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A REVIEW ON PHARMACOLOGICAL ACTIVITIES OF *Citrus medica* L LEAVES

R. Suja Pandian* and A. Thajun Noora

Department of Biochemistry, Rabiammal Ahamed Maideen College for Women, Thiruvarur, Tamil Nadu, India.

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***Corresponding Author**
R. Suja Pandian
Department of Biochemistry, Rabiammal Ahamed Maideen College for Women, Thiruvarur, Tamil Nadu, India.

ABSTRACT

The plant kingdom is a rich source of structural biodiversity and offers a variety of natural products. Plants have been utilized to produce various types of medicines for thousands of years. *Citrus medica.* L has been used successfully in Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use. *Citrus medica.* L (commonly known as citron) one of the important citrus fruits of the world, is considered a native of India. Flowers and leaves of Citrus are usually strong scented, the extracts of which contain many useful flavonoids and other compounds that are effective insecticides, fungicides, and medicinal agents. *Citrus medica*.L extracts and compound have shown antioxidant, anti-inflammatory, estrogenic activity, antiulcer activity, antidiabetic activity, antihypertensive effect, antithyroid activity, antihyperglycemic activity, antianxiety effect, anticancer activity, prevention of anemia, central nervous effect, insecticidal activity, anthelmintic and repellent effects, antifungal effect and antimicrobial effect.

KEYWORDS: *Citrus medica*. L, leaves, antidiabetic, antithyroid, pharmacological activities.

INTRODUCTION

India has a very long, safe and continuous usage of many herbal drugs in the officially recognized alternative systems of health such as Ayurveda, Unani, Siddha and Homoeopathy. These systems have rightfully existed side-by-side with Allopathy and are not ‘in the domain of obscurity’. Millions of Indians use herbal drugs regularly, as spices, home-remedies, health foods as well as self-medication or also as drugs prescribed in the non-allopathic systems.[1,2]

The plant kingdom is a rich source of structural biodiversity and offers a variety of natural products. Plants have been utilized to produce various types of medicines for thousands of years. More recently, the use of plants as medicines hasfocused on the isolation of active compounds from them. Plants have different chemical compounds like secondary metabolites with many biochemical and bioactivity properties showing applications in various industries such as pharmaceuticals.[3]

Citrus medica. L

C. medica is a bushy small shrub or tree of irregular habit of growth with twigs angled and purplish when young and cylindrical at maturity, glabrous, with stout, short, single spines in the axils of the leaves. The inflorescences are short. The fruits were large, oblong or oval, with acid or sweetish pulp Seed swere monoembryonic in nature, numerous in numbers, small, pointed at the base, smooth with spheroid or ovoid shape; cotyledon white and reddish chalazal cap. All citrus species have dark green, waxy leaves with a characteristic citrus odour and sweet smelling flowers. Most species are easy to differentiate by their fruits. [4]Flowers and leaves of Citrus are usually strong scented, the extracts of which contain many usefulflavonoids and other compounds that are effective insecticides, fungicides, and medicinal agents.[5]

Taxonomical Classification

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Sapindales
Family	:	Rutaceae
Genus	:	Citrus
Species	:	C. medica
Binomial name	:	Citrus medica. L

Vernacular Names

Hindi name : Bijoura, baraneebu
English name : Citron, wild lemon
Bengali name : Begpur
Kannada name : Maadala, deva maadala
Telugu name : Nimmakaya, matulungamu,

Tamil name : kadara-Narathai, kommattimaatulai

Malayalam name : Ganapathi Narakam, cerunaarakam

Fig 1: Citrus medica. L leaves.

Common Uses

The root, flowers, fruit and leaves of *Citrus medica*.Lis used in the form of juice and decoction to treat tastelessness due to fever, intrinsic haemorrhage, anaemia, jaundice, hiccough, asthma, vomiting, pain in cardiac region, gulma, colic, pox, gravels, caries, for easy delivery, foul smell in flatus, erysipelas, head-disease, anorexia during pregnancy and earache.

Pharmagological Studies

Around the world researchers have worked on different varieties of *Citrus medica*L. The findings related to thepharmagological studies are summarized.

1. Antiinflammatory and antioxidant activity

The chemical composition and the antioxidant, anti-inflammatory and hypoglycemic potential of flowers, leaves, and fruits of *Citrus medica* Lcv Diamante at two maturity stages has been reported. Flowers and leaves were characterized with the highest total phenol and flavonoid content. A declining trend was observed during maturity of fruits for both phenols and flavonoids.[6] Theinvestigation on bioassay-guided anti-inflammatory principles from the stem and root barks of *C. medica*L. var. *sarcodactylis* Swinglehas led to the isolation of a new coumarin, namely citrumedin-B and thirty known compounds. The anti-inflammatory components were xanthyletin, nordentatin, atalantoflavon and lonchocarpol A, which displayed potent nitric oxide (NO)-reducing activity in microglial cells.[7] The antioxidative, anti-inflammatory and analgesic potential of *C. medica* was evaluated from the peel extract.

Antioxidant activity in different solvent systems was evaluated. Leaves are externally used in case of pains and inflammation on the external body part. It is also used on skin disorders and also relieves from itching.[8]

2. Antioxidant effect

The aqueous methanol extract of the defatted powdered leaves of *Citrus medica*.Lexerted significant reduction in blood glucose level and antioxidant activity in diabetic rats after one month of treatment. The methanol extract of the defatted powdered leaves of *Citrus medica*.L exhibited significant antihyperglycemic activity which might be attributed to the presence of flavonoid compounds The significant antioxidant activity of *Citrus medica*. Lextractwas verified by different assays (DPPH test, β-carotene bleaching test and bovine brain peroxidation assay) in a dose dependent manner as compared to ascorbic acid.[9,10,11]

3. Cytotoxic activity

The photo-induced cytotoxic activity of *C. medica* L. cv. *Diamante*was evaluated the peel essential oils and two coumarins, bergapten and citropten. Essential oil was obtained by hydrodistillation and analyzed by GC and GC/MS. The study suggested that UV irradiation is effective in activating essential oils. This photo-toxicity may be considered as a treatment option in some cases of lentigomaligna or lentigomaligna melanoma.[12] It has been concluded that the C. medica oil, is nontoxic to test animals and do not induce any adverse effects to the blood, liver function, kidney function, protein, carbohydrate and lipid metabolism of the animals.[13]

4. Antiulcer activity

Aqueous extract of the fruits of C. medica Lshowed statistically significant decrease in the ulcer scores, percentage of ulcers and ulcer index against ethanol-induced ulcers in rats. The antiulcer effect of C. medica could be due to the presence of flavonoids as one of its constituents, as polyphenolic compounds are known to exhibit gastro protective effect by virtue of their antioxidant property. These observations were further substantiated by the histopathological findings wherein, decreased mucosal ulceration, inflammatory infiltration in mucosa and edema in sub mucosa were observed in the extract pretreated groups compared to untreated group. It is concluded the C. medica fruit extract possesses antiulcer activity and also validated the traditional use of aqueous extract of C. medica an antiulcer remedy.[14]

5. **Estrogenic activity**

Oral administration of petroleum ether extract of Citrus medica leaves increased the weight of the uterus and showed estrogen like activity in the ovariectomized rats. It exhibited a significant estrogenic activity (P<0.05) at a dose of 400mg/kg b.wt. Petroleum ether extract of leaves could be useful as a safe natural source for estrogenic activity for Postmenopausal women.[7,15]

6. Antidiabetic Activity

Citrus medica contains citroflavonoids that have been found to possess antidiabetic activity.[16] Measurements of the effects of Citrus medicacv Diamante peel extract on the mouse insulinoma MIN6 β-cells indicated that it exerted direct stimulatory effects on the exocytotic release of insulin in a concentration-dependent manner. Citrus medicacv Diamante peel extract reduced plasma glucose concentration in mice.[17]

The antidiabeticand hypolipidemic activity of petroleum ether extract of Citrus medica L seeds was studied in streptozotocin (STZ) induced diabetic model in rats. The petroleum ether extract of Citrus medica seeds induced significant reduction ($p < 0.05$) of fasting blood glucose, serum cholesterol, serum triglycerides, LDL and VLDL in dose dependent manner after 15 days of drug administration.[18] Insulin secretagogue effect of Citrus medica L. var. SarcodactylisHortfruits was confirmed by kinetic analysis on the hypoglycemic patterns of the intraperitoneal glucose tolerance and the insulin-glucose tolerance tests.[19]

7. Antihypertensive effect

The antihypertensive effect of C. medica L leaves was investigated against the acute response of blood pressure to angiotensin II administration The results showed that different concentrations of the aqueous extract prevented the raise of systolic and diastolic blood pressure and mean blood pressure with a dose dependent effect for diastolic pressures. The 500 and 1000 mg/kg doses inhibited the action of Angiotensin II in similar extent to telmisartan.[20]

8. Antithyroid activity

The increase in thyroid hormones level may be due to the absorption of L-T4 well by gut, thus increasing the level of thyroxine (T4) in circulation, which is then converted into triiodothyronine (T3) by iodothyroninedeiodinases. However, when Citrus medica leaves extract was administered with L-T4, it reversed the concentration as evidenced by a marked

decrease in the level of both the thyroid hormones with an increase in TSH, indicating the antithyroidic nature of the extract. Since both the thyroid hormones, T3 and T4 were decreased by the test material, it appears that the *Citrus medica* extract is capable of inhibiting thyroid function both at glandular (major source of T4 synthesis) as well as at the peripheral level of T4 to T3 conversion, the principal pathway of T3 generation.[21]

9. Antihyperglycemic Activity

Experimental induction of diabetes in rats showed a significant increase in serum glucose, LDL and triglycerides levels together with a significant decrease in serum HDL and no effect on Cholesterol level as compared to normal rats. Treatment with methonolicextract of the *Citrus medic* leaf powder, showed a significant and a dose dependent decrease in serum level of glucose when compared to the standard Gliclazideand the diabetic control groups.[22]

10. Antianxiety effect

Aromatherapy is the use of essential oils as an alternative treatment for medical purposes. Citrus fragrances have been used by aromatherapists particularly for the treatment of anxiety symptoms. Based on this claim, Faturihas investigated the effects of Citrus sinensis essential oil on Wistar male rats.[19]

11. Anticancer activity

The vital capacity test and Ames test were used to evaluate the anticancer effect of Citrus medica, with special emphasis on the application of Salmonella typhimurium to identify antimutagenesis and anticancer levels of chemicals. In vitro study on fruit juice effect on cancerous cell culture revealed that the fruit juice severely repressed division of cancerous cells.[23] The potential of citrus limonoids as anticancer agent in micehas been investigated by Jacoband it was found that five limonoidsaglycones (limonin, nomilin, obacunone, isoobacunoic acid, ichangin) induced significant amounts of glutathione-S-transferase (GST) in the liver and intestinal mucosa.[24]

12. Prevention of Anemia

Anemia is often caused by iron deficiency, and it is most common in premenopausal women.Citrus contains small amounts of iron, but are great sources of vitamin C and citric acid, which can increase the absorption of iron from other foods, helping indirectly to prevent anemia.[25]

13. Central nervous effect

Factors that enhance the intrinsic growth potential of neurons play a major role in the regeneration and repair of adult neurons following an injury. Fibroblast growth factor (FGF-2) is one of the key players in the origin and growth of neuronal and glialcells through autocrine and paracrine signaling. Aqueous extract of *Citrus medica*var. sarcodactylis,was found to activate the FGF-2 promoter in transgenic luciferase expression models. *Citrus medica* treatment on Schwann cells (RSC96) transfected with luciferase reporter plasmid under a FGF-2 promoter was found to induce the FGF-2 promoter and showed enhanced luciferase expression. The FGF-2 expression was accompanied with an increase in the expression of proteins involved in cell migration and cell proliferation in a dose dependent manner.[26]

14. Toxicity and side effects

The toxicity of *Citrus medica* leaves essential oil was studied in rats. The effect of chronic ingestion of a diet treated with different concentrations of essential oil of Citrus medica was studied on body weight, diet consumption, haemoglobin, total and differential leucocyte count, blood glucose, protein, cholesterol, urea levels and serum glutamic oxaloacetic transaminase, serumglutamic pyruvic transaminase and alkaline phosphatase activity in albino rats. It was found that the *Citrus medica* oil was nontoxic to test animals and did not induce any adverse effects to the blood, liver function, kidney function, protein, carbohydrate and lipid metabolism of the animals.[27]

15. Anthelmintic and repellent effects

Petroleum ether and methanolic extracts of *Citrus medica*leaves possessed dose dependant anthelmintic activity against the Indian adult earthworms (*Pheretimaposthumad*).Various concentrations of extract were tested and results were expressed in terms of time for paralysis and time for death of worms The effect which could be attributed to inhibition of glucose uptake in the parasites and depletion of its glycogen synthesis. Alcoholic extracts of the rind of Citrus medica showed *in vitro* anthelmintic activity against human Ascarislumbricoides. It also activated nicotinic cholinergic receptor in the worms resulting in either persistent depolarization or hyperpolarization.[28,29,30]

16. Insecticidal activity

Leaves of *C. medica* are reported to have potential to paralyze and kill earthworm (*P. posthuma*). The shortest time of paralysis and time of death was observed at higher dose (80 mg/ml) of petroleum ether extract was found to 30.86 min.[29]

17. Antimicrobial effect

The physicochemical properties and *invitro*antifungal effect of the essential oil of the leaves of *C. medica*L was reported by Essien.[31] Essential oil from the fresh leaf of *Citrus medica* L. var. *sarcodactylis*possessed strong antimicrobial activity against *Staphylococcus aureus*and *Bacillus subtilis* (MIC 2,500 ppm).[32]

CONCLUSION

Citrus has a long history of cultivation - more than 4000 years. However, the huge controversy over the phylogeny of key wild species, and the genetic relationship between the cultivated species and their putative wild progenitors have remained unresolved, mainly due to the sexual compatibility between Citrus and related genera, the high frequency of bud mutations, the long history of cultivation, and wide dispersion. The extract of the different parts of the plant shows various activities likeantioxidant, anti-inflammatory, estrogenic activity, antiulcer activity, antidiabetic activity, antihypertensive effect, antithyroid activity, antihyperglycemic activity, antianxiety effect, anticancer activity, prevention of anemia, central nervous effect, insecticidal activity, anthelmintic and repellent effects, antifungal effect and antimicrobial effect.

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