

Review

An overview of *Citrus aurantium* used in treatment of various diseases

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Citrus aurantium (bitter orange) is a plant belonging to the family Rutaceae, The most important biologically active constituents of the *C. aurantium* fruits are phenethylamine alkaloids octopamine, synephrine, tyramine, N-methyltyramine and hordenine. It is rich in vitamin C, flavonoids and volatile oil. Synephrine is a primary synthesis compound with pharmacological activities such as vasoconstriction, elevation of blood pressure and relaxation of bronchial muscle. whose fruit extracts have been used for the treatment of various diseases such as gastrointestinal disorders, insomnia, head aches, cardiovascular diseases, cancer, antiseptic, anti-oxidant, antispasmodic, aromatic, astringent, carminative, digestive, sedative, stimulant, stomachic and tonic and by research novel use is found in obesity and related risks even life threatening are continuously increasing through out world in all age groups. Many marketed formulations claim to possess antiobesity actions, but still many herbs which have claims to this need to be investigated and their claims to be authenticated. In recent era there is a great thrust on screening of herbal extracts and formulations for antiobesity action. In this article efforts have been taken to discuss the photochemistry, constituents, ethnobotany, pharmacology safety and toxicity of citrus plant. The motto is to discuss *C. aurantium* here more research attention should be given on this that would increase its use in various chronic and acute diseases

Key words: Bitter orange, synephrine, obesity, thermogenesis, ethnobotany.

INTRODUCTION

Citrus plant is native to tropical Asia but it is also found in all tropical and subtropical country. It is easily available plant showing a wide range of uses in treatment of various diseases. The major active biological constituents in Citrus herbs are flavonoids, especially hesperidin, naringin and alkaloids, mainly synephrine, with beneficial medical effects on human health (Pellati et al., 2002). It has been used for their essential oil in foods and perfumes. *Citrus aurantium* is also used in herbal medicine as a stimulant and appetite suppressant. It has also been used in traditional Chinese medicine to treat nausea, indigestion, and constipation, cancer, cardiovascular effect, sedative. However, what has made bitter orange well known and popularized is the claim that it replaces the banned ephedra stimulant, without the ephedra side effects. Because of this, *C. aurantium* is a popular weight loss ingredient used in a wide variety of diet pills and fat. Bitter orange has been substituted into "ephedra-free" herbal weight-loss products by dietary supplement manufacturers. The National Center for

Complementary and Alternative Medicine found that "there is currently little evidence that bitter orange is safer to use than ephedra". It is easily available and comparatively safe.

PLANT DESCRIPTION OF *C. AURANTIUM*

Common name: Bitter orange, Seville orange, Zhi Shi, Chongcao, Ch'Eng, Chin Ch'lu, Hua Chu Hung, Kuang Chu, Orange bitters, Naranja Agria, Neroli, Petitgrain, Seville orange, Orange bitters, Neroli.

Family: Rutaceae

Botanical names: *Citrus aurantium* (Citrus x aurantium)

Botanical source: *Citrus aurantium* L.

Genus: *Citrus* L.

Species: *Citrus aurantium*

Subspecies: *Citrus amara*, *Citrus bergamia*, *Citrus bigaradia*, and *Citrus vulgaris*.

Habitat and cultivation: Native to tropical Asia, this tree is now grown throughout the tropics and subtropics. Orchards of bitter orange are found along the Mediterranean coast, especially in Spain.

A valuable medicinal herb, the orange originated in China and by the middle Ages was a favorite with Arabian physicians. In the 16th century, an Italian princess named Anna-Marie de Nerola reputedly discovered oil extracted from the flowers, which she used to scent her gloves; today neroli oil, as it became known, it is prohibitively expensive. The Chinese remain the greatest enthusiasts of medicinal oranges: the bitter Seville orange (*C. aurantium*) and sweeter tangerines and satsumas (*Citrus reticulata*) that are mainly used and grown are as follows:

(i) *Citrus aurantium* subsp. *amara* is a spiny evergreen tree native to southern Vietnam, but widely cultivated. It is used as grafting stock for citrus trees, in marmalade, and in liqueur like triple sec, Grand Marnier and Curacao. It is also cultivated for the essential oil expressed from the fruit, and for neroli oil and orange flower water, which are distilled from the flowers.

(ii) Seville orange (or *bigarade*) is a widely-known, particularly tart orange which is now grown throughout the Mediterranean region. It has a thick, dimpled skin, and is prized for making marmalade, being higher in pectin than the sweet orange, and therefore giving a better set and a higher yield. It is also used in compotes and for orange-flavored liqueurs. Once a year, oranges of this variety are collected from trees in Seville and shipped to Britain to be used in marmalade. However, the fruit is rarely consumed locally in Andalusia.

(iii) Bergamot orange, *C. aurantium* subsp. *bergamia* is cultivated in Italy for the production of bergamot oil, a component of many brands of perfume and tea, especially Earl Grey tea.

(iv) Chinotto, from the myrtle-leaved orange tree, *C. aurantium* var. *myrtifolia*, native to Italy, is used for the namesake Italian soda beverage. This is sometimes considered a separate species.

(v) Daidai, *C. aurantium* var. *daidai*, is used in Chinese medicine and Japanese New Year celebrations. The aromatic flowers are added to tea.

(vi) Wild Florida sour orange is found near small streams in generally secluded and wooded parts of Florida. It was introduced to the area from Spain.

MEDICINAL USES

Part used: Dry unripe fruit. Fruit, peel, leaves, flowers, seeds, essential oil. The dried outer peel of the fruit of bitter orange, with the white pulp layer removed, is

used medicinally. The leaves are also commonly used in many folk traditions. The bitter orange tree is indigenous to eastern Africa. The different parts of citrus aurantium used as a drug is as shown in Figure 1.

Photochemical and constituents

Bitter orange has a complex chemical makeup, though it is perhaps most known for the volatile oil in the peel. The familiar oily residue that appears after peeling citrus fruit, including bitter orange, is this volatile oil. It gives bitter orange its strong odor and flavor, and accounts for many of its medicinal effects. Besides the volatile oil, the peel contains flavones, the alkaloids synephrine, octopamine, and N-methyltyramine, and carotenoids.

Main content: synephrine, C₉H₁₃NO₂, 0.24 to 1.45% (g/g); N-methyltyramine, C₉H₁₃NO, 0.19 to 0.83% (g/g). Other Phytochemicals: neohesperidin; nobiletin; 5-o-desmethyl nobiletin; quinoline; narcotin; noradrenline; tryptamine; tyramine; naringin; rhoifolin; lonicerin. *C. sinensis* Osbeck (Sweet orange) a variety of citrus also contains hesperitin; naringenin; isosakuranetin; carotene; riboflavine; tengeretin; 3, 5, 6, 7, 8, 3'4'-methoxyflavone. Fruit peel contains volatile oil composed of d-limonene; d-linalool, N-acetyloctopamine; gamma-aminobutyric acid.

Bitter orange peel contains a volatile oil with limonene (about 90%), flavonoids, coumarins, triterpenes, vitamin C, carotene, and pectin. The flavonoids have several useful properties, being anti-inflammatory, antibacterial, and antifungal. The composition of the volatile oils in the leaves, flowers, and peel varies significantly. Linalyl acetate (50%) is the main constituent in oil from the leaves (petit grain), and linalool (35%) in oil from the flowers (neroli). The unripe fruit of the bitter orange contains cirantin, which reputedly is a contraceptive. Include: (+)-auraptental, 4-terpineol, 5-hydroxyauranetin, acetaldehyde, acetic-acid, alpha-humulene, alpha-ionone, alpha-phellandrene, alpha-pinene, alpha-terpineol, alpha-terpinyl-acetate, alpha-ylangene, ascorbic-acid, aurantiamene, aurapten, benzoic acid, beta-copaene, beta-elemene, beta-ocimene, beta-pinene, butanol, cadinene, camphene, caprinaldehyde, carvone, caryophyllene, cinnamic acid, *cis*-ocimene, citral, citronellal, citronellic acid, citronellol, cryptoxanthin, d-citronellic acid, d-limonene, d-linalool, d-nerolidol, decanal, decylaldehyde, decylpelargonate, delta-3-carene, delta-cadinene, dipentene, dl-linalool, dl-terpineol, dodecanal, dodecen-2-al (1), duodecylaldehyde, ethanol, farnesol, formic acid, furfural, gamma-elemene, gamma-terpinene, geranic acid, geraniol, geranyl acetate, geranyl oxide, hesperidin, hexanol, indole, isolimononic acid, isoscutellarein, isosinensetin, isotetramethylether, l-linalool, l-linalylacetate, l-stachydrine, lauric aldehyde, limonene,



Citrus aurantium L.

Figure 1. Bitter orange plant from Wikipedia.com.

limonin, linalool, linalyl acetate, malic acid, mannose, methanol, myrcene, naringenin, naringin, neral, nerol, nerolidol, neryl acetate, nobiletin, nomilin, nonanol, nonylaldehyde, nootkatone, octanol, octyl acetate, *p*-cymene, *p*-cymol, palmitic acid, pectin, pelargonic acid, pentanol, phellandrene, phenol, phenylacetic acid, pyrrol, pyrrole, rhoifolin, sabinene, sinensetin, stachydrine, tangeretin, tannic acid, terpenyl acetate, terpinen-4-ol, terpinolene, tetra-*o*-methyl-scutellarein, thymol, *trans*-hexen-2-al-1, *trans*-ocimene, umbelliferone, undecanal, valencene, and violaxanthin.

Applications

Bitter orange was found therapeutically effective in application of various diseases such as;

- i) It aid in digestion and relieves flatulence.
- ii) Cardiovascular health.
- ii) Anti-Cancer.
- iii) Treatment of Stroke.

iv) An antianxiety and sedative: The essential oil of *C. aurantium* contains linalool and the fragrant substance limonene have antianxiety and sedative effects (Carvalho-Freitas et al., 2002). Antidepressant-Synephrine-rich *Citrus aurantium* extracts have antidepressant effects (Kim et al., 2001) and (Song et al., 1996).

Antiviral -whole *C. aurantium* peel contains citral, limonene, and several citrus bioflavonoids, including hesperidin, neohesperidin, naringin, and rutin. Weak evidence hints that these substances might have antiviral effect (Kim et al., 2001) and (Song et al., 1996). Worldwide it is used in treatment of various diseases some of which are listed in Table1.

Properties

Digestion and flatulence: Bitter orange is used similarly in a wide variety of traditions. In Mexico and South America the leaf is used as a tonic, as a laxative, as a sedative for insomnia, and to calm frazzled nerves. The peel of the fruit is used for stomach aches and high bloodpressure. The Basque people in Europe use the leaves for stomach aches, insomnia, and palpitations and the bitter orange peel as an anti-spasmodic. In traditional Chinese medicine, the peel of the immature fruit is used for indigestion, abdominal pain, constipation, and dysenteric diarrhea. Where the patient is weak, the milder, mature fruit is used similarly. However, six bitter orange continues to be widely used for insomnia and indigestion in many parts of the world.

Dosage

Many health professionals recommend 1 to 2 g of dried bitter orange peel simmered for 10 to 15 min in a cup of water. Three cups are usually recommended as a daily dosage. As a tincture, 2 to 3 ml is usually recommended, also to be taken three times a day.

The strongly acidic fruit of the bitter oranges stimulates the digestion and relieves flatulence: An infusion of the fruit is thought to soothe headaches, calm palpitations, and lower fevers. The juice helps the body eliminate waste products, and, being rich in vitamin C, which helps the immune system ward off infection. If taken to excess, however, its acid content can exacerbate arthritis. In Chinese herbal medicine, the unripe fruit, known as zhi shi, is thought to "regulate the qi" helping to relieve flatulence and abdominal bloating, and to open the bowels. The essential oils of bitter orange, especially neroli, are sedative. In Western medicine, these oils are used to reduce heart rate and palpitations, to encourage sleep, and to soothe the digestive tract. Diluted neroli is applied as a relaxing massage oil. The distilled flower water is antispasmodic and sedative.

Table 1. Ethnobotany of citrus plant.

Country	Ethnobotany: Worldwide uses
China	Abdomen, Ache, Antidote, Anodyne, Antiseptic, Bactericide, Bubo, Cancer, Cancer (Breast), Cancer (Stomach), Carminative, Chest, Congestion, Deobstruent, Diarrhea, Dysmenorrhea, Dyspepsia, Dyspnea, Emmenagogue, Freckle, Fungicide, Gas, Prolapse, Nausea, Marasmus, Panacea, Pectoral, Pimple, Rectocele, Refrigerant, Rib, Sedative, Sore, Spasm, Splenitis, Stomach, Stomachic, Thirst, Urogenital, Uterus, Vermifuge, Wine-Nose.
Curacao	Gall-Bladder, Hypertension, Nerve, Shampoo, Tea, Tranquilizer
Elsewhere	Ache (Stomach), Antifertility, Carminative, Carminative, Chest, Expectorant, Emmenagogue, Gall-Bladder, Heart, Hemostat, Medicine, Nerve, Spasm, Stimulant, Stomach, Stomachic, Styptic, Sudorific, Tonic.
Haiti	Antiseptic, Fever, Laxative, Purgative
India	Ache (Stomach), Hypertension, Liver, Megalospleny, Menorrhagia
Mexico	Ache, Antiseptic, Apertief, Nerve Tonic, Tranquilizer, Tea
Trinidad	Depurgative, Dyspepsia, Expectorant, Flatulence, Mouthwash, Oliguria, Purgative, Sedative, Sore, Thrush
Turkey	Antiseptic, Aperitif, Narcotic, Nervine, Sedative, Scurvy, Stomachic, Tonic
US	Cancer, Fatality

Source: Alexander and Paul (1995).

Cardiovascular health: An orange a day promotes cardiovascular health. One health study found that drinking one daily glass of orange juice reduced the risk of stroke by 25%. Countless other studies have confirmed similar benefits from regular consumption of citrus. For example, oranges are rich in vitamin C. They are also rich in flavonoids, such as hesperidin, that work to revive vitamin C after it has quenched a free radical. In other words, the hesperidin strengthens and amplifies the effect of vitamin C in your body. In an interesting human clinical trial, orange juice was shown to elevate HDL cholesterol ("good" cholesterol) while lowering LDL (so-called bad) cholesterol.

The fiber in oranges is another major contributor to heart health. Citrus fruit (especially tangerines) are one of the richest sources of high quality pectin - a type of dietary fiber. Pectin is a major component of the kind of fiber that is known to lower cholesterol. Pectin is also helpful in stabilizing blood sugar. A single orange provides 3 g of fiber, and dietary fiber has been associated with a wide range of health benefits.

Oranges also help prevent cardiovascular disease by supplying folate, also called "folacin" or "folic acid" when used in supplementary form. Folate is one of the B vitamins. The total folic acid content in the average diet has been found to be below the recommended daily allowances, and mild-to-moderate folate deficiency is common. In fact, folate deficiency is known to be among the most common vitamin deficiencies in the world. We know that dietary folate can play an important role in the prevention of cardiovascular disease; it is essential for the maintenance of normal DNA and also plays a role in the prevention of colon and cervical cancers, and

possibly even breast cancer.

Folate plays an important role in lowering blood concentrations of homocysteine. Homocysteine is an amino acid by-product of protein metabolism and its role in cardiovascular disease is significant. High levels of homocysteine have been implicated in cardiovascular disease and even vascular disease of the eye. Folate works with the other B vitamins B12 and B6 and probably betaine (a plant-derived compound that seems to lower homocysteine) to remove homocysteine from the circulatory system. The homocysteine that is allowed to build up in your body can damage your blood vessels and ultimately precipitate a "cardiovascular event" Interestingly, there is evidence that increased folate intake can actually improve heart health in people who have already developed heart disease.

Cancer: Recent news from researchers has demonstrated that oranges can play a significant role in preventing cancer. We know, for example, that the Mediterranean diet, which includes a considerable amount of citrus, is associated with a low incidence of cancers of the breast, lung, pancreas, colon, rectum, and cervix. Indeed, citrus fruits have been found to contain numerous known anticancer agents-possibly more than any other food. The anticancer power of oranges is most effective when the whole fruit is eaten; it seems that the anticancer components of oranges work synergistically to amplify one another's effects. The soluble fiber, or pectin, which is so effective for heart health, is also an anticancer agent (Miyazawa et al., 1999). It contains antagonists of growth factors, which in the future may be shown to have a positive effect decreasing the growth of tumors. We know

that in animals pectin has been shown to inhibit the metastasis of prostate and melanoma cancers.

One particular phytonutrient has attracted attention lately as a health promoting agent. Amazingly, we routinely throw out this most potent part of the orange. In the oil of the peel of citrus fruits is a phytonutrient known as limonene. Oranges, mandarins, lemons, and limes contain significant amounts of limonene in the peel and smaller quantities in the pulp. Limonene stimulates our antioxidant detoxification enzyme system, thus helping to stop cancer (Sato et al., 1996) before it can even begin. Limonene also reduces the activity of proteins that can trigger abnormal cell growth. Limonene has blocking and suppressing actions that, at least in animals, actually cause regression of tumors. Mediterranean people suffer lower rates of certain cancers than others, and researchers now believe this can partly be ascribed to their regular consumption of citrus peel.

Vitamin C, abundantly available in oranges, also plays a role in fighting cancer. In fact, there is a relatively consistent inverse association of vitamin C with cancer of the stomach, oral cancer, and cancer of the esophagus. This makes sense, as vitamin C protects against nitrosamines, cancer-causing agents found in food that are thought to be responsible for instigating cancers of the mouth, stomach, and colon. Orange and stroke: Orange seems to have a protective ability against stroke. In one case study citrus and citrus juice were major contributors to the stroke-risk reduction from fruits and vegetables. It has been estimated that drinking one glass of orange juice daily may lower the risk of stroke in healthy men by 25% while the risk is reduced only 2% from other fruits. It is very interesting that consumption of vitamin C in supplement form does not appear to have the same benefits as the whole fruit when it comes to stroke prevention. This suggests that there must be some other protective substances in citrus juices to account for their power to protect from strokes. The current assumption at this point is that it is the power of the polyphenols that make the difference. More than 350 to 400 mg a day of supplemental vitamin C for a period of at least ten years seems to be an effective means of lowering risk of developing cataracts.

OTHER MEDICAL USES

Obesity

Antiobesity effect of *C. aurantium* contains synephrine which is a stimulant with similar properties as caffeine and ephedrine. It claims to have similar effects by increasing energy expenditure, increasing metabolism, and suppressing appetite (Haaz et al., 2006) and it has been labeled as the ephedra replacement. Banning of ephedra has paved the way for bitter orange to become a very widely used stimulant in fat burners (Hedrej et al.,

1997). Although you will see marketing material claiming *C. aurantium* to have similar benefits but none of the side effects of ephedra, clinical research and case reports have proven otherwise. There are reported cases of stroke and angina. In a clinical review of various studies done on *C. aurantium*, the researchers reviewed numerous available clinical weight loss trials, physiological studies, and case reports of bitter orange.

From the review of synephrine studies, Haaz et al., (2006) found some promising evidence for synephrine in treatment of obesity, but concluded that more rigorous studies are needed to draw adequate conclusions.

Another *C. aurantium* study conducted by the department of physiology, medicine and pathology at the George town university found that *C. aurantium* aided in weight loss in two studies and increase thermogenesis, at least to some extent, in three studies. Colker et al. (1999) reported that in a double-blind, placebo-controlled, randomized study of *C. aurantium*, caffeine and St John's Wort, lost significant amounts of total body weight while on a strict diet and exercise. Those in the placebo and control groups who also were on the same restricted diet did not. However, intergroup analysis showed no statistical significance among the weight changes in the three groups. In contrast, the loss of fat mass in the test group was significantly greater compared to the placebo and control groups.

Cosmetic uses

It is commented in some glossary that bitter orange extract can have antioxidant properties when eaten; however, used topically its methanol content makes it potentially irritating for skin. *C. aurantium* Amara (bitter orange) peel extract is an extract of the peel of the bitter orange, *C. aurantium* Amara, as a raw material, it has reported used in cosmetic related products such like sunless tanning, conditioner, bar soap, shampoo, makeup remover, exfoliant/scrub, blush, mask, facial cleanser.

As from related research and application suggestions, *C. aurantium* can be used to prevent skin fragility and perks up skin tone, and metabolism boosting. *C. aurantium* Amara (bitter orange) peel extract is classed as a biological product and is used as a miscellaneous skin-conditioning agent as well as a fragrance ingredient. The skin (the epicarp) is used for extraction. The epicarp is a very versatile compound and is used for its astringent quality, as well as the fact that it helps to prevent skin fragility and perks up skin tone. *In vitro* tests have shown that limonene derived from citrus peels may have relevant anti-cancer, anti-tumor, and cell-differentiation promoting activities, as well as helping to increase metabolism (thermogenesis) due to its synephrine content. In traditional western medicine, *C. aurantium* has been used to treat digestive and circulatory problems. *C. aurantium* is widely used for stimulating the breakdown of

cholesterol by causing the release of nor-adrenaline (a stress hormone) at beta-3 receptor sites creating chemical reactions that increase fat breakdown.

The aforementioned properties make this material good for purpose of cellulite treatment. Normally combined with many other herbs such like butchers broom, horsetail, rosemary leaf, *Centella asiatica*, black pepper seed extracts, etc.

Side effects or interactions

Bitter orange oil may possibly cause light sensitivity (photosensitivity), especially in fair-skinned individuals. Generally this occurs only if the oil is applied directly to the skin and then exposed to bright light; in rare cases it has also been known to occur in people who have taken bitter orange internally. The oil should not be applied topically and anyone who uses it internally should avoid bright light, including tanning booths. Internal use of the volatile oil of bitter orange is also potentially unsafe and should not be undertaken without expert guidance. Large amounts of orange peel have caused intestinal colic, convulsions, and death in children. The amounts recommended above for internal use should not be exceeded.

One text on Chinese medicine cautions against the use of bitter orange in pregnancy. This concern is not raised in any other reference, and the American Herbal Products Association classifies the herb as "class 1" an herb that can be safely consumed during pregnancy when used appropriately.

Decoctions of bitter orange substantially increased blood levels of cyclosporine in pigs, causing toxicity. Bitter orange also inhibited human cytochrome P450 3A (CYP3A) in the test tube. This is an enzyme that helps the liver get rid of numerous toxins, and strongly affects metabolism of certain drugs. Bitter orange might, therefore, interact with drugs that are metabolized by CYP3A. To be on the safe side, bitter orange should not be combined with prescription medications, unless someone is under the care of an experienced natural medicine clinician.

Safety and toxicity

Decoctions of bitter orange substantially increased blood levels of cyclosporine, causing toxicity (Bent et al., 2004). Bitter orange contains synephrine and octopamine, these chemicals may cause high blood pressure (hypertension) (Nykamp et al., 2004) and heart rhythm disturbances (arrhythmias) which can lead to heart attack (Bui et al., 2006), stroke and even death (Bouchard et al., 2005).

CONCLUSION

C. aurantium is easily available and shows their effect in

treatment of various diseases. It also shows its effect in obesity. It control access body weight by natural ways which is cheap and easily available, apart from the fact that it is used in treatment of various disease like cancer, cardiovascular diseases, circulatory diseases, digestion and in cosmetic. So it is essential to give more research attention towards the safety and efficacy of this herbal drug that will increase its utilization in therapeutic purpose to a more extent.

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