Bitter Orange (*Citrus aurantium* var. amara) Extracts and Constituents (±)-*p*-Synephrine [CAS No. 94-07-5] and (±)-*p*-Octopamine [CAS No. 104-14-3]

Review of Toxicological Literature

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Abstract

Citrus aurantium (bitter orange, Seville orange, sour orange) and extracts of its dried fruit and peel have been used for years in traditional Western medicines, Chinese and Japanese herbal medicines, and as flavorings in foods and beverages. Bitter orange is regulated by the U.S. FDA; the peel, oil, extracts, and oleoresins are Generally Recognized as Safe as a direct additive to food. The peel is used in many pharmacopoeial preparations for flavoring and treatment of digestive problems. Oils from the fruit, peel, and other plant parts are also used for flavoring and fragrance and do not contain alkaloids. *p*-Octopamine and *p*-synephrine, the most frequently mentioned biogenic amines found in bitter orange extract, are agonists for both α- and β-adrenoceptors (octopamine has weak β-adrenergic activity). Octopamine is used as a cardiotonic and to treat hypotension. Synephrine is used as a vasoconstrictor in circulatory failure. 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. Health concerns about bitter orange and other compounds in dietary supplements led to the FDA's collection of product labels for the Center for Food Safety and Applied Nutrition to evaluate possible health risks. Concentrations of synephrine measured in several dietary products were generally lower than that declared on the label. Following intraveous administration of tritiated synephrine to patients, ~66 and 10% of the administered dose was recovered in the urine as deaminated *p*-hydroxymandelic acid and unchanged synephrine, respectively (2.5% of the dose was recovered as unchanged synephrine following ingestion). Trace amounts of *p*- and *m*-octopamine and *p*- and *m*-synephrine were found in plasma and platelets of healthy human subjects. Low concentrations of octopamine, thought to be a metabolic byproduct of catecholamine biosynthesis, are present in the central nervous system and peripheral tissues of vertebrates. Oral exposure of mice to extracts of *C. aurantium* peel suppressed cell viability of splenocytes and thymocytes. Oral exposure of rats to aqueous extracts of the immature fruit caused decreased food intake and body weight gain, ventricular arrhythmias, and inhibited Type I allergic reactions. Synephrine affected the sense organs and caused convulsions, dyspnea, cyanosis, and respiratory stimulation in other animal studies. Octopamine and synephrine were not mutagenic in *Aspergillus nidulans* diploid strains or L5178Y mouse lymphoma cells, respectively.

Executive Summary

Nomination

Bitter orange extract was nominated in 2002 for toxicological studies by a private individual based on its widespread and increasing use in "ephedra-free" dietary supplements and limited data to demonstrate its safety for this use. Bitter orange peel and its constituent synephrine are present in dietary supplements with and without ephedra (ma huang) for weight loss. Synephrine and other bitter orange biogenic amine constituents—octopamine, *N*-methyltyramine, tyramine, and hordenine—have adrenergic activity and may result in cardiovascular or other adverse effects similar to those induced by ephedra alkaloids.

Nontoxicological Data

Citrus aurantium var. [or subspecies] amara belongs to the order Geraniales and the family Rutaceae. It is a native to Southeast Asia and a wild crop in Venezuela. Bitter orange peel (also called bitter orange, sour orange, *Aurantii cortex*, *Aurantii Amari Cortex*, Bigarade orange, and Seville orange) consists of the fresh or dried outer portion of the pericarp of the ripe fruit of *C. aurantium*, var. Bigaradia, Hook. f. The main constituents of orange peel are the volatile oil and an amorphous, bitter glucoside called aurantiamarin. Other constituents include hesperidin, a colorless, tasteless, crystalline glucoside occurring mainly in the white zest of the peel, isohesperidin, hesperic acid, aurantiamaric acid, and a bitter acrid resin. In the peel of immature fruits, the chief constituents are naringin and hesperidin, while in the fruit flesh it is umbelliferone. *p*-Octopamine and *p*-synephrine, both adrenergic agonists, are the most frequently mentioned biogenic amines found in bitter orange peel and other *C. aurantium* preparations and other species such as *C. reticulata* Blanco (mandarin orange).

Chemical Analysis: The essential oils from bitter orange peel have been examined by thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), and gas chromatography (GC), alone or accompanied with flame ionization detector (GC-FID) or mass spectrometry (GC-MS). Methods for the quantitation of synephrine in the peel of citrus fruit (mature and immature) and decoctions of Chinese crude drugs include GC, TLC, and HPLC, alone or with various detectors. Using capillary electrophoresis (CE) with a chiral selector, synephrine enantiomers can be separated. Liquid chromatography-mass spectrometry (LC-MS) and LC-tandem MS methods allow the measurement of synephrine in dietary supplements.

Commercial Availability: *C. aurantium* var. amara is chiefly cultivated in southern Spain and Sicily. In the United States, they are grown as a crop in Arizona, where the peak of production is in January. Two companies in the United Kingdom supply bitter orange products. Additionally, there are numerous suppliers of multicomponent dietary supplements (especially for weight loss) containing bitter orange.

Uses: Bitter oranges are grown mainly for processing as preserves (especially, marmalade) and syrup due to their tart flavor. The essential oil is used to add fragrance to beverages and liqueurs (e.g., Curacao and Grand Marnier), sweet foods like candies and cakes, soaps, detergents, cosmetics, perfumes, and in sauces for meats and poultry. Orange peel is used in many pharmacopoeial preparations as a flavoring agent, stomachic, and carminative. Additionally, bitter orange is reported to be an expectorant, laxative, hypertensive, nervine, tonic, and diuretic. The extract has been added to many dietary supplements and herbal weight loss formulas (as an alternative to ephedra). Synephrine is the "active" ingredient of bitter orange and functions as a stimulant. It is also used as a vasoconstrictor in circulatory failure. Octopamine is used as a cardiotonic and to treat hypotension.

Human Exposure: Exposure to bitter orange peel and its constituents occurs primarily via ingestion of the fruit itself or its products (e.g., orange juice, marmalade, flavorings and fragrances, and dietary supplements). Weight loss formulas usually contain 100-200 mg bitter orange extract, which provides

10-40 mg synephrine per dose. Extracts can contain up to 95% synephrine. Exposure can also result from peel oil used in aromatherapy and flavoring.

Regulations: Bitter orange is regulated by the Food and Drug Administration (FDA). Although *C. aurantium* is listed in its Poisonous Plants Database, *C. aurantium* orange oil extract, peel, flowers, and leaf are listed in its food additive database, an inventory often referred to as "Everything" Added to Food in the United States (EAFUS). Additionally, bitter orange peel, oil, oleoresins, and extracts are Generally Recognized as Safe (GRAS) as a direct additive to food. In frozen concentrated orange juice, the volume of bitter orange that may be added cannot exceed 5%.

The International Fragrance Association (IFRA) standard for bitter orange peel oil is 1.25% in products applied to areas of the skin that are exposed to the sun. The National Collegiate Athletic Association (NCAA) has included synephrine from *C. aurantium*, zhi shi, and bitter orange on its list of substances banned for student athletes.

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.

In volunteers receiving skin applications of bitter orange peel oil expressed (5 $\mu L/cm^2$ of 100% oil) under occlusion followed by exposure to visible light or ultraviolet A, all subjects exhibited phototoxic reactions.

Toxicological Data

Chronic exposure, cytotoxicity, carcinogenicity, or tumor initiation/promotion studies were not available.

Chemical Disposition, Metabolism, and Toxicokinetics: Low concentrations of octopamine are present in the central nervous system and peripheral tissues of vertebrates; it is thought to be a metabolic byproduct of catecholamine biosynthesis. In rats, *m*- and *p*-octopamine are present in equal concentrations in the heart, spleen, and liver. Both are also present in the adrenals, vas deferens, brain, kidney, large intestine, bladder, and lungs, although the concentration of *m*-octopamine is 30 to 60% of the levels of *p*-octopamine in the these organs. The main urinary metabolites of the *o*-, *p*-, and *m*-octopamine (norfenefrine) are *o*-hydroxymandelic acid (OHMA), *p*-hydroxymandelic acid (PHMA), and *m*-hydroxymandelic acid (MHMA), respectively.

Following i.v. administration of tritiated synephrine to six patients, about 66% and 10% of the administered dose was recovered in the urine as deaminated PHMA and unchanged synephrine, respectively. Oral ingestion by ten patients followed a similar elimination pattern, except that only 2.5% of the dose was recovered as unchanged synephrine. The biological half-life was about two hours. Three healthy adult males given a plant free, controlled diet for three days provided urine samples containing no synephrine. After eating *Citrus unshiu* pulp, all three excreted the conjugated form of synephrine in the urine. The authors concluded that *l*-synephrine in fruit was converted to the conjugated form of synephrine, and that *l*-synephrine underwent chiral conversion to *d*-synephrine *in vivo*.

Trace amounts of *p*- and *m*-octopamine and *p*- and *m*-synephrine were found in plasma and platelets of healthy human subjects. There were no significant differences in the urinary concentrations of *p*- and *m*-

octopamine or *p*- and *m*-synephrine in a study comparing both hypertensive and normotensive human subjects. The metabolism of both amines to dopamine is mediated by human CYP2D6.

Acute Exposure: In male mice treated by gavage with essential oil from *C. aurantium* peel (0.5 or 1.0 g/kg), the latency period of tonic seizures was increased. In addition, treatment with the higher dose significantly increased hypnotic activity and anxiolytic activity. Sprague-Dawley rats orally administered a single dose of TJ-41 (up to 10 g/kg) or TJ-43 (2 or 8 mg/kg), herbal drug mixtures containing ~10% of *C. aurantium* peel, showed no toxic signs. Additionally, no deaths were reported.

Subcutaneous (s.c.) injection of *p*-synephrine (1500 mg/kg [8.971 mmol/kg]) caused effects on the sense organs, convulsions, and respiratory stimulation in mice. Administration of (*R*)-(-)-*p*-synephrine (700 mg/kg [4.19 mmol/kg]) and the *S*-enantiomer (1500 mg/kg [8.971 mmol/kg]) by s.c. injection also caused convulsions, as well as dyspnea and cyanosis in mice; oral administration of the compounds (1 mg/kg [6 µmol/kg] *R* and 0.3 mg/kg [2 µmol/kg] *S*) increased body temperature.

Short-term and Subchronic Exposure: No drug-related abnormalities in body or organ weights, food consumption, ophthalmology, urinalysis, hematological examination, blood biochemical examination, gross pathological examination, or microscopic examination were observed in Sprague-Dawley rats orally given TJ-41 (500 or 2500 mg/kg), an herbal drug mixture containing ~10% of *C. aurantium* peel, daily for 13 weeks. Similar results were seen with another herbal mixture containing ~10% peel, TJ-43 (125, 500, or 2000 mg/kg).

Daily oral administration (gavage) of *C. aurantium* fruit extracts standardized to 4 or 6% synephrine to male Sprague-Dawley rats for 15 days caused a significant dose-dependent decrease in food intake and body weight gain. Some deaths occurred in all treatment groups. No marked changes were seen in blood pressure; however, ventricular arrhythmias with enlargement of the QRS complex were observed.

In a study of *p*-synephrine stereoisomers, *S*-(+)-*p*-synephrine appeaed to possess more antidepressant-like acitivity than *R*-(-)-*p*-synephrine.

Reproductive and Teratological Effects: In rats, daily intramuscular injection of synephrine (55 or 110 mg/kg [0.33 or 0.66 mmol/kg]) on days 7-16 of pregnancy decreased the number of uterine implants and viable fetuses, increased mean fetal weight and the number of micro fetuses, and retarded cranial and thoracic ossification. Additionally, renal and intestinal hemorrhage, brain hypoplasia, and unilateral microphthalmia were reported in some fetuses.

Genotoxicity: In *Aspergillus nidulans* diploid strains, octopamine (dose not provided [n.p.]) did not induce non-disjunction or crossing-over. In the L5178Y mouse lymphoma assay, synephrine (20-3600 µg/mL [120 µM-21.53 mM]) was inactive.

Immunotoxicity: Oral administration of extracts of the peel of the *C. aurantium* fruit, as well as of the immature fruit, led to decreased cell viability of splenocytes and thymocytes in BALB/c mice. Oral administration of aqueous extracts of the immature fruit also inhibited Type I allergic reactions in rats.

Other Data

Effects on Cell Growth

Compounds isolated from extracts of immature *C. aurantium* fruit inhibited cell growth in mouse leukemia L1210 and human erythroleukemia K562 cells *in vitro*, while methoxylated flavones isolated from extracts of the peel induced cell differentiation in mouse myeloid leukemia (M1) and human promyelocytic leukemia (HL-60) cells.

Neurological Effects
Neurological effects reported for synephrine and octopamine included increased locomotor activity, pre- and postsynaptic effects, anti-depressive activity, agonistic response toward trace amine receptors, inhibition of smooth muscle contraction, and depression of neurological function.

Effects on Enzymes
Sour orange juice inhibited microsomal CYP3A-mediated testosterone 6β-hydroxylation, whereas sweet orange juices did not. *C. aurantium* crude drugs showed the same effects. Octopamine, but not synephrine, inhibited cytochrome P450c11 *in vitro*. In a study of the inhibitory effects of citrus fruit extracts from 42 species and cultivars on rat platelet cyclooxygenase and lipoxygenase, the albedo extract of *C. aurantium* had the highest lipoxygenase inhibitory activity. Additionally, bitter orange juice extract had an inhibitory effect on intestinal P-glycoprotein-related efflux carriers *in vitro*.

Cardiovascular Effects
In humans, rats, guinea pigs, cats, and/or dogs, synephrine, octopamine, and extracts of *C. aurantium* have been evaluated for effects on the cardiovascular system that include changes in blood pressure, cardiovascular toxicity, contractility and excitability of the heart muscle, and/or adrenergic activity.

Effects on Blood and Hematopoietic System
Hypertensive rats administered synephrine via gavage for eight days had significantly reduced portal venous pressure, portal tributary blood flow, and cardiac index. When infused into hypertensive rats, synephrine dose-dependently reduced portal venous pressure and elevated mean arterial pressure.

Bitter orange peel (in Jupi, a Chinese herbal prescription) promoted human platelet aggregation.

Miscellaneous Studies
In white fat cells of the rat, hamster, and dog, synephrine partially stimulated lipolysis. Octopamine was fully lipolytic in garden dormouse, rat, hamster, and dog fat cells but was inefficient in guinea pig or human fat cells. Bitter orange peel stimulated lipolysis in mature 3T3-L1 cells.

Synephrine (dose n.p.), isolated from the leaves and juice of immature fruit, inhibited uterine contraction induced by serotonin in rats. D,L-Synephrine (10 μM [1.7 μg/mL]) stimulated aromatization of testosterone in Sertoli cell-enriched cultures from 19-day-old rats. Additionally, octopamine and synephrine (1 μM - 1 mM) enhanced progesterone production in bovine luteal cells *in vitro*; addition of norepinephrine and epinephrine significantly increased the effect.

<u>Receptor Pharmacology of Biogenic Monoamines</u>
Terminology in the NLM MeSH Database indicates that structural analogs of ephedrine, epinephrine, and norepinephrine are agonists for both α- and β-adrenoceptors, while synephrine and octopamine are α-adrenoceptor agonists and tyramine is an indirect sympathomimetic. However, some studies report that synephrine and octopamine were also agonists for β-adrenoceptors. Results from studies of both receptors are discussed.

In vitro studies of the adrenergic activity of *p*-octopamine and *p*-synephrine compared to that of norepinephrine showed that p-octopamine and p-synephrine were generally orders of magnitude less active than norepinephrine on both the α- and β-adrenoceptors. *p*-Octopamine was more active than *p*-synephrine in some studies and less or equally active in other studies. *m*-Octopamine (norfenefrine) and *m*-synephrine (phenylephrine) were generally more potent than their para counterparts.

Structure-Activity Relationships

This 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.

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1.0 Basis for Nomination

Bitter orange extract was nominated in 2002 for toxicological studies by a private individual based on its widespread and increasing use in "ephedra-free" dietary supplements and limited data to demonstrate its safety for this use. Bitter orange peel and its constituent synephrine are present in dietary supplements with and without ephedra (ma huang) for weight loss. Synephrine and other bitter orange biogenic amine constituents—octopamine, *N*-methyltyramine, tyramine, and hordenine—have adrenergic activity and may result in cardiovascular or other adverse effects similar to those induced by ephedra alkaloids.

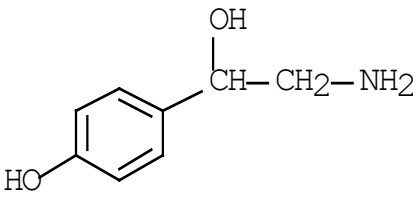
2.0 Introduction

Citrus aurantium var. [or subspecies] amara belongs to the order Geraniales and the family Rutaceae. It is a native to Southeast Asia and a wild crop in Venezuela (Quintero et al., 2003). The Latin name for the peel of the citrus fruit is *Aurantii Nobilis Pericarpium*, and that for the immature fruit is *Aurantii Fructus Immaturus* (Takei et al., 1999). The pharmacopoeial name for bitter orange peel is *Aurantii pericarpium*, and the fruit is called zhi shi in traditional Chinese medicine (Am. Botanical Council, 2000; Supplement Watch, undated). Constituents of *C. aurantium* include flavonone glycosides and flavone aglycones, coumarins, psoralens, polymethoxyflavones, waxes, aldehydes, amines, and monoterpenes (ARS USDA, 1999; Boelens and Jimenez, 1989; Chouchi et al., 1996). Many studies have reported results from the determination of bitter orange peel constituents, often noting differences in oil composition from unripe and ripe fruit (e.g., Boelens and Jimenez, 1989). The cold-pressed oil from the cortex contains mainly monoterpenes (chiefly limonene [77.9%]), sesquiterpenes, aldehydes, alcohols, and one ketone (nootkatone) (Quintero et al., 2003). The psoralens found in *Citrus* species include bergapten and epoxybergamottin (Dugo et al., 1996).

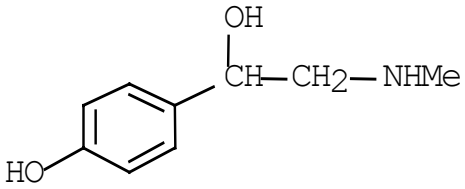
This report presents data on bitter orange peel, its essential oil, and its constituents, *p*-octopamine and *p*-synephrine, the most frequently noted biogenic amines found in the peel. Unless otherwise stated, "octopamine" and "synephrine" will be used to designate the *para* isomers; in most cases, when authors did not specify the form, the *para* form was meant.

Source: http://www.rain-tree.com/orange.htm

(±)-*p*-Octopamine
[104-14-3]



(±)-*p*-Synephrine
[94-07-5]



2.1 Chemical Identification and Analysis

2.1.1 Chemical Identification

Bitter Orange Peel

Bitter orange peel (also called bitter orange, sour orange, *Aurantii cortex*, *Aurantii Amari Cortex*, Bigarade orange, and Seville orange) consists of the fresh or dried outer portion of the pericarp of the ripe fruit of *Citrus aurantium*, var. Bigaradia, Hook. f. In traditional Chinese medicine, zhi qiao is prepared from the dried peel of immature green fruit, and zhi shi is prepared from dried fruit. Bitter oragnge is distinguished from the sweet orange by its deeper orange-red color, rough rind, bitter peel, sour pulp, and more broadly winged leaf stalk. The main constituents of the orange peel are the volatile oil and an amorphous, bitter glucoside called aurantiamarin. Other constituents include hesperidin ($C_{44}H_{28}O_{14}$), a colorless, tasteless, crystalline glucoside occurring mainly in the white zest of the peel, isohesperidin ($C_{44}H_{26}O_{24}\cdot 5H_2O$), hesperic acid, aurantiamaric acid, and a bitter acrid resin (Am. Botanical Council, 2000; Br. Pharm. Codex, 1911; Budavari, 1996; Felter and Lloyd, 1898). In the peel of immature fruits, the chief constituents are naringin and hesperidin, while in the fruit flesh it is umbelliferone (Wu and Sheu, 1992).

The CAS Registry Number for bitter orange peel oil is 68916-04-1 and for bitter orange peel extract is 977081-87-0.

p-Octopamine and *p*-Synephrine

p-Octopamine and *p*-synephrine, both adrenergic agonists, are the most frequently mentioned biogenic amines found in bitter orange peel and other *C. aurantium* preparations and *Citrus* species such as *C. reticulata* Blanco (mandarin orange). Most of the literature is indexed with the CAS RNs of the racemic mixtures of these agents; however, the enantiomers have also been reported. Octopamine is the phenol analog of norepinephrine (noradrenaline). Tyramine, *N*-methyltyramine, and, less often, hordenine are often determined. The widely occurring stachydrine—unlike the other amines in bitter orange, which are 4-hydroxyphenylethanolamine derivatives—is a 2-carbonyl-1,1-dimethylpyrrolinium inner salt (Am. Botanical Council, 2000; Budavari, 1996).

Octopamine ([$C_8H_{11}NO_2$]; mol. wt. = 153.18) is also called:

1-(*p*-Hydroxyphenyl)-2-aminoethanol
4-Hydroxyphenethanolamine
4-(2-Amino-1-hydroxyethyl)phenol
α-(Aminoethyl)-*p*-hydroxybenzyl alcohol

α-(Aminomethyl)-4-hydroxybenzenemethanol
α-(Aminomethyl)-*p*-hydroxybenzyl alcohol
Analet
Benzenemethanol, α-(aminomethyl)-4-hydroxy- (9CI)
Benzyl alcohol, α-(aminomethyl)-*p*-hydroxy- (6CI, 8CI)
β-Hydroxy-β-(4-hydroxyphenyl)ethylamine
p-Hydroxyphenylethanolamine
ND50
Norden
Norfen
Norphen
Norsympathol
Norsympatol
p-Norsynephrin
Norsynephrine
Norton
Octapamine
(±)-Octopamine
DL-Octopamine
p-Octopamine
p-Oxyphenyl aminoethanol
(*RS*)-Octopamine
Win 5512
WV-569 (drug code)

Sources: Budavari (1996); ChemIDplus (undated-a); Registry (2003a)

Synephrine ([$C_9H_{13}NO_2$]; mol. wt. = 167.21) is also called:

1-Hydroxy-4-[(1-hydroxy-2-methylamino)ethyl]benzene
1-(4-Hydroxyphenyl)-2-methylaminoethanol
1-(4-Hydroxyphenyl)-*N*-methylethanolamine
4-Hydroxy-α-[(methylamino)methyl]benzenemethanol
4-[1-Hydroxy-2-(methylamino)ethyl]phenol
dl-1-(4-Hydroxyphenyl)-2-methylaminoethanol
RS-1-(4-Hydroxy-2-(methylamino)ethanol
Analeptin
Benzenemethanol, 4-hydroxy-α-[(methylamino)methyl]- (9CI)
Benzyl alcohol, *p*-hydroxy-α-[(methylamino)methyl]- (8CI)
Ethaphene
p-Hydroxy-α-[(methylamino)methyl]benzyl alcohol
p-Hydroxyphenylmethylaminoethanol
p-Methylaminoethanolphenol
(±)-*N*-Methyloctopamine
β-Methylamino-α-(4-hydroxyphenol)ethyl alcohol
Methylaminomethyl 4-hydroxyphenyl carbinol
NSC 166285
NSC 170956
Oxedrine
p-Oxedrine

α-(4-Oxyphenyl)-α-oxy-β-methylaminoaethan (German)
Parakorper (German)
Parasympatol
Pentedrin (German)
(±)-S38537-9
Simpalon
Simpatol
Sympaethamine
Sympathol
Synefrin (Czech)
Synephrin
(±)-Synephrine
DL-Synephrine
p-Synephrine
Synthenate

Sources: Budavari (1996); ChemIDplus (undated-b); Registry (2003b)

2.1.2 Chemical Analysis

The essential oils from bitter orange peel have been examined by thin-layer chromatography (TLC) and by gas chromatography (GC), alone or accompanied with flame ionization detector (GC-FID) or mass spectrometry (GC-MS) (Quintero et al., 2003; Salib et al., 1978; Tuzcu et al., 1985; Veriotti and Sacks, 2002). The composition of the oxygen heterocyclic fraction of bitter orange essential oil has been obtained by high-performance liquid chromatography (HPLC) (Dugo et al., 1996; Fisher and Trama, 1979).

Methods for the quantitation of synephrine in the peel of citrus fruit (mature and immature) and decoctions of Chinese crude drugs include GC, TLC, and HPLC (Takei et al., 1999; Hashimoto et al., 1992), alone or with various detectors (e.g., HPLC with electrospray MS detection [He et al., 1997]). Additionally, its presence in crude drugs and dried fruit and fruitpeel was determined by ion-pair HPLC [sodium dodecyl sulfate as the ion-pair reagent] (Ohta et al., 1994; Zheng et al., 1983). Hesperidin and synephrine can be quantitated in the dried rind of the ripe fruit of mandarin oranges (*C. reticulata Blanco*; Chinese traditional herbal drug, *Pericarpium Citri Reticulatae*) using capillary electrophoresis with electrochemical detection (CE-ED). The detection limits were 6.54×10^{-7} and 4.96×10^{-7} M, respectively (Chen et al., 2002). Using CE with a chiral selector, synephrine enantiomers can be separated (De Boer et al., 1999). Volatile compounds and methyl esters in bitter orange have been identified using GC; limonene was the main compound in the monoterpenes, and the mean concentration of fatty acids was 678 mg/L (Moufida and Marzouk, 2003). The content of the adrenergic amines *dl*-octopamine, *dl*-synephrine, and tyramine in fruits, extracts, and herbal products of *C. aurantium* L. var. amara were determined using HPLC with UV detection; the direct separation of synephrine enantiomers was done with HPLC on a β-cyclodextrin stationary phase (Pellati et al., 2002; Kusu et al., 1996).

FDA scientists have developed liquid chromatography-mass spectrometry (LC-MS) and LC-tandem MS methods for the measurement of synephrine in dietary supplements (Niemann and Gay, 2003). Octopamine and synephrine levels have been determined in urine by gas chromatography-negative ion chemical ionization mass spectrometry (GC-NICIMS) (Watson et

al., 1990). HPLC with electrochemical detection has also been used to assess synephrine and octopamine concentrations in human plasma and platelets (D'Andrea et al., 2003a).

2.2 Physical-Chemical Properties

Property	Information	Reference(s)
	Oil	
Physical State	pale yellow liquid	Budavari (1996)
Density (d_{25}^{25})	0.842-0.848	
Water Solubility	very slightly	
Soluble in:	alcohol (absolute or 4:1 with glacial acetic acid)	
	p-Octopamine [104-14-3]	
Boiling Point (ºC)	360.7±27.0 @ 760.0 Torr	Registry (2003a)*
Flash Point (ºC)	172.0±42.7	
Vapor Pressure (Torr)	7.82×10^{-6} @ 25 ºC	
K_{OC}	1 @ pH 1, 4, 7; 2.86 @ pH 8; 5.00 @ pH 10	
logP	-0.276±0.259	
Molar Solubility	≥ 1 M @ pH 1, 4, 7, 8, 10	
	D(-)-*Octopamine [876-04-0]*	
Physical State	crystals from hot water	Budavari (1996)
Melting Point (ºC)	>250 (decomposes) for a compound formed at ~160 ºC	
	DL-*Octopamine hydrochloride [770-05-8]*	
Physical State	crystals	Budavari (1996)
Deompositin Point (ºC)	170	
Soluble in:	water	
	p-Synephrine [94-07-5]	
Physical State	crystals	Budavari (1996)
Melting Point (ºC)	184-185	
Boiling Point (ºC)	341.1±27.0 @ 760 Torr	Registry (2003b)*
Flash Point (ºC)	163.4±25.7	
Vapor Pressure (Torr)	3.18×10^{-5} @ 25 ºC	
K_{OC}	1 @ pH 1, 4, 7, 8; 6.04 @ pH 10	
logP	-0.030±0.269	
Molar Solubility	≥ 1 M @ pH 1, 4, 7, 8, 10	
	p-Synephrine hydrochloride [5985-28-4]	
Physical State	crystals	Budavari (1996)
Melting Point (ºC)	151-152	
Soluble in:	water	
	p-Synephrine tartrate [16589-24-5]	
Physical State	crystals	Budavari (1996)
Melting Point (ºC)	188-190 (some decomposition)	
Soluble in:	alcohol and water	

*calculated properties using Advanced Chemistry Development (ACD) Software Solaris V4.67 (©1994-2003ACD)
Note: Calculated properties for the other chemicals are available from Registry.

Synephrine is stable to air and light (Budavari, 1996). It is chemically similar to ephedrine and pseudoephedrine (Supplement Watch, undated).

Although the available literature indicates that the synephrine content of the bitter orange originates in the peel, publications regarding peel extraction and analytical techniques that

describe synephrine concentrations were not found. Information about peel constituents was limited to flavonoid content, for example peels extracted for hesperidin/hesperetin (Nguyen and Lee, 1987; Nakabayashi, 1960 [Japanese patent]). Concentrations of synephrine and other constituents, in extracts of bitter orange fruit, peel, and/or oil are given **Table 1**. The concentration of synephrine in the dried fruit extracts are more than ten fold higher than that reported for the fresh fruit extracts. Additional constituents found in *C. aurantium* are listed in Appendix B.

Nieman and Gay [FDA] (2003) determined ephedrine alkaloids in 48 trade-named dietary supplements containing ephedra and/or (+/-)-synephrine. The analytical concentration of (+/-)-synephrine generally differed from that declared on the label. Energy Fuel (ephedra-free) contained 13.4% (+/-)-synephrine and the label declared 19.5%. In two other products, (+/-)-synephrine concentrations of 20% and 25% were declared, yet none were found. The product with the highest (+/-)-synephrine concentration, 16.9%, had a declared concentration of 16%. In ten other synephrine-containing products, (+/-)-synephrine concentrations ranged from 2.02 to 6.75% compared to declared concentrations of 3.0 to 5.2%. Clembutrx contained 12.7% (+/-)-synephrine, but a declared concentration could not be found.

Table 1. Concentrations of Constituents in Fruit, Peel, Oil, and Extracts

Sample Matrix	Extraction Method	Analytical Method	Synephrine Concentration	Other Constituents	Reference(s)
fresh fruit pulp	water	RP-HPLC/UV detector	0.020 % (92.389 % *l*-enantiomer)	Octopamine < 0.9 ng/µl[a] Tyramine < 1.2 ng/µl[a]	Pellati et al. (2002)
fresh fruit pulp	water	HPLC-DAD on β-cyclodextrin stationary phase	(*dl*-): 0.027 % (*l*-): 0.025 % (*d*-): 0.002 %	NG	Pellati et al. (2002)
Seville (sour) orange juice	freshly squeezed	HPLC/UV detector; direct injection	56.9 +/- 0.52 µg/mL	Octopamine not detected	Penzak et al. (2001)
pulverized dried fruits	water	RP-HPLC/UV detector	0.352 %	Octopamine < 0.9 ng/µl[a] Tyramine < 1.2 ng/µl[a]	Pellati et al. (2002)
pulverized dried fruits	water	HPLC-DADon β-cyclodextrin stationary phase	(*dl*-): 0.380 % (*l*-): 0.380 % (*d*-): < 2.3 ng/µl[a]	NG	Pellati et al. (2002)
powdered peel and fruit	methanol	TLC/UV absorbance	0.12-1.98 % (aggregate range for 11 samples of fruit & peel)	NG	Chen and Hou (1984)
dried immature fruits	1.2 g. powd. fruit; 80% ethanol at 90 °C for 2 hr	HPLC/UV detector/ES/MS for flavonoids	detected but not quanitated in a 120 mg residue	Flavonoids	He et al. (1997)
pulverized dried extracts from local Italian markets (unspecified matrix)	water	RP-HPLC/UV detector	3.003-3.079 % (100% *l*-enantiomer)	Octopamine 0.023-0.028 % Tyramine 0.055-0,056 %	Pellati et al. (2002)
pulverized dried extracts from local Italian markets (unspecified matrix)	water	HPLC β-cyclodextrin stationary phase	(*dl*-): 2.847-2.996 % (*l*-): 2.847-2.996 % (*d*-): < 2.3 ng/µl[a]	NG	Pellati et al. (2002)

Table 1. Concentrations of Constituents in Fruit, Peel, Oil, and Extracts (Continued)

Sample Matrix	Extraction Method	Analytical Method	Synephrine Concentration	Other Constituents	Reference(s)
immature fruit peel extract (see text)	water/ethanol	HPLC	6.0-10%	NG	Renaissance Herbs (2003)
oil from fresh Tunisian bitter orange juice	fruits cold pressed 1:1 diethyl ether-pentane extraction of juice	GC/FID detector	NG	α-Pinene 1.498 % Limonene 90.335 % Linalool 1.461 % α-Terpineol 1.068 % 3-Heptanone 1.2467 % other constituents <1%	Moufida and Marzouk (2003)
peel oil	steam distillation	GC/TOF MS	NG	Myrcene 2.05% Limonene 3.42% *p*-Cymene 7.24% Linalool 0.10 %	Veriotti and Sacks (2002)
peel oils from on-tree fruits	NG	NG	NG	Limonene 92-95% Linalol & linalyl acetate 0.3-3.2%	Boelens and Jimenez (1989)

[a] Level of detection. Abbreviations: DAD = diode array detectio; FID = flame ionization detection; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; NG = not given; RP = reverse phase; TLC = thin layer chromatography; TOF = time of flight; UV = ultraviolet

2.3 Commercial Availability

C. aurantium var. amara is chiefly cultivated in southern Spain Seville oranges) and Sicily (Palermo). In the United States, they are grown as a crop in Arizona (Br. Pharm. Codex, 1911; Luckett, 2003). The oil from *C. aurantium* flowers is imported from the West Indies and sold in amounts from 0.5 to 32 oz. by CedarVale Natural Health Inc. (Cedar Vale, KS) (CedarVale Nat. Health, 2003). Two companies in the United Kingdom supply bitter orange products: bitter orange essential oil is sold as 2.5-mL up to 1-L volumes from Alexander Essentials, and bitter orange peel tincture is available from Artemis Herbs Limited in 50- and 100-mL quantities (Alexander Essentials, 2003; Artemis Herbs Ltd., 2003).

A bulk supplier of powdered *C. aurantium* "peel" extract sells their product as Zhi Shi with 6% or 10% synephrine in 25-kg quantities. Zhi shi is the immature bitter orange fruit, and is likely the actual starting material for these products. (The details for this extract were similar to the descriptions of immature fruit extracts sold in bulk.) Despite the numerous dietary supplements advertised on the Internet as containing "bitter orange peel extract," the additive used is more likely the dried alcohol-water extracts of the immature fruit that is sold as a powder in bulk quantities. Other bulk suppliers of *C. aurantium* powder extract include Hainan Zhongxin Chemical Co., Ltd. (100 kg [220 lb]), Shanghai Herbsea Nutraceutical Inc., and Zhejiang Sinour Industry Co., Ltd., and (Shanghai Herbsea Nutraceutical Inc., 2004; Zhejiang Sinour Industry Co., 2003; ZXCHEM, 2002). In the United States, FCC Products, Inc. (Livingston, NJ) sells the extract with 10% synephrine (FCC Products, Inc., undated). A bulk supplier of *C. aurantium* peel tincture (alcohol-water; maximum quantity sold is five gallons) was also found but there was no mention of synephrine or other constituents in the material safety data sheet (Liberty Natural Products, 2004).

Numerous suppliers of multicomponent dietary supplements for weight loss and other purposes exist, with many of the products containing bitter orange. Examples include the following:

- Bitter Orange Extract [standardized to 6% synephrine],

- Xenadrine®-EFX™ [bitter orange standardized for synephrine, *N*-methyltyramine, hordenine, octopamine, and tyramine],
- Ultra Diet Phen Calm Mood [bitter orange peel standardized extract 570 mg, yielding 24 mg synephrine],
- Lipotrim [27 mg bitter orange peel]
- Dexatrim Natural [12 mg bitter orange peel powdered extract per caplet], and
- MRM Meta-Burn™ XTP [300 mg octopamine hydrochloride (bitter orange and synephrine not listed)]

Sources: Nature's Way (2003); Cytodyne Technologies (2003); HerbsMD (2002); Integra Nutrition Inc. (undated); SlimStore.com (undated); and 1fast400.com (2004), respectively.

(±)-Synephrine is available from Boehringer Ingelheim Pharma GmbH and Company (Germany) in 25-kg fiber drums (Boehringer Ingelheim, 2003). Synephrine extract, with 4% to 95% content, is supplied by Northwest Botanicals, Inc. (Grants Pass, OR) in 5-kg/bag or 25-kg/drum (Northwest Botanicals, Inc., 2003). Authentic synephrine for experimental use is available from Sigma (St. Louis, MO) (Huang et al., 1995; Takei et al., 1999).

3.0 Production Processes

For pharmaceutical preparation, the recommended formula for bitter orange peel fluid extract or tincture consists of a menstruum composed of two parts alcohol and one part water (Hughes, 1926; Martin et al., 1961; Robbins, 1883).

p-Synephrine is prepared synthetically by the hydrogenation of ω-methylamino-4-hydroxyacetophenone in water in the presence of platinum or palladium. *p*-Octopamine is biosynthesized by β-hydroxylation of tyramine by the enzyme dopamine β-hydroxylase (Budavari, 1996).

4.0 Production and Import Volumes

No data were available.

5.0 Uses

Bitter Orange Peel and Its Oil

Bitter oranges are grown mainly for processing as preserves (especially, marmalade) and syrup due to their tart flavor. Their flesh is also used in baking. The essential oil extracted from the cortex of *C. aurantium* amara is used to add fragrance to beverages and liqueurs, sweet foods like candies and cakes, soaps, detergents, cosmetics, and perfumes. Specifically, oil of Seville (from the leaves and zest) is used as a flavoring agent in Curacao, Grand Marnier, Cointreau, and orange flower water, as well as in sauces for meats and poultry (Am. Botanical Council, 2000; Lin et al., 1986; Luckett, 2003; Quintero et al., 2003; Victoria Packing Corp., 2001).

Orange peel is used in many pharmacopoeial preparations as a flavoring agent, stomachic, and carminative (Br. Pharm. Codex, 1911). Bitter orange is also an expectorant, laxative, hypertensive, nervine, tonic, and diuretic. In the United States, its purported uses include prevention of cancer of the skin, breast, colon, etc. [Worldwide uses are presented—e.g., use as an antiseptic and purgative in Haiti or as a narcotic, sedative, and treatment for scurvy in Turkey] (Flora Manufacturing and Distributing Ltd., undated; Raintree Nutrition, Inc., 2002). Oil of

bitter orange is used as a remedy for treatment-resistant fungal skin diseases. Bitter orange tincture or extract is primarily used for heartburn (Am. Botanical Council, 2000).

Powdered extracts (water/alcohol) of dried immature fruit and/or peel have been added to many dietary supplements and herbal weight loss formulas (as an alternative to ephedra) (Am. Botanical Council, 2000). Synephrine is the "active" ingredient of bitter orange and functions as a stimulant (Brooks et al., 2003). Consequently, products containing synephrine or octopamine (or other alkaloids, such as *N*-methyltyramine) obtained from bitter orange peel (as well as the leaves and immature, ripe fruit) have been manufactured to produce and/or maintain weight loss, improve physical fittness, and increase lean muscle mass (Jones 2002a,b). Patented methods and "thermogenic" compositions for weight loss also contain bitter orange, synephrine, ephedrine, or other norepinephrine-stimulating compounds (Kuhrts, 2002). However, the claims that synephrine is a safe and effective weight-loss substitute for ephedra have not been proven (Brooks et al., 2003). Additionally, one paper reports that the peel oil extracts of bitter orange may contain potential insecticides (Mwaiko, 1992).

Octopamine

Octopamine is used in Chinese medicine as a cardiotonic and to treat hypotension. The natural *D(-)* form is more potent that the *L(+)* form in producing cardiovascular adrenergic responses. In some invertebrates, it can also serve as a neurotransmitter (ChemIDplus, undated-a).

Synephrine

Pharmacologically, synephrine is similar to ephedrine but does not have its central nervous system (CNS) effects (NDPSC, 2003). It is therefore being considered as an alternate for ephedrine in dietary supplements (Am. Botanical Council, 2000). Synephrine and *N*-methyltyrosamine (chemicals found in immature *C. aurantium* fruit) have been shown to be effective antishock (i.e., primarily cardiotonic and vasoconstrictive) agents. In one study, 48 of 50 children with infective shock were cured when treated with synthetic synephrine and *N*-methyltyrosamine (1.66 to 24 mg/kg) (Zhao et al., 1989).

6.0 Environmental Occurrence and Persistence

In addition to their presence in bitter orange, octopamine and synephrine have been found in higher plants such as Amaryllidaceae and Cyperaceae (Wheaton and Stewart, 1970). Synephrine also occurs in the flower of *C. aurantium* (Huang et al., 2001a).

7.0 Human Exposure

Exposure to bitter orange peel and its constituents occurs primarily via ingestion of the fruit itself or its products (e.g., orange juice, marmalade, and dietary supplements). Bitter orange peel is added to various foods (beer and other beverages, cakes, etc. [see Section 5.0]). The Florida Department of Citrus regularly monitors the concentrations of synephrine and its precursor tyrosine among several other compounds in citrus juices (Cancalon, 1999). The daily dosage for bitter orange peel is 4-6 g (dry peel) in drugs, 2-3 g in tincture, and 1-2 g in extract. Weight loss formulas usually contain 100-200 mg bitter orange extract, which provides 10-40 mg synephrine per dose (Am. Botanical Council, 2000; Smartinfo, undated; Ther. Res. Faculty, 2003).

8.0 Regulatory Status

Bitter orange is regulated by the U.S. Food and Drug Administration (USFDA). *C. aurantium* is listed in its Poisonous Plants Database, however, *C. aurantium* orange oil extract, peel, flowers, and leaf are listed in its food additive database, an inventory often referred to as "Everything" Added to Food in the United States (EAFUS) (FDA CFSAN, 1996, 2003). Additionally, bitter orange peel is Generally Recognized as Safe (GRAS) as a direct additive to food (21 CFR 182.20 and 21 CFR 582.20). The oils, extracts, and oleoresins of bergamot, bitter orange flowers and peel, and petitgrain (all of *C. aurantium* L.) are also designated as GRAS (21 CFR 172, 182, 184, and 186) (ars-grin.gov, undated). In frozen concentrated orange juice, the volume of bitter orange that may be added cannot exceed 5% (21 CFR 146.146). Table syrup may contain ground orange peel (no specific species) as an ingredient (21 CFR 168.180). FDA's guidance for the preparation of orange marmalade, suggesting that bitter orange marmalade be prepared by mixing at least 25 lb of fruit (peel and juice) to each 75 lb of sweetening ingredient, is in agreement with the standards first issued by the U.S. Department of Agriculture in 1974 (FDA CFSAN, 1997; USDA, 1974).

Concerns about bitter orange and other compounds in dietary supplements led to the FDA's collection of product labels for the Center for Food Safety and Applied Nutrition (CFSAN) to determine the conditions of product use and the levels of product ingredients in order to evaluate possible health risks. Products shipped in bulk not for use in manufacturing other dietary supplements in accordance with section 101.36(h)(3) are exempt from nutrition labeling (i.e., "Supplement Facts") (FDA CFSAN, 2000). Zhishin, LLC (South Burlington, VT), who manufactures three of the four name brand dietary supplements they package, ZHI-Slim™, ZHI-Thermo™, ZHIshape™, and DynamicTrim™, submitted "Notification of a Structure/Function Statement" to the FDA/CFSAN, noting that bitter orange contains small amounts of synephrine and octopamine (Jones, 2001). In 2004, the FDA Commissioner stated that the agency will investigate other herbal diet supplements, including bitter orange, that have replaced the now banned ephedra as substitutes (Healthfinder, 2004a,b; schumer.senate.gov, undated).

The International Fragrance Association (IFRA) standard for bitter orange peel oil is 1.25% in products applied to areas of the skin that are exposed to the sun (IFRA, 2002). The National Collegiate Athletic Association (NCAA) has included synephrine from *C. aurantium*, zhi shi, and bitter orange on its list of substances banned for student athletes (NCAA, undated).

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

In one study, a 28-year-old man abusing synephrine tablets (dose not provided [n.p.]) suffered a massive myocardial infarction (Keogh and Baron, 1985; NDPSC, 2003). In another study, an overdose of synthetic synephrine and *N*-methyltyramine in children caused side effects that included a rapid increase in blood pressure, nausea, vomiting, irritation, and tachycardia; the symptoms, however, were short-lived (Zhao et al., 1989).

With the increasing use of dietary supplements by the general population, many studies have been conducted regarding the effects of these products, especially those formulas whose ingredients include both ephedrine and bitter orange. Some report no adverse effects (e.g., Kalman et al., 2002), while others report that the use of bitter orange with stimulants such as

ephedra causes cardiotoxicity (Keogh and Baron, 1985 [cited by Moore, 2003 lett.]; Penzak et al., 2001). When used in products for weight loss, which may include ephedra, identified adverse effects were sensitivity to light and an increase in blood pressure (Heinrich, 2002). The product Xenadrine RFA-1 (containing 85 mg bitter orange [standardized for 5 mg (30 µmol) synephrine] and ephedrine) produced heightened anxiousness, elevated heart rate, and a feeling of "warmed blood" in obese adults. The supplement caused reductions in fat mass, percent fat, and body mass but had little effect on energy expenditure, changes in appetite, or blood chemistries (Armstrong et al., 2001). Xenadrine was also implicated in a 26-year-old woman suffering from ischemic colitis (Ryan et al., 2002). A 55-year-old woman (noted smoker) who ingested the multicomponent dietary supplement Edita's Skinny Pill (containing 300 mg bitter orange) for weight loss over a one-year period, was diagnosed with acute lateral-wall myocardial infarction. Based on the analysis, *C. aurantium* was possibly associated with the cardiovascular event (Nykamp et al., 2004).

Similar to the study results of supplements containing both bitter orange and ephedra, those for supplements containing synephrine plus caffeine are 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 (Marcus and Grollman, 2003 lett.). In one study, however, when *C. aurantium* extract (975 mg; synephrine content not reported), caffeine, and St. John's Wort was given to obese adults, significant reductions in body weight and body fat occurred with no changes in blood pressure, heart rate, electrocardiographic findings, serum chemistries, or urinalysis findings [note: patients were also undergoing mild caloric restriction and exercise] (Colker et al., 1999).

When applied topically as a 25% emulsion, 20% oil in alcohol, or in pure form, oil of bitter orange reportedly cured patients with tinea corporis, cruris, and pedis within one to four weeks. The pure form produced mild irritation but no other side effects were reported (Ramadan et al., 1996). In volunteers receiving skin applications of bitter orange peel oil expressed (5 µL/cm^2 of 100% oil) under occlusion followed by exposure to visible light or ultraviolet A, phototoxic reactions in all subjects were observed (Kaidbey and Kligman, 1980; cited by IFRA, 2002).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

No studies evaluating disposition, metabolism, or kinetics of administered bitter orange products were available.

Octopamine

Rossi-Fanelli et al. (1976) reported that normal subjects had <1 ng octopamine per milliliter blood. Kobayashi et al. (1980) reported normal human urinary concentrations of free and total octopamine were 5.7 and 3.48 ng/mg creatinine, respectively.

A number of authors have indicated that low concentrations of octopamine are present in the CNS and peripheral tissues of vertebrates (Paterson et al., 1990; Tallman et al., 1976 [both cited by Bunzow et al., 2001]; Watson et al., 1990; Yonekura et al., 1988); it is thought to be a metabolic byproduct of catecholamine biosynthesis (Bunzow et al., 2001). A study in rats indicated that levels of *p*-octopamine drastically decrease in the hypothalamus and telencephalon after 20 months of age; the change appears to be related to a decrease in aromatic *L*-amino acid

decarboxylase activity (David et al., 1989). The authors concluded that *p*-octopamine may have some pathways that are independent of catecholamine metabolism, and that it may have a role in the normal activity of the brain.

In rats, *m*- and *p*-octopamine are present in similar concentrations in the heart, spleen, and liver. Both are also present in the adrenals, vas deferens, brain, kidney, large intestine, bladder, and lungs, although the concentration of *p*-octopamine is 30 to 60% higher than that of *p*-octopamine in the these organs. Endogenous concentrations of *p*-octopamine (measured by GC/MS) in tissues of Sprague-Dawley rats were reported as the following: 0.8 ng/g in brain; 1.1 ng/g in liver; 2.0 ng/g in lung, large intestine, heart, spleen, bladder, and kidney; 9.2 ng/g in vas deferens; and 103 ng/g in adrenals. After monoamine oxidase inhibition, concentrations rose to 163 – 370 ng/g in spleen, heart, adrenals, and vas deferens and to 18 – 76 ng/g in the other organs (Ibrahim et al., 1985).

The main urinary metabolites of the *o*-, *p*-, and *m*-octopamine in rats are *o*-hydroxymandelic acid (OHMA), *p*-hydroxymandelic acid (PHMA), and *m*-hydroxymandelic acid (MHMA), respectively. Intraperitoneal administration of 6-hydroxydopamine (which causes long lasting depletion of norepinephrine) caused the daily urinary output of PMHA and MHMA to drop by 50%; levels of PHMA were restored to normal more rapidly than MHMA. The authors concluded that *m*- and *p*- (but not *o*-) octopamine coexist with the catecholamines in sympathetic nerve terminals. Both follow the same biosynthetic pathway following chemical sympathectomy; turnover of *p*-octopamine is more rapid (Ibrahim and Williams, 1985). The excretion rate of PHMA in vertebrates was similar to that of norepinephrine and vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid). Octopamine concentrations were lower than those of norepinephrine suggesting that the turnover rate may be very high. When octopamine biosynthesis was inhibited by blocking dopamine β-hydroxylase [involved in conversion of *p*-tyramine to octopamine], endogenous octopamine concentrations decreased by 50% within 2.6 hours, much faster than the 50% decrease in norepinephrine observed at 13 to 15 hours (David and Coulon, 1985).

Endogenous octopamine concentrations in mammalian brain and heart reported between 1963 and 1982 were generally in the range 1 to 100 ng/g wet tissue (most values were less than 50 ng/g). Concentrations reported for the human brain were 2 ng/g for the parietal lobe, 10.4 ng/g for the temporal lobe, 20 ng/g for the locus ceruleus, and 80 ng/g for the hypothalamus. Human blood platelets contained 0.007 ng/organ and serum contained 4.6 ng/organ. Reported plasma octopamine concentrations in humans, monkeys, and dogs were 0.45, 0.34, and 0.69 ng/mL, respectively. Concentrations in cerebrospinal fluid were 0.50 ng/mL in the monkey and 0.25 ng/mL in the dog (David and Coulon, 1985).

Synephrine

Following i.v. administration of tritiated synephrine to six patients (given by infusion for 10-63 min), about 66% and 10% of the administered dose (0.399 to 0.878 mg) was recovered in the urine as deaminated PHMA and unchanged synephrine, respectively. Free synephrine concentrations in serum ranged from 0.05 to 0.52 ng/mL six hours after dosing. A similar elimination pattern was seen following oral ingestion of synephrine by ten patients, except that only 2.5% of the dose was recovered as unchanged synephrine. The biological half-life was about two hours. Peak concentrations were observed between one and two hours after oral

administration. Free synephrine in the serum ranged from 0.14 to 2.48 ng/mL six hours after oral doses of about 6 mg. The pharmacokinetic parameters after i.v. infusion were said to be similar to those of structurally analogous sympathomimetics. The area under the curve (AUC) for the individual subjects ranged from 191.8 to 808.6 ng/mL, the volume of distribution (V_d,β) ranged from 132 to 647 L, and the total clearance ranged from 493 to 2940 mL/min. Renal clearance (Cl_{ren}) ranged from 37.0 to 283.2 mL/min (Hengstmann and Aulepp, 1978).

In rats given 62 µg tritiated synephrine per 100 g body weight i.v., the highest tissue concentrations were seen after 30 minutes in the heart (178.7 ng/g), adrenals (150.8 ng/g), kidneys (102.4 ng/g); liver (58.7 ng/g) and plasma (44.9 ng/g). After four hours, tissue concentrations were: adrenals (72.5 ng/g); kidneys (33.2 ng/g); liver (54.8 ng/g); and plasma (13.4 ng/g). Concentrations in other rat organs four hours after dosing ranged from 7.3 ng/g in brain to 68.2 ng/g in spleen (Hengstmann and Aulepp, 1978).

Octopamine and Synephrine

Trace amounts of *p*- and *m*-octopamine and *p*- and *m*-synephrine were determined in the plasma and platelets of healthy subjects by a multi-channel electrochemical HPLC system (D'Andrea et al., 2003a). Mean plasma concentrations of synephrine were 4.06 ng/mL in six of eight male subjects and 5.02 ng/mL in five of eight female subjects. Mean intra-platelet concentrations were 0.26 ng/10^8 platelets in all males and 0.41 ng/10^8 platelets in all females. Mean plasma concentrations of octopamine were 1.95 ng/mL in males (8/8) and 3.12 ng/mL in females (8/8). Mean concentrations in platelets were 0.25 ng/10^8 in males (8/8) and 0.42 ng/10^8 in females (7/8). [Note that the plasma concentrations detected in this study by HPLC were an order of magnitude higher than those found by Andrew et al. (1993).]

Low and inconsistent concentrations of unconjugated *p*-synephrine, *p*-octopamine, and other noncatechol monoamines were determined in the plasma of normotensive subjects by GC/negative-ion chemical ionization MS. *p*-Synephrine was found at a mean concentration of 58 pg/mL (range not detected [ND] to 235 pg/mL) in 14 subjects and *p*-octopamine was found at a mean concentration of 53 pg/mL (ND to 300 pg/mL) in 12 subjects (Andrew et al., 1993). In a study comparing hypertensive to normotensive human subjects, there were no significant differences in the concentrations of *p*- and *m*-octopamine and *p*- and *m*-synephrine in the urine (Watson et al., 1990).

Synephrine and octopamine were found to be common substrates for both type A and type B monoamine oxidases in rat brain mitochondria *in vitro*. For synephrine, the Michaelis-Menten constant (K_m) and maximum velocity of the reaction (V_{max}) were 250 µM and 32.6 nmol/mg protein/30 min, respectively (Suzuki et al., 1979a,b). Pharmacokinetic studies of octopamine were published by Gillis and Roth (1977) (rabbit perfused lung) and Egashira et al. (1984) (monkey brain mitochondria) but K_m and V_{max} values were not given in the abstracts.

In a study investigating the biochemical parameters of tyrosine hydroxylase deficiency, the authors indicated that biosynthetic pathways from *l*-tyrosine to norepinephrine and epinephrine are possible via *p*-tyramine, octopamine, and synephrine (Bräutigam et al., 1998).

The metabolism of octopamine and synephrine to dopamine is mediated by human CYP2D6 (Hiroi et al., 1998; cited by Tyndale et al., 1999).

Tyramine

Because tyramine is rapidly metabolized by monoamine oxidase (MAO) in the gut and liver, ingested tyramine does not exert its sympathomimetic effects. However, patients taking MAO inhibitors may experience hypertensive crisis. For example, an "average meal of natural or aged cheeses contains enough tyramine to provoke a marked rise in blood pressure and other cardiovascular changes" in such patients. Effects of an antihypertensive drug have also been studied in volunteers given high tyramine doses (20 mg/kg) to induce pressor effects (HSDB, 2002).

9.1.3 Acute Exposure

Acute toxicity values for octopamine and synephrine and its hydrochloride are given in **Table 2**.

Table 2. Acute Toxicity Values for Octopamine, Synephrine, and Its Hydrochloride

Route	Species (sex and strain)	$LD_{Lo}/LD_{50}/TD_{Lo}$	Reference(s)
(±)-*p*-Octopamine [104-14-3]			
s.c.	mouse (sex and strain n.p.	LD_{50} = 2070 mg/kg (13.51 mmol/kg)	RTECS (1996a)
i.p.		LD_{50} = 600 mg/kg (3.92 mmol/kg)	
i.v.		LD_{50} = 75 mg/kg (0.49 mmol/kg)	
i.c.		LD_{50} = 2100 mg/kg (13.71 mmol/kg)	
oral		LD_{50} = 4200 mg/kg (27.42 mmol/kg)	
s.c.	rat (sex and strain n.p.)	LD_{50} = 350 mg/kg (2.28 mmol/kg)	
i.p.		LD_{50} = 1350 mg/kg (8.813 mmol/kg)	
oral		LD_{50} = 1240 mg/kg (8.095 mmol/kg)	
i.v.	guinea pig (sex and strain n.p.)	LD_{Lo} = 200 mg/kg (1.31 mmol/kg)	
(±)-*p*-Synephrine [94-07-5]			
s.c.	mouse (sex and strain n.p.)	LD_{Lo} = 1500 mg/kg (8.971 mmol/kg)	RTECS (1996b)
	rat (sex and strain n.p.)	LD_{Lo} = 1500 mg/kg (8.971 mmol/kg)	
i.p.	mouse (sex and strain n.p.)	LD_{50} = 1000 mg/kg (5.981 mmol/kg)	
i.v.	mouse (sex and strain n.p.)	LD_{50} = 270 mg/kg (1.61 mmol/kg)	
	rabbit (sex and strain n.p.)	LD_{Lo} = 150 mg/kg (0.897 mmol/kg)	
(*R*)-(-)-*p*-Synephrine [614-35-7]			
s.c.	mouse (sex and strain n.p.)	LD_{Lo} = 700 mg/kg (4.19 mmol/kg)	RTECS (2003a)
oral	mouse (sex and strain n.p.)	TD_{Lo} = 1 mg/kg (6 µmol/kg)	
(*S*)-(+)-*p*-Synephrine [532-80-9]			
s.c.	mouse (sex and strain n.p.)	LD_{50} = 1500 mg/kg (8.971 mmol/kg)	RTECS (2003b)
oral	mouse (sex and strain n.p.)	TD_{Lo} = 0.3-3 mg/kg (2-18 µg/kg)	

Table 2. Acute Toxicity Values for Octopamine, Synephrine, and Its Hydrochloride (Continued)

Route	Species (sex and strain)	$LD_{Lo}/LD_{50}/TD_{Lo}$	Reference(s)
(±)-*p*-Synephrine hydrochloride [5985-28-4]			
s.c.	mouse (sex and strain n.p.)	LD_{Lo} = 400 mg/kg (1.96 mmol/kg)	RTECS (1997)
	rat (sex and strain n.p.)	LD_{Lo} = 320 mg/kg (1.57 mmol/kg)	
	guinea pig (sex and strain n.p.)	LD_{Lo} = 500 mg/kg (2.45 mmol/kg)	

Abbreviations: i.c. = intracerebral; i.p. = intraperitoneal; i.v. = intravenous; LD_{50} = lethal dose for 50% of test animals; LD_{Lo} = lethal dose, low; n.p. = not provided; s.c. = subcutaneous; TD_{Lo} = toxic dose low of any route, other than inhalation, over any period of time and reported to produce carcinogenic, neoplastigenic, or teratogenic effects in animals or humans or to produce any toxic effect in humans

Bitter Orange Peel

In adult male Swiss mice treated orally by gavage with essential oil from *C. aurantium* peel (0.5 or 1.0 g/kg), the latency period of tonic seizures (induced by pentylenetetrazole or maximum electroshock) was increased. In addition, treatment with the higher dose significantly increased hypnotic activity (induced by sodium pentobarbital) and anxiolytic activity (i.e., permanence in the open arms of the maze) (Carvalho-Freitas and Costa, 2002).

Sprague-Dawley rats orally administered a single dose of TJ-41 (up to 10 g/kg) or TJ-43 (2 or 8 mg/kg), herbal drug mixtures containing ~10% of the fruit peel, showed no toxic signs and no deaths were reported (Iijima et al., 1995; Kanitani et al., 1995).

Synephrine

Subcutaneous (s.c.) injection of *p*-synephrine (1500 mg/kg [8.971 mmol/kg]) caused sensory organs effects (not specified), convulsions, and respiratory stimulation in mice (RTECS, 1996b). Administration of (*R*)-(-)-*p*-synephrine (700 mg/kg [4.19 mmol/kg]) and the *S*-enantiomer (1500 mg/kg [8.971 mmol/kg]) by s.c. injection also caused convulsions, as well as dyspnea and cyanosis in the animals; oral administration of the compounds (1 mg/kg [6 µmol/kg] *R* and 0.3 mg/kg [2 µmol/kg] *S*) increased body temperature (RTECS, 2003a).

9.1.4 Short-term and Subchronic Exposure

When Sprague-Dawley rats were orally given TJ-41 (500 or 2500 mg/kg), an herbal drug mixture containing ~10% of the *C. aurantium* fruit peel, daily for 13 weeks, no drug-related abnormalities in body or organ weights, food consumption, ophthalmology, urinalysis, hematological examination, blood biochemical examination, gross pathological examination, or microscopic examination were observed (Iijima et al., 1995). A similar experiment with another herbal medicinal preparation containing ~10% peel, TJ-43 (125, 500, or 2000 mg/kg), produced the same results (Kanitani et al., 1995). [Note: The Japanese herbal mixtures, TJ-41 and TJ-43, are a dried decoctum of ten and eight herbal drugs, respectively.]

Oral administration (gavage) of *C. aurantium* fruit hydroalcoholic extracts standardized to 4 or 6% synephrine (doses of 2.5, 5, 10, or 20 mg/kg for each extract) to male Sprague-Dawley rats for 15 days caused a significant and dose-dependent decrease in food intake and body weight gain. Deaths occurred in all treatment groups: at the low dose, 10% mortality was seen with both extracts; at the high dose, 30 and 50% mortalities were reported for extracts standardized to 4

and 6%, respectively. No marked changes were seen in blood pressure; however, ventricular arrhythmias with enlargement of the QRS complex were observed (Calapai et al., 1999).

9.1.5 Chronic Exposure
No data were available.

9.1.6 Synergistic/Antagonistic Effects
The ability of citrus juice to inhibit organic anion transporting polypeptide-mediated drug uptake and other drug interactions has been reported (Dresser et al., 2002; Malhotra et al., 2001; Mohri and Uesawa, 2001; Zychlinski and Montgomery, 1984). Similar to grapefruit juice, sour orange juice may interact with other drugs. When healthy volunteers drank Seville orange juice after receiving a single oral dose of felodipine, a drug to lower blood pressure, peak concentrations of felodipine were two times greater than individuals drinking only common orange juice (UNC 2001, press release). In another experiment, *C. aurantium* was able to attenuate acute intoxication of cyclosporine in swine (Hou et al., 2000).

9.1.7 Cytotoxicity
No data were available.

9.2 Reproductive and Teratological Effects
In rats, daily intramuscular injection of synephrine (55 or 110 mg/kg [0.33 or 0.66 mmol/kg]) on days 7-16 of pregnancy decreased the number of uterine implants and viable fetuses, increased mean fetal weight and the number of micro fetuses, and retarded cranial and thoracic ossification. Additionally, renal and intestinal hemorrhage, brain hypoplasia, and unilateral microphthalmia were reported in some fetuses (Scrollini et al., 1970).

9.3 Carcinogenicity
No data were available.

9.4 Initiation/Promotion Studies
No data were available.

9.5 Anticarcinogenicity
No data were available.

9.6 Genotoxicity
Only two genotoxicity studies were identified. In *Aspergillus nidulans* diploid strains, octopamine (dose n.p.) did not induce non-disjunction or crossing-over (Bignami et al., 1974). In the L5178Y mouse lymphoma assay, synephrine (20-3600 µg/mL [120 µM-21.53 mM]) was inactive (McGregor et al., 1988).

9.7 Cogenotoxicity
No data were available.

9.8 Antigenotoxicity
No data were available.

9.9 Immunotoxicity

Oral administration of extracts of the peel of bitter oragne, as well as of the immature fruit, led to decreased cell viability of splenocytes and thymocytes in BALB/c mice (Yum and Eun, 1998). Oral administration of aqueous extracts of the immature fruit also inhibited Type I allergic reactions in rats (Koda et al., 1982).

9.10 Other Data

Synephrine, octopamine, *A. nobilis pericarpium*, and/or extracts of *C. aurantium* have also been studied for effects on cellular function, neurological activity, enzyme activity, the cardiovascular system, and the blood and hematopoietic system.

Effects on Cell Growth

Octopamine was assessed for inhibitory effects on human keratinocyte mitosis *in vitro*; no details were provided in the abstract (Harper and Flaxman, 1975). Compounds isolated from extracts of the immature *C. aurantium* fruit inhibited cell growth in mouse leukemia L1210 and human erythroleukemia K562 cells *in vitro*, while methoxylated flavones isolated from extracts of the peel induced cell differentiation in mouse myeloid leukemia (M1) and human promyelocytic leukemia (HL-60) cells (Satoh et al., 1996; Sugiyama et al., 1993).

Neurological Effects

Neurological effects reported for synephrine and octopamine included increased locomotor activity, pre- and postsynaptic effects, anti-depressive activity, agonistic response toward trace amine receptors, inhibition of smooth muscle contraction, and depression of neurological function (Bulach et al., 1984; Bunzow et al., 2001; Celuch and Juorio, 1988; Chance et al., 1985; Cho et al., 1996; Coulon et al., 1989; Jagiello-Wojtowicz, 1979; Jagiello-Wojtowicz and Chodkowska, 1984; Kim et al., 2001; Lafi and Leake, 1988; Song et al., 1996).

Effects on Enzymes

Sour orange juice inhibited microsomal CYP3A-mediated testosterone 6β-hydroxylation, whereas sweet orange juices did not. *C. aurantium* crude drugs showed the same effects (Guo et al., 2000, 2001). Octopamine, but not synephrine, inhibited cytochrome P450c11 *in vitro* (Louw et al., 2000).

In a study of the inhibitory effects of citrus fruit extracts from 42 species and cultivars on rat platelet cyclooxygenase and lipoxygenase, the albedo extract of *C. aurantium* had the highest lipoxygenase inhibitory activity (Nogata et al., 1996). Additionally, bitter orange juice extract had an inhibitory effect on intestinal P-glycoprotein-related efflux carriers *in vitro* (Deferme et al., 2002).

In rat jejunal mucosa, octopamine (10 mM) inhibited histamine-*N*-methyltransferase. It was suggested that the compound might play a vital role in the chemical potentiation of histamine toxicity (Taylor and Leiber, 1979).

Cardiovascular Effects

In humans, rats, guinea pigs, cats, and/or dogs, synephrine, octopamine, and extracts of *C. aurantium* have been evaluated for effects on the cardiovascular system that include changes in blood pressure, cardiovascular toxicity, contractility and excitability of the heart muscle, and/or adrenergic activity (e.g., Calapai et al., 1999 [see subsection 9.1.4]; Ress et al., 1980; Yen and Chung, 1981). Pressor effects and the ability to restore contractility and excitability to heart muscle were reported for synephrine and octopamine (Altura, 1975; Chen et al., 1990; Jia et al., 1983; Ledda et al., 1980).

Effects on Blood and Hematopoietic System

Hypertensive rats administered synephrine (1 mg/kg) via gavage for eight days had significantly reduced portal venous pressure, portal tributary blood flow, and cardiac index. Mean arterial pressure, vascular resistance, and systemic and portal territory were improved (Huang et al., 2001b). When infused into hypertensive rats, synephrine (0.095, 0.19, or 0.38 mg/kg/min) dose-dependently reduced portal pressure and elevated mean arterial pressure (Huang et al., 1995).

Bitter orange peel (in Jupi, a Chinese herbal prescription) promoted human platelet aggregation (Okuyama et al., 1987).

Miscellaneous Studies

In white fat cells of the rat, hamster, and dog, synephrine partially stimulated lipolysis. Octopamine was fully lipolytic in garden dormouse, rat, hamster, and dog fat cells but was inefficient in guinea pig or human fat cells; its effects were similar to those of β3-adrenoceptor agonists (Carpéné et al., 1999; Fontana et al., 2000). At high concentrations, it can reduce the lipolytic effect of norepinephrine (David and Coulon, 1985). In mature 3T3-L1 cells, bitter orange peel stimulated lipolysis (Sakuramata and Kusano, 1998).

Synephrine (dose n.p.), isolated from the leaves and juice of immature *C. aurantium* fruit, inhibited uterine contraction induced by serotonin in rats (Kinoshita et al., 1979). D,L-Synephrine (10 μM [1.7 μg/mL]) stimulated aromatization of testosterone in Sertoli cell-enriched cultures from 19-day-old rats; the effect was inhibited by propranolol and phenoxybenzamine, potent α-adrenergic antagonists (Verhoeven et al., 1979). Additionally, octopamine and synephrine (1 μM - 1 mM) enhanced progesterone production in bovine luteal cells *in vitro*; addition of norepinephrine and epinephrine significantly increased the effect (Battista and Condon, 1986).

9.11 Receptor Pharmacology of Octopamine, Synephrine, and Other Biogenic Monoamines

Adrenergic Receptors (Adrenoceptors)

According to terminology in the NLM MeSH Database, structural analogs of ephedrine, epinephrine, and norepinephrine are agonists for both α- and β-adrenoceptors, while synephrine, octopamine, and phenylephrine are α-adrenoceptor agonists and tyramine is an indirect sympathomimetic. However, some studies were found in which synephrine and octopamine were also agonists at β-adrenoceptors. Appendix C lists the physiological effects observed with activation of the various types of α- and β-adrenoceptors. [Note: No original primary publications were retrieved. This discussion is largely limited to PubMed records with abstracts

for mammalian studies that included epinephrine or norepinephrine as well as synephrine or octopamine.]

In vitro studies of the adrenergic activity of *p*-octopamine and *p*-synephrine compared to that of norepinephrine showed that *p*-octopamine and *p*-synephrine were generally orders of magnitude less potent than norepinephrine. *p*-Octopamine was more active than *p*-synephrine in some studies and less or equally active in other studies. *m*-Octopamine (norfenefrine) and *m*-synephrine (phenylephrine) were generally more potent than their para counterparts.

In a review of the older literature, David and Coulon (1985) noted that the effects of octopamine in the rat were blocked by alprenolol (a β-adrenoceptor antagonist), phentolamine (a nonselective α-adrenoceptor antagonist), phenoxybenzamine (a long-acting α-adrenoceptor antagonist), and yohimbine (an α2-adrenoceptor antagonist) but were unchanged in the presence of propranolol (a nonspecific β-adrenoceptor antagonist).

α-Adrenergic Activity

In studies of α-adrenergic activity, octopamine was between 60 and 15,000 times less active than norepinephrine in inducing contractions in rat arteriole and metarteriole preparations *in vitro* (Altura, 1975). The activities of *o*-, *m*-, and *p*-octopamine in contracting rat aortic smooth muscle *in vitro* were 0.7500, 0.0075, and 0.0038 times that of *m*-synephrine (Ress et al., 1980).

Brown et al. (1988) studied the relative activity of the (-)- and (+)-forms of *m*- and *p*-octopamine and *m*- and *p*-synephrine, compared to that of norepinephrine, on α1-adrenoceptors from rat aorta and anococcygeus and α2-adrenoceptors from rabbit saphenous vein. In rat aorta, the (-)-*m*-isomers were 6-fold less active than norepinephrine and the (-)-*p*-isomers were 1000-fold less active on the α1-andrenoceptors. In rat anococcygeus, the (-)-*m* isomers were also more potent than the (-)-*p*-isomers, which were 30-fold less active than norepinephrine. The (-)-*m*-isomers were 150-fold less active than norepinephrine and the (-)-*p*-isomers were 1000-fold lest active on the α2-adrenoceptors from rabbit saphenous vein. In tests with the (+)-isomers, the potencies were 1 to 2-fold lower than those of their (-)-counterparts. The relative potency of the (+)-isomers was norepinephrine > *m*-octopamine > *m*-synephrine > *p*-octopamine > *p*-synephrine.

At the α1- and α2-binding sites in rat cerebral cortex, the (-)-forms of *m*- and *p*-synephrine and octopamine were more active than the (+)-forms. The relative order of activity of the (-)-forms for both binding sites was norepinephrine > *m*-octopamine = *m*-synephrine > *p*-synephrine > *p*-octopamine (Brown et al., 1988).

In aortic smooth muscle of spontaneously hypertensive rats with α1- or α2-adrenoceptors blocked by prazosin and yohimbine, respectively, the octopamine isomers and *m*-synephrine were shown to exert contractile responses by stimulating the α1-adrenoceptors. The relative potencies in the presence of prazosin were *p*-octopamine > *m*-octopamine > *m*-synephrine > *o*-octopamine (Rahmani et al., 1987).

Racemic *o*-, *m*-, and *p*-octopamine increased blood pressure in pentolinium-blocked rats, with racemic *m*-octopamine having the greatest α-adrenergic activity, which was 100-fold less than

that of norepinephrine. The activities *o*-, *m*-, and *p*-octopamine were 0.01, 0.005, and 0.007 times that of norepinephrine, respectively (Fregly et al., 1979).

In a study of the α-adrenoceptor subtypes, norepinephrine and racemic *m*- and *p*-octopamine showed the same rank order in their agonist potencies for human cloned α1A-, α1B-, and α1D-adrenoceptors expressed in CHO cell lines: norepinephrine > *m*-octopamine > *p*-octopamine (Richardson et al., 2003).

β-Adrenergic Activity

In isolated, perfused rabbit heart, *p*-octopamine and *m*-synephrine showed preference for chronotropic (increased rate of heart contractions) and inotropic (increased force of heart contractions) stimulation, respectively. The actions were antagonized by propranolol but not by pretreatment with reserpine, cocaine, butoxamine, or phenoxybenzamine, which indicated that the selective actions were exerted directly at β1-receptors (Ferguson and Vazquez, 1984).

Racemic *o*-, *m*-, and *p*-octopamine did not show significant β-adrenergic activity in rats compared to that of the β-adrenergic agonist isoproterenol as determined by initiation of thirst and increase of tail skin temperature (Fregly et al., 1979).

The potency of the (-)-forms of *m*- and *p*-octopamine and *m*- and *p*-synephrine, relative to norepinephrine, on β1 adrenoceptors in guinea pig atria and trachea was norepinephrine > *m*-synephrine > *m*-octopamine = *p*-octopamine > *p*-synephrine. Norepinephrine was 100-fold more active than *m*-synephrine, 6000-fold more active than *m*- and *p*-octopamine, and 40,000-fold more active than *p*-synephrine. The (+)-forms of the isomers were about one to two orders of magnitude less active than norepinephrine on the β1 adrenoceptors Norepinephrine activity on β2 adrenoceptors was more than four orders of magnitude greater than the activities of the (-)-forms, while concentrations of the (+)-forms up to 0.0001 *M* had no effect on β2 adrenoceptors (Jordan et al., 1987).

Octopamine was reported to be a selective β3-adrenoceptor agonist, stimulating fat cell lipolysis by β3-adrenoceptor activation rather than by activation of other adrenoceptor subtypes (Galitzky et al., 1993; Carpéné et al., 1999; Fontana et al., 2000). However, octopamine given to genetically obese Zucker rats (i.p. injection with 81 μmol/kg per day for four weeks) elicited a 19% decrease in body weight gain, but it was not accompanied by changes in lipolytic response or stimulation of glucose transport by insulin. The dosed rats did show lower plasma insulin than that of the untreated rats. The authors concluded "that octopamine can reduce body weight gain in obese rats, without apparent adverse effects, but with less efficacy than β3-adrenoceptor agonists" (Bour et al., 2003). Synephrine was only a partial β3-adrenoceptor agonist (Carpéné et al., 1999).

Trace Amine Receptors

David and Coulon (1985) reviewed several older studies that indicate specific receptors for octopamine and other trace amines may exist in vertebrates. For example, one study reported that octopamine activity was inhibited by specific blocking agents that had no effect on norepinephrine and dopamine activity. At the time of the review, an octopamine-sensitive

adenylate cyclase had been found in only the caudate nucleus of the rat brain, and no specific octopamine antagonist had been identified.

Using appropriate antagonists for different types of receptors, Varma et al. [publication not identified] showed that octopamine-induced relaxation in rat aorta preparations was not mediated via α1-, α2-, β1-, or β2-adrenoceptors or via 5-hydroxytryptamine (serotonin; 5-HT), histamine, or adenosine receptors. In further experiments, catecholamines were inactive in endothelium-denuded rat aortic strips when α1-and β1-receptors were blocked but the noncatecholamines were active with a relative potency of methoxyphenamine > tyramine > *p*-hydroxyephedrine, L-amphetamine > L-ephedrine > phenethylamine > synephrine > methoxamine > octopamine. The authors suggested that novel tyramine receptors might explain the rat aorta relaxation activity they observed (Varma et al., 1995).

More recent evidence for a family of G protein-coupled receptors specific for trace amines in human, rat, and mouse tissues was published in 2001 (Borowsky et al. [Synaptic Pharmaceutical Corporation], 2001). These trace amine receptors are related to the classical biogenic amine receptors. Four human receptors (designated TA_1, TA_3, TA_4, and TA_5) and 14 rat receptors (TA_{1-4} and TA_{6-15}) were identified. The TA_1 receptor is coupled to the stimulation of adenylate cyclase via a $G_{\alpha s}$ G protein. Human TA_1 is moderately expressed in the stomach and, to a lesser degree, the kidney, lung, and small intestine; and traces are expressed in numerous other tissues. TA_1 receptors are more widespread in the brain of mice than of humans. Tyramine and β-phenethylamine (β-PEA) are potent activators while octopamine, dopamine, and tryptamine have lower agonist activity. Tryptamine and β-PEA also activate the rat TA_2 receptor.

Bunzow et al. [Oregon Health and Science University] (2001) also discovered a rat G-protein-coupled trace amine receptor (rTAR1 = rat TA_1). Drugs that stimulated cAMP production mediated by this receptor included racemic synephrine and octopamine; amphetamines; ergoline; and dopamine, as well as a few dopamine-, adrenergic-, and serotonin- receptor drugs. These findings support a "novel intercellular signaling system found widely throughout the vertebrate brain and periphery" in which the effects of trace amines, catecholamine metabolites, and amphetamines may be partially mediated. In assays with human embryonic kidney cells (HEK293) stably expressing the rTAR1 sequence, the relative potency for the stimulation of cAMP production was *p*-tyramine > β-PEA > tryptamine > synephrine > octopamine > *m*-tyramine ≥ dopamine > 5-HT >>epinephrine > norepinephrine.

Other sources have stated that trace amine receptors may be important in drug discovery for treatment of disorders such as schizophrenia, depression, attention deficit disorder, and Parkinson's disease (Branchek and Blackburn, 2003; Premont et al., 2001; Travis, 2001). According to a newsletter published by the National Institute on Drug Abuse, the results of the study by Bunzow et al. (2001) "indicate that the activation of TAR may be responsible for some of the psychological effects of psychostimulants; therefore TAR may represent an important new target for the development of anti-psychostimulant medications" (NIDA, 2002). D'Andrea et al. (2003b) summarized evidence that supports a role for trace amines in migraine and cluster headache pathogenesis, which has been recently bolstered by the findings of the trace amine

receptors and the ability to measure endogenous concentrations of the amines with non-radioactive methods.

Dopamine Receptors

A few studies have implicated dopamine receptors in the physiological activities of octopamine and other trace amines. For example, *p*-octopamine, *p*-tyramine, and PEA lowered prolactin levels (hypoprolactinemic effect) induced in rats by immobilization stress or by swimming. The effect may have been mediated by dopamine release or direct dopaminergic action since blocking dopaminergic receptors *in vitro* prevented the hypoprolactinemic effects of octopamine and PEA (Becu-Villalobos et al., 1992). The relaxant effect of octopamine on isolated rabbit intestinal smooth muscle, accompanied by direct stimulation of adenylate cyclase and cAMP production, may also be mediated by dopamine D-1 receptors. Octopamine-induced effects were not altered by antagonists of any type of adrenergic receptor or by antagonists of dopamine D-2, but were totally blocked by a dopamine D-1 antagonist (Cheng and Hsieh-Chen, 1988). In the rat striatum *in vitro* octopamine also bound and blocked the dopamine D-1 receptor (Cheng and Tsai, 1991; Cheng et al., 1990).

10.0 Structure-Activity Relationships

This subsection discusses the physiological effects, including toxicity, of certain structural analogs of synephrine that have been extensively tested. Abstracts of several primary studies that compared the adrenergic effects of synephrine and/or octopamine with those of other biogenic amines were described in subsection 9.11. No attempt was made to be comprehensive. Much of the focus has been on cardiovascular effects because the bitter orange dietary supplements are promoted as safer than the ephedra preparations, which have cardiotoxic potential. Terminology regarding adrenergic receptors (also called adrenoceptors) and other receptors that may be involved in the physiological activity of synephrine, octopamine, and their structural analogs is explained in Appendices C and D.

The compounds discussed in this section were selected primarily from phenylethylamine and phenylpropanolamine analogs in *The Merck Index* (Budavari, 1996) and in a recent edition of *Casarett and Doull's Toxicology* (Klaassen, 2001). The latter source discussed mechanisms of cardiotoxicity of positive inotropic drugs and related agents. Among these, structural analogs of synephrine and octopamine included the catecholamines; several bronchodilators including ephedrine and terbutaline; nasal decongestants including phenylephrine, phenylpropanolamine, and pseudoephedrine; and appetite suppressants such as amphetamines.

A general Markusch structure represents the group of compounds in **Table 3** that are mentioned in this subsection. The physiological activities/therapeutic uses of the compounds in the table are generally those listed in *The Merck Index* (Budavari, 1996). **Table 4** summarizes the structure-adrenergic activity relationships for various substitution patterns on this basic structure.

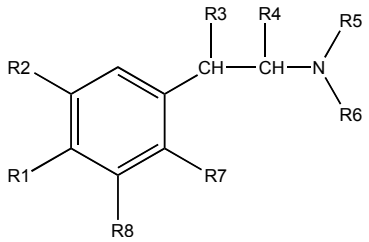


Table 3. Phenylethylamine and Phenylpropanolamine Structural Analogs of Synephrine and Octopamine (Primary Sources: Budavari, 1996; Griffith, 2003; Klaassen, 2001)

Names	CAS RN	Adreno-ceptor	R1	R2	R3	R4	R5	R6	R7	R8	Comments
(±)-*p*-Synephrine	94-07-5	α and β	OH	H	OH	H	H	CH_3	H	H	Vasopressor
(±)-*p*-Octopamine	104-14-3	α and β	OH	H	OH	H	H	H	H	H	Adrenergic (listed if no other therapeutic category). Weak β1 agonist (Jordan et al., 1987). Selective β3 agonist (Carpéné et al., 1999).
Phenylephrine; *m*-Synephrine	59-42-7	α1 and β1	H	OH	OH	H	H	CH_3	H	H	Primarily a direct-acting α-adrenoceptor agonist. Phenylephrine was the only adrenergic phenethylamine listed as an α1-adrenoceptor agonist by Griffith (2003). Hydrochloride is a mydriatic and decongestant. β1 agonist (Jordan et al., 1987).
Norfenefrine; *m*-Octopamine; Norphenylephrine	536-21-0	α1 and weak β1	H	OH	OH	H	H	H	H	H	Adrenergic. α1 (Brown et al., 1988); weak β1 (Jordan et al., 1987)
Norepinephrine	51-41-2	α and β	OH	OH	OH	H	H	H	H	H	Vasopressor, antihypotensive. α1,2- and β-adrenoceptor agonist (Flechtner-Mors et al., 2004). Positive inotropic effect mediated by only α receptors whereas the positive inotropic effects of epinephrine and dopamine are mediated by both α- and β-adrenoceptors (Wagner et al., 1980).
l-Epinephrine; Adrenalin(e)	51-43-4	α and β	OH	OH	OH	H	H	CH_3	H	H	Bronchodilator; cardiostimulant, and mydriatic. Structure is (*R*)-(-)-.
L-(-)-Ephedrine; (*R*-(*R**,*S**))-α-(1-(methylamino)ethyl) benzenemethanol; L-*erythro*-2-(Methylamino)-1-phenylpropan-1-ol	299-42-3	α and β	H	H	OH	CH_3	H	CH_3	H	H	Bronchodilator
Dopamine	51-61-6	α and β	OH	OH	H	H	H	H	H	H	
β-Phenethylamine; β-Phenylethylamine; PEA	64-04-0	α2 & β1	H	H	H	H	H	H	H	H	Pharmacologically related to amphetamine. α2 (Matsuoka et al., 1993); β1, pos. inotropic (Ferguson & Vazquez, 1984)
Methoxamine; 2,5-Dimethoxynorephedrine	390-28-3	α1	H	CH_3O	OH	CH_3	H	H	CH_3O	H	Antihypotensive. Used in surgery to maintain adequate arterial blood pressure (Dutta, 2003).
N-Methyltyramine; Methyl-4-tyramine	370-98-9	α; α2 antagonist	OH	H	H	H	H	CH_3	H	H	*N*-Methyltyramine is a bitter orange peel constituent and said by some to be the active principle. Koda et al. (1999) reported that *N*-methyltyramine was an α2 antagonist in mice. The anti-shock effect on the heart is similar to that of synephrine (Zhao et al., 1989).
Methamphetamine; (*S*)-(+)-*N*,α-Dimethylphenethylamine	537-46-2	α2A and α1B	H	H	H	CH_3	H	CH_3	H	H	Anorexic, CNS stimulant, used in attention deficit disorder with hyperactivity. α2A agonist (Nishio et al., 2003). α1B agonist (Battaglia et al., 2003). Adrenergic and dopamine uptake inhibitor (ChemIDplus). Direct negative inotropic effect and indirect positive inotropic effect on cardiac tissues (Ishiguro and Morgan, 1997).
Norpseudoephedrine; Pseudonorephedrine	36393-56-3	Weak α2Note I	H	H	OH	CH_3	H	H	H	H	Anorexic. D,L-*threo*-form of phenylpropanolamine. Weak α2 (Rothman et al., 2003).

Table 3. Phenylethylamine and Phenylpropanolamine Structural Analogs of Synephrine and Octopamine (Continued)

Names	CAS RN	Adreno-ceptor	R1	R2	R3	R4	R5	R6	R7	R8	Comments
Isoproterenol; Epinephrine isopropyl homolog	7683-59-2	β1 and β2	OH	OH	OH	H	H	*i*-Pr	H	H	*i*-Pr = -CH(CH_3)$_2$ [isopropyl]. Bronchodilator
Methoxyphenamine	93-30-1	β	H	H	H	CH_3	H	CH_3	CH_3O	H	Bronchodilator
Terbutaline	23031-25-6	β2	H	OH	OH	H	H	*t*-Bu	H	OH	*t*-Bu = -C(CH_3)$_3$ Bronchodilator.
Albuterol: Salbutamol	18559-94-9	β2	OH	-CH_2OH	OH	H	H	*t*-Bu	H	H	Bronchodilator
Phenylethanolamine	7568-93-6	β3	H	H	OH	H	H	H	H	H	Sulfate is a topical vasoconstrictor. β3 agonist (Carpéné et al., 1999). β antagonist (Wong et al., 1987).
L-(+)- or *d*-Pseudoephedrine; *threo*-2-(Methylamino)-1-phenylpropan-1-ol	90-82-4	Note I	H	H	OH	CH_3	H	CH_3	H	H	Nasal decongestant
Phenylpropanolamine; *l*-Norephedrine	492-41-1	Note I	H	H	OH	CH_3	H	H	H	H	Hydrochloride is used as an anorexic, decongestant, and bronchodilator.
Hordenine; *N,N*-Dimethyltyramine	539-15-1	Note I	OH	H	H	H	CH_3	CH_3	H	H	Hordenine is a bitter orange peel constituent that is also found in barley.
p-Tyramine	51-67-2	Note I	OH	H	H	H	H	H	H	H	Adrenergic
Amphetamine: Phenedrine	300-62-9	Note I	H	H	H	CH_3	H	H	H	H	
Fenfluramine	458-24-2	[Seroton-ergic or serotonin-releasing]	H	H	H	CH_3	H	Et	H	CH_3	Et = CH_3CH_2- Anorexic. A constituent of the diet drug Fen-Phen (with phentermine). Dexfenfluramine (Redux) and fenfluramine were associated with valvular heart disease. All three drugs have been removed from the market (Fen-Phen-Legal-Resources.com, 2003). Sympathetic overactivity in Fen-Phen combination (Koury et al., 1999) [case report of an overdose]. Racemic fenfluramine has catecholamine effects, but the *d*-enantiomer does not. It is a noradrenergic uptake inhibitor (Cleare et al., 1997). Serotonergic (Carek and Dickerson, 1999); serotonin uptake inhibitor (ChemIDplus). "Fenfluramine evokes 5-HT2A receptor-mediated responses but does not displace [^{11}C]MDL 100907, a specific receptor binding agent" (Hirani et al., 2003).
Phentermine	122-09-8	[Dopamin-ergic]	H	H	H	CH_3 (two)	H	H	H	H	The second methyl would replace the H shown in the generic structure at the carbon α to the amino group. Anorexic. Dopaminergic (Rowland et al., 2001). Not catecholaminergic. Probably potentiates synaptic serotonin release. Additive with fenfluramine in enhancing extracellular serotonin in hypothalamus (Tao et al., 2002).

Note I: Indirect-acting sympathomimetic that induces norepinephrine release.

Table 4. Structure-Activity Relationships Among Adrenergic Receptor Agonists

Structure*	Agonist Activity at Adrenergic Receptors
R1 = R2 = OH (catecholamines; 3,4-dihydroxy-)	α,β
R2 = OH (*m*- or 3-hydroxy-)	More α activity
R3 = OH (*p*- or 4-hydroxy-)	More β activity
R2 = R8 = OH (3,5-dihydroxy-) + large R5	β2 selectivity
R1 = R2 = R8 = H	No sympathomimetic activity. Increased blood-brain barrier permeability and oral availability
Larger R5 or R6	Increased β selectivity with larger *N*-alkyl group
R5 = R6 = H (primary amino group) or R5 = H (secondary amino group)	Potent agonists, whereas tertiary and quaternary amines are poor agonists.
R4 = CH_3- OR CH_3CH_2- (methyl or ethyl)	Selectivity increased: α2 > α1 and β2 > β1. Longer acting since greater stability against monoamine oxidase (MAO) metabolism.
No OH in aromatic ring, β-OH present on side chain	Sympathomimetics with mixed mechanism of action, e.g., D-(-)-ephedrine
α-CH_3-, *N*-substitution, β-OH	Substituents that increase activity as indirect-acting sympathomimetics, e.g., amphetamines, 4-hydroxyamphetamine, and L-(+)-pseudoephedrine

Source: Dutta (2003)
*Refer to the Markusch structure on page 22 of this report.

Specific Compounds or Compound Classes

Appetite Suppressants

Appetite suppressants such as amphetamines, fenfluramine, and phentermine may induce tachycardia, pulmonary hypertension, and valvular disease, possibly by elevating serotonin concentrations and inducing sodium ion channel blockade (Klaassen, 2001).

Catecholamines

Cardiotoxic effects induced by high circulating concentrations of endogenous catecholamines epinephrine and norepinephrine or by high doses of exogenous catecholamines such as isoproterenol include cardiac myocyte death *in vivo* and hypertrophic growth *in vitro*. The catecholamines increase heart rate, enhance myocardial oxygen demand, and increase systolic arterial blood pressure. Isoproterenol, however, has a hypotensive effect. Mechanisms of cardiotoxicity include:

- Activation of β1-adrenergic receptors
- Coronary vasoconstriction
- Mitochondrial dysfunction
- Elevated calcium ion concentrations
- Oxidative stress
- Apoptosis (Klaassen, 2001)

Dopamine (CAS RN 51-61-6)
The NTP testing status report (2003) stated that dopamine was weakly positive in *Salmonella* tests.

Ephedrine
A recent nomination background document for Dietary Supplements Containing Ephedrine Alkaloids (http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPdf/ephedrinealkaloids.pdf) provided an extensive toxicity review for ephedrine, pseudoephedrine, and ephedra preparations (TRI, Inc., 2001). Prolonged use of ephedrine depletes norepinephrine stores in sympathetic nerves and may lead to hypotension due to direct cardiac depression and vasodilation. Toxic effects from ephedrine alkaloid supplements or ephedrine diet pills reported in the literature include vasculitis, hypersensitivity myocarditis, myocardial necrosis, cerebral infarct, thalamic infarct, hemorrhagic stroke, myocardial infarction, and deaths. Ephedrine has milder CNS stimulating activity than the amphetamines.

Large doses of ephedra alkaloids may induce tachycardia and increase the potential for occurrence of ventricular arrhythmias in the myocardium. Ephedrine, ephedrine alkaloids, ma huang, phenylephrine, phenylpropanolamine, pseudoephedrine, and bronchodilators such as albuterol, salmeterol, and terbutaline induce tachycardia by nonselective activation of β1-adrenergic receptors (Klaassen, 2001).

Ephedrine activates adrenergic receptors in two ways: by direct agonist activity and by release of norepinephrine via a carrier-mediated exchange mechanism. Ephedrine and ephedrine-type compounds such as pseudoephedrine, norephedrine (phenylpropanolamine), and pseudonorephedrine are most potent as substrates of the norepinephrine transporter. Their next most potent activity is as substrate activity at the dopamine transporter. They have weak affinity at α2-adrenergic and 5-hydroxytryptamine7 [sic] (5-HT=serotonin) receptors (Ki values 1-10 μM) but no significant activity at α1-adrenergic or β-adrenergic receptors. The pharmacological effects of ephedrine and ephedrine-like phenylpropanolamine analogs are probably mediated by release of norepinephrine (Rothman et al., 2003).

Ephedrine and other vasopressor agents, including *m*-octopamine (norfenefrine) showed a direct effect on arterial vessels during extracorporeal circulation in clinical trials, raising perfusion pressure. Norfenefrine induced a large, but short-lived increase in perfusion pressure (Boldt et al., 1986).

Ephedrine sulfate (CAS RN 134-72-5) was tested by the NTP in 14 day, 13 week, and 2 year studies in B6C3F1 mice and F344 rats with dosed feed. In the 13-week studies, mice were given ephedrine sulfate at concentrations of 310-5000 ppm in the feed, and rats were given 125-2000 ppm in the feed (NTP TR-307, 1986 abstr.). Changes in heart and adrenal weights were observed in rats (RTECS, 2002), but the major response was reduction in weight gain (NTP TR-307, 1986 abstr.).

There was no evidence of carcinogenicity in the two-year bioassay (NTP TR-307, 1986 abstr.), in which both species were fed a diet with 125 or 250 ppm ephedrine sulfate in their feed. For rats, the average doses were estimated to be equivalent to 4 mg/kg bw and 9 mg/kg bw for males

and 5 mg/kg bw and 11 mg/kg bw for females. The average doses for mice were 14 mg/kg bw and 29 mg/kg bw for males and 12 mg/kg bw and 25 mg/kg bw for females. Throughout the study, rats and mice of both sexes showed lower mean body weight gains than controls.

Ephedrine sulfate was negative in a mouse lymphoma assay (NTP Testing Status Report) and SCE and chromosomal aberration assays in CHO cells. Ephedrine sulfate was not mutagenic in *Salmonella* strains TA100, TA1535, TA97, and TA98 with and without metabolic activation (NTP TR-307, 1986 abstr.). One 1996 study in RTECS (2002) reported DNA damage in rat hepatocytes at a concentration of 3 mmol/L.

_l_-Epinephrine (CAS RN 51-43-4) and _l_-Epinephrine Hydrochloride (CAS RN 55-31-2)

l-Epinephrine did not induce chromosomal aberrations in CHO cells with or without metabolic activation. In *Salmonella*, *l*-epinephrine was mutagenic in strain TA100 in the presence of metabolic activation, but results were equivocal without activation. The compound was not mutagenic in *Salmonella* strains TA98, TA1535, and TA1537 with or without metabolic activation (NTP TR-380, 1990 abstr.).

In 14-day inhalation tests, B6C3F1 mice and F344 rats were exposed to 12.5 to 200 mg/m^3. Deaths occurred in male rats exposed in all dose groups and in female rats at concentrations of 25 mg/ m^3 or higher. All groups showed increased respiratory rate. At 100 and 200 mg/m^3, rats showed excessive lacrimation and dyspnea and mice showed exaggerated visual and auditory reflexes (NTP TR-380, 1990 abstr.).

In the 13-week inhalation tests, mice and rats were exposed to 2.5 to 40 mg/m^3. At the highest dose, the animals showed increased respiratory rates, increased heart and adrenal gland weights, increased liver weight (only in mice), squamous metaplasia of the respiratory epithelium of the nasal mucosa, and uterine atrophy (only in 7/10 female mice). Rats showed degenerative lesions of the laryngeal muscle at 20 and 40 mg/m^3, and mice showed glandular stomach inflammation at 10 to 40 mg/m^3 (NTP TR-380, 1990 abstr.)

In 15-month studies with rats and mice, compound-related changes were not observed in the hematologic analyses. Absolute and relative decreases in liver and kidney weights were seen in one or both species at 3 and/or 5 mg/m^3 but no compound-related lesions were observed (NTP TR-380, 1990 abstr.).

No carcinogenic effects were observed in the 2-year inhalation study (NTP TR-380, 1990 abstr.) in these strains; however, these studies were considered "inadequate studies of carcinogenic activity." Doses were "too low for the animals to have received an adequate systemic challenge." Mice were exposed to 1.5 or 3.0 mg/m^3 and rats were exposed to 1.5 or 5.0 mg/m^3. Mean body weights and survival of exposed and control animals were similar.

_N_-Methyltyramine (CAS RN 370-98-9)

Intraperitoneal injections of *N*-methyltyramine increased cAMP (cyclic adenosine monophosphate) concentration in mice and cGMP (3',5'-guanosine monophosphate) concentrations in mice and guinea pigs (tissues unspecified) *in vivo.* *N*-Methyltyramine had a

positive inotropic effect *in vitro* in guinea pig atrium, which was blocked by phentolamine, and in perfused guinea pig heart (Yen and Chung, 1981).

N-Methyltyramine was positively inotropic when given i.v. to dogs at 0.25 and 0.5 mg/kg while racemic *p*-synephrine was positively inotropic at 0.5 and 1.0 mg/kg (Chen et al., 1980).

Norfenefrine (*m*-Octopamine) (CAS RN 536-21-0)
Subcutaneous dosing of rats with norfenefrine for 90 days induced unspecified cardiac and gastrointestinal changes and some mortality. The TD_{LO} was 810 mg/kg (probably a cumulative dose of 9 mg/kg/day since the rat s.c. LD_{50} from the same 1968 Japanese reference was 28.1 mg/kg) (RTECS, 1996c).

(*R*)-(-)-Phenylephrine (*m*-Synephrine) Hydrochloride (CAS RN 61-76-7)
In NTP testing, (*R*)-(-)-phenylephrine hydrochloride induced mutations in mouse lymphocytes (mouse lymphoma assay) and SCE in CHO cells at 1500 mg/L (RTECS, 1996d). The NTP testing status report also states that the compound was negative in chromosomal aberration and micronucleus tests *in vitro*, and in *Salmonella*.

In 14-day studies, no toxic effects were observed in F344 rats and B6C3F1 mice dosed with up to 2000 ppm phenylephrine hydrochloride in their feed.

In one subchronic study, F344 rats and B6C3F1 mice were given (*R*)-(-)-phenylephrine hydrochloride for 12 weeks at concentrations of 1250 to 20,000 ppm feed. Some male rats and mice at the 10,000- and 20,000-ppm dose levels died and one of the 10 male rats fed a diet with 5000 ppm died. Body weights decreased with increasing dietary concentrations. Feed consumption by rats was reduced. Inflammatory eye lesions were the only organ toxicity noted (NTP TR-322, 1987 abstr.).

No evidence of carcinogenicity was found in either strain in the 2-year bioassays (NTP TR-322, 1987 abstr.). Mice were given concentrations of 1250 and 2500 ppm in the feed (average doses of 133 and 270 mg/kg bw/day), and rats were given 620 and 1250 ppm in the feed (average doses of 24 and 50 mg/kg bw/day). Dosed mice and rats were 3 to 15% lighter than controls. Dosed male rats showed more frequent liver and prostate gland inflammation than did the controls.

In other studies, the (*R*)-(-)-phenylephrine hydrochloride induced DNA damage in rat hepatocytes at 7 mmol/L (~1500 mg/L). Rabbits dosed s.c. with (*R*)-(-)-phenylephrine hydrochloride on days 22-31 of gestation showed fetotoxicity; adverse effects on parturition were also noted (RTECS, 1996d).

Phenylpropanolamine (CAS RN 492-41-1)
Phenylpropanolamine, a structural analog of ephedrine and amphetamine, increases peripheral vascular resistance and blood pressure. It acts by stimulating adrenergic receptors directly and by stimulating norepinephrine release from neurons and is potentially toxic in treated hypertensive patients and in patients with cardiomyopathy (Bravo, 1988). At high doses, nasal decongestants may induce tachycardia. Deaths have been reported (Klaassen, 2001).

A clinical study indicated that phenylpropanolamine in appetite suppressants was an independent risk factor for hemorrhagic stroke in women (Kernan et al., 2000, cited by TRI, Inc., 2001). FDA issued a public health advisory in early 2001 that asked companies to stop marketing phenylpropanolamine-containing products.

11.0 Online Databases and Secondary References

11.1 Online Databases

National Library of Medicine Databases (TOXNET)
ChemIDplus
EMIC and EMICBACK
HSDB
TOXLINE

STN International Files

AGRICOLA	LIFESCI
BIOSIS	MEDLINE
CABA	Registry
EMBASE	RTECS
HSDB	TOXCENTER

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSHTIC®	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

National Archives and Records Administration
Code of Federal Regulations (CFR)

In-House Databases
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

11.2 Secondary References

Budavari, S., Ed. 1996. The Merck Index, 12th ed. Merck and Company, Inc., Whitehouse Station, NJ. CD-ROM version 12:1 1996, Chapman & Hall Electronic Publishing Division (monographs of synephrine, octopamine, and selected structural analogs).

Hughes, I., Ed. 1926. Tablets to Uguentum. In: The National Formulary, USD, 21st ed. Available at Internet address: http://www.herbdatanz.com/nf_usd_t-u.htm. Last accessed on October 23, 2003.

Klaassen, C.D., Ed. 2001. Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed. McGraw-Hill Medical Publishing Division, New York, NY.

Martin, E.W., Cook, E.F., Leuallen, E.E., Osol, A., Tice, L.F., and Van Meter, C.T., Eds. 1961. Remington's Practice of Pharmacy, 12th ed. Mack Publishing Company, Easton, PA, pp. 369, 374-376, 1303, and 1324.

12.0 References

1fast400.com. 2004. Meta-Burn XTP. Reviews. Available at Internet address: http://www.1fast400.com?products_id=753. Last accessed on June 3, 2004.

Alexander Essentials. 2003. Bitter orange essential oil. Available at Internet address: http://wholesale.alexander-essentials.com/orangebitter.php3. Last accessed on October 22, 2003.

Altura, B.M. 1975. Pharmacological effects of α-methyldopa, α-methylnorepinephrine and octopamine on rat arteriolar, arterial, and terminal vascular smooth muscle. Circ. Res. 26(6 Suppl. 1):233-240. Abstract from PubMed 1093755.

American Botanical Council. 2000. Expanded Commission E: Orange peel, bitter. Available at Internet address: http://www.herbalgram.org/iherb/expandedcommission/he072.asp. Last accessed on October 6, 2003.

Andrew, R., Best, S.A., Watson, D.G., Midgley, J.M., Reid, J.L., and Squire, I.B. 1993. Analysis of biogenic amines in plasma of hypertensive patients and a control group. Neurochem. Res. 18(11):1179-1182.

Armstrong, W.J., Johnson, P., and Duhme, S. 2001. The effect of commercial thermogenic weight loss supplement on body composition and energy expenditure in obese adults. JEPonline (Journal of Exercise Physiologyonline) 4(2):28-34. Available at Internet address: http://www.ephedrafacts.com/media/Attachment8.pdf.

ARS USDA (Agricultural Research Service, U.S. Department of Agriculture). 1999. Survey of phenolic compounds produced in citrus. Appendix 2. Taxonomic literature review of flavonoids found in Citrus (amblycarpa through cleopatra). Available at Internet address:

http://www.ars.usda.gov/is/np/phenolics/ap2/ca-c.htm. Original posting on April 1, 1999. Last accessed on October 22, 2003.

ars-grin.gov. Undated. Module 19. Botanicals Generally Recognized As Safe. Dr. Duke's Phytochemical and Ethnobotanical Databases. Available at Internet address: http://www.ars-grin.gov/duke/sullabus/gras.htm. Last accessed on June 1, 2004.

Artemis Herbs Limited. 2003. Bitter orange peel died herb. Available at Internet address: http://www.artemisherbs.co.uk/info/bitter_orange_peel_dried_herb.html. Last accessed on October 23, 2003.

Battaglia, G., Fornai, F., Busceti, C.L., Lembo, G., Nicoletti, F., and De Blasi, A. 2003. Alpha-1B adrenergic receptor knockout mice are protected against methamphetamine toxicity. J. Neurochem. 86(2):413-421. Abstract from PubMed 12871582.

Battista, P.J., and Condon, W.A. 1986. A role for alternative pathway catecholamines in the regulation of steroidogenesis in cow luteal cells. J. Reprod. Fertil. 78(1):275-280. Abstract from PubMed 3093678.

Becu-Villalobos, D., Thyssen, S.M., Rey, E.B., Lux-Lantos, V., and Libertun, C. 1992. Octopamine and phenylethylamine inhibit prolactin secretion both *in vivo* and *in vitro*. Proc. Soc. Exp. Biol. Med. 199:230-235. Abstract from PubMed 1741415.

Bignami, M., Morpurgo, G., Pagliani, R., Carere, A., Conti, G., and di Giuseppe, G. 1974. Non-disjunction and crossing-over induced by pharmaceutical drugs in *Aspergillus nidulans*. Mutat. Res. 26:159-170.

Boehringer Ingelheim. 2003. (±)-Synephrine. Available at Internet address: http://www.boehringer-ingelheim.com/finechem/products/Osy/Synephrine.pdf.

Boelens, M.H., and Jimenez, R. 1989. The chemical composition of the peel oils from unripe and ripe fruits of bitter orange, citrus. Flav. Fragr. J. 4(3):139-142.

Boldt, J., Muller, H., Borner, U., Kling, D., Moosdorf, R., and Hempelmann, G. 1986. Isolated modification of the vascular system by vasopressor agents (akrinor, etilefrin, ephedrine, norfenefrine, amezinium) during extracorporeal circulation in man (Ger.). Anaesthesist 35(2):93-8. Abstract from PubMed 2870661.

Borowsky, B., Adham, N., Jones, K.A., Raddatz, R., Artymyshyn, R., Ogozalek, K.L., Durkin, M.M., Lakhlani, P.P., Bonini, J.A., Pathirana, S., Boyle, N., Pu, X., Kouranova, E., Lichtblau, H., Ochoa, F.Y., Branchek, T.A., and Gerald, C. 2001. Trace amines: Identification of a family of mammalian G protein-coupled receptors. Proc. Natl. Acad. Sci. 98:8966-8971.

Bour, S., Visentin, V., Prevot, D., and Carpene, C. 2003. Moderate weight-lowering effect of octopamine treatment in obese Zucker rats. J. Physiol. Biochem. 59:175-182. Abstract from PubMed 15000448.

Branchek, T.A., and Blackburn, T.P. 2003. Trace amine receptors as targets for novel therapeutics: legend, myth and fact. Curr. Opin. Pharmacol. 3:90-97. Abstract from PubMed 12550748.

Bräutigam, C., Wevers, R.A., Janse, R.J.T., Smeitink, J.A.M., de Rijk-van Andel, J.F., Gabreëls, F.J.M., and Hoffmann, G.F. 1998. Biochemical hallmarks of tyrosine hydroxylase deficiency. Clin. Chem. 44(9):1897-1904.

Bravo, E.L. 1988. Phenylpropanolamine and other over-the-counter vasoactive compounds. Hypertension 11(3 Pt 2):II7-10. Abstract from PubMed 3280497.

British Pharmaceutical Codex. 1911. Aurantii Cortex. Bitter orange peel. Published by direction of the Council of the Pharmaceutical Society of Great Britain. Available at Internet address: http://www.ibiblio.org/herbmed/eclectic/bpc1911/citrus-aura.htm. Last accessed on October 23, 2003.

Brooks, J., Nagelin-Anderson, E., and Zuckerman, D. 2003. Examining the safety of natural supplements. National Center for Policy Research (CPR) for Women and Families, Washington, DC. Available at Internet address: http://www.center4policy.org/supplements2.html. Last accessed on October 23, 2003.

Brown, C.M., McGrath, J.C., Midgley, J.M., Muir, A.G., O'Brien, J.W., Thonoor, C.M., Williams, C.M., and Wilson, V.G. 1988. Activities of octopamine and synephrine stereoisomers on alpha-adrenoceptors. Br. J. Pharmacol. 93(2):417-29. Abstract from PubMed 2833972.

Bulach, C., Doare, L., Massari, B., and Simon, P. 1984. Antidepressive effects of 3 endogenous monoamines: Psychopharmacologic profiles of noradrenaline, octopamine, and phenethylamine (Fr.). J. Pharmacol. 15(1):1-15. Abstract from PubMed 6425565.

Bunzow, J.R., Sonders, M.S., Arttamangkul, S., Harrison, L.M., Zhang, G., Quigley, D.I., Darland, T., Suchland, K.L., Pasumamula, S., Kennedy, J.L., Olson, S.B., Magenis, R.E., Amara, S.G., and Grandy, D.K. 2001. Amphetamine, 34-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Mol. Pharmacol. 60(6):1181-1188.

Calapai, G., Firenzuoli, F., Saitta, A., Squadrito, F., Arlotta, M.R., Costantino, G., and Inferrera, G. 1999. Antiobesity and cardiovascular toxic effects of *Citrus aurantium* extracts in the rat: A preliminary report. Fitoterapia 70:586-592.

Cancalon, P.F. 1999. Analytical monitoring of citrus juices by using capillary electrophoresis. J. AOAC Int. 82(1):95-106. Abstract from PubMed 10028677.

Carek, P.J., and Dickerson, L.M. 1999. Current concepts in the pharmacological management of obesity. Drugs 57(6):883-904. Abstract from PubMed 10400403.

Carpéné, C., Galitzky, J., Fontana, E., Atgie, C., Lafontan, M., and Berlan, M. 1999. Selective activation of β3-adrenoceptors by octopamine: Comparative analysis studies in mammalian fat

cells. Naunyn. Schmiedebergs Arch. Pharmacol. 359(4):310-321. Abstract from PubMed 10344530.

Carvalho-Freitas, M.I., and Costa, M. 2002. Anxiolytic and sedative effects of extracts and essential oil from *Citrus aurantium* L. Biol. Pharm. Bull. 25(12):1629-1633.

CedarVale Natural Health Inc. 2003. Bitter orange oil. Available at Internet address: http://www.cedarvale.net/essentialoils/orangebitter.htm. Last accessed on October 22, 2003.

Celuch, S.M., and Juorio, A.V. 1988. Pre- and postsynaptic effects of *p*-tyramine and *p*-octopamine in the prostatic portion of the rat vas deferens. Naunyn. Schmiedebergs Arch. Pharmacol. 338(1):39-46. Abstract from PubMed 2907098.

Chance, W.T., Bernardini, A.P., James, J.H., Edwards, L.L., Minnema, K., and Fischer, J.E. 1985. Behavioral depression after intraventricular infusion of octopamine in rats. Am. J. Surg. 150(5):577-584. Abstract from PubMed 2415012.

ChemIDplus. Undated-a. Octopamine. Available at Internet address: http://www.chem.sis.nlm.nih.gov/chemidplus/all.html?DetailIndex=1&DetailCount=2. Last accessed on October 24, 2003.

ChemIDplus. Undated-b. Synephrine. Available at Internet address: http://www.chemsis.nlm.nih.gov/chemidplus/all.html?DetailIndex=1&DetailCount=2. Last accessed on October 24, 2003.

Chen, F., and Hou, L. 1984. Determination of synephrine in citrus plants (Chin.). Yaowu Fensi Zazhi 4(3):169-171. Abstract from HCAPLUS 1984:497731.

Chen, G., Zhang, L., Zhao, J., and Ye, J. 2002. Determination of hesperidin and synephrine in *Pericarpium Citri Reticulatae* by capillary electrophoresis with electrochemical detection. Anal. Bioanal. Chem. 373(3):169-173. Abstract from PubMed 12043020.

Chen, J.-C., Min, Y., Gao, Y., and Pan, X.-X. 1990. Hemodynamic effects of Shen-Zhi lyophilized injection on endotoxin-induced shock dogs (Chin.). Chin. J. Pharm. 21(4):165-167. Abstract from TOXLINE (secondary source ID: BIOSIS/91/03356).

Chen, X., Huang, Q.X., Zhou, T.J., and Dai, H.Y. 1980. Studies of *Citrus autantium* and its hypertensive ingredients on the cardiac functions and hemodynamics in comparison with dopamine and dobutamine (Chin.). Yao Hsueh Hsueh Pao 15:71-77. Abstract from NAPRALERT 92:80692.

Cheng, J.T., and Hsieh-Chen, S.C. 1988. Octopamine relaxes rabbit jejunal smooth muscle by selective activation of dopamine D1 receptors. Naunyn. Schmiedebergs. Arch. Pharmacol. 338:373-378. Abstract from PubMed 2854205.

Cheng, J.T., and Tsai, J.T. 1991. Octopamine: An endogenous blocker of dopamine D-1 receptors. Adv. Exp. Med. Biol. 287:237-240.

Cheng, J.T., Shen, C.L., and Jou, T.C. 1990. Inhibitory effect of octopamine on dopamine D-1 receptor in striatal homogenates of the rat. Neurosci. Res. 9:202-207. Abstract from PubMed 1963678.

Cho, S.-K., Park, H.-R., and Kim, C.-J. 1996. Spasmolytic and anti-peptic ulcer activities of crude drugs acting on gastrointestinal tract in rats (Korean). Yakhak Hoeji 40(5):591-598. Abstract from BIOSIS 1997:24455.

Chouchi, D., Barth, D., Reverchon, E., and della Porta, E. 1996. Bigarade peel oil fractionation by supercritical carbon dioxide desorption. J. Agric. Food Chem. 44(4):1100-1104. Abstract from CABA 96:108238.

Cleare, A.J., Murray, R.M., and O'Keane, V. 1997. Do noradrenergic reuptake inhibitors affect serotonergic function in depression? Psychopharmacology 134:406-410. Abstract from PubMed 9452184. Abstract from PubMed 9452184.

Colker, C.M., Kalman, D.S., Torina, G.C., Perlis, T., and Street, C. 1999. Effects of *Citrus aurantium* extract, caffeine, and St. John's Wort on body fat loss, lipid levels, and mood states in overweight healthy adults. Curr. Ther. Res. Clin. Exp. 60(3):145-153. Abstract from EMBASE 1999117569.

Coulon, J.F., Cavoy, A., Delacour, J., and David, J.C. 1989. Prenatal ontogenesis of brain phenolamines and catecholamines in relation to their metabolizing enzymes in Roman avoider strains of rats. J. Neurochem. 52(5):1418-1424. Abstract from PubMed 2565373.

Cytodyne Technologies. 2003. Xenadrine®-EFX: Supplemental facts. Available at Internet address: http://www.cytodyne.com/products/EFX/supp_facts.asp. Last accessed on October 22, 2003.

D'Andrea, G., Terrazzino, S., Fortin, D., Farruggio, A., Rinaldi, L., and Leon, A. 2003a. HPLC with electrochemical detection of trace amines in human plasma and platelets and expression of mRNA transcripts of trace amine receptors in circulating leukocytes. Neurosci. Lett. 346(1-2):89-92.

D'Andrea, G., Terrazzino, S., Fortin, D., Cocco, P., Balbi, T., and Leon, A. 2003b. Elusive amines and primary headaches: historical background and prospectives. Neurol. Sci 24(Suppl. 2):S65-S67.

David, J.C., and Coulon, J.F. 1985. Octopamine in invertebrates and vertebrates: A review. Prog. Neurobiol. 24(2):141-185.

David, J.C., Coulon, J.F., Cavoy, A., and Delacour, J. 1989. Effects of aging on *p*- and *m*-octopamine, catecholamines, and their metabolizing enzymes in the rat. J. Neurochem. 53(1):149-154. Abstract from PubMed 2566654.

De Boer, T., Bijma, R., and Ensing, K. 1999. Modeling of conditions for the enantiomeric separation of β2-adrenergic sympathicomimetics by capillary electrophoresis using cyclodextrins

as chiral selectors in a polyethylene glycol gel. J. Pharm. Biomed. Anal. 19(3-4):529-537. Abstract from TOXLINE (secondary source ID IPA/00/1190525).

Deferme, S., Van Gelder, J., and Augustijns, P. 2002. Inhibitory effect of fruit extracts on P-glycoprotein-related efflux carriers: An *in vitro* screening. J. Pharm. Pharmacol. 54(9):1213-1219. Abstract from Life Sci. w/Abstracts Reference Ed. (2002 annual).

Dresser, G.K., Bailey, D.G., Leake, B.F., Schwarz, U.I., Dawson, P.A., Freeman, D.J., and Kim, R.B. 2002. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin. Pharmacol. Ther. 71(1):11-20. Abstract from PubMed 11823753.

Dugo, P., Mondello, L., Cogliandro, E., Verzera, A., and Dugo, G. 1996. On the genuineness of citrus essential oils. 51. Oxygen heterocyclic compounds on bitter orange oil (*Citrus aurantium* L.). J. Agric. Food Chem. 44(2):544-549. Abstract from AGRICOLA 1998:9088.

Dutta, A. 2003. Medicinal Chemistry II: MDCM 626 (Spring 2003). Homeostatic agents. I. Cholinergics; II. Autonomic and cardiovascular agents. [Required text Foye et al. *Principles of Medicinal Chemistry*, 5th ed.]. Course syllabus, Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, Kansas. Available at Internet address: http://www.pharm.ukans.edu/medchem/mdcm626/dutta/Adrenergics.pdf. Last accessed December 17, 2003.

Egashira, T., Yamamoto, T., and Yamanaka, Y. 1984. Some interrelated properties of A and B form monoamine oxidase in monkey brain mitochondria. Jpn. J. Pharmacol. 34(3):327-334. Abstract from PubMed 6427500.

FCC Products, Inc. Undated. Certificate of analysis: *C. aurantium* extract 10% synephrine. Available at Internet address: http://www.fccproducts.com/analysis/Citrus%20Aurantium%2010%.htm. Last accessed on June 4, 2004.

FDA CFSAN (Food and Drug Administration, Center for Food Safety and Applied Nutrition). 1996. Poisonous Plant Database. Available at Internet address: http://www.cfsan.dfa.gov/~djw/plantnam.html. Last accessed on October 22, 2003.

FDA CFSAN. 1997. What guidance does FDA have for manufacturers of fruit jams (preserves), jellies, fruit butters, and marmalades? [Excerpt from Requirements of Laws and Regulations Enforced by the U.S. Food and Drug Administration.] Available at Internet address: http://www.cfsan.fda.gov/~dms/qa-ind5c.html. Last accessed on October 22, 2003.

FDA CFSAN. 2000. Food Compliance Program: Food composition, standards, labeling and economics; dietary supplements—import and domestic. Issued on February 17, 2000. Available at Internet address: http://www.cfsan.fda.gov/~comm/cp21008.html. Last accessed on October 22, 2003.

FDA CFSAN. 2003. EAFUS: A food additive database. Available at Internet address: http://www.cfsan.fda.gov/~dms/eafus.html. Last accessed on October 22, 2003.

Felter, H.W., and Lloyd, J.U. 1898. King's American Dispensatory. Aurantii Amari Cortex (U.S.P.)—Bitter orange peel. Available at Internet address: http://www.ibiblio.org/herbmed/eclectic/kings/citrus-aura_cortex.html. Last accessed on October 23, 2003.

Fen-Phen-Legal-Resources.com. 2003. Advancing the rights of patients. (Summary of Fen Phen recall, health information, and lawsuits) Website of lawyers and attorneys Lieff Cabraser Heimann & Bernstein, LLP. Available at Internet address: http://www.fen-phen-legal-resources.com. Last accessed on December 19, 2003.

Ferguson, D.M., and Vazquez, A.J. 1984. Pharmacodynamic differentiation of chronotropic and inotropic beta-adrenergic receptors in rabbit heart. J. Cardiovasc. Pharmacol. 6(1):151-158. Abstract from PubMed 6199598.

Fisher, J.F., and Trama, L.A. 1979. High performance liquid chromatographic determination of some coumarins and psoralens found in citrus peel oils. J. Agric. Food Chem. 27(6):1334-1337. Abstract from BIOSIS 1980:161849.

Flechtner-Mors, M., Jenkinson, C.P., Alt, A., Biesalski, H.K., Adler, G., and Ditschuneit, H.H. 2004. Sympathetic regulation of glucose uptake by the alpha1-adrenoceptor in human obesity. Obes. Res. 12:612-620. Abstract from PubMed 15090628.

Flora Manufacturing and Distributing Limited. Undated. Bitter-orange peel, herb monograph—Flora Health Herb Encyclopedia. Available at Internet address: http://www.florahealth.com/flora/home/canada/healthinformation/encyclopedias/BitterOrangePeel.asp. Last accessed on October 23, 2003.

Fontana, E., Morin, N., Prevot, D., and Carpéné, C. 2000. Effects of octopamine on lipolysis, glucose transport and amine oxidation in mammalian fat cells. Comp. Biochem. Physiol. C Toxicol. Pharmacol. 125(1):33-44. Abstract from PubMed 11790328.

Fregly, M.J., Kelleher, D.L., and Williams, C.M. 1979. Adrenergic activity of ortho-, meta-, and para-octopamine. Pharmacology 18(4):180-187. Abstract from PubMed 37530.

Galitzky, J., Carpene, C., Lafontan, M., and Berlan, M. 1993. Specific stimulation of adipose tissue adrenergic beta 3 receptors by octopamine (Fr.). C R Acad. Sci. III 316:519-523. Abstract from PubMed 8106131.

Gillis, C.N., and Roth, J.A. 1977. The fate of biogenic monoamines in perfused rabbit lung. Br. J. Pharmacol. 59(4):585-590. Abstract from PubMed 322781.

Griffith, R.K. 2003. Chapter one. Adrenergics and adrenergic-blocking agents. In: Burger's Medicinal Chemistry and Drug Discovery, 6th ed. Vol. 6: Nervous System Agents, D.J. Abraham, Ed., John Wiley & Sons, Inc., New York, New York, pp. 1-37. Available at Internet address http://media.wiley.com/product_data/excerpt/11/04712740/0471274011.pdf. Last accessed December 17, 2003.

Guo, L.Q., Fukuda, K., Ohta, T., and Yamazoe, Y. 2000. Role of furanocoumarin derivatives on grapefruit juice-mediated inhibition of human CYP3A activity. Drug Metab. Disp. 28(7):766-771.

Guo, L.Q., Taniguchi, M., Chen, Q.Y., Baba, K., and Yamazoe, Y. 2001. Inhibitory potential of herbal medicines on human cytochrome P450-mediated oxidation: Properties of umbelliferous or citrus crude drugs and their relative prescriptions. Jpn. J. Pharmacol. 85(4):399-408. Abstract from PubMed 11388644.

Harper, R.A., and Flaxman, B.A. 1975. Effect of pharmacological agents on human keratinocytes mitosis *in vitro*. 2. Inhibition by catecholamines. J. Cell. Physiol. 82:293-300. Search result from TOXLINE (secondary source ID EMIBACK/22024),

Hashimoto, K., Yasuda, T., and Ohsawa, K. 1992. Determination of synephrine from Chinese medicinal drugs. J. Chromatogr. 623(2):386-389.

He, X.-G., Lian, L.-Z., Lin, L.-Z., and Bernart, M.W. 1997. High-performance liquid chromatography-electrospray mass spectrometry in phytochemical analysis of sour orange (*Citrus aurantium* L.). J. Chromatogr. A 791(1-2):127-134. Abstract from EMBASE 1998044111.

Healthfinder. 2004a. Health Highlights: January 21, 2004. FDA plans closer look at diet supplements. Available at Internet address: http://www.healthfinder.gov/news/newsstory.asp?docID=517061. Last accessed on June 1, 2004.

Healthfinder. 2004b. Health Highlights: April 8, 2004. "Natural" supplements aren't necessarily safe: Magazine. Available at Internet addres: http://www.healthfinder.gov/news/newsstory.asp?docID=518328. Last accessed on June 1, 2004.

Heinrich, J. 2002. Dietary supplements for weight loss. Limited federal oversight has focused more on marketing than on safety. Report No. GAO-02-985T. U.S. General Accounting Office (Chen et al.). Available at Internet address: http://www.gao.gov/new.items/d02985t.pdf.

Hengstmann, J.H., and Aulepp, H. 1978. Pharmacokinetics and metabolism of ^{3}H-synephrine (Ger.). Arzneimittelforschung 28(12):2326-2331.

HerbsMD. 2002. Ultra Diet Phen Calm Mood by Source Naturals. Available at Internet address: http://www.herbsmd.com/shop/xq/asp/pid.1075/qx/productdetail.htm. Last accessed on October 23, 2003.

Hirani, E., Sharp, T., Sprakes, M., Grasby, P., and Hume, S. 2003. Fenfluramine evokes 5-HT2A receptor-mediated responses but does not displace [11C]MDL 100907: Small animal PET and gene expression studies. Synapse 50:251-260. Abstract from PubMed 14515343.

Hiroi, T., Imaoka, S., and Funae, Y. 1998. Dopamine formation from tyramine by CYP2D6. Biochem. Biophys. Res. Commun. 249:838-843. Cited by Tyndale et al. (1999).

Hou, Y.C., Hsiu, S.L., Tsao, C.W., Wang, Y.H., and Chao, P.D. 2000. Acute intoxication of cyclosporin caused by coadministration of decoctions of the fruits of *Citrus aurantium* and the Pericarps of Citrus grandis. Planta Med. 66(7):653-5. Abstract from MEDLINE 2001090897.

HSDB (Hazardous Substances Data Bank). 2002. Tyramine [51-67-2]. Produced by the National Library of Medicine (NLM) on STN. Profile last updated on May 13, 2002.

Huang, S., Hu, S., Shi, J., and Yang, Y. 2001a. Studies on chemical constituents from the flower of *Citrus aurantium* (Chin.). Chung Yao Tsai [J. Chin. Med. Mater.] 24(12):865-867. Abstract from MEDLINE 2002186144.

Huang, Y.-T., Lin, H.-C., Chang, Y.-Y., Yan, Y.-Y., Lee, S.-D., and Hong, C.-Y. 2001b. Hemodynamic effects of synephrine treatment in portal hypertensive rats. Jpn. J. Pharmacol. 85(2):183-188. Abstract from BIOSIS 2001:161212.

Huang, Y.-T., Wang, G.F., Chen, C.F., Chen, C.C., Hong, C.Y., and Yang, M.C. 1995. *Fructus aurantii* reduced portal pressure in hypertensive rats. Life Sci. 57(22):2011-2020.

Ibrahim, K.E., and Williams, C.M. 1985. Effect of 6-hydroxydoopamine on the metabolism of endogenous octopamines and catecholamines. J. Pharm. Pharmacol. 37(7):496-497.

Ibrahim, K.E., Couch, M.W., Williams, C.M., Fregly, M.J., and Midgley, J.M. 1985. *m*-Octopamine: Normal occurrence with *p*-octopamine in mammalian sympathetic nerves. J. Neurochem. 44(6):1862-1867.

IFRA (International Fragrance Association). 2002. Notification of IFRA Standards No. 2. 36th Amendment to the IFRA Code of Practice. Available at Internet address: http://www.ifraorg.org/Enclosures/News/36th%20Amendment_IFRA%20Code%20of%20Practice.pdf.

Iijima, O.T., Minematsu, S., Maemura, S., Waterson, L.A., and Gopinath, C. 1995. A single oral dose toxicity study and a 13-week repeated dose study with a 4-week recovery period of TSUMURA Hochn-ekki-to (TJ-41) in rats. Jpn. Pharmacol. Ther. 23(Suppl. 7):209-224. Abstract from EMBASE 95321104.

Integra Nutrition Inc. Undated. Lipotrim. Available at Internet address: http://www.integranutrition.com/lipotrim.html. Last updated on November 15, 2002. Last accessed on October 23, 2003.

Ishiguro, Y., and Morgan, J.P. 1997. Biphasic inotropic effects of methamphetamine and methylphenidate on ferret papillary muscles. J. Cardiovasc. Pharmacol. 30:744-749. Abstract from PubMed 9436813.

Jagiello-Wojtowicz, E. 1979. Mechanism of central action of octopamine. Pol. J. Pharmacol. Pharm. 31(5):509-516. Abstract from PubMed 121158.

Jagiello-Wojtowicz, E., and Chodkowska, A. 1984. Effects of octopamine on GABA-ergic transmission in rats. Pol. J. Pharmacol. Pharm. 36(6):595-601. Abstract from PubMed 6100132.

Jia, H., Zong, H., and Guo, Z. 1983. Effect of "Zhi shi" (*Citrus aurantium*) and its active principles on the contractility and automaticity of cat papillary muscle in endotoxic shock (Chin.). Hunan Yixueyuan Xuebao 8(3):267-271. Abstract from TOXCENTER 1984:94801.

Jones, D. 2001. Notification of a Structure/Function Statement, FFDCA 403(r)(6); 21 U.S.C. 343(r)(6). Forms for four dietary supplements: ZHI-Thermo™, ZHI-Slim™, ZHIshape™, and DynamicTrim™. Submitted on April 20, 2001. Letters are available at Internet address: http://www.fda.gov/ohrms/dockets/dailys/01/Jun01/061801/let7649.pdf. …let7650, …let7653, and …let7647, respectively.

Jones, D. 2002a. Methods for inducing weight loss in a human with materials derived from Citrus varieties. Off. Gaz. U.S. Pat. Trademark Of. Pat. Vol. 1254, No. 4. Abstract from BIOSIS 2002:179980.

Jones, D. 2002b. Regulation of athletic function with materials derived from Citrus varieties. Off. Gaz. U.S. Pat. Trademark Of. Pat. Vol. 1254, No. 4. Abstract from BIOSIS 2002:161757.

Jordan, R., Midgley, J.M., Thonoor, C.M., and Williams, C.M. 1987. Beta-adrenergic activities of octopamine and synephrine stereoisomers on guinea-pig atria and trachea. J. Pharm. Pharmacol. 39(9):752-4. Abstract from PubMed 2890747.

Kaidbey, K.H., and Kligman, A.M. 1980. Identification of contact photosensitizers by human assay. Report No. 1995. In: Current Concepts in Cutaneous Toxicity. Academic Press, New York, NY, pp. 55-68. Cited by IFRA (2002).

Kalman, D., Incledon, T., Gaunaurd, I., Schwartz, H., and Krieger, D. 2002. An acute clinical trial evaluating the cardiovascular effects of herbal ephedra-caffeine weight loss product in healthy overweight adults. Int. J. Obesity 26:1363-1366.

Kanitani, M., Minematsu, S., Maemura, S., Perry, C.J., and Mulhern, M. 1995. A single oral dose toxicity study and a 13-week repeated dose study with a 4-week recovery period of TSUMURA Rikkunshi-to (TJ-43) in rats. Jpn. Pharmacol. Ther. 23(Suppl. 7):225-240. Abstract from EMBASE 95321105.

Keogh, A.M., and Baron, D.W. 1985. Sympathomimetic abuse and coronary artery spasm. Br. Med. J. 291:940. Also cited by Moore (2003 lett.).

Kernan, W.N., Viscoli, C.M., Brass, L.M., Broderick, JP., Brott, T., Feldmann, E., Morgenstern, L.B., Wilterdink, J.L., Horwitz, R.I. 2000. Phenylpropanolamine and the risk of hemorrhagic stroke. New Engl. J. Med. 343:1826-1832. Cited by TRI, Inc. (2001).

Kim, K.W., Kim, H.D., Jung, J.S., Woo, R.S., Kim, H.S., Suh, H.W., Kim, Y.H., and Song, D.K. 2001. Characterization of antidepressant-like effects of *p*-synephrine stereoisomers. Naunyn. Schmiedebergs Arch. Pharmacol. 364(1):21-26. Abstract from PubMed 11485034.

Kinoshita, T., Sameshima, M., and Sankawa, U. 1979. Isolation of a sympathomimetic substance from Chinese medicinal drugs originated from Citrus species (Jpn.). Shoyakugaku Zasshi 33(3):146-149. Abstract from BIOSIS 1980:212280.

Kobayashi, K., Foti, A., Dequattro, V., Kolloch, R., and Miano, L. 1980. A radioenzymatic assay for free and conjugated normetanephrine and octopamine excretion in man. Clin. Chim. Acta 107(3):163-173. Abstract from PubMed 6777088.

Koda, A., Nishiyori, T., Nagai, H., Matsuura, N., and Tsuchiya, H. 1982. Anti allergic actions of crude drugs and blended chinese traditional medicines effects of type I and type IV allergic reactions (Jpn.). Folia Pharmacologica Japonica 80(1):31-42. Abstract from BIOSIS 1983:294326.

Koda, H., Yokoo, Y., Matsumoto, N., Suwa, Y., Fukazawa, H., Ishida, H., Tsuji, K., Nukaya, H., and Kuriyama, K. 1999. Antagonistic effect of *N*-methyltyramine on alpha2-adrenoceptor in mice. Jpn. J. Pharmacol. 81:313-315. Abstract from PubMed 10622222.

Koury, R., Stone, C.K., Stapczynski, J.S., and Blake, J. 1999. Sympathetic overactivity from fenfluramine-phentermine overdose. Eur. J. Emerg. Med. 6(2):149-152. Abstract from PubMed 10461560.

Kuhrts, E.H. 2002. Methods and compositions for producing weight loss. Off. Gaz. U.S. Pat. Trademark Of. Pat. Vol. 1264, No. 1. Abstract from BIOSIS 2003:42073.

Kusu, F., Matsumoto, K., Arai, K., and Takamura, K. 1996. Determination of synephrine enantiomers in food and conjugated synephrine in urine by high-performance liquid chromatography with electrochemical detection. Anal. Biochem. 235:191-194.

Labrid, C., Rocher, I., and Guery, O. 1989. Structure-activity relationships as a response to the pharmacological differences in beta-receptor ligands. Am. J. Hypertens. 2:245S-251S. Abstract from PubMed 2573372.

Lafi, M.A., and Leake, L.D. 1988. Actions of dopamine and related amines on reserpinized and chronically denervated vasa deferentia of the rat. Comp. Biochem. Physiol. C 89(2):141-146. Abstract from PubMed 2898988.

Ledda, F., Mantelli, L., and Mugelli, A. 1980. α-Sympathomimetic amines and calcium-mediated action potentials in guinea-pig ventricular muscle. Br. J. Pharmacol. 69(4):565-571. Abstract from PubMed 6254592.

Liberty Natural Products. 2004. Orange peel USA. Bulk wholesale price list. Available at Internet address: http://libertynatural.com/bulk/715.htm. MSDS: Orange peel, USA - Product No. 715. Available at Internet address: http://libertynatural.com/msd/715.htm. Both pages last updated on March 18, 2004. Both pages last accessed on June 16, 2004.

Lin, Z.K., Hua, Y.F., and Gu, Y.H. 1986. Chemical constituents of the essential oil from the flowers, leaves and peel of *Citrus aurantium* (Chin.). Acta Botanica Sinica 28(6):635-640. Abstract from CABA 87:18331.

Lohse, M.J., Engelhardt, S., and Eschenhagen, T. 2003. What is the role of beta-adrenergic signaling in heart failure? Circ. Res. 93:896-906. Abstract from PubMed 14615493.

Louw, A., Allie, F., Swart, A.C., and Swart, P. 2000. Inhibition of cytochrome P450c11 by biogenic amines and an aziridine precursor, 2-(4-acetoxyphenyl)-2-chloro-*N*-methyl-ethylammonium chloride. Endocr. Res. 26(4):729-736. Abstract from PubMed 11196449.

Luckett, P. 2003. Bitter Seville oranges perfect for cooking. The Halifax Herald Limited. January 26, 2003. Available at Internet address: http://www.herald.ns.ca/stories/2003/01/26/pYourTime255.raw.html. Last accessed on October 23, 2003.

Malhotra, S., Bailey, D.G., Paine, M.F., and Watkins, P.B. 2001. Seville orange juice-felodipine interaction: Comparison with dilute grapefruit juice and involvement of furocoumarins. Clin. Pharmacol. Ther. 69(1):14-23. Abstract from PubMed 11180034.

Marcus, D.M., and Grollman, A.P. 2003 lett. Ephedra-free is not danger-free (letter). Science 301(2640):1669-1670.

Matsuoka, Y., Sugioka, T., Terawaki, Y., Uruno, T., and Kubota, K. 1993. Characteristics of antinociception induced by noncatecholic phenylethylamine derivatives: The involvement of alpha-2-adrenoceptors. Jpn. J. Pharmacol. 63(1):101-108. Abstract from PubMed 7903717.

McGregor, D.B., Riach, C.G., Brown, A., Edwards, I., Reynolds, D., West, K., and Willington, S. 1988. Reactivity of catecholamines and related substances in the mouse lymphoma L5178Y cell assay for mutagens. Environ. Mol. Mutagen. 11(4):523-544.

MeSH (Medical Subject Headings) Database. 2003. (Terminology for selected structural analogs of synephrine and octopamine and for selected terms related to adrenergic receptors.) Database of indexing terminology used in MEDLINE/PubMed. Produced by the National Library of Medicine (NLM). Available at Internet address http://www.ncbi.nih.gov/entrez/query.fcgi?db=mesh.

Mohri, K., and Uesawa, Y. 2001. Effects of furanocoumarin derivatives in grapefruit juice on mifedipine pharmacokinetics in rats. Pharm. Res. 18(2):177-182. Abstract from PubMed 11405288.

Molinoff, P.B. 1984. Alpha- and beta-adrenergic receptor subtypes properties, distribution and regulation. Drugs 2:1-15. Abstract from PubMed 6098436.

Moore, B.J. 2003 lett. Letter to J.H. Cohen dated June 24, 2002. Available at Internet address: http://www.faseb.org/ascn/gaoresponse.pdf.

Moufida, S., and Marzouk, B. 2003. Biochemical characterization of blood orange, sweet orange, lemon, bergamot and bitter orange. Phytochemistry 62(8):1283-1289.

Mwaiko, G.L. 1992. Citrus peel oil extracts as mosquito larvae insecticides. East Afr. Med. J. 69(4):223-226. Abstract from MEDLINE 92354539.

Nakabayashi, T. 1960. Extraction of hesperidin from the citrus plant. Makiji Hata. Japanese Patent No. 35011200 dated August 15, 1960. Abstract from HCAPLUS 1961:50836.

Nature's Way. 2003. Bitter orange extract (standardized). Available at Internet address: http://www.n101.com/Static/Products/bitter_orange_extract_standardized_643006-1… Last accessed on October 6, 2003.

NCAA (National Collegiate Athletic Association). Undated. NCAA banned-drug classes, 2003-2004. Available at Internet address: http://www1.ncaa.org/membership/ed_outreach/health-safety/drug_testing/banned_drug_classes.pdf.

NDPSC (National Drugs and Poisons Schedule Committee). 2003. Record of the Reasons, 37th meeting, February 25-26, 2003. Available at Internet address: http://www.health.gov.au/tga/ndpsc/record/rr200302.pdf.

Nguyen, T.C., and Le, V.T. 1987. Conditions for the extraction of hesperidin from the peel of citrus fruits (Vietnamese). Tap Chi Duoc Hoc 1:18-21. Abstract from HCAPLUS 1988:403339.

NIDA (National Institute on Drug Abuse). 2002. News Scan: NIDA Addiction Research News. Newly discovered receptor may be important in the development of antipsychostimulant medications. NIDA, NIEHS, U.S. Department of Health and Human Services. Available at Internet address: http://www.nih.gov/news/pr/jan2002/nidanewsscan01032002.pdf. Last updated on January 3, 2002.

Niemann, R.A., and Gay, M.L. 2003. Determination of ephedrine alkaloids and synephrine in dietary supplements by column-switching cation exchange high-performance liquid chromatography with scanning-wavelength ultraviolet and fluorescence detection. J. Agric. Food Chem. 51(19):5630-5638. Abstract from PubMed 12952412.

NIOSH (National Institute of Occupational Safety and Health). Undated. National Occupation Exposure Survey (1981-1983). Agent Name: Oils, bitter-orange. Available at Internet address: http://www.cdc.gov/noes/noes2/x2707occ.html. Last accessed on June 1, 2004.

Nishio, M., Kuroki, Y., and Watanabe, Y. 2003. Role of hippocampal alpha(2A)-adrenergic receptor in methamphetamine-induced hyperlocomotion in the mouse. Neurosci. Lett. 341(2):156-160. Abstract from PubMed 12686389.

Nogata, Y., Yoza, K.I., Kusumoto, K.I., Kohyama, N., Sekiya, K., and Ohta, H. 1996. Screening for inhibitory activity of citrus fruit extracts against platelet cyclooxygenase and lipoxygenase. J. Agric. Food Chem. 44(3):725-729. Abstract from CABA 96:107783.

Northwest Botanicals, Inc. 2003. Synephrine extract—*Citrus aurantium*. Available at Internet address: http://www.nwbotanicals.org/nwb/synephrine.htm. Last accessed on October 31, 2003.

NTP Testing Status Reports. 2003. Synopses of NTP testing for dopamine, epinephrine, epinephrine hydrochloride, ephedrine sulfate, ephedrine alkaloid dietary supplements, and phenylephrine hydrochloride. Available at Internet address http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/Res_Stat/iH_Res_Stat_Frames.html. [Enter individual search terms.] Reports updated November 26, 2003. Last accessed on December 9, 2003.

NTP TR-307. 1986 abstr. Toxicology and Carcinogenesis Studies of Ephedrine Sulfate (CAS No. 134-72-5) in F344/N Rats and B6C3F1 Mice (Feed Studies). National Toxicology Program Technical Report 307. Abstract of long-term study available at Internet address http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr307.html. Last accessed on December 9, 2003.

NTP TR-322. 1987 abstr. Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride (CAS No. 61-76-7) in F344/N Rats and B6C3F1 Mice (Feed Studies). National Toxicology Program Technical Report 322. Abstract of long-term study available at Internet address http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr322.html. Last accessed on December 9, 2003.

NTP TR-380. 1990 abstr. Toxicology and Carcinogenesis Studies of *l*-Epinephrine Hydrochloride (CAS No. 55-31-2) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). National Toxicology Program Technical Report 322. Abstract of long-term study available at Internet address http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr380.html. Last accessed on December 9, 2003.

Nykamp, D.L., Fackih, M.N., and Compton, A.L. 2004. Possible association of acute lateral-wall myocardial infarction and bitter orange supplement (May). Ann. Pharmacother., March 16, 2004 [Epub ahead of print]. Abstract from PubMed 15026566.

Ohta, I., Ogawa, K., Saito, H., and Ohsawa, K. 1994. Determination of synephrine in Oriental pharmaceutical decoctions containing *Aurantii Fructus Immaturus* by ion-pair high-performance liquid chromatography (Jpn.). Yakugaku Zasshi 114(9):691-696. Abstract from EMBASE 94327036.

Okuyama, T., Takata, M., Shibata, S., Hoson, M., Kawada, T., Masaki, H., and Noguchi, T. 1987. Effect of Sino-Japanese medicine on platelet aggregation. IV. Chinese medical prescriptions employed for angina pectoris like symptom (Jpn.). Shoyakugaku Zasshi 41(2):147-152. Abstract from BIOSIS 1988:7779.

Paterson, IA, Juorio, AV, and Boulton, AA. 1990. 2-Phenylethylamine: A modulator of catecholamine transmission in the mammalian central nervous system? J. Neurochem. 55:1827-1837. Cited by Bunzow et al. (2001).

Pellati, F., Benvenuti, S., Melegari, M., and Firenzuoli, F. 2002. Determination of adrenergic agonists from extracts and herbal products of *Citrus aurantium* L. var. amara by LC. J. Pharm. Biomed. Anal. 29(6):1113-1119.

Penzak, S.R., Jann, M.W., Cold, J.A., Hon, Y.Y., Desai, H.D., and Gurley, B.J. 2001. Seville (sour) orange juice: Synephrine content and cardiovascular effects in normotensive adults. J. Clin. Pharmacol. 41(10):1059-1063.

Premont, R.T., Gainetdinov, R.R., and Caron, M.G. 2001. Following the trace of elusive amines. Proc. Natl. Acad. Sci. 98(17):9474-9475.

Quintero, A., de Gonzalez, C.N., Sanchez, F., Usubillaga, A., Rojas, L., Szoke, E., Mathe, I., Blunden, G., and Kery, A. 2003. Constituents and biological activity of *Citrus aurantium amara L*. essential oil. Acta Horticult. (597):115-117. Abstract from CABA 2003:94821.

Rahmani, M.A., Cheema, I.R., Sen, S., and Peoples, B. 1987. Evaluation of isomers of octopamine for in vitro alpha-adrenergic stimulation of the aortic smooth muscle from spontaneously hypertensive rats. Cytobios 52(208):7-16. Abstract from PubMed 2824134.

Raintree Nutrition, Inc. 2002. Orange bitters. Available at Internet address: http://www.rain-tree.com/orange.htm. Last accessed on October 22, 2003.

Ramadan, W., Mourad, B., Ibrahim, S., and Sonbol, F. 1996. Oil of bitter orange: New topical antifungal agent. Int. J. Dermatol. 35(6):448-449. Abstract available from PubMed 8737885.

Registry. 2003a. 140-14-3. Octopamine. Provided by the American Chemical Society on STN.

Registry. 2003b. 94-07-5. Synephrine. Provided by the American Chemical Society on STN.

Renaissance Herbs. 2003. Product Information SHeet (PIS): Zhi Shi 6%. Available at Internet address: http://www.renaissanceherbs.com/products/ZhiShi6PIS.pdf. PIS: Zhi Shi 10%. Available at Internet address: http://www.renaissanceherbs.com/products/ZhiShi10PIS.pdf.

Ress, R.J., Rahmani, M.A., Fregly, M.J., Field, F.P., and Williams, C.M. 1980. Effect of isomers of octopamine on *in vitro* reactivity of vascular smooth muscle of rats. Pharmacology 21(5):342-347. Abstract from PubMed 6776546.

Richardson, J., Chatwin, H., Hirasawa, A., Tsujimoto, G., and Evans, P.D. 2003. Agonist-specific coupling of a cloned human alpha1A-adrenoceptor to different second messenger pathways. Naunyn Schmiedeberg's Arch. Pharmacol. 2003. 367(4):333-341. Abstract from PubMed 12690424.

Robbins, A. 1883. Fluid extracts of the new pharmacopoeia. Part I. Am. J. Pharm. 55(2):12 ff.

Rossi-Fanelli, F., Cangiano, C., Attili, A., Angelico, M., Cascino, A., Capocaccia, L., Strom, R., and Crifo, C. 1976. Octopamine plasma levels and hepatic encephalopathy: A re-appraisal of the problem. Clin. Chim. Acta 67(3):255-261. Abstract from PubMed 770031.

Rothman, R.B., Vu, N., Partilla, J.S., Roth, B.L., Hufeisen, S.J., Compton-Toth, B.A., Birkes, J., Young, R., and Glennon, R.A. 2003. *In vitro* characterization of ephedrine-related stereoisomers at biogenic amine transporters and the receptorome reveals selective actions as norepinephrine transporter substrates. J. Pharmacol. Exp. Ther. 307(1):138-45. Abstract from PubMed 12954796.

Rowland, N.E., Lo, J., and Robertson, K. 2001. Acute anorectic effect of single and combined drugs in mice using a non-deprivation protocol. Psychopharmacology 157:193-196. Abstract from PubMed 11594445.

RTECS (Registry of Toxic Effects of Chemical Substances). 1996a. Database record for 104-14-3. (±)-*p*-Octopamine. Profile provided by DOC on STN.

RTECS. 1996b. Database record for 94-07-5. (±)-*p*-Synephrine. Profile provided by DOC on STN.

RTECS. 1996c. Database record for racemic *m*-octopamine (norfenefrine). RTECS on STN International RTECS Number DN7250000.

RTECS. 1996d. Database record for (*R*)- or D-(-)-Phenylephrine hydrochloride. RTECS Number DO7525000. Available at http://www.cdc.gov/niosh/rtecs/do72d288.html. Last accessed December 19, 2003.

RTECS. 1997. 5985-28-4. Synephrine hydrochloride. Profile provided by DOC on STN.

RTECS. 2002. Database record for (-)-ephedrine sulfate. RTECS Number KB2625000. Available at http://www.cdc.gov/niosh/rtecs/kb280de8.html. Last accessed December 19, 2003.

RTECS. 2003a. 614-35-7. (*R*)-(-)-*p*-Synephrine. Profile provided by DOC on STN.

RTECS. 2003b. 532-80-9. (*S*)-(+)-*p*-Synephrine. Profile provided by DOC on STN.

Ruffolo, R.R., Jr. 1984. Interactions of agonists with peripheral alpha-adrenergic receptors. Fed. Proc. 43:2910-2916. Abstract from PubMed 6149156.

Ryan, C.K, Reamy, B., and Rochester, J.A. 2002. Ischemic colitis associated with herbal product use in a young woman. JABFP 15(4):309-312.

Sakuramata, Y., and Kusano, S. 1998. Screening of plant extracts with potential to stimulate lipolysis in 3T3-L1 cells (Jpn.). J. Jpn. Soc. Nutr. Food Sci. (Nippon Eiyo Shokuryo Gakkaishi) 51(6):361-364. Abstract from CABA 1999:70192.

Salib, A.G., Saleh, M.A., and Abdel-Malik, G.S. 1978. Chemical and physical studies on peel essential oils of some Egyptian citrus fruits. Ann. Agric. Sci. Moshtohor 9:65-72. Abstract from CABA 79:9648.

Satoh, Y., Tashiro, S., Satoh, M., Fujimoto, Y., Xu, J.Y., and Ikekawa, T. 1996. Studies on the bioactive constituents of *Aurantii Fructus Immaturus* (Jpn.). Yakugaku Zasshi 116(3):244-250. Abstract from PubMed 8721353.

Schumann, H.J. 1983. What role do alpha- and beta-adrenoceptors play in the regulation of the heart? Eur. Heart J. 4(Suppl. A):55-60. Abstract from PubMed 6301837.

schumer.senate.gov. Undated. Schumer, Sweeney: New US ephedra ban doesn't go far enough—ephedra copycats dodge ban and 15 ephedra clones already on sale in NY. Available at Internet address: http://schumer.senate.gov/SchumerWebsite/pressroom/press_releases/PR02373.pf.html. Last accessed on June 1, 2004.

Scrollini, F., Sangiovanni, M., and Torchio, P. 1970. Comparative teratogenic effects of dimethophrine and synephrine. Atti Acc. Med. Lomb. 25(2-3):203-207. Abstract from HCAPLUS 1972:54426.

Shangai Herbsea Nutraceutical Inc. 2004. *Citrus aurantium* powder extract (synephrine). Available at Internet address: http://herbsea.en.alibaba.com/product/50016115/50086697/Herbal_Extracts__Stimul… Last accessed on June 4, 2004.

SlimStore.com. 2002. Ephedrine-free Dexatrim Natural. Available at Internet address: http://www.slimstore.com/dexatrimnatural.htm. Last accessed on October 23, 2003.

Smartinfo. Undated. *Citrus Aurantium*. Available at Internet address: http://www.sirius.nl/en/smartinfo?Plants=Citrus%20Aurantium. Last accessed on October 22, 2003.

Song, K.D., Suh, H.W., Jung, J.S., Wie, M.B., Son, K.H., and Kim, Y.H. 1996. Antidepressant-like effects of *p*-synephrine in mouse models of immobility tests. Neurosci. Lett. 214(2-3):107-110. Abstract from PubMed 8878095.

Sugiyama, S., Umehara, K., Kuroyanagi, M., Ueno, A., and Taki, T. 1993. Studies on the differentiation inducers of myeloid leukemic cells from citrus species. Chem. Pharm. Bull. 41(4):714-719. Abstract from CABA 94:25487.

Supplement Watch. Undated. Synephrine. Available at Internet address: http://www.supplementwatch.com/supatoz/supplement.asp?supplementID=273. Last accessed on October 22, 2003.

Suzuki, O., Katsumata, Y., and Oya, M. 1979a. Oxidation of phenylethanolamine and octopamine by type A and type B monoamine oxidase. Biochem. Pharmacol. 28(15):2327-2332.

Suzuki, O., Matsumoto, T., Oya, M., and Katsumata, Y. 1979b. Oxidation of synephrine by type A and type B monoamine oxidase. Experientia 35(10):1283-1284.

Takei, H., Hirabuki, M., and Yoshizaki, F. 1999. Analysis of synephrine in the peel of Citrus fruit, immature Citrus fruit and decoctions of Chinese medicinal prescriptions containing these crude drugs by capillary electrophoresis. Anal. Sci. 15:1017-1020.

Tallman, J.F., Saavedra. J.M., and Axelrod, J. 1976. Biosynthesis and metabolism of endogenous tyramine and its normal presence in sympathetic nerves. J. Pharmacol. Exp. Ther. 199:216-221. Cited by Bunzow et al. (2001).

Tao, R., Fray, A., Aspley, S., Brammer, R., Heal, D., and Auerbach, S. 2002. Effects on serotonin in rat hypothalamus of D-fenfluramine, aminorex, phentermine and fluoxetine. Eur. J. Pharmacol. 445:69-81. Abstract from PubMed 12065196.

Taylor, S.L, and Leiber, E.R. 1979. *In vitro* inhibition of rat intestinal histamine-metabolizing enzymes. Food Cosmet. Toxicol. 17(3):237-240. Abstract from TOXLINE (secondary source ID HEEP/80/04232).

Therapeutic Research Faculty. 2003. Natural medicines in clinical management of obesity. Natural Medicines Comprehensive Database: Clinical Management Series. Available at Internet address: http://www.naturaldatabase.com/ce_natmeds.asp?pg=main. Last accessed on October 23, 2003.

Travis, J. 2001. Obscure brain chemicals draw new attentions. (Trace amines). Science News, July 21, 2001. Available at Internet address: http://www.findarticles.com/cf_dls/m1200/3_160?77074764/print.jhtml. Last accessed on April 30, 2004.

TRI (Technical Resources International), Inc. 2001. Summary Data for Chemical Selection. Dietary Supplements Containing Ephedrine Alkaloids. Prepared for NCI by Technical Resources International, Inc. to support chemical nominations under contract no. N02-CB-07007, October 2001. Available at Internet address: http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPdf/ephedrinealkaloids.pdf. Last accessed on December 19, 2003.

Tuzcu, O., Neubeller, J., and Buchloh, G. 1985. Essential oil contents in the rinds of Eastern Mediterranean sour oranges (*Citrus aurantium* L.) (Turkish). Doga Bilim Dergisi, D2 9(1):34-39. Abstract from CABA 85:115116.

Tyndale, R.F., Li, Y., Li, N.-Y., Messina, E., Miksys, S., and Sellers, E.M. 1999. Characterization of cytochrome P-450 2D1 activity in rat brain: High-affinity kinetics for dextromethorphan. Drug Metab. Disp. 27(8):924-930.

UNC (University of North Carolina). 2001. Press release: Like grapefruit, sour oranges boost drug effectiveness, scientists find, and also why. Public release date: February 6, 2001. Available at Internet address: http://www.eurekalert.org/pub_releases/2001-02/UoNC-Lgso-0602101.php. Last accessed on October 23, 2003.

USDA (U.S. Department of Agriculture). 1974. United States Standards for Grades of Orange Marmalade. Effective date: December 31, 1974. Available at Internet address: http://www.ams.usda.gov/standards/cnorangm.pdf.

Varma, D.R., Deng, X.F., Chemtob, S., Nantel, F., and Bouvier, M. 1995. Characterization of the vasorelaxant activity of tyramine and other phenylethylamines in rat aorta. Can. J. Physiol. Pharmacol. 73(6):742-6. Abstract from PubMed 7585347.

Verhoeven, G., Dierickx, P., and de Moor, P. 1979. Stimulation effect of neurotransmitters on the aromatization of testosterone by Sertoli cell-enriched cultures. Mol. Cell. Endocrinol. 13(3):241-253.

Veriotti, T., and Sacks, R. 2002. High-speed characterization and analysis of orange oils with tandem-column stop-flow GC and time-of-flight MS. Anal. Chem. 74(21):5635-5640.

Victoria Packing Corporation. 2001. Fruits Information Center: Citrus. Available at Internet address: http://www.victoriapacking.com/fruitinfo.html. Last accessed on October 23, 2003.

Wagner, J., Schumann, H.J., Knorr, A., Rohm, N., and Reidemeister, J.C. 1980. Stimulation by adrenaline and dopamine but not by noradrenaline of myocardial alpha-adrenoceptors mediating positive inotropic effects in human atrial preparations. Naunyn. Schmiedebergs Arch. Pharmacol 312:99-102. Abstract from PubMed 6248799.

Watson, D.G., Midgley, J.M., Chen, R.N., Huang, W., Bain, G.M., McDonald, N.M., Reid, J.L., and McGhee, C.N.J. 1990. Analysis of biogenic amines and their metabolites in biological tissues and fluids by gas chromatography-negative ion chemical ionization mass spectrometry (GC-NICIMS). J. Pharm. Biomed. Anal. 8(8-12):899-904.

Wheaton, T.A., and Stewart, I. 1970. The distribution of tyramine, *N*-methyltyramine, hordenine, octopamine, and synephrine in higher plants. Florida Agricultural Experiment Stations Journal Series No. 3355. Appl. Environ. Microbiol. 33(2):244-254.

Wong, A., Hwang, S.M., Cheng, H.Y., and Crooke, S.T. 1987. Structure-activity relationships of beta-adrenergic receptor-coupled adenylate cyclase: Implications of a redox mechanism for the action of agonists at beta-adrenergic receptors. Mol. Pharmacol. 31:368-376. Abstract from PubMed 2883567.

Wu, F.-J., and Sheu, S.-J. 1992. Analysis and processing of Chinese herbal drugs. XII. The study of *Fructus Aurantii Immaturus* (Chin.). Chin. Pharm. J. 44(3):257-263. Abstract from BIOSIS 1992:435981.

Yen, Y.F., and Chung, W.P. 1981. Preliminary study of the effect on receptors and of the positive inotropic effects of *N*-methyltyramine, an active principle of Zhi shi (*Citrus aurantium*) (Chin.). Hu-nan I Hsueh Yan Hsueh Pao 6:131-134. Abstract from NAPRALERT 92:82017. Also available from Chem. Abstr. 95:91117.

Yonekura, T., Kamata, S., Wasa, M., Okada, A., Yamatodani, A., Watanabe, T., and Wada, H. 1988. Simultaneous determination of plasma phenethylamine, phenylethanolamine, tyramine and octopamine by high-performance liquid chromatography using derivatization with fluorescamine. J. Chromatogr. 427(2):320-325.

Yum, J.Y., and Eun, J.S. 1998. Effect of *Arantii nobilis pericarpium* and *Arantii immaturi* on immunocytes in mice (Korean). Korean J. Pharmacog. 29(3):173-178. Abstract from CABA 1999:1247.

Zhao, X.W., Li, J.X., Zhu, Z.R., Sun, D.Q., and Liu, S.C. 1989. Anti-shock effects of synthetic effective compositions of *Fructus aurantii immaturus*. Experimental study and clinical observation. Chin. Med. J. 102(2):91-93.

Zhejiang Sinour Industry Co., Ltd. 2003. Worldbid International trade leads import export b2b marketplace. View offers to sell: Health products/supplements--weight loss. Available at Internet address: http://www.worldbid.com/tradeleads/details.htm?session=&search_type=Sell&search… Last accessed on June 4, 2004.

Zheng, H.J., Liu, Y.F., and Zhou, Y.Y. 1983. Determination of synephrine and *N*-methyl-tyramine in Citrus crude drugs and Zhi Shi (immature Citrus fruit) injections by reversed-phase

ion-pairing HPLC (Chin.). Chung Ts'ao Yao 14(5):200-204. Abstract from NAPRALERT 92:85106.

ZXCHEM. 2002. Certificate of analysis: *C. auratium* extract. Available at Internet address: http://www.chineseherbalextract.com/Products/COA/CitrusAurantium_Synephrine_HPLC30.pdf.

Zychlinski, L, and Montgomery, M.R. 1984. Alterations in monoamine oxidase activity after single and repeated exposure of rats to chlorphentermine. Toxicol. Lett. 22(2):133-138. Abstract from PubMed 6474505.

13.0 References Considered But Not Cited

Bergner, E.A., and Dougherty, R.C. 1981. Detection of urinary primary amines through negative chemical ionization mass spectrometry of fluorescamine derivatives. Biomed. Mass Spectrom. 8(5):208-210.

Boulton, A.A. 1978. The tyramines: Funtionally significant biogenic amines or metabolic accidents? Life Sci. 23(7):659-671.

DiMarco, M.P., Edwards, D.J., Wainer, I.W., and Ducharme, M.P. 2002. The effect of grapefruit juice and Seville orange juice on the pharmacokinetics of dextromethorphan: The role of gut CYP3A and P-glycoprotein. Life Sci. 71(10):1149-1160. Abstract from Life Sciences with Abstracts Reference Edition, 2002 annual.

Edwards, D.J., and Antelman, S.M. 1980. Mono amine oxidase and the metabolism of phenyl ethanolamine tyramine and octopamine. In: Mosnaim, A.D., and Wolf, M.E., Eds. Modern Pharmacology-Toxicology, Vol. 12. Noncatecholic phenylethylamines, Part 2. Phenylethanol-amine, tyramines, and octopamine. Marcel Dekker, Inc., New York, NY, pp. 53-80.

Edwards, D.J., Bellevue, F.H., III, and Woster, P.M. 1996. Identification of 6′,7′-dihydroxybergamottin, a cytochrome P450 inhibitor, in grapefruit juice. Drug Metab. Dispos. 24(12):1287-1290. Abstract from PubMed 8971132.

Edwards, D.J., Fitzsimmons, M.E., Schuetz, E.G., Yasuda, K., Ducharme, M.P., Warbasse, L.H., Woster, P.M., Schuetz, J.D., and Watkins, P. 1999. 6′,7′-Dihydroxybergamottin in grapefruit juice and Seville orange juice: Effects on cyclosporine disposition, enterocyte CYP3A4, and P-glycoprotein. Clin. Pharmacol. Ther. 65(3):237-244. Abstract from PubMed 10096255.

Grana, E., Zonta, F., and Santagostino Barbone, M.G. 1980. Magnitude of the maximal response in the rat vas deferens. Part 1. Study of adrenergic amines with different action mechanisms and influence of Ca^{2+} concentration in the physiological solution (Ita.). Farm. Ed. Sci. 35:269-278. Abstract from TOXLINE (secondary source ID IPA/81/416072).

Ikegawa, T., Ushigome, F., Koyabu, N., Morimoto, S., Shoyama, Y., Naito, M., Tsuruo, T., Ohtani, H., and Sawada, Y. 2000. Inhibition of P-glycoprotein by orange juice components, polymethoxyflavones in adriamycin-resistant human myelogenous leukemia (K562/ADM) cells. Cancer Lett. 160(1):21-28. Abstract from PubMed 11098080.

Kimura, T., Iwasaki, N., Yokoe, J.-I., Haruta, S., Yokoo, Y., Ogawar, K.-I., and Higaki, K. 2000. Analysis and prediction of absorption profile including hepatic first-pass metabolism of *N*-methyltyramine, a potent stimulant of gastrin release present in beer, after oral ingestion in rats by gastrointestinal-transit-absorption model. Drug Metab. Disp. 28(5):577-581.

Murphy, D.L., Cahan, D.H., and Molinoff, P.B. 1975. Occurrence, transport, and storage of octopamine in human thrombocytes. Clin. Pharmacol. Ther. 18(5, Pt. 1):587-593. Abstract from PubMed 1102236.

Schardein, J.L. 1993. Drugs used in respiratory and allergic disorders. Chemically Induced Birth Defects 2:340-360. Search result from TOXLINE (secondary source ID DART/TER/ 93001534).

Scrollini, F., Sangiovanni, M., and Torchio, P. 1970. Comparative teratogenic effects of dimethophrine and synephrine—two sympathomimetic amines. (Ita.). Atti. Accad. Med. Lombarda 25:203-207. Search result from TOXLINE (secondary source ID ETICBACK/ 37401).

Stockamp, K., Schreiter, F., and Altwein, J.E. 1974. alpha-Adrenergic drugs in retrograde ejaculation. Fertil. Steril. 25:817-820. Abstract available from TOXLINE (secondary source ID: IPA/75/161011).

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Appendix A: Units and Abbreviations

°C = degrees Celsius
µg/L = microgram(s) per liter
µg/m^3 = microgram(s) per cubic meter
µg/mL = microgram(s) per milliliter
µM = micromolar
CNS = central nervous system
DAD = diode array detection
FDA = Food and Drug Administration
FID = flame ionization detection
g = gram(s)
g/mL = gram(s) per milliliter
GC = gas chromatography
h = hour(s)
HPLC = high performance liquid chromatography
i.c. = intracerebal(ly)
i.p. = intraperitoneal(ly)
i.v. = intravenous(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LC = liquid chromatography
LC_{50} = lethal concentration in air for 50% of test animals (calculated)
LD_{50} = lethal dose for 50% of test animals (calculated)
LD_{Lo} = lethal dose low of any route, other than inhalation, over any given period of time, and reported to have caused death in humans or animals
LOD = limit of detection
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
MS = mass spectrometry
NOEL = no observable effect level
nm = nanometer(s)
n.p. = not provided
ppb = parts per billion
ppm = parts per million
p.o. = peroral(ly), *per os*

s.c. = subcutaneous(ly)
TD_{Lo} = toxic dose low of any route, other than inhalation, over any period of time and reported to produce any toxic effect in humans or to produce carcinogenic, neoplastigenic, or teratogenic effects in animals or humans
TLC = thin layer chromatography
TSCA = Toxic Substances Control Act
TWA = time-weighted average
USEPA = U.S. Environmental Protection Agency
UV = ultraviolet
wk = week(s)
yr = year(s)

Appendix B: Chemicals Found in *Citrus Aurantium* (from the Phytochemical and Ethnobotanical Database)

Chemicals in Essential Oil
AUROPTENOL* Essential Oil

Chemicals in the Flower (Orange Blossom)
EO Flower 1,000 - 2,000 ppm
ANTHRANILIC-ACID-METHYL-ETHER Flower 4 - 26 ppm
LINALYL-ACETATE Flower 80 - 520 ppm
ACETIC-ACID Flower
BETA-OCIMENE Flower
DECYL-ALDEHYDE Flower
HESPERIDIN Flower
INDOL Flower
JASMONE Flower
L-CAMPHENE Flower
MYRCENE Flower
PHENYLACETIC-ACID Flower
PHENYLETHANOL Flower
PHENYL-ETHYL-ALCOHOL Flower

Chemicals in the Fruit
BETA-CAROTENE Fruit 1 - 27 ppm
RIBOFLAVIN Fruit 1 - 3 ppm
THIAMIN Fruit 1 - 6 ppm
PHOSPHORUS Fruit 120 - 1,600 ppm
ZINC Fruit 16 ppm
CALCIUM Fruit 18 - 4,230 ppm
NIACIN Fruit 3 - 24 ppm
IRON Fruit 3 - 260 ppm
COPPER Fruit 4 - 10 ppm
ASCORBIC-ACID Fruit 420 - 3,947 ppm
ASH Fruit 5,000 - 64,000 ppm
SODIUM Fruit 54 - 116 ppm
PROTEIN Fruit 6,000 - 56,000 ppm
EO Fruit 7,000 - 25,000 ppm
POTASSIUM Fruit 7,020 - 13,800 ppm
HESPERIDIN Fruit 700 - 2,500 ppm
MANGANESE Fruit 8 ppm
FAT Fruit 8,000 ppm
MAGNESIUM Fruit 800 - 1,730 ppm
WATER Fruit 857,000 - 892,000 ppm
CARBOHYDRATES Fruit 97,000 - 909,000 ppm
6,7-DIMETHOXYCOUMARIN Fruit
AURANETIN* Fruit
AURANTIAMARIN* Fruit
BERGAPTEN Fruit
CITRANTIN* Fruit
CITRIC-ACID Fruit
COUMARIN Fruit
DELTA-LIMONENE* Fruit
GERANYL-ACETATE Fruit
ISOHESPERIDIN* Fruit
L-LINALYL-ACETATE Fruit
NARINGIN Fruit
NEOHESPERIDIN Fruit
NERYL-ACETATE Fruit
NOBILETIN* Fruit
TANNIN Fruit
LIMONIN Fruit JBH
ZEAXANTHIN Fruit JBH

Chemicals in the Leaf
TERPINOLENE Leaf 1 - 10 ppm
CIS-OCIMENE Leaf 1 - 110 ppm
ALPHA-PHELLANDRENE Leaf 1 - 20 ppm
TRANS-OCIMENE Leaf 1 - 332 ppm
SABINENE Leaf 1 - 40 ppm
ALPHA-PINENE Leaf 1 ppm
ALPHA-TERPINENE Leaf 1 ppm
CIS-3-HEXENOL Leaf 1 ppm
DECANAL Leaf 1 ppm
GERANIAL Leaf 1 ppm
NERAL Leaf 1 ppm
THYMOL Leaf 1 ppm
STACHYDRINE Leaf 1,000 ppm
L-STACHYDRINE╪ Leaf
LINALOL Leaf 1,990 - 2,795 ppm
NEROL Leaf 100 - 150 ppm
p-CYMENE Leaf 100 - 270 ppm
MYRCENE Leaf 130 - 550 ppm
ALPHA-TERPINYL-ACETATE Leaf 20 - 229 ppm
GERANIOL Leaf 200 - 350 ppm
GERANYL-ACETATE Leaf 261 ppm
ASCORBIC-ACID Leaf 3,000 ppm
EO Leaf 3,000 ppm
LINALYL-ACETATE Leaf 4,429 - 5,500 ppm
ALPHA-TERPINEOL Leaf 460 - 760 ppm
GAMMA-TERPINENE Leaf 50 - 110 ppm
TERPINEN-4-OL╪ Leaf 50 - 80 ppm
NERYL-ACETATE Leaf 55 - 755 ppm
LIMONENE Leaf 70 - 110 ppm
BETA-PINENE Leaf 70 - 170 ppm
ANTHRANILIC-ACID-METHYL-ETHER Leaf
BETA-OCIMENE Leaf
CADINENE Leaf
CAMPHENE Leaf Plant
CITRONELLIC-ACID Leaf
DIPENTENE Leaf
D-LINALOL Leaf
DL-LINALOL Leaf
DL-TERPINEOL Leaf
D-NEROLIDOL Leaf

FARNESOL Leaf Plant
FURFUROL Leaf
GERANIC-ACID Leaf
GERANYL-OXIDE Leaf
HESPERIDIN Leaf
L-LINALYL-ACETATE Leaf
PYRROL Leaf

Chemicals in the Pericarp
4-TERPINENOL Pericarp
DUODECYLALDEHYDE Pericarp
FORMIC-ACID Pericarp
GAMMA-TERPINENE Pericarp
NONANOL Pericarp
NONYL-ALDEHYDE Pericarp
OCTALDEHYDE** Pericarp
OCTANOL Pericarp
PELARGONALDEHYDE╪ Pericarp
PELARGONIC-ACID Pericarp
PENTANOL Pericarp
PHELLANDRENE Pericarp
SABINENE Pericarp
SINENSETIN╪ Pericarp
TANGERETIN Pericarp
TERPENYL-ACETATE Pericarp
TERPINOLENE Pericarp
VIOLAXANTHIN Pericarp

Chemicals in the "Plant," Not Otherwise Specified
LIMONENE Plant 1,000 - 8,000 ppm
FIBER Plant 3,000 - 160,000 ppm
(+)-AURAPTENAL Plant
4-TERPINEOL Plant
5-HYDROXYAURANETIN Plant
ACETALDEHYDE Plant
ACETIC-ACID Plant
ALPHA-HUMULENE Plant
ALPHA-IONONE Plant
ALPHA-PINENE Plant
ALPHA-TERPINEOL Plant
ALPHA-YLANGENE Plant
AURANTIAMENE Plant
AURAPTEN Plant
BENZOIC-ACID Plant
BETA-COPAENE Plant
BETA-ELEMENE Plant
BETA-OCIMENE Plant
BETA-PINENE Plant
BUTANOL Plant
CADINENE Plant
CAPRINALDEHYDE Plant
CARVONE Plant
CARYOPHYLLENE Plant
CINNAMIC-ACID Plant
CITRAL Plant
CITRIC-ACID Plant
CITRONELLAL Plant
CITRONELLOL Plant
CRYPTOXANTHIN Plant
D-CITRONELLIC-ACID Plant
DECYL-ALDEHYDE Plant
DECYLPELARGONATE Plant
DELTA-3-CARENE Plant
DELTA-CADINENE Plant
DIPENTENE Plant
D-LIMONENE Plant
D-NEROLIDOL Plant
DODECANAL Plant
DODECEN-2-AL-(1) Plant
DUODECYLALDEHYDE** Plant
ETHANOL Plant
FORMALDEHYDE Plant
FORMIC-ACID Plant
FURFUROL Plant
GAMMA-ELEMENE Plant
GAMMA-TERPINENE Plant
GERANIAL Plant
GERANIOL Plant
GERANYL-OXIDE Plant
GUM Plant
HEXANOL Plant
INDOLE Plant
ISOLIMONIC-ACID Plant
ISOSCUTELLAREIN* Plant
ISOSINENSETIN* Plant
ISOTETRAMETHYLETHER Plant
LAURIC-ALDEHYDE Plant
LIMONIN Plant JBH
L-LINALOL Plant
MALIC-ACID Plant
MANNOSE Plant
METHANOL Plant
MYRCENE Plant
NARINGENIN Plant
NERAL Plant
NEROL Plant
NEROLIDOL Plant
NOBILETIN Plant
NOMILIN Plant
NONANOL Plant
NONYL-ALDEHYDE Plant
NOOTKATONE Plant
OCTANOL Plant
OCTYL-ACETATE Plant
PALMITIC-ACID Plant
p-CYMENE Plant
p-CYMOL Plant
PECTIN Plant
PELARGONIC-ACID Plant
PENTANOL Plant
PHELLANDRENE Plant
PHENOL Plant

PHENYLACETIC-ACID Plant
PYRROLE Plant
RHOIFOLIN Plant
SABINENE Plant
SINENSETIN Plant JBH
TANGERETIN Plant
TANNIC-ACID Plant
TERPENYL-ACETATE Plant
TERPINOLENE Plant
TETRA-O-METHYL-SCUTELLAREIN╪ Plant
TRANS-HEXEN-2-AL-1 Plant
UMBELLIFERONE Plant
UNDECANAL Plant
VALENCENE Plant
VIOLAXANTHIN Plant

Chemicals in the Root and Seed
SESELIN Root JBH
FAT Seed 448,600 ppm

Source: ARS GRIN Phytochemical and Ethnobotanical Database. Specific sources:

JBH Jeffery B. Harborne and H. Baxter, eds. 1983. Phytochemical Dictionary. A Handbook of Bioactive Compounds from Plants. Taylor & Frost, London. 791 pp.

All others from **DUKE1992A** Duke, James A. 1992. Handbook of phytochemical constituents of GRAS herbs and other economic plants. Boca Raton, FL. CRC Press.

Symbols
* *C. aurantium* is the species with the highest concentration of this chemical.
** *C. aurantium* is the only species with this chemical in the pericarp.
╪ *C. aurantium* is one of only two or three plants containing this chemical.

Appendix C: Summary of Physiological Responses to Adrenoceptor Stimulation

(Sources: Dutta, 2003; MeSH Database; Lohse et al., 2003; Labrid et al., 1989; Ruffolo, 1984; Molinoff, 1984; Schumann, 1983)

α: Phenylethylamines and imidazolines (e.g., clonidine) are the major chemical classes of α-receptor agonists. Postsynaptic α1 and α2 receptors are present in the vasculature and mediate vasoconstriction, apparently by different mechanisms. Agonists of α-adrenoceptors in the heart produce positive inotropic effects (increase the force of muscular contractions).

α1: Constricts arterioles; contracts pregnant uterus; high affinity for **phenylephrine**. Clinically important in heart, blood vessels, liver, intestines, genitourinary, smooth muscle, CNS, and peripheral nervous system. Receptors are located postsynaptically and mediate the excitatory effects of catecholamines at α receptors, and mediate the response of the effector organ. May mediate phosphoinositide breakdown in some systems (phosphotidylinositide diphosphate-inositol triphosphate system).

α2: Found in vascular smooth muscle, pre- (usually) and postsynaptically in CNS and peripheral nervous system, and in pancreatic β cells. Involved in regulation of norepinephrine release. These receptors modulate neurotransmitter liberation via a negative feedback mechanism and may act through adenylate cyclase inhibition. High affinity for clonidine.

β: Catecholamine effects are most frequently mediated by adenylate cyclase activation and cAMP accumulation. Ligands for β-adrenoceptors (agonists and antagonists) are generally aryl- or heteroaryl substituted ethanolamines or oxypropanolamines. Phenylethanolamine agonists must have a secondary amine in the side chain. Catecholamine structural analogs may include replacement of the hydroxyl (OH) group by a hydroxymethylene ($-CH_2OH$) or a carbamo ($-NHCONH_2$) group. β-adrenoceptor agonists induce positive inotropic (increased force of contraction), chronotropic (increased rate of contraction), dromotropic (increased nerve conductivity), and bathmotropic (increased response to stimuli, increased excitability of muscle tissue) effects (Schumann, 1983).

β1: Agonists induce inotropic and chronotropic actions in the heart and stimulate renin secretion in kidney. They are present in the heart, juxtaglomerular cells of the kidney, CNS, peripheral nervous system. These receptors are equally sensitive to **norepinephrine** and **epinephrine**; **isoproterenol** is more potent. Agonist selectivity is "strongly and negatively correlated with lipophilicity" (Labrid et al., 1989). This is the most prominent β-adrenergic receptor subtype in cardiomyocytes. They are the receptors chiefly responsible for the positive chronotropic and inotropic effects of catecholamines.

β2: Found in vascular, bronchial, gastrointestinal, and genitourinary smooth muscle, and skeletal muscle. Involved in smooth muscle relaxation and metabolic effects of catecholamines. Dilates arterioles; dilates bronchioles; relaxes uterus. They bind **terbutaline** with high affinity. **Isoproterenol** and **epinephrine** are more active at these receptors than **norepinephrine**. β2-adrenergic receptor agonists also increase cardiac function. They activate nonclassical signaling pathways, which suggests a function distinct from the β1 subtype (Lohse et al., 2003).

β3: Increases fat lipolysis. β3 receptors are the predominant receptor type expressed in white and brown adipocytes. They are involved in modulation of energy metabolism and thermogenesis. **Isoproterenol** and **norepinephrine** have comparable activities (both higher than that of **epinephrine**).

α,β: Increases glycogenolysis and gluconeogenesis in the liver; increases fat lipolysis (see β3); decreases intestinal motility

Indirect-acting sympathomimetics induce norepinephrine release. Neuronal cells take them up actively followed by norepinephrine replacement in storage vesicles (Dutta, 2003).

Appendix D: Definitions from the MeSH Database

Proteins and Receptors

Membrane Proteins

Proteins which are found in membranes including cellular and intracellular membranes. They consist of two types, peripheral and integral proteins. They include most membrane-associated enzymes, antigenic proteins, transport proteins, and drug, hormone, and lectin receptors.
Year introduced: 1977

GTP-Binding Proteins [retrieved in MESH database by the phrase "g proteins"]

Regulatory proteins that act as molecular switches. They control a wide range of biological processes including: receptor signaling, intracellular signal transduction pathways, and protein synthesis. Their activity is regulated by factors that control their ability to bind to and hydrolyze GTP to GDP. EC 3.6.1.-.
Year introduced: 1997

Receptors, Cell Surface

Cell surface proteins that bind signalling molecules external to the cell with high affinity and convert this extracellular event into one or more intracellular signals that alter the behavior of the target cell (From Alberts, Molecular Biology of the Cell, 2nd ed, pp693-5). Cell surface receptors, unlike enzymes, do not chemically alter their ligands.
Year introduced: 1994

Receptors, G-Protein-Coupled

The largest family of cell surface receptors involved in SIGNAL TRANSDUCTION. They share a common structure and signal through HETEROTRIMERIC G-PROTEINS.
Year introduced: 2004

Receptors, Neurotransmitter

Cell surface receptors that bind signalling molecules released by neurons and convert these signals into intracellular changes influencing the behavior of cells. Neurotransmitter is used here in its most general sense, including not only messengers that act to regulate ion channels, but also those which act on second messenger systems and those which may act at a distance from their release sites. Included are receptors for neuromodulators, neuroregulators, neuromediators, and neurohumors, whether or not located at synapses.
Year introduced: 1994

Receptors, Biogenic Amine

Cell surface proteins that bind biogenic amines with high affinity and regulate intracellular signals which influence the behavior of cells. Biogenic amine is a chemically imprecise term which, by convention, includes the catecholamines epinephrine,

norepinephrine, and dopamine, the indoleamine serotonin, the imidazolamine histamine, and compounds closely related to each of these.
Year introduced: 1994

Receptors, Catecholamine

Cell surface proteins that bind catecholamines with high affinity and trigger intracellular changes which influence the behavior of cells. The catecholamine messengers epinephrine, norepinephrine, and dopamine are synthesized from tyrosine by a common biosynthetic pathway.
Year introduced: 1994

Receptors, Dopamine

Cell-surface proteins that bind dopamine with high affinity and trigger intracellular changes influencing the behavior of cells.
Year introduced: 1977

Receptors, Adrenergic, alpha

One of the two major pharmacological subdivisions of adrenergic receptors. The alpha-beta distinction was originally based on cellular effects of receptor activation but now relies on the relative affinities for certain synthetic ligands. alpha-Adrenergic receptors are further subdivided into several subclasses based on studies of endogenous and cloned receptors.
Year introduced: 1984. ["The effects of catecholamines at alpha-receptors generally involve other second messenger systems (Molinoff, 1984)."]

Receptors, Adrenergic, alpha-1

A subclass of alpha-adrenergic receptors (RECEPTORS, ADRENERGIC, ALPHA). alpha-1 Adrenergic receptors can be pharmacologically discriminated, e.g., by their high affinity for the agonist phenylephrine and the antagonist prazosin. They are widespread, with clinically important concentrations in the liver, the heart, vascular, intestinal, and genitourinary smooth muscle, and the central and peripheral nervous systems.
Year introduced: 1994. [α1-receptors are located postsynaptically and mediate the excitatory effects of catecholamines at alpha receptors. α1-adrenoceptor stimulation may mediate breakdown of phosphoinositide in some systems (Molinoff, 1984).]

Receptors, Adrenergic, alpha-2

A subclass of alpha-adrenergic receptors (RECEPTORS, ADRENERGIC, ALPHA). alpha-2 Adrenergic receptors can be pharmacologically discriminated, e.g., by their high affinity for the agonist clonidine and the antagonist yohimbine. They are found on pancreatic beta cells, platelets, and vascular smooth muscle, as well as both pre- and postsynaptically in the central and peripheral nervous systems.
Year introduced: 1994. [These autoreceptors are involved in the regulation of

norepinephrine release and may act through adenylate cyclase inhibition (Molinoff, 1984.)]

Receptors, Adrenergic, beta

One of the two major pharmacologically defined classes of adrenergic receptors. The alpha-beta distinction was originally based on the cellular effects of receptor activation but now relies on the relative affinities for characteristic synthetic ligands. Beta adrenergic receptors are further subdivided based on information from endogenous and cloned receptors.
Year introduced: 1984 [Catecholamine effects at β-receptors are most frequently mediated by adenyl cyclase activation and cAMP accumulation (Molinoff, 1984).

Receptors, Adrenergic, beta-1

A subclass of beta-adrenergic receptors (RECEPTORS, ADRENERGIC, BETA). beta-1 Adrenergic receptors are equally sensitive to epinephrine and norepinephrine and bind the agonist dobutamine and the antagonist metoprolol with high affinity. They are found in the heart, juxtaglomerular cells, and in the central and peripheral nervous systems.
Year introduced: 1994

Receptors, Adrenergic, beta-2

A subclass of beta-adrenergic receptors (RECEPTORS, ADRENERGIC, BETA). beta-2 Adrenergic receptors are more sensitive to epinephrine than to norepinephrine and have a high affinity for the agonist terbutaline. They are widespread, with clinically important roles in skeletal muscle, liver, and vascular, bronchial, gastrointestinal, and genitourinary smooth muscle.
Year introduced: 1994. [β2-receptors are involved in smooth muscle relaxation, including vascular relaxation, and catecholamine metabolic effects (Molinoff, 1984).]

Receptors, Adrenergic, beta-3

A subclass of beta-adrenergic receptors (RECEPTORS, ADRENERGIC, BETA). beta-3 Adrenergic receptors are the predominant beta-adrenergic receptor type expressed in white and brown ADIPOCYTES and are involved in modulating ENERGY METABOLISM and THERMOGENESIS.
Year introduced: 2001

Receptor Agonists and Antagonists

By class

Adrenergic Agents

Drugs that act on adrenergic receptors or affect the life cycle of adrenergic transmitters. Included here are adrenergic agonists and antagonists and agents that affect the synthesis, storage, uptake, metabolism, or release of adrenergic transmitters.
Year introduced: 1995

Adrenergic Agonists

Drugs that bind to and activate adrenergic receptors.
Year introduced: 1995

Adrenergic alpha-Agonists

Drugs that selectively bind to and activate alpha adrenergic receptors.
Year introduced: 1995

Adrenergic Antagonists

Drugs that bind to but do not activate ADRENERGIC RECEPTORS. Adrenergic antagonists block the actions of the endogenous adrenergic transmitters EPINEPHRINE and NOREPINEPHRINE.
Year introduced: 1995

Adrenergic alpha-Antagonists

Drugs that bind to but do not activate alpha-adrenergic receptors thereby blocking the actions of endogenous or exogenous adrenergic agonists. Adrenergic alpha-antagonists are used in the treatment of hypertension, vasospasm, peripheral vascular disease, shock, and pheochromocytoma.
Year introduced: 1995

Adrenergic beta-Antagonists

Drugs that bind to but do not activate beta-adrenergic receptors thereby blocking the actions of beta-adrenergic agonists. Adrenergic beta-antagonists are used for treatment of hypertension, cardiac arrythmias, angina pectoris, glaucoma, migraine headaches, and anxiety.
Year introduced: 1995

Catecholamines

A general class of ortho-dihydroxyphenylalkylamines derived from tyrosine

Neurotransmitter Agents

Substances used for their pharmacological actions on any aspect of neurotransmitter systems. Neurotransmitter agents include agonists, antagonists, degradation inhibitors, uptake inhibitors, depleters, precursors, and modulators of receptor function.
Year introduced: 1998

<u>Some Receptor Agonists</u>

Dopamine

One of the catecholamine NEUROTRANSMITTERS in the brain. It is derived from tyrosine and is the precursor to NOREPINEPHRINE and EPINEPHRINE. Dopamine is a

major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of receptors (RECEPTORS, DOPAMINE) mediate its action.

Ephedrine

An alpha- and beta-adrenergic agonist that may also enhance release of norepinephrine. It has been used in the treatment of several disorders including asthma, heart failure, rhinitis, and urinary incontinence, and for its CNS stimulatory effects in the treatment of narcolepsy and depression. It has become less extensively used with the advent of more selective agonists.

Epinephrine

The active sympathomimetic hormone from the adrenal medulla in most species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics.

Norepinephrine

Precursor of epinephrine that is secreted by the adrenal medulla and is a widespread central and autonomic neurotransmitter. Norepinephrine is the principal transmitter of most postganglionic sympathetic fibers and of the diffuse projection system in the brain arising from the locus ceruleus. It is also found in plants and is used pharmacologically as a sympathomimetic.

Octopamine

An alpha-adrenergic sympathomimetic amine, biosynthesized from tyramine in the CNS and platelets and also in invertebrate nervous systems. It is used to treat hypotension and as a cardiotonic. The natural D(-) form is more potent than the L(+) form in producing cardiovascular adrenergic responses. It is also a neurotransmitter in some invertebrates.
Year introduced: 1991

Phenylephrine

An alpha-adrenergic agonist used as a mydriatic, nasal decongestant, and cardiotonic agent.

Synephrine

Sympathetic alpha-adrenergic agonist with actions like PHENYLEPHRINE. It is used as a vasoconstrictor in circulatory failure, asthma, nasal congestion, and glaucoma.
Year introduced: 1980

Tyramine

An indirect sympathomimetic. Tyramine does not directly activate adrenergic receptors, but it can serve as a substrate for adrenergic uptake systems and monoamine oxidase so it

prolongs the actions of adrenergic transmitters. It also provokes transmitter release from adrenergic terminals. Tyramine may be a neurotransmitter in some invertebrate nervous systems.

Related Terms

Second Messenger Systems

Systems in which an intracellular signal is generated in response to an intercellular primary messenger such as a hormone or neurotransmitter. They are intermediate signals in cellular processes such as metabolism, secretion, contraction, phototransduction, and cell growth. Examples of second messenger systems are the adenyl cyclase-cyclic AMP system, the phosphatidylinositol diphosphate-inositol triphosphate system, and the cyclic GMP system.
Year introduced: 1989

Adenylate Cyclase

An enzyme of the lyase class that catalyzes the formation of CYCLIC AMP and pyrophosphate from ATP. EC 4.6.1.1. Year introduced: 1998

Cyclic AMP

An adenine nucleotide containing one phosphate group which is esterified to both the 3'- and 5'-positions of the sugar moiety. It is a second messenger and a key intracellular regulator, functioning as a mediator of activity for a number of hormones, including epinephrine, glucagon, and ACTH.
Year introduced: 1994

Appendix E: Description of Search Strategy and Results

Bitter Orange (*Citrus aurantium* var. amara) (ILS Code X0020) and Constituents (±)-*p*-Synephrine (CAS RN 94-07-5; ILS CODE X0021) and (±)-*p*-Octopamine (CAS RN 104-14-3; ILS Code X0022)

Nomination

Bitter orange peel and its constituent synephrine are being widely used in dietary supplements with and without ephedra (ma huang) for weight loss. Synephrine and other bitter orange biogenic amine constituents—octopamine, *N*-methyltyramine, tyramine, and hordenine—have adrenergic activity and may induce cardiovascular problems similar to those induced by ephedrine.

Search Strategy

About 3 days were spent scanning the Internet. Besides the Google search engine general searches (often with specification that retrievals should be limited to the pdf format), the searcher visited specific U.S. government agency web sites and checked botanic web sites used in previous assignments on dietary supplements. Dates searched and URLs for retrieved pdf and certain other types of files may be found in Attachment A. Fee-based searches started by identifying CAS RNs and molecular structures for compounds of interest, particularly forms of synephrine and octopamine (racemic mixtures, stereo isomers (enantiomers), and *m*-, *o*-, and *p*-isomers and their salts and esters) with the major focus on the para forms. (Little information was collected about the ortho forms.) The numbers of records on synephrines and octopamines in the biomedical databases were large. The original focus was to limit retrievals to their association with bitter orange peel and to restrict the interest to the para isomers of synephrine and octopamine. Later strategies tried to limit retrievals to toxicity. Thus, terms in PubMed were combined with "tox [sb]," and toxicity-specific databases such as RTECS, DART, EMIC, and TOXLINE were searched for synephrines and octopamines. No systematic searches were done for the other bitter orange amine constituents (the tyramines and hordenine). The following table summarizes the numbers of search results by database.

Database Results Matrix

Databases	Approximate No. of Titles Examined	No. Selected for Printing	No. in Search Package[a]	
			A-B	B- and C
STN				
AGRICOLA	23	5	3	2
BIOSIS	65	24	18	6
CABA	150	19	15	4
EMBASE	78	17	10	7
MEDLINE	51	17	13	4
NAPRALERT	24	7	5	2
TOXCENTER	13	3	1	2
Total	**404**	**98**	**63**	**25**
PubMed	(Not tracked)	(Not tracked) >122	96	26
TOXLINE	59	59	23	19
CCoD	51	17	11	6
Internet (no strategy explained)		7	6	1

[a]Others were entirely irrelevant or duplicates.

Specific keywords and search strategies used for STN International databases, Current Contents® on Diskette (CCoD), Google, PubMed, and TOXLINE are shown in Attachment B. Further details include the relative numbers of titles/citations examined for each strategy and the numbers that appear in the search package from the standard databases. These are further aggregated by report-value codes.

In brief, the STN International search strategy combined the following concepts in a simultaneous search of the databases in the above matrix: (A) a limited number of terms and CAS RNs for *p*-octopamine and (B) for *p*-synephrine, (C) several terms for bitter oranges and herbal preparations from *C. aurantium*, (D) "peel? OR pericarp? OR rind," and (E) reviews published between 2000 and 2003. The combination of concepts "C AND D" [bitter orange peel] retrieved 275 records (answer set L30) that included the 7 results retrieved with the combination C AND D AND (A OR B) (L45) [bitter orange peel AND (synephrine OR octopamine)]. The combination "(C AND (A OR B)) NOT (L30 OR L45)" [bitter orange AND (synephrine OR octopamine) minus the records already seen] retrieved 38 hits (L52). The combination "(A OR B) AND E" [recent reviews on synephrine OR octopamine] retrieved 30 records. Because so many records were about invertebrates, the synephrine (B) OR octopamine (A) terms were combined with the names of several common mammalian laboratory species. Of the 73 hits, only 11 were selected to print.

Search Results

The database records, web pages, and pages from other references in this package are grouped by ILS subject code number. Most of the material within groups is organized alphabetically by first author surname. The hard copy contains green divider pages between the subjects. The order of topics in the following summary corresponds to the order in which they will appear in the ILS toxicology review.

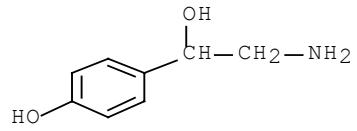
Authoritative Reviews (Subject Code 05)

The only authoritative review found was the brief Commission E Monograph on Bitter Orange Peel (American Botanical Council, 1998 [excerpt]).

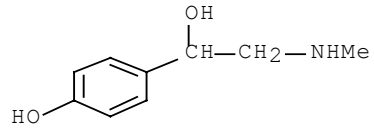
Other Reviews (11)

Brief reviews were found in newspapers and at web sites selling bitter orange peel formulations as weight-loss products. Referenced general reviews found included American Botanical Council (undated) [on bitter orange peel]; Cheng and Tsai (1991), David and Coulson (1985), and Williams et al. (1987) [on octopamines]; Preuss et al. (2002) [*C. aurantium* as an ephedra replacement]; and Pietrzak et al. (2002) (German) [biogenic amines in animal nutrition]. The following reviews covered trace amines as neurotransmitters (many focus on invertebrates): Branchek and Blackburn (2000), Coyle (1977), Nguyen and Juoria (1989), Robertson (1981), Saavedra and Axelrod (1976), and Walker et al. (1996). Breda and Zattoni (1976) and Fogel et al. (1990) reviewed the hepatic renal syndrome and Farmer and Mulakken (1990) reviewed hepatic encephalopathy. Fulenwider et al. (1978) covered deranged tyrosine metabolism in cirrhosis. D'Andrea et al. (2003b) reviewed the possible role of biogenic amines in headache. Others reviewed the physiological actions of structural analogs and other bitter orange constituents (e.g., Camp, 1970, on *N*-methyltyramine).

Chemical Identification (13a)



(±)-*p*-Octopamine



(±)-*p*-Synephrine

Bitter orange, Seville orange, and sour orange are common names for *Citrus aurantium* var. [or subspecies] amara, described by Quintero et al. (2003) as a native of southeast Asia. Extracts, tinctures, and oils of peel, leaves, and flowers as well as dried immature fruit that are used as medicines and for perfumes and flavorings have various synonyms and Latin designations (see the keywords used in the STN International searches in Attachment B). Many preparations have appeared in older English-language pharmacopoeias and formularies (e.g., Felter and Lloyd, 1898, and the British Pharmaceutical Codex, 1911, entry for *Aurantii Cortex*). Much literature is on Chinese and Japanese preparations such as Zhi shi and multicomponent preparations. *p*-Synephrine and *p*-octopamine are the most frequently mentioned biogenic amines found in bitter orange peel, other *C. aurantium* preparations, and other *Citrus* species such as *C. reticulata* Blanco (mandarin orange) (Chen et al., 2002). Most of the literature is indexed with the CAS RNs of the racemic mixtures; however, the enantiomers have also been reported. Tyramine, *N*-methyltyramine, and, less often, hordenine are often determined. The widely occurring stachydrine—unlike the other amines in bitter orange, which are 4-hydroxyphenylethanolamine derivatives—is a 2-carbonyl-1,1-dimethylpyrrolinium inner salt (Budavari, 1996). Several sources list other constituents of *C. aurantium*, including flavonone glycosides and flavone aglycones (e.g., ARS USDA, 1999); coumarins, psoralens, polymethoxyflavones, and waxes (Chouchi et al., 1996); and aldehydes and terpenes (e.g., Boelens and Jimenez, 1989). Many studies have reported the determination of bitter orange peel constituents, often noting differences in oil composition from unripe and ripe fruit (e.g., Boelens and Jimenez, 1989). The cold-pressed oil from the easily detachable cortex contains mainly monoterpenes (chiefly limonene [77.9%], alcohols, and one ketone, nootkatone) (Quintero et al., 2003). The limonene concentration reported by Salib et al. (1978) was lower (24%) and was matched by that of citronellal. The psoralens found in *Citrus* species include bergapten and epoxybergamottin (Dugo et al., 1996). Njorge et al. (2003) also reported the presence of epoxy compounds in *C. aurantium* var. Cyathifera, but they attributed them to artifactual formation during storage. Records from the Registry file, *The Merck Index* (Budavari, 1996), and ChemIDplus have been organized into subgroups: (13a-1) bitter orange preparations; free base, enantiomers, and derivatives of (13a-2) *p*-synephrine, (13a-3) *p*-octopamine, (13a-4) *m*-synephrine (phenylephrine), and (13a-5) *m*-octopamine (norfenefrine); and (13a-6) some related compounds involved in metabolism of monoamines (dopamine, tyramine, epinephrine, norepinephrine, etc.).

Chemical-Physical Properties (13b)

Properties of the *C. aurantium* amines and some structural analogs may be found in the Registry records and *The Merck Index* monographs (Budavari, 1996) in the 13a subgroups of compounds. Properties of some of the *C. aurantium* preparations may also be found in the studies described in 13a.

Analytical Methods (13c)

Analytical methods information in this package may also be found among references in Groups 12 and 13a. Takei et al. (1999) determined the synephrine content in citrus fruit peels, immature fruit, and Chinese medical decoctions by capillary electrophoresis. DeBoer et al. (1999) used capillary electrophoresis with a chiral selector to separate synephrine enantiomers. FDA scientists developed LC/MS (liquid chromatography/mass spectrometry) and LC/tandem MS methods for ephedrine and synephrine determination in dietary supplements (Niemann and Gay, 2003). Other methods used include thin layer chromatography (TLC) (e.g., Pachaly, 1999) and high-performance liquid chromatography (HPLC) with various detectors. For example, He et al., (1997) used HPLC with electrospray MS detection.

Commercial Availability (01)

Producers (01a)

C. aurantium var. amara is chiefly cultivated in southern Spain and Sicily. They are grown as a crop in Arizona where the peak of production is in January (Luckett, 2003; Tantillo, undated). Boehringer-Ingelheim may be a producer of racemic synephrine. The oil from *C. aurantium* flowers is imported from the West Indies and sold in amounts from 0.5 to 32 oz. (±)-Synephrine is sold in 25-kg fiber drums.

Suppliers (01b)

Alexander Essentials (undated) of the UK offers bitter orange essential oil in amounts up to 1 L. Suppliers of multicomponent dietary supplements for weight loss and other purposes include Cytodyne Technologies (Xenadrine® EFX with Bitter Orange [said to be standardized for synephrine, *N*-methyltyramine, hordenine, octopamine, and tyramine]); Herbs MD (Ultra Diet Phen Calm Mood with 24 mg synephrine per 570 mg bitter orange peel extract); SlimStore.com (DexaTrim Natural with bitter orange peel powdered extract, 12 mg/caplet (1 serving); Integra Nutrition, Inc. (Lipotrim); and Nature's Way (bitter orange [dried fruit] extract standardized to 6% synephrine). Niemann and Gay (2003) of FDA CFSAN determined (-)-ephedrine and synephrine concentrations of 25 samples of finished dietary supplement products and compared results to content declaration for 48 finished products. Suppliers may be identified in this publication.

Production Processes (01d)

Production process may include syntheses of octopamine (Somanathan and Guerrero, 1985) and manufacture of various pharmaceutical preparations (e.g., Martin and Cook, 1961; Robbins, 1883; and *National Formulary*, 1926).

Production and Import Volumes (01c)

Specific data were not found so far. The American Society for Clinical Nutrition, Inc. (Moore, 2000) estimated that 17.2 million Americans used weight-loss supplements in the period 1996-1998. Further searches may find the volumes of oil imported.

Other Processes (01e)

Halmekoski and Pekkala (1977) used synephrine tartrate, octopamine, and tyramine as chemical intermediates in the preparation of either butyramides or butanoic acid esters.

Uses (01f)

Luckett (2003) described culinary uses other than orange marmalade, a major use of bitter orange peel. Lin et al. (1986) (Chinese) stated that bitter orange peel oil is used in drinks, confectionery, and cakes. [The NAPRALERT record for this publication stated that the peel oil contained 96.41% limonene.]

Lists of uses of bitter orange preparations for medicines and dietary supplements may be found in many groups in this package. Raintree Nutrition Inc. (2002) listed Ethnobotanical uses for orange bitters in China, Curacao, Haiti, India, Mexico, Trinidad, and Turkey. A series of U.S. patents assigned to Zhishin, LLC, South Burlington, VT (Jones, 2001, 2002a,b) covered compositions for "regulation of appetite, body weight and athletic function with compositions from *C. aurantium* and *C. reticulata*." Kuhrts (2002) patented methods and "thermogenic" compositions for producing weight loss that contained bitter orange, synephrine, ephedrine, or other norepinephrine (noradrenaline)-stimulating compound(s).

Environmental Releases, Occurrence, and Fate (04)

Little relevant information was found on these topics. Synephrine and octopamine occur in the tissues of vertebrates and invertebrates. Wheaton and Stewart (1970) reported on the distribution of tyramine, *N*-methyltyramine, hordenine, octopamine, and synephrine in nearly 200 species of higher plants, including *Citrus* species. All citrus species analyzed contained 15 to 58 ppm *N*-methyltyramine. Katty et al. (1977) and Veeraswamy et al. (1976) (same research group) reported that a highly specific enzyme from the soil bacterium *Arthrobacter synephrinum* degraded racemic synephrine to *p*-hydroxyphenylacetaldehyde and methylamine.

Exposure Potential (02)

Synephrine is present in citrus fruits, juice, and peel of the bitter orange and some other orange species. Bitter orange juice may be added in limited amounts to sweet orange juice (see FDA, 2003). Bitter orange peel may be added to beer and other beverages such as Curacao liqueur (http://www.curacaoliqueur.com/). The Florida Department of Citrus regularly monitors the concentrations of synephrine and its precursor tyrosine among several other compounds. The capillary electrophoretic method can simultaneously analyze most orange juice components (Cancalon, 1999). The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, undated) mentioned vasoactive amines in food, including octopamine, synephrine, tyramine, β-phenylethylamine, serotonin, and histamine. Octopamine, synephrine, tyramine, dopamine, epinephrine, and norepinephrine were indexed in the database record for a publication by Lovenberg (1973) on vaso- and psychoactive substances in food. Food spoilage organisms in dry sausage might generate synephrine (Maijola, 1994) before the

sausage is deemed unfit for consumption due to masking of unpleasant odors by the sausage spices [ILS conjecture]. Smartinfo (undated) and Therapeutic Research Faculty (2003) discuss usual doses of bitter orange peel, peel extract, and synephrine from dietary supplements. Endogenous octopamine concentrations in the brain may be perturbed by injury or perturbations of other brain chemicals by diseases such as cirrhosis (e.g., Bendahan et al., 1993).

Regulations (24)

Bitter orange peel is Generally Regarded as Safe (GRAS) as a direct additive to food (21 CFR 182.20 and 21 CFR 582.20). Limits for bitter orange juice in frozen concentrated orange juice were promulgated in 21 CFR 146.146. Ground orange peel (no specific species) may be added to table sirup (FDA, 2003). FDA lists *C. aurantium* in its Poisonous Plants database. The USDA (1974) issued standards for grades of orange marmalade containing bitter orange peel, and FDA offered guidance for preparation of orange marmalade (FDA CFSAN, 1997). FDA concerns about bitter orange and other compounds in dietary supplements led to collection of product labels (FDA CFSAN, 2000). The FDA/CFSAN EAFUS (2003) list of substances directly added to food includes *C. aurantium* orange oil extract, peel, flowers, and leaf but no entries for the terms Curacao, bitter, Seville, or sour oranges. The International Fragrance Association (IFRA, 2002) recommended in the 36th Amendment to the IFRA Code of Practice concentration limits for expressed peel oil from *C. aurantium* due to the potential for photoirritation. The National Collegiate Athletic Association (NCAA, undated) included synephrine from *C. aurantium*, Zhi shi, or bitter orange on its list of substances banned for student athletes.

Human Studies (18)

Supplements that include bitter orange were found to be effective in weight loss in obese adults (Colker et al., 1999; Armstrong et al., 2001; Duhme et al., 2001; Johnson et al., 2001). A report of a woman taking Xenadrine, an herbal weight loss formulation containing bitter orange (5 mg synephrine), described a case of ischemic colitis potentially induced by the formulation (Ryan et al., 2002). The oil of bitter orange is an effective topical antifungal agent, producing no side effects except for mild irritation (Ramadan et al., 1996). The effects of bitter orange, synephrine tartrate, or mixtures containing bitter orange on the cardiovascular system have also been investigated (Glatzel, 1968; Hofstetter et al., 1985; Penzak et al., 2000, 2001; Kalman et al., 2002; Seifert et al., 2003). Four Chinese papers describe the anti-shock effects of *Fructus aurantii* (Anonymous, 1981; Yen et al., 1983; Huang et al., 1984; Zhao et al., 1989).

Seville orange juice was found to be an inhibitor of CYP3A/P-glycoprotein (DiMarco et al., 2002; Penzak et al., 2002; Lemahieu et al., 2003).

The Australian National Drugs and Poisons Schedule Committee (2003) noted in their recent meeting that there were inadequate data available to fully understand the pharmacological profile of synephrine. Estimated human exposure to synephrine as a flavoring agent was 0.16-1.6 µg/kg/day.

Additionally, synephrine has been used to treat retrograde ejaculation; it was effective in 1 of 6 cases and was thought to be attributable to an increase of bladder neck tone with prevention of backflow of semen into the bladder (Stockamp et al., 1974).

ADME (12)

Many of the studies in this group do not discuss metabolic pathways but rather indicate the presence of the 4-hydroxyphenylethanolamines of interest in human and other mammalian tissues and body fluids. For example, D'Andrea et al. (2003a) reported that plasma concentrations of octopamine, synephrine, and tyramine "vary among individuals.": Andrew et al. (1993) found both para and meta isomers in the plasma of human hypertensives and controls (see also Watson et al., 1990). Arai et al. (1997) followed the time course of urinary excretion of synephrine and its metabolites 4-hydroxymandelic acid and conjugated synephrine enantiomers after ingestion of *C. unshui*. Crowley et al. (1981) reported that hypertensive patients excreted ortho, meta, and para isomers of hydroxymandelic acid. Patients that excreted high concentrations of the meta isomer used medications containing phenylephrine. Other analogs found in human plasma were metanephrine and normetanephrine (Andrew et al., 1993). Boulton and Wu (1972) reviewed the *in vivo* formation of the para forms of tyramine, octopamine, and synephrine in the brain. Octopamine synthesis may be increased in hepatic encephalopathy, a frequent complication of cirrhosis, due to "cerebral excess of aromatic amino acids" (Felaco et al., 1997) (Italian). Hengstrom and Aulepp (1978) (German) studied the pharmacokinetics and metabolism of tritiated synephrine in 10 patients. Apparently, oral doses were 100% absorbed. Pharmacokinetic parameters were comparable to those of other "sympathomimetics with similar structure." Kimura et al. (2000) studied the bioavailability of oral *N*-methyltyramine. Octopamine and synephrine oxidation by monoamine oxidases (MAO) types A and B was studied by Suzuki et al. (1979a,b).

Acute Toxicity (03)

LD_{Lo} and LD_{50} data are reported in RTECS (2003) for synephrine, synephrine HCl, synephrine tartrate, stereo isomers of synephrine, and octopamine for mouse, rat, rabbit, and/or guinea pig. Adverse effects and contraindications reported for *C. aurantium* in weight loss supplements include sensitivity to light and increased blood pressure (Heinrich, 2002). Synephrine induced cardiac hypertrophy and functional changes in rats (Zimmer, 1997), and aqueous extracts of *F. aurantii* (unripe fruit of *C. aurantium*), as well as synephrine, reduced portal pressure in rats (Huang et al., 1995). LC_{50} values for *C. aurantium* L. in a brine shrimp were reported to correlated well with *in vivo* mouse LD_{50}s (Logarto et al., 2001). Essential oil from peels of *C. aurantium* L. increased the latency period of induced-tonic seizures, barbiturate-induced sleeping time, and anxiolytic activity in mice. Hydroethanolic extracts from leaves also enhanced barbiturate-induced sleeping time but had no effect on tonic seizures (Carvalho-Freitas and Costa, 2002). Synephrine caused inotropic but not chronotropic effects in guinea pigs (Anonymous, 1978).

Short-Term and Subchronic Toxicity (06a)

Two herbal drug mixtures, TJ-41 and TJ-43, each containing ~ 10% *Aurantii nobilis pericarpium*, were reported to be toxic at doses > 2500 mg/kg bw and > 2000 mg/kg bw, respectively (Iijma et al., 1995; Kanitani et al., 1995). Synephrine was reported to have beneficial pressor effects on portal hypertensive rats in an eight-day treatment study (Huang et al., 2001).

Chronic Toxicity (06b)

No data were available.

Synergistic/Antagonistic Effects (22)

The role of octopamine as a neuromodulator or neurotransmitter has been studied in invertebrates, rats, and insects (Adamo, 2002; Druse, 1981; Duffield et al., 1986; Mesce, 2002; Waldeck, 1970). Orange juice components have been found to inhibit P-glycoprotein in human leukemia cells (Ikegawa et al., 2000). Additionally, the ability of fruit juices to inhibit organic anion transporting polypeptide-mediated drug uptake and other drug interactions have been reported (Dresser et al., 2002; Li et al., 2002; Malhotra et al., 2001; Maskalyk, 2002; Mohri and Uesawa, 2001; UNC Press Release, 2001; Zychlinski and Montgomery, 1984).
One paper reviewed the ability of *C. aurantium* to attenuate acute intoxication of cyclosporine (Hou et al., 2000). Another study investigated the radioprotective properties of aryl alkyl amine adrenomimetics in mice (Kalinski and Iashunskii, 1979).

Reproductive and Developmental Toxicity (10)

Octopamine affected uterine contractility in pregnant women (Senties et al., 1970) and in rat vas deferens (Grana et al., 1980). Synephrine had a stimulatory effect on aromatization of testosterone in Sertoli cell-enriched rat cell cultures (Verhoeven et al., 1979). Birth defects and teratogenic effects of synephrine have also been studied (Schardein et al, 1993; Scrollini et al., 1970). Both octopamine and synephrine enhanced progesterone production in bovine luteal cells *in vitro* (Battista and Condon, 1986).

Carcinogenicity (07a)

No data were available.

Genotoxicity (09)

Only two genotoxicity studies were identified. One reported results for octopamine in tests for genetic crossing-over and nondisjunction in *Aspergillus nidulans* (Bignami et al., 1974), and the other reported that synephrine was not mutagenic in the mouse lymphoma L5178Y cell assay (McGregor et al., 1988).

Immunotoxicity (08)

The Atlas on Mechanisms in Adverse Reactions to Food (Andrea et al., 1995) appears to have immunotoxicity data for octopamine. Information on allergic reactions to oranges is addressed in a draft report by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Some aromatherapy oils that contain extracts from the subspecies *C. aurantium bergmia* have been shown to be phototoxic due to the presence of 5-methoxypsoralen (Kaddu et al., 2001). The cell viability of splenocytes and thymocytes was suppressed in BALB/c mice by oral administration of extracts of *A. nobilis pericarpium* (Yum et al., 2003). Aqueous extracts of *A. Fructus immaturus* were reported to inhibit Type I allergic reactions in rats (Koda et al., 1983).

Other Biological Activities (14)

Synephrine, octopamine, *A. nobilis pericarpium*, and/or extracts of *C. aurantium* have also been studied for effects on cellular function, neurological activity, enzyme activity, the cardiovascular system, and the blood and hematopoietic system.

Effects on Cell Growth (17)

Octopamine was assessed for inhibitory effects on human keratinocyte mitosis in vitro (Harper & Flaxman, 1975). Compounds isolated from extracts of C. aurantium L. inhibited cell growth in mouse leukemia L1210 and human erythroleukemia K562 cells in vitro (Satoh et al., 1996) while methoxylated flavones isolated from extracts of A. nobilis pericarpium induced cell differentiation in mouse myeloid leukemia and human promyelocytic leukemia cells (Sugiyama et al., 1993).

Neurological Effects (19)

Neurological effects reported for synephrine and octopamine included increased locomotor activity, pre- and postsynaptic effects, anti-depressive activity, agonistic response toward trace amine receptors, inhibition of smooth muscle contraction, and depression of neurological function (Bulach et al., 1984; Bunzow et al., 2001; Celuch and Juorio, 1988; Chance et al., 1985; Cho et al., 1996; Coulon et al., 1989; Jagiello-Wojtowicz, 1979; Jagiello-Wojtowicz and Chodkowska, 1984; Kim et al., 2001; Lafi and Leake, 1988; Song et al., 1996).

Effects on Enzymes (28)

6′,7′-Dihydroxybergamottin, found in grapefruit juice and to a lesser extent in some orange juices, inhibited the metabolism of substrates for enzymes of the CYP3A subfamily (Edwards et al., 1996, 1999; Bailey, 2000; Guo et al., 2000, 2001; Wangensten et al., 2003). Octopamine, but not synephrine, inhibited cytochrome P450 c11 *in vitro* (Louw et al., 2000).

In a study of the inhibitory effects of citrus fruit extracts from 42 species and cultivars on rat platelet cyclooxygenase and lipoxygenase, *C. aurantium* had the highest lipoxygenase inhibitory activity (Nogata et al., 1996). Additionally, the inhibitory effects of fruit extracts (including Seville orange juice) on P glycoprotein-related efflux carriers *in vitro* have been reported (Deferme et al., 2002).

The multiple roles of monoamine oxidase inhibitors (including octopamine) in the therapy of neurodegenerative disorders, based on their ability to alter catecholamine catabolism in the central nervous system, have been investigated (Foley et al., 2000). In rat jejunal mucosa, octopamine inhibited histamine-N-methyltransferase. It was suggested that the compound might play a vital role in the chemical potentiation of histamine toxicity (Taylor and Leiber, 1979).

Cardiovascular Effects (29)

Synephrine, octopamine, and extracts of *C. aurantium* have been evaluated for effects on the cardiovascular system which includes changes in blood pressure, cardiovascular toxicity, contractility and excitability of the heart muscle, and/or adrenergic activity. Humans, dogs, cats, guinea pigs, and/or rats were used in these studies (Carpéné et al., 1999; Fontana et al., 2000; Fregly et al., 1979; Ress et al., 1980; Yen and Chung, 1981). Extracts of *C. aurantium* caused cardiovascular toxicity in rats (Calapai et al., 1999). Pressor effects and the ability to restore

contractility and excitability to heart muscle was reported for synephrine and octopamine (Altura, 1975; Chen et al., 1990; Jia et al., 1983; Keogh and Baron, 1985; Ledda et al., 1980).

Effects on Blood and Hematopoietic System (30)

Human platelet aggregation was studied in individuals taking herbal prescriptions that included *A. nobilis pericarpium* (Okuyama et al., 1987). Polymethoxy-flavonoids extracted from *C. aurantium* L. were evaluated for their effect on erythrocyte sedimentation rate (Quarenghi et al., 1985).

Miscellaneous

The activation of lipolysis by octopamine and extracts of *C. aurantium* was assessed in mammalian white fat cells as an indicator of adrenergic activity (Carpéné et al., 1999; Fontana et al., 2000; Sakuramata and Kusano, 1998).

Structure-Activity Relationships (25)

Monographs for structural analogs ephedrine and amphetamine and related compounds, which contain aminopropyl rather than aminoethyl side chains, are included in the subgroups following the Group 25 collection of studies. Among the studies, Jordan et al. (1987) found that *in vitro* adrenergic activities of the meta and para isomers of octopamine and synephrine on β1- and β2-adrenoreceptors in guinea pig atria and trachea were 100 (phenylephrine) to 40,000-fold less active than norepinephrine. *Casarett and Doull's Toxicology* (Klaassen, 2001) listed the cardiotoxic manifestations and proposed mechanisms of cardiotoxicity for phenylephrine, ephedrine, amphetamines, and other structural analogs on pages 614-615 with a discussion on page 618.