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Citrus maxima (Burm.)Merr. A Traditional Medicine: Its Antimicrobial Potential And Pharmacological Update For Commercial Exploitation in Herbal Drugs – A Review

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Abstract : Ethno-botanical and traditional uses of natural compounds, mainly of plant origin established much interest as they are well tested for their efficacy and generally believed to be safe for human use.The extracts of differet parts might be added value in the scientific evalution of medicinal application of C. Maxima. Extensive literature survey revealed many pharmacological properties includes antimicrobial, antihelmintic antioxidant, antidiabetic, and central nervous system activity, hepatoprotective, and anticancer activities of the extract and isolated molecules of Citrusmaxima (Burm) Merr. The conversion of these pharmacological activities in to the modern drugs, proper scientific evalution includes isolation of answerable phytochemicals, their mechanism of actions and appropriate standardization need to be explored.
Key words : Citrusmaxima, Traditional uses, Antimicrobial activity, herbal medicine and phytochemistry.

Introduction

Plants have unlimited capacity to synthesize secondary metabolites such as tannins, terpenoids, alkaloids, flavo-glycosides and phenols which have been found to have antimicrobial properties [1-3].Plants derived substances attracted the attention owing to their resourceful applications. It has been estimated that 14-28 % of higher plant species are used in medicinal purposes and that 74 % of pharmacologically active plant derived components were discovered after following up on ethnomedicinal use of the plants. In the last couple of decades, it is evident that there is a new development in the research and promotion of plants based drugs. The interest of peoples has become increasingly towards the herbal medicines[4-6].

Plant Introduction

Citrus maxima(Burm).Merr. (syn. *C. grandis*) belonging to family Rutaceae. It is commonly known as shaddock, papanus or pummelo or chakotra. Although *C. grandis* (L.) Osbeck is more frequently used, *C. maxima* (Burm.) merr. is correct under the International Code of Botanical Nomenclature. It is a perennial tree and edible fruit. The round shape and big sized fruit is of two types i.e. pink and white fleshed and named accordingly. In traditional medicine, the fruit peel has been widely used for cough, swelling and epilepsy. *Citrus* is one of the most important mercantile fruit crops grown in all continents of the world[7-9,3].

Taxonomy

Kingdom – Plantae

Division - Magnoliophyta
Class – Magnoliopsida
Order – Rosidae
Family – Rutaceae
Common name – Pomelo
Vernacular name – Madhukarkati (Sanskrit), Mahanimbu (hindi)
Botanical name – *Citrusmaxima*

Distribution and Habitat

It is a crop plant of India, China, Japan, Indonesia, USA, Philippine and Thailand. It is widely distributed indigenous plant found in Indian subcontinent. It is a native plant of Asia and commercially grown in India. It is indigenous to East of India.*C. maxima* is with a height of 5-15 m, and having thickness 10-30 cm [10]. The tree has large evergreen leaves are dotted, glandular, alternate, ovate and elliptic, 10.5 to 20 cm long, with winged petiole. The flowers and fruits are borne singly. The fruits are pear- shaped with a width of 10-30 cm and pale-yellow or greenish yellow in colour [10-12].

Traditional Uses

C. maxima have been recommended in traditional herbal medicine as source of diabetic medication for diabetes. It is well recognized for their various ethno-medicinal uses. It has been used as a folk medicine in many countries as antimicrobial, antioxidant, larvicidal, hepatoprotective, anticancer, antiplatelet, antidiabetic and anti-inflammatory [13-15]. It can cure fever, gout, arthritis, kidney disorders and ulcers. The fruits pulp and peels are used as an appetizer, stomach-tonic, inflammation, cardiac stimulant and coughs. The fruits juice has potential in influencing weight loss and promoting cholesterol reduction[16-17]. The fruit juice is used in stomach tubules. The fruit is nutritive, cardiotonic and refrigent [19-20]. Fruits of *C. maxima* are also used in food, cosmetic, perfume and pharmaceutical industries as flavouring or fragrance-enhancing agents[16]. The essential oil from the fruits and the leaves of *C. maxima* is used as one of the components of various toiletry products. Highly aromatic character of its flowers is routinely exploited by perfume manufactures. Pomelo peel has also been traditionally used for beauty purposes [21-22]. Leaves are reported to use inepilepsy, chorea, and convulsive cough. Oil from fresh leaves posses antidermatophytic activity, fungicidal activity [23, 18-19]. Leaves are also useful in stomach pain due to indigestion [24]. Flowers are reported to use as sedative in nervous affection. Fruits are reported to use inleprosy, asthma, cough, mental aberration, epilepsy, cardiotonic. Rinds are used in antiasthmatic, sedative in nervous affection, brain tonic, useful in vomiting; griping of abdomen, diarrhoea, headache and eye troubles [25-26,23]. The hot leaf decoction is useful on swellings and ulcers. The fruit juice is taken as a febrifuge. The seeds are employed against dyspepsia, coughs and lumbago and fruit used in the treatment of coughs, fevers, cardiotonic, cancer and gastrointestinal disorders [10,26,5].

Antimicrobial Activities

Antibacterial Activity

Borah *etal*., (2012) studied antibacterial activity of EtOH extracts of *C.maxima* against *S.aureus, E.coli* and *P.aeruginosa*. Antibacterial activities of the phytochemical constituents of the pericarp, mesocarp and segment membrane crude EtOH extracts of *C.maxima* fruit were tested against *E.coli* and *Salmonella typhimurium*[27]. The antibacterial activity of the EtOH extract of *C. maxima* leaves against *E. coli* and *P. aeruginosa* was investigated by Das *et al*.,(2013) [28]. Similar antibacterial activity of *C. maxima* oil was reported against *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Salmonella typhi* at 1000 ppm concentration with 52.0, 62.2, 57.4, 52.5 and 53.3%, respectively [29]. Abirami *etal*., (2013) reported the *in vitro* antibacterial activity of MeOH extracts of *C. maxima* (red and white fruit) extract against *S. aureus, K.penumoniae, P. aeruginosa, S. typhi* and *E. coli*. MeOH extract of leaves and pulp were found to have maximum activity as compared to peel extracts against all tested microorganisms [30]. In another similar study the antibacterial activity of the volatile constituents of *C. maxima* (fruit epicarp) against *Bacillus pumilus, B.subtilis, S.aureus, Escherchia coli, Klebseilla pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhi* was reported by Pandey *etal*., (2010) [31].Kichaoi *etal*., (2015)reported *invitro* antimicrobial activity of EtOH, MeOH and H_2O extracts of *C.maxima* pulp against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans* and MIC (Micro-dilution method) at different concentrations

(100-0.195mg/mL) for *S. aureus*, *E. coli* and *P. aeruginosa*, and (200- 0.39mg/mL) for *Candida albicans* [32].The antibacterial activity of the phytochemical constituents of the pericarp, mesocarp and segment membrane crude EtOH extracts of *C.maxima* fruit were tested against *E. coli* and *S. typhimurium*. In terms of antimicrobial activity, the pericarp, mesocarp and segment membrane extracts generated zone of inhibitions measuring 17.10, 18.00 and 17.03 mm for *Salmonella typhimurium*, respectively at 100% concentration. *E. coli* was noted to be inactive in all three sample extracts at 100% concentration [33].The antibacterial activity of pomeloethyl alcohol (EtOH) and ethyl acetate extracts. All *Citrus* peels showed antibacterial activities against pathogenic bacteria with MIC(minimum inhibitory concentration) and MBC (minimum bactericidal concentration) ranged between 0.4 to 50.0 mg/ml[34]. Hindi *etal*., (2014) reported the antimicrobial activity of different types and part of Citrus species against different microbial isolates. The antimicrobial effects of H_2O extracts of peel, juice and leaves from fresh *C.grandis* against *S. aureus, S. pyogenes, E. feacalis, P. aeruginosa, K. pneumoniae, E. coli, S. typhi, Proteus* spp., *M. catarrhalis*, all of them were studied. Citrus juices showed the highest antibacterial activity against most of the study bacterial isolates. Moderate activity produced by the *Citrus* peels and the lowest effect produced by the extract of the Citrus leaves [35].In a study it was also assayed that the distilled *C. grandis* oil exhibited better antimicrobial activities than distilled *C. paradisi* oil, especially against *E.coli* and *Salmonella* enteric subsp. [36].

The antimicrobial activities of five different extract of peel and pulp of *C. maxima* fruits have also been investigated against isolated *E.faecalis* and *P. putida*. Kinnow peel and pulp showed maximum antimicrobial activity in methanolic (MeOH) extracts form, against *P.putida*, which was ~73% and ~64% respectively comparatively to gentamicin. The orange peel and pulp showed maximum antimicrobial activity in MeOH and EtOH(ethanolic or ethyl alcohol) extracts form respectively, against *P.putida*. The maximum antimicrobial activity among the chakotra peel and pulp was showed in EtOH extracts against *E. faecalis* [37].Singh and Navneet (2016) reported the antibacterial activities of seeds extracts of *C.maxima*. MeOH extract showed highest antibacterial activity among all solvents followed by acetone (ACE), aqueous (H_2O) and petroleum ether (PET). Maximum inhibition zone was found against *S. aureus* (24±0.88 mm) followed by *S. pneumoniae* (21.78±0.36 mm), *H. influenzae* (19.74±0.22 mm), *P. aeruginosa* (18.54±0.62), *S. pyogens* (10.93±0.69 mm)and *C. albicans* (7.66±0.32 mm). The MICs values for MeOH extract were observed between 3.12 mg/mL to 25 mg/mL. MIC values were observed against S. *aureus* at 3.12 mg/mL followed by *S. pneumoniae* and *P. aeruginosa* at 6.25 mg/mL *H. Influenzae*, *S. pyogens* at 12.5 mg/mL and 25mg/mL for *C. albicans*[5].

Antifungalactivity

Antiaflatoxigenic activity of *C.maxima* essential oil (EO) reported broad fungitoxic spectrum against different food contaminating moulds. The EOs and their combination completely inhibited aflatoxin B1 (AFB1) production at 500 ppm, whereas, DL-limonene, the major component of EOs showed better antiaflatoxigenic efficacy even at 250 ppm. The EOs were found non-mammalian toxic showing high LD_{50} for mice (oral, acute). The oils may be recommended as safe plant based antimicrobials as well as antioxidants for enhancement of shelf life of food commodities by checking their fungal infestation, aflatoxin production. Complete inhibition of *Aspergillus flavus* was found at 750 ppm of both the EOs and their combination. At 500 ppm, *A. flavus* was inhibited 48.1%, 46.2% and 44.0% against EO of *C.maxima*, *C. sinensis* and their combination, respectively. DL-Limonene, completely inhibited the growth of *A. flavus* at 500 ppm[38]. In another study antifungal activity of seeds extracts in percentage inhibition was observed maximum with 37.01% of H_2O extract followed by MeOH (22.47%), PET (8.36%) and ACE (1.56%). The control mycelia growth diameter was determined between 34.23±0.46 to35.4±0.28 mm[5].

Antiaflatoxigenic Activity

The EOs of C. *maxima*, C. *sinensis* and their combination completely inhibited AFB1 production at 500 ppm in SMKY broth while DL-limonene could inhibit at 250 ppm. At 500 ppm, mycelia growth was recorded in all the EOs and DL-limonene treated sets, but aflatoxin B1 production was completely inhibited [38].

Pharmacological Properties

Analgesic activity

Analgesic activity was studied in acetic acid induced, hot plate methods in mice and tail flick method in rats. Ethanol extract of leaves and bark 300 mg/kg extracts exhibits significant analgesic activity in acetic acid-

induced writhing test. The extracted compounds exhibited analgesic activity against chemically and a thermal noxious stimulus on both early and late phases of pain by the *C. maxima* extracts[39].

Antioxidant activities

Antioxidant potential was tested for the juice of *C.maxima* in rats. The enhanced antioxidant status observed in *C. maxima* treated rats and its protective role against H_2O_2, STZ and nitric oxide generating system induced DNA damages might be due to the effect of different types of active principles acting individually or synergistically, each with a single or a diverse range of biological activities against oxidative stress [40].Antioxidants including total phenolic content, total flavonoid content and ascorbic acid content were determined using Folin-Ciocalteu reagent assay, aluminium chloride colorimetric assay and AOAC method, respectively. The peels of both Citrus fruits had higher antioxidant content and capacity than their pulps. It was also reported that the white variety of Citrus had higher antioxidant content and capacity compared to the pink counterpart. Citrus peel from white variety possessed higher antioxidant properties and it is potentially rich sources of natural antioxidants [41]. The peel of *Citrus* fruit contained higher amount of antioxidant as compared to its pulp as the peel is to protect the antioxidants in the fruit from oxidation. In anotherstudy it was assayedthat EO exhibited DPPH radical scavenging activity in dose dependent manner[38].

Aimee *et al*., (2014) reported the antioxidant activity of the phytochemical constituents of the pericarp, mesocarp and segment membrane crude EtOH extracts of *C.maxima* fruit. The strongest antioxidant activity was obtained by the pericarp extract (29.64 expressed as % lipid peroxidation)[33].The antioxidant effects of different tropical *Citrus* peel extracts (kaffir lime, lime and pomelo) obtained from EtOH and ethyl acetate extraction in raw chicken drumettes during storage at 4°C were studied. The total viable counts, 2-thiobarbituric acid reactive substances values of KEa-treated chicken wing samples were lower than those of control samples while the sensory properties maintained significantly ($p < 0.05$) higher values during 14 days of storage [34].

Antidiabetic activities

Ethyl alcoholic (EtOH) extract of stem bark of *C. maxima* was reported antidiabetic activity studied in the Alloxan, streptozotocin induced antidiabetic activity and Oral glucose tolerance test. Acute toxicity assayed showed that LD_{50} values were too high thus it showed the safety of the extract. Oral glucose tolerance test in rats showed the significant decrease in the blood glucose level. Serum biomarker SGPT, SGOT was decreased significantly in the glibenclamide treated and *C.maxima* extract treated animals. Fruit juice of *C.maxima* was studied for the glucose tolerance and the lipid profile in the type II diabetic rats[42-43].

Anti-inflammatory activities

Acute and Chronic inflammatory activities were studied in rats by formalin induced paw edema models respectively. In both models, the standard drug used was diclofenac sodium 10 mg/kg, 100 mg/kg. A dose of 300 mg/kg ethanolic extract of leaves and bark exhibited significant anti-inflammatory activity in formalin induced paw edema models in comparison to control [39].

Hepatoprotective activity

Leaves of*C. maxima* were studied for hepatotoxicity in rats against paracetamol induced hepatotoxicity. Standard drug silymarin was compared with the MeOH extract leaves. The effect of the MeOH extract of *C. maxima* had significant effect on thiobarbituric acid reactive substances. Reduced levels of the glutathione and catalase activity were restored to normal levels using MeOH extract. The histopathological studies have also showed that the hepatocellular vacuolization and focal hepatic necrosis in paracetomol control animals is significantly reduced in the methanol extract 400 mg/kg treated animals and silymarin treated animals. CCl4 (carbon tetrachloride) induced hepatotoxicity model were used and *C. maxima* peels were found to posses the protective action against hepatic damage induced by CCl4. Antioxidant compound like caffeic acid and epicatechin are found to be responsible for the effectiveness of *C. maxima* peel powder against liver disorder [40,44].

Hypocholesterolemic and ACE inhibitory activity

C. maxima juice was studied for inhibition of the angiotensin converting enzyme and hypocholesterolemic activity. The interaction of the citrus fruit juice with ACE revealed that the juice inhibited ACE activity in a dose-dependent manner. The juices had lower inhibition of the enzyme activity than captopril [45].

Larvicidalactivity

Three different solvents (n- hexane, ethyl acetate, and methanol)crude fruit peel extracts of *C. maxima* were applied at dose dependent manner for larvicidal bioassay against *Culex quinquefasciatus* Say, 1823 (*Cx. quinquefasciatus*) mosquito. Crude fruit peel extract of *C. maxima* showed strong lethal activity against all instars larvae of*Cx. quinquefasciatus*. 1st instar larvae were most susceptible to crude fruit peel extract and showed 100% mortality only at 0.2% concentration of crude fruit peel extract after 72 h of exposure. 100% mortality of 3rd instar larvae were observed at 400 ppm concentration of n-hexane fruit peel extract after 24 h of exposure whereas, ethyl acetate and MeOH fruit peel extracts showed 100% mortality at 800 ppm concentration after 72 and 24 h of exposure respectively. LC_{50} values of n-hexane, ethyl acetate and MeOH fruit peel extracts were 204.60, 640.95, and 336.36 ppm, respectively against 3rd instar larvae after 24 h of exposure without any mortality on control treatments [46].In another similar study the larvicidal effects of leaf and stem/bark extracts of *C.grandis* was tested on the larvae of the dengue-vector, *Aedesaegypti*. Various concentrations (20 mg/mL, 40 mg/mL and 60 mg/mL) of the plant extracts were tested against third instar larvae of *A. aegypti* [47].

Antitumouractivity

C. maxima leaves were tested for antitumor activity in Ehrlich's Ascites carcinoma cell(EAC)-treated mice. Intraperitonial administration of MeOH extract of *C. maxima* showed to increase the life span, nonviable tumour cell count and decrease in the tumour volume. Hematological parameters were towards normal level [40,48]. The flavonoids and limnoids present in *Citrus* plants are postulated to be the cause of their anticancer and anti-inflammatory effects [49].

Anticanceractivity

Shivananda *etal*., (2013) were reported the anticancer property of plant extracts were analysed using HeLa cell line. EtOH fraction of *C.maxima* leaf is selected to establish the IC_{50} and IC_{50} value is found approximately closer to 50%.Whereas, EtOH fraction of *C. maxima* leaf has showed high anticancer property (69.1% deadcells), EtOH fraction of *C.maxima* bark has shown 15.3% of dead cells, while, ACE andH_2O fractions of *C.maxima* fruit peel have showed 23.3% and 22.1% of dead cells respectively [39].

Antiarthritic activity

Antiarthritic activity was studied using Formalin induced paw oedemas in rats. The EtOH extract was found to compatible with the standard drug diclofenac [39,40].

Central Nervous System(CNS) activity

Central Nervous System activities were studied with the extracts of *C.maxima* leaf on the Rodents. Acute toxicity was performed, which was observed after 5 h of administration, and for 14 days. It was reported to be safe even at 2000mg/kg and no delayed toxicity was observed. Various parameters like anti-depressant activity, anxiolytic, Anticonvulsant, hypnotic, muscle relaxant activity were studied for the central nervous system activity [50-51].

a. Anti-depressant activity

The EtOH leaf extract of *C. maxima* was reported the antidepressant activity studied with Forced Swim test and Tail suspension test. There was significant decrease in the immobility time and increase in the climbing behaviour was observed with the EtOHleaf extract of *C.maxima*. The Light and dark test measured the increase in the number of crossing. EtOH extract of *C.maxima* showed increase in the frequency of open arm entry and the time spent in the open arm. The effect of extract was comprised with the standard Diazepam in the each test [50-51].

b. Anticonvulsant activity

In a study it was reported that the administration of the EtOH extract of *C.maxima* leaf increase in the latency of the seizure, dose dependant increase in anticonvulsant activity, dose dependant increase in the delay of seizure respectively was observed. Hypnotic activity was assayed using the pentobarbitone induced sleeping time. Significant increase in the duration of the sleep was observed with the EtOH extract of C.*maxima*. Muscle relaxant studies were done using Rotarod model, Climbing test, inclined screen test. EtOH extract of *C.maxima* showed potential muscle relaxant activity with all of models [50-51].

Phytochemistry

Preliminary phytochemical test revealed the presence of phenols, tannins, saponins expressed as catechine quivalent (CE)/100ml and flavonoid expressed as gallic acid equivalent (GAE)/100ml [33]. Singh and Navneet (2016) assayed the MeOH and ACE extracts showed the presence of different kinds of phytochemicals. MeOH extract showed the presence of glycosides, lignins,steroids, terpenoids, phenols, flavonoids, proteins, amino acids and ACE extract revealed the presence of glycosides, saponins, flavonoids, tannins, proteins. Water (H_2O) and petroleum ether (PET) extract showed amino acids, steroids terpenoids and alkaloids [3].In another similar study Gutierrez *etal*., (2014) reported the phytochemical screening revealed the presence of alkaloids, flavonoids and steroids in the leaf bark/stem extracts of *C.grandis* is rich in alkaloids, saponins, tannins, flavonoids and steroids [47]. 5-hydroxyacronycine, acriginine A, Atalafoline, Baiyumine A and B, Buntanine, Buntanmine, Grandisine I and II, Pumiline, honyumine, natsucrin, Prenyl citpressine, Citropone A and B, Glycocitrine I werereported in the roots and the bark. Whereas the caffeine are assayed in the flowers of the *C. maxima* [52-57].Alanine, Asparigine, Aspartic acid, Coline, Glutamic acid, Glycine And proline are reported in the leaves [58-59]. Phytol, Synephrine, Methyl antralinate, Fructose, Glucose and Pectin are present in the leaf, peel and flowers [60-63]. Carotenoids are one of the most important by-products in citrus fruits. More than 115 different carotenoids were reported in the peel and pulp of citrus fruits [64-65]. Carotene [66] and Roseoside [67] reported in the peels. 5-Geranoxy-7-methoxy-Coumarin, Aurapte, Auraptene, bergamottin [68-70] are reported in the peels and 5-methoxy seselin[56], 5-methyltodannol, 6-hydroxy methylherniarin are present in the roots and stem bark. Acacetin, rutin, tangeretin, cosmosiin, diosmetin, diosmin, eriocitrin, hespeidin, naringin [71-73].α-pinene, α-terpineol, anethole, β-pinene, camphene, camphor, citral, citronellal, citroonellol, farnesol, geraniol, myrcene, neral, terpinene [74-76].

Conclusion

C. maxima depicted the fact that it is used as a cure for different types of diseases. Subsequent the traditional and folk claims, very little efforts have been made by the researchers to discover the therapeutic potential of *Citrusmaxima*. It is appealing to note that pure compounds and crude organic extracts of leaves, seeds, peels, pulp, fruits and roots of *C. maxima* have been screened for some pharmacological activities and found to possess analgesic, anti-inflammatory, antitumor, CNS activity, anti-diabetic activity, hypocholesterolemic, antioxidant activity, anti-diarrheal, hepato-protective, antibacterial, analgesic and anti inflammatory activity. The detailed information as provided in this review might be added value in the scientific evaluation of medicinal application of *C.maxima*. In future study, the conversion of these pharmacological activities in to the modern drugs, proper scientific evaluation includes isolation of answerable phytochemicals, their mechanism of actions, toxicity and appropriate standardization need to be explored.

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Conflict of Interest

Authors are no conflict of interest.

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