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Review Article

Citrus aurantium (Bitter Orange): A Review of its Traditional Uses, Phytochemistry and Pharmacology

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Abstract
Citrus aurantium L commonly called as bitter orange. Economically, *C.aurantium* is of appreciable importance as a source of edible fruit and is widely used in folk medicines. The aim of the present review is to present comprehensive information of the ethno medical information, chemical constituents, biological and pharmacological research on *C. aurantium* which will be presented and critically evaluated. The close connection between traditional and modern sources for ethno pharmacological uses of *C.aurantium* is especially for treatment against inflammation, malarial fever, diarrhoea, digestive and fever. Essential oil from the whole plant, flower and seeds has conclusively established their mode of action in treatment of various diseases and other health benefits. Strong interdisciplinary programmes that incorporate conventional and new technologies will be critical for the future development of *C. aurantium* as a promising source of medicinal products. In the present review, attempts on the important findings have been made on whole plant, bark, flower, seed and root of *C. aurantium*.

Key Words: *Citrus aurantium*, Rutaceae, Whole plant, Root, Seed, Flower, Bark.

Introduction
Citrus aurantium commonly known as bitter orange is widely and easily available plant belonging to the family Rutaceae. The leaves, fruit, barks, flower and root are used traditionally for the treatment of wide panel of diseases. It is also known as sour orange, Seville orange, bigarade orange [1]. *Citrus aurantium* (Khatta: Hindi, Narangam, Narattai: Tamil) is a tree with greenish white, glabrous shoots which cultivated in India for its fruit and used for various medicinal purposes. Bitter orange is regularly cultivated in Khasi hills and cacher. It is native to southeastern Asia. It is 3rd most important fruit crop in India. Its ethno-medicinal application has been well known for a long time [2]. It is traditionally known to be useful for the treatment of wide panel of diseases like stomach ache, vomiting, blood pressure, cough, cold, bronchitis, ear ache, dysentery, diarrhea, abdominal pain and fever. Bark used for UTI ailments. Infusion of dried flower is orally used for influenza, insomnia, as a cardiovascular analeptic, anti spasmodic, for cold, sedative, digestive. Root is used as treat boils and urinary tract infections. Flower is used as cardiovascular analeptic, sedative, antispasmodic and digestive. This plant is much more popular in India and widely cultivated. In India fruits used for pickles. The economic aspect of this crop evidently proved that as commercial crop. In fact the revenue generated by this crop can be further magnified by many folds, if its medicinal applications are scientifically explored well. By a well coordinated effort, we can exploit properly this plant. It may be further envisaged that the revenue generated by this plant would easily exceed that generated by any major crop of the country even with a present level of traditional agro economic practices. Though there is good level of traditional and experimental evidences to support various claims and advantages of this plant, still it needs proper evaluation and exploitation.

The exceptional medicinal value of *C.aurantium* has long been recognized and economically appreciable importance as a source of edible fruit; the present review assesses the potential of *C.aurantium* in relation to its traditional uses and in terms of findings based on modern bioscientific research. The link between conventional remedies and recent research in various areas has been well established in other plants [3, 4] which facilitate to determine effective mode of action of plant derived products. The present plant is known to contain several pharmacological important biomolecules whose efficacy is well established by several biochemical and pharmacological studies. This review indents to compile various studies on this plant and critically evaluates the issues related to the ethno botanical, ethno medical and ethno pharmacology of *C.aurantium* whole plant, seed, root, bark and flower.

Taxonomy

Kingdom	:	Plantae
Division	:	Eudicots
Class	:	Rosids
Order	:	Sapindales
Family	:	Rutaceae
Genus	:	*Citrus*
Species	:	*aurantium*
Binomial name	:	*Citrus aurantium* L.

Botanical information [5]

Name of the plant: *Citrus aurantium* L.
Synonym : Bitter orange, Sour orange, Seville orange, Bigarade orange

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Vernacular names

Sanskrit	:	Brihatjambhira
Hindi	:	Khatta
Urudu	:	Nagorongo
Telugu	:	Mallikanarangi
Tamil	:	Narangam, Narattai
Kannada	:	Heralay
Malayalam	:	Karna

Plant description [6, 7]

A tree or rarely a shrub; young shoots glabrous, greenish white. Leaves foliate; Leaflets 7.5-15cm. Long, elliptic or ovate, obtuse, acute or acuminate; petioles naked or winged, the wing often obovate and nearly as large as the blade. Flower bisexual, pure white. Stamens 20-30. Fruit is globose, generally oblate, not mamillate, usually orange-coloured; rind loose or adherent; Pulp sweet, yellow, rarely red.

History and Geographical distribution

Widely cultivated in India - said to be indigenous in the Mothronwala Swamp Dehradun, Garhwal, Kumaon, Sikkim, Khasia hills, Manipur mountain forests of the Peninsula. It is growing in semi-wild state particularly in the Naga and Khasi hills.

The sour orange is native of south eastern Asia. Natives of the South Sea Islands, especially Fiji, Samoa, and Guam, believe the tree to have been brought to their shores in the prehistoric period. Arabs are thought to have been carried it to Arabia in the 9th Century. It was reported that to be growing in the Sicily in 1002 A.D and it was cultivated around Seville, Spain, in the end of 12th Century. For 500 years, it was the only orange in Europe, and it was the first orange to reach to the New World. It was naturalized in Mexico by 1568 and in the Brazil by 1587, and not long after it was running wild in Cape Verde Islands, Bermuda, Jamaica, Puerto Rico and Barbados. Sir Walter Raleigh has taken sour orange seeds to England; they were planted in the Surrey and the trees began bearing regular crops in 1595, but were killed by cold in 1739.

Spaniards were introduced the sour orange into St. Augustine, Florida. It was quickly accepted by the early settlers and local Indians in the 1763, sour oranges were being exported from the St. Augustine to England.

Cultivation

Area and production

Citrus is the 3rd most important fruit crop in India and the area under its cultivation is estimated at 2.4 lakhs hectares with a production of 19 lakhs tones. It occupies about 9% of the area under fruit cultivation. With regard to production of citrus fruits, India occupies a significant position in the world productivity. India's orange (sweet, mandarin and sour) production amounts to15% of the orange production in Asia, next only to China. The major citrus producing states, viz. Andhra Pradesh, Bihar, Gujarat, Maharashtra, Punjab, Tamil Nadu and Madhya Pradesh contribute 82 % of the total citrus production in India with Andhra Pradesh leading with a contribution of 39%.

Climate

Citrus crop thrives well in frost-free sub-tropical to semi-tropical climate. However, most of the species tolerate light frost. Being evergreen, it has no specific requirement of winter chilling but cessation of growth during winter helps in flower bud induction resulting in spring flowering. Best growth occurs within 29-35°C. An annual rainfall of 700 mm is sufficient if it is well-distributed. Unevenly distributed rainfall can be supplemented by irrigation and best quality fruits are obtained in semi-arid, sub-tropical regions.

Soil

Citrus thrives well in deep, loose, well-aerated soils devoid of any hard pan of calcium carbonate in the rooting zone. The ideal soil p^H is 5.5 to 7.5 but with proper management it can grow with success even in highly acidic soils up to 4.5 and those containing free lime with p^H 8. The crop is highly sensitive to water-logging in the root zone and is susceptible to salt injury; hence it does not thrive in saline and alkaline soils. Loamy soils with comparatively heavier sub-soils or even heavy soils with good drainage are ideal for the crop.

Propagation

Citrus trees are propagated both by seed and vegetative means. Vegetative propagation is preferred because it ensures true to type plants, uniform quality, regular bearing, etc. Notwithstanding the merits of vegetative propagation, seed propagation is still in vogue in the case of certain *citrus* species. Many citrus species can be raised from cutting when they are desired to be clonally propagated on their own roots. A large number of graft compatible species and varieties are available in India.

Seed Propagation

It requires collection of seed from fruits of healthy, virus-free old trees which have a good pedigree performance. The extracted seeds are mixed with ash and dried in the shade. The nursery is located away from old existing orchards to reduce the hazards of pests. Soil which is free of soil-borne pathogens and nematodes is selected and properly fertilized with adequate organic manures and laid out into beds of convenient size. Bold seeds collected from desired trees are treated with fungicides before sowing to prevent seed-borne infections. The seeds have no dormancy and are sown immediately after extraction; treating them with IAA (100ppm) improves germination. Sowing is done in May-June or September-October in Southern and Western India, in spring or rainy season in Northern India and in July-August in Assam. The seeds are sown 2-3cm deep in lines 8-25 cm apart.

Planting

Planting of seedlings or budding in orchards is usually done after the initial rains. Pits of 50-75 cm are dug in a square system 5-8 m apart in summer. The soil is replaced after adding to it about 40kg of farmyard manure.

Irrigation

Citrus requires irrigation in places where the annual rainfall is below 890 mm. The trees are sensitive to excessive moisture and water-logging, and moisture stress is avoided during growth period and in flowering and fruiting as it reduces the fruit size. The soil is allowed to dry out only during spring and summer months but wilting is avoided. Irrigations absolutely essential tlll the fruits attain 2 cm diameter.

Manures and Fertilizers

Nutrients	Quantity/hectare
Nitrogen	21Kg
Phosphorus	5 Kg
Potassium	41 Kg
Calcium	19 Kg
Magnesium	3.6 Kg
Sulphur	3 Kg
Copper	9 g
Iron	50 g
Manganese and Zinc	13 g

Interculture

Interculture is chiefly done to remove weeds which compete with the trees for moisture and nutrients, and for incorporating manure.

Harvesting and yield

Harvesting is done in most of the citrus species the fruits remain fresh for several weeks in the tree without any deterioration after attaining fruit maturity. They do not improve their quality after harvest, and are, therefore, harvested when fully riped citrus fruits are considered fully mature for harvesting when they turn from green to golden yellow even tough colour break is not reliable index of fruit maturity.

Storage

Citrus fruits can be stored well for a few days at room temperature and in cold storage for several months without any appreciable depreciation in quality.

Ethno medical Information

Plant orally used for fever, epilepsy, emotional shock, cold, rheumatism, digestive and gall bladder problems, hepatic disorder, in food preparation and externally used for skin blemishes, externally and internally for bruising in Haiti [8]. Hot aqueous extract of dried plants orally used for malaria in Sudan [9]. Hot aqueous extract of entire plants orally used for menorrhagia in India [10]. Juice of branches orally used to treat convulsions in children in Cook Island, the scraped branches of the *Citrus* and *Psidium guajava* are squeezed through cloth in to water to treat convulsion in children, the medicine is considered best prepared at the time of a full or new moon, but not between a breast feeding baby and mother drink a sweetened solution once. Other fits and convulsions use the scraped bark of new shoots with the Guava bark. The solution is given daily for three days and repeated in a month. Effects described are from a multi-component remedy. Decoction of fresh branches used orally to treat Gonorrhea in Cook Island. Gonorrhea may be treated with the following medicine scraped bark with two ripe and unripe *Morinda citrifolia* fruits are pounded a tablespoon measure of powdered *Piper methysticum* are mixed, squeezed through a cloth into half a gallon of water and boiled. The cooled solution is drunk daily for two days. Effects described are from a multi-component remedy [11]. Branches used for vomiting by oral route in Mexico. Branches used for stomach ache by oral route in Mexico [12].

Phytochemical studies

Dried whole plant contains Isoquinoline alkaloid- Synephrine, 5-methyl tyramine was reported in China [13]. Alkaloid- Diphenylamine confirmed in whole plant extract by chromatographic method [14] and Triterpene - Limonin, Nomilin was isolated in Sudan [9].

Essential oil review

Monoterpene- Limonene was found to be main constituents of essential oil of *C.aurantium* whole plant [15, 16] and Sesquiterpene- α-Bergamotene, β-Bisabolene, β-Caryophyllene were reported as constituents of EO [17]. Monoterpene- Linalool, Linalool acetate [18] and Alkaloid- 3-(but-cis-1-enyl) pyridine is present in commercial sample of essential oil [19] were reported.

Pharmacological studies

Laxative

Decoction of mixture of rheum species, *Mangolia officinalis* and *Citrus aurantium* screened for laxative effect in China [20]. It is active. Effects described are from a multi-component prescription.

Antiulcer Activity

Aqueous extract of plant screened for antiulcer activity in rat and found inactive against Hcl/Ethanol induced gastric ulcers at 500mg/kg dose [21].

Neuraminidase Inhibition Activity

Methanol extract of whole plant screened for neuraminidase inhibition activity and found active at 1ppm concentration [22].

Whole plant Essential oil

Antifungal Activity

Essential oil screened in Paraguay for antifungal activity (plant pathogens) by agar plate method. It is active against *Polyporus versicolor, Lentinus lepideus and Lenzites trabea* [23]. Essential oil screened in Egypt for antifungal activity in agar plate method and found inactive against *Trichoderma viride, P.cyclopium* [24].

Antibacterial Activity

Essential oil screened for antibacterial activity in Egypt by agar plate method and found active against *S. aureus, P.aeruginosa* and inactive against *E.coli, B.areus* [24]. Essential oil screened in Thailand for antibacterial activity in agar plate method and found that active against *S. pyogenes* and *S. aureus* [25].

Antiyeast activity

Commercial sample of essential oil screened in Australia for antiyeast activity in agar plate method 0.25% found active against *C. albicans* [26].

Smooth Muscle Relaxant activity

Essential oil of plant screened for smooth muscle relaxant activity and found active in guinea pig trachea at ED_{50} 64mg/liter dose and also found inactive in guinea pig ileum at 100mg/liter [27].

Insect Repellent Activity

Essential oil screened in India for insect repellent activity in Apis florae. It is active in 0.0125% by Olfactometer test [28].

Antiulcer Activity

Essential oil screened for glutathione-S-transferase induction in mouse liver. Dose of 30mg/animal given by intragastric route every 2 days for total of 3 doses is inactive in ulcer in liver, stomach and small intestine [29].

Anti tumor Activity

Essential oil screened for tumor promotion inhibition in rat. Dose 1% of diet is active in CA-mammary-DMBA [8]. Essential oil of plant screened for Glutathione-S-transferase induction activity in mouse stomach, small intestine, liver by intragastric route at dose 30mg/animal and find inactive. Dose was given every 2 days for a total of 3 doses [29].

Action on CNS

Essential oil of plant screened for tranquilizing effect in mouse by inhibition (1.897mg/L) and found active. Greatest activity was seen within 30 minutes of dosing. Air concentration of compound at end of exposure of 1hour was given [30]. Essential oil screened in Yugoslavia for CNS depressant activity by using gold fish externally used and found that it is inactive [31].

STEM PITH

Immunosuppressant Activity

Aqueous extract of dried stem pith screened for immunosuppressant activity in mouse by intra gastric route (500mg/kg) and found active against con-A induced proliferation in thymocytes, also active against LPS induced proliferation in splenocytes [32]. Statistical data in report indicate significant results.

Nitric Oxide Synthesis activity

Aqueous extract of dried stem pith screened for nitric oxide synthesis stimulation activity and found inactive in macrophages and inactive against LPS induced proliferation in macrophages with gamma interferon [32]. Statistical data in report indicate significant results.

BARK REVIEW

Ethno medical information

Dried bark is boiled and used for urinary tract ailments by oral route in Cook Islands [33].

Phytochemical studies

Fungus infected bark contains coumarin- Scoporane in Israel were reported [34, 35].

Pharmacological studies

Cytotoxic Activity

Aqueous and methanolic extract of dried bark screened in Japan for cytotoxic activity (5%) by cylinder plate method and found equivocal against CA-*Ehrlich-Ascites* and inhibition is found to be 28 mm and 27 mm for respective extracts [36]. Methanolic and Acetone extract of dried bark screened in Japan for cytotoxic activity by cylinder plate method and found equivocal in CA-*Ehrlich-Ascites* and inhibition is found to be 27 mm and 30 mm for respective extracts [36].

FLOWER REVIEW

Ethno medical information

Infusion of dried flower of *C.aurantium* var amara orally used for influenza, insomnia and as a tranquilizer in Canary Islands [37]. Extract of dried flowers of *C.aurantium* var amara orally used as a cardiovascular analeptic in Tunisia [38]. Infusion of dried flower orally used for cold and antispasmodic in Brazil [39]. Infusion of flower and leaf were used orally as a sedative and digestive in Italy [40]. Infusion of dried flowers orally used as a digestive in Spain [41].

Phytochemical studies

Dried flower contains Steroid- Desmosterol, Ergosterol, β-Sitosterol, Stigmasterol and 'O' Saponins (unspecified type or hemolytic absent) [42]. Alkaloid- caffeine was reported in dried flower extract [43]. Flower essential oil contains Monoterpene- β-limonene, Linalool, Linalool acetate [44].

Pharmacological studies

Anti amoebic Activity

Essential oil of flower screened (1.0µl/ml) for anti amoebic activity in Broth culture method and found active against *Entamoeba histolytica* [45].

SEED REVIEW

Pharmacological studies

Cytotoxic Activity

Aqueous extract of dried seed screened in China for cytotoxic activity by cell culture method (500mcg/ml) and found inactive in human embryonic cells HE-1 and weak activity in CA-mammary micro alveolar [46].

Antigen Activation Activity

Hexane and 95% ethanolic extract of dried seed screened in Japan for Epstein-Barr virus early antigen activation inhibition activity (10µg/ml) by cell culture method and found inactive against 12-O-tetradecanoylphorbol-13-acetate (TPA) induced carcinogenesis in lymphoblasts human [47].

Antimicrobial Activity

Oil of dried seed screened for antibacterial, antifungal, antiyeast activity by agar plate method (10mg/ml) and found inactive against *S. viridans, Diplococcus pneumoniae, C. diphtheriae, S. aureus, Streptococcus pyogenes, Piedraia hortae, Microsporum canis, Microsporus gypseum, Trichophyton mentagrophytes, Phialophora jeanselmei, Candida albicans, Candida tropicalis* and also screened for anthelmintic activity and found inactive against Anthelmintic parasite [48].

Phytochemical studies

Triterpene - Limonin, Nomilin, Deacetyl nomilin, Obacunone was reported in seed extract [49], Triterpene – Ichangin-17- β-D-glucoside, Isolimonic acid, β-D-Glucoside, Limonin-17-o- β- D-glucoside, Deacetyl nomilin-17-o-β-D-glucoside, Nomilin-17- β-D-glucoside, Deacetyl nomilinic acid-17- β-D-glucoside, Deacetyl nomilinic acid-19-(OH)-17-β-D-glucoside, Nomilinic acid -17- β-D-glucoside, Obacunone-17- β-D-glucoside was reported earlier [50]. Triterpene- Ichangin, Isolimonic acid, Limonin, Nomilin, Nomilin glycoside, Deacetyl nomilin, Nomilinic acid, 19-(OH) deacetyl nomilinic acid aglycone, Deacetyl nomilinic acid, Obacunone Nomilinic acid was present in seed extract [51]. Triterpene- Ichangin, Isolimonic acid, Nomilinic acid, Deacetyl nomilinic acid was found to be important constituents in other study [52]. Seed extract contains Triterpene- Limonin, Deacetyl nomilin [53].

ROOT REVIEW

Ethno medical information

Extract of dried root and fruit of *C aurantium* aff are orally used for polio in Tanzania. Aqueous extract of dried root of *C.aurantium* aff orally used for stomach upset in Tanzania [54]. Decoction of dried root, fruit and leaf are orally used for fever, hypertension, diarrhea, ulcers and digestive for stomach ache in Nicaragua [55].

Pharmacological studies

Protein Binding Activity

Dichloromethane extract of dried root screened in France for P-glycoprotein binding activity and found active in erythroleukemia (K562) [56].

Mutagenesis

Dried root screened in France for multi drug resistance efflux pump inhibition by cell culture method (017.5µg/ml) and found active in erythroleukemia (K562) against DMBA induced mutagenesis [56].

Phytochemical studies

Fresh root contains Coumarin- Seselin was reported [57]. Dried fruit + leaf + root contain 'O'alkaloid [58]. Coumarin- Braylin, Geranyl-oxy pyranocoumarin, Seselin, Suberosin, Xanthoxyletin, Xanthyletin was isolated from root extract [59].

Conclusion

The present review discusses the significance of *C.aurantium* as a valuable source for medicinally important compounds besides its edible fruit which is a store house of minerals, vitamins, antioxidants and other nutrients. Correlation between the ethno medical employment and the pharmacological activities has been duly observed and described in the present review.

There is a need to minimize the gap between the studies conducted so far and to exploit fully medicinal properties of *C.aurantium*. However, there is a need to study the acute toxicity, sub acute toxicity, chronic toxicity and pharmacological safety profiling of plants. Detailed animal acute and chronic toxicity studies of compounds are required prior to clinical testing.

Two goals seem to be largely open for future exploitation. First, once the accurate and precise chemical composition of these compounds is known, will lead further studies to understand metabolic pathways of these useful products, and second, understanding metabolic engineering will enhance the synthesis and accumulation of these compounds considerably.

C.aurantium is a very important part of biodiversity and it's sustainably use for future generations. The bitter orange plant still is a rather an untapped source for isolation and characterization of novel useful products; however, at the same time it also opens up new avenues for novel therapeutics for fighting against dreadful disease.

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