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PHARMACOLOGICAL AND NUTRACEUTICALS PROFILE OF *CITRUS MEDICA*: A VITAMIN C RICH SOURCE

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Abstract

Citrus medica commonly known as citron is widely distributed in the himalayan regions of India. It contains various phytoconstituents like limonene, hesperetin, Vitamin C, phenolics, flavonones, iso-limonene, pectin, linalool, decanal, and nonanal etc. It is frequently used in traditional systems of medicine for the treatment of cardiac, thyroid, and oestrogen disorders. These activities is due to presence of phenolic and flavanoids content in it. It is also mutagenic and exhibits good antioxidant properties. The plant leaves, peels, fruits and their seeds have several pharmacological effects such as antioxidant (reduces reactive oxygen species and malondialdehyde), analgesic and anti-inflammatory activities (inhibitis DPPH and hydrogen peroxide radical scavenging), antilipidaemic (by inhibiting HMG-CoA reductase) and estrogenic activity (increase vaginal epithelial cell cornification and uterine weight) etc. The purpose of this review is to highlight the source, geographical indication, phytochemistry, traditional uses, pharmacological effects and numerous nutraceuticals application of *Citrus medica* and its main constituent Vitamin C.

INTRODUCTION

Citrus medica is an evergreen shrub or small tree belonging to family Rutacae, commonly known aschakotra, citron in English, bara nimbu in Hindi and bijapura in Ayurvedic literature, which is about 3.6 m in hight with small, thick and spiny branches (Figure:1). It is cultivated all over warm and humid areas of India [1,2,3]. It has been used for many years in the Unani, Ayurvedic, and Siddha systems of medicine to treat a variety of illnesses. In order to promote health, it is also utilised in the treatment of chronic conditions viz: cancer, heart disease, and metabolic syndrome [4,5,6].

Juice and fruits of citrus are an essential derivation of pectin, phenolic compounds, ascorbic acid, flavonoids, are important for human sustenance. Nearly half of the citrus fruit's mass, which contains the greatest flavonoids, is found in the peel and shows a good antioxidant potential [7,8].

CLASSIFICATION

Citrus medica is a well-known genus of the citrus, belongs to the family Rutaceae and Aurantioideae. Theophrastus coined medica derived early names medium, middle apple, etc [9].

TAXONOMY [10]

Kingdom : Plantae
Class : Magnoliopsida
Sub-class : Rosidae
Order : Sapindales
Family : Rutaceae
Genus : *Citrus*
Species : *medica*

VERNACULAR NAMES [11]

Hindi - Bara nimbu
English - Citron
Sanskrit-Beejapoorna

Urdu- Poastturanj

Bengali-Begpur

Gujarati-Turanj
Marathi-Mahalunga

GEOGRAPHICAL DISTRIBUTION

Citrus medica is widely spread over the Western Ghats, Pachamarhi, Garhwal, Kumaon, , Khasia Hills, Garo Hills, Sikkim, Chittagong, Upper Yunzalin valley, Mediterranean Region, central and southern regions of America, Satpura range in Central India [2,9].

TRADITIONAL USES

Citrus medica was reported as a poisonous antidote in early literature [12]. Arab civilizations, Unani, Ayurvedic system of medicine, used peel and fruit of *Citrus medica* as stomachic, cardiotonic, carminative, refrigerant, appetizer, etc. Furthermore, it is also useful in the in duration of spleen tumors [13]. Historically and throughout the Middle Ages, the it was used in several disorders, viz: intestinal problems, lung issues, seasickness also used to treat dysentery and halitosis in India. In China, the sugared peel of *Citrus medica* is consumed as stomachic, stimulant, expectorant and tonic. *Citrus medica* is used only as a medicine. In West Tropical Africa it is mostly used in rheumatism [12].

PHYTOCHEMICAL PROPERTIES

It peels, fruit decoction, and leaves have been shown to contain the phytochemicals alkaloids, flavonoids, phenols, carbohydrates, and mucilage. Essential oils of *Citrus medica* which is the main constituents are given in figure 2. There are 43 components that have been identified in peel oil, include citral (23.12%), neryl alcohol and acetate (2.25%, 2.51%), isolimonene (39.57%), limonene (21.78%), -myrcene (2.70%), as well as beta-Bisabolene (0.71%), linalool (0.94%), caryophyllene (0.59%), β -terpenyl acetate(0.52%), nonanal (0.25%), alpha-bergamotene (0.48%),α- pinene(0.41%), decanal (0.33%) [14,15].

PHARMACOLOGICAL ACTIVITY

As outlined above, outcomes from several studies (Table 2) shows that in addition to having anthelmintic and estrogenic effects, *Citrus medica* leaves, and peel also contain analgesic, anticancer, ulcer protective, free redical scavenging, cardiotonic, hypoglycaemic, anticholinesterase, hypolipidemic, antibacterial, and anthelmintic properties.

ANTIULCER ACTIVITY

Ulcer protective activity was performed in fruits of citrus in rat. Result of phytochemical screening showed carbohydrates, proteins, amino acids and flavonoids content. The pretreatment of extract was given orally to the rats in two doses (250, 500 mg/kg) and compared with standard drug ranitidine (20 mg/kg p.o.). Rats receiving ethanol treatment showed a significant reduction in mucosal ulceration, inflammatory mucosal alterations, and submucosal edoema, which may be attributed to the presence of flavonoids [16].

ANTIBACTERIAL ACTIVITY

Bioactive components of citron fruit were evaluated qualitatively and quantitatively. Peel extracts and juice were tested for antibacterial activity. The study's findings showed that saponins, terpenoids, and anthracenedione were absent in it. While flavonoids, carbohydrates, tannins, phenols, steroids, cardioactive glycosides were present in the peel and juice. Peel indicates the maximum quantity of tannin whereas juice showed a higher quantity of phenol, and fruits contain more phenolic content. At a dose 100 mg/ml citron has greatest inhibitory zone (12 mm) and the lowest minimum inhibitory and bactericidal concentration (1.5625 mg/ml and 3.125 mg/ml) against *Staphylococcus auricularis*. Peel extract significantly represent antibacterial activity against all four bacterial strain (*Escherichia coli, Klebseilla pneumoniae, Staphylococcus aureus and Streptococcus pneumoniae*) while ethanol 80% showed activity only against two bacteria

(*Escherichia coli*, *Staphylococcus auricularis*). It manifest maximum inhibition zone (10 & 22mm) at (100mg/ml) and lowering MIC value (25mg/ml & 12.5mg/ml) and MBC (50 mg/ml) opposed to *Escherichia coli* [17,18].

ANTIOXIDANT AND FREE RADICAL SCAVENGING ACTIVITY

Total phenol concentration, 2,2 diphenyl-1 picrylhydrazyl (DPPH), and radical scavenging effect were chosen for the experimental study. The concentration of extract inhibits the generation of DPPH radicals by 50% and radicals of nitric oxide. Outcomes of study showed that the extracts have a significant amount of antioxidant activity [19]. Citron curtailed reactive oxygen species (ROS) and malondialdehyde therefore amplifying the efficiency of the enzymes superoxide dismutase (SOD) and catalase (CAT) in C. elegans. Study discovered three key compounds in pure citron and established its exceptional antiaging properties, which are ascribed to its potent antioxidant activity and impact on ROS homeostasis [20].

ANTI-IMPLANTATION ACTIVITY

The ethanolic and chloroform oil extract of the peels of Citron were examined for antifertility activity. On days 1-7 post-coital, on female wistar rats, the alcoholic (2.5gm/kg) and chloroform extract (1.0 gm/kg) displayed substantial anti-implantation activity. Similarly On days 1-7, at the dose of 100mg/kg it did not show substantial anti-implantation activity [21].

CARDIOTONIC EFFECT IN CONGESTIVE HEART FAILURE (CHF)

Digoxin is beneficial in high output failure and Cardio tonics are beneficial in low output failure. Force of contraction can be increased by Citrus to increase the activity of cardiac muscles and also has a diuretic impact. Thus, it may ameliorate CHF. Its positive ionotropic effects were measured by in-vitro Langen dorff's method [22].

ANTIMUTAGENICITY AND ANTICANCER EFFECT

The antimutagenic and anticancer fruit juice effect of citron was evaluated. 10% foetal calf serum, peniciline-streptomycin, and L-glutamine were added to DMEM (Gibco) in order to supplement the human astrocytoma cancer cells, incubated at 37 oC for two days. In addition, its fruit juice was applied to cancer cell lines when they were partially or fully mature, and MTT assay was used to measure the cellular capacity of the cells. Citron fruit juice was assessed in respect of antimutagenicity and anticancer potential by using standard reverse mutation assay (ames test). This was accomplished using the *Salmonella typhimurium* histidine auxotroph strain (TA100), produces reverted colonies adainst sodium azide. The human astrocytoma cell line showed significant expressive cell death. The fruit juice prevents the reversal of mutations in ames test. Riped citrus (34.4%), half-riped (71.7%) were found to be in antimutagenicity test similar as in anticancer test (83.3%) and (50%). The effects were greater in half-ripe *Citrus medica* in comparison to the ripened one [23].

ESTROGENIC ACTIVITY

In this investigation, albino rats' responses to a petroleum ether seeds extract of *Citrus medica* were tested for anti-oestrogenic action and estrogenic. The rats given the extract (200 and 400 mg/kg) showed increase in uterine weight and cornification of the vaginal epithelial cells. When 30-days-old immature rats were given extract, showed emergence of the vagina and cornification

of vaginal epithelial cells on 5th day, before 10 days earlier than controls. findings may indicate that *Citrus medica* seed petroleum ether extract has strong estrogenic properties and can be employed as an antifertility agent [24].

ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY

Although citron peel ethanol extract, in a dose-dependent manner, reduced the potential DPPH and hydrogen peroxide radical scavenging effect. In the paw oedema test, peel's ethyl acetate extract showed analgesic and anti-inflammatory action against carrageenan-induced inflammation in rats. Ethyl acetate extract (400mg/kg) has potency comparable to diclofenac, reduced paw volume and pain. Therefore, it can used as antioxidant and amend inflammation and pain due to presence of flavonoids and phenolic compounds [4].

HYPOGLYCAEMIC AND ANTICHOLINESTERASE ACTIVITY

In diabetes and alzheimer's disease, Free radicals act as primary factor in their pathogenesis. Using various tests, the monoterpenes (limonene and gamma-terpinene) and sesquiterpenes found in the n-hexane extract of the peel of the diamante citron demonstrated antioxidant activity. According to the study diamante citron can improve Alzheimer's and diabetes [2, 25].

ANTIDIABETIC AND ANTILIPIDAEMIC ACTIVITY

Antidiabetic, antilipidemic, and antioxidant effects of *Citrus medica* peel extract against oxidative stress in Zucker diabetic fatty (ZDF) rats were evaluated. The biological antioxidant potential test (BAP) and the reactive oxygen metabolites-derived compounds (d-ROMs) test were used to assess these activities. At a dose of 600 mg/kg it expressly, triglyceride, cholesterol and lower blood glucose in type -2 diabetic animals due to naringine, apigenin, hesperitin, and quercetin, inhibits Co A (HMG-Co A) reductase improves lipid metabolism in ZDF rats [26].

Inhibition assays for amylase and glucosidase were utilised to evaluate the in vitro hypoglycemic potential of Citrus peel extract. It also inhibited carbohydrate-hydrolyzing enzymes in vitro and stimulated insulin release. Administration of the extract reduced blood glucose concentrations, cholesterol levels, and triglyceride levels. It is concluded that Citron could be exploited as a new source with beneficial characteristics for foods or nutraceutical items [27,28].

ANTITHYROID EFFECT

In the hyperthyroid mice induced by L-thyroxine, level of thyroid stimulating hormone (TSH) and thyroid hormones (T3 & T4) was assessed at a dose of 200mg/kg, for 15 days. In mice treated with L-thyroxine, lowered T3, T4, and TSH blood levels changed, following administration of Citrus medica leaf extract toward normal, demonstrating it can treat thyroid [29].

VARIOUS SPECIES OF *CITRUS*

Citrus medica L.:*Aurantium medicum* (L.) M. Gómez; *Citreum vulgare* Torn. ex Mill.; *Citrus x aurantium subvar*. amilbed Engl.; *Citrus x aurantium subvar*. ckakotra Engl.; Citrus x limon (L.) *Citrus sacrodactulis* Hoola van Nooten; *Citrus tuberosa Mill*; Sarcodactilis helicteroides Gaertn Osbeck; Citrus x limon var. digitata Risso; Citrus x limonia (L.) Osbeck; Citrus x limonum Risso; *Citrus alata* (Tanaka) Tanaka; *Citrus cedra* Link; Citrus cedrata Raf.; *Citrus fragrans Salisb*.; Citrus limon (L.) Osbeck; *Citrus medica* fo. monstrosa Guillaumin; *Citrus medica* subsp. bajoum H. Perrier; *Citrus medica var. alata Tanaka*; *Citrus medica var. digitata Risso*; *Citrus medica* var.

ethrog Engl.; *Citrus medica var. limon* L.; *Citrus medica* var. proper Hook. f.; *Citrus medica var. sarcodactylis* (Hoola van Nooten) Swingle; *Citrus odorata Roussel*; [30]. Othar than *Citrus medica* there are some other species of citrus viz; *Citrus aurantifolia*, *Citrus maxima, Citrus aurantium, Citrus reticulate* [31], Emblica officinalis, Citrus sinesis, Citrus limon which contain Vitamin C [32].

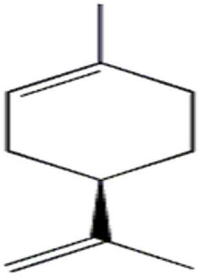
NUTRACEUTICALS APPLICATION OF *CITRUS MEDICA* AND VITAMIN C

Products of citrus possess a number of health benefits. Citrus fruits, which have health-promoting effects, include a variety of essential nutrients, including Vitamin C, folate, dietary fibre, minerals (potassium), and phytochemicals. Citrus's capacity as an antioxidant and synergestic is significantly influenced by its constituent Vitamin C [33]. Fruits juices of citron available those are highly stable at variable temperature [34]. Because of functional properties ascorbic acid and flavonoids, food stuffs rely on the raw material composition as well machine used. In two different lemon varieties these two nutraceuticals in juice were identified. The maximum content of ascorbic acid was found in Fino lemon juice. Different techniques of extract lead impact on separation of several flavanoids [35]. In persian traditional medicine system citron juice obtained by citrus medica boiled with sugar used to improve headache problem. Qarabadin-e-kabir is a most important pharmacopoeia introduced several formulation of *Citrus medica* in which sharbat-e baling is well known, used as a tonic for headache and stomach problems [36].Various marketed preparations of *Citrus medica* are available in the market such as carbonated drinks, jams, jellies, alcoholic beverages, syrup, candied peels, marmalade, tea, squashes, jellies, cordials [28]. A wide variety of marketed drug of Vitamin C obtained from *Citrus medica* and other citrus species are available in market like cream, serum, transdermal patches [37] cecon, celin, ascor, vitron etc [38]. Other formulation of Vitamin C in oral dosage forms effervescent tablet, capsule, chewable, syrup, supplements and injection form are also available [39,40,41,42].

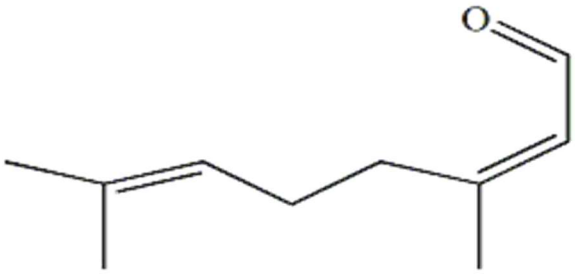
(a) (b)

(c)

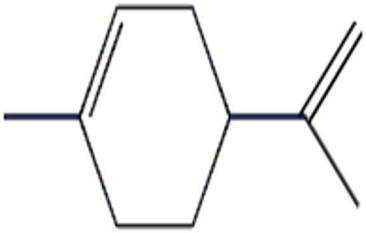
Figure 1: (a) Whole plant of *Citrus medica* L. (b) Riped Fruit of *Citrus medica* (c) Peel of *Citrus medica* fruit



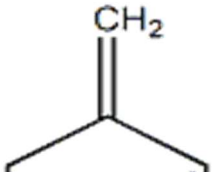
Isolimonine



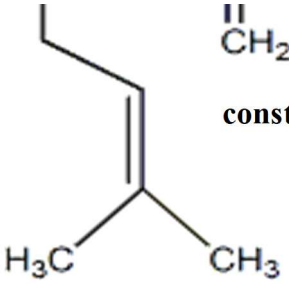
Citral

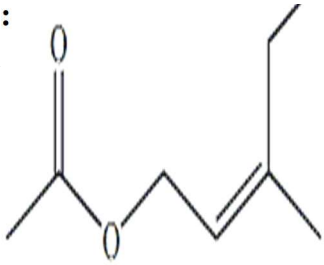


Limonene

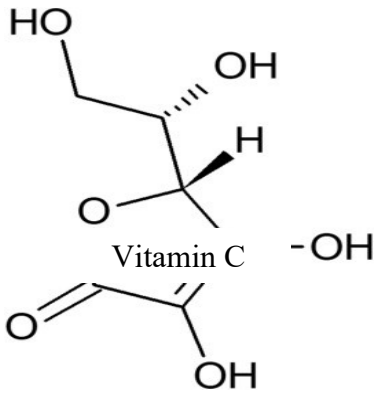


β-myrcene





Neryl acetate



Vitamin C

Figure 2: Main constituent of *Citrus medica*

TABLE 1: DIFFERENT TYPES OF PHYTOCONSTITUENT PRESENT IN *CITRUS MEDICA*

Part used	Phytochemicals								
	Alkaloids	Flavonoids	Tannins	Terpenoids	Steroids	Glycosides	Phenols	Carbohydrates	Mucilage
Fruit	+	+	–	–	–	–	+	+	+
Leaves	+	+	–	–	+	+	–	–	–
Peels	–	+	–	–	+	–	+	+	–

(+) sign indicate presence and (-) indicate absence

TABLE 2: VARIOUS PHARMACOLOGICAL EFFECTS OF *CITRUS MEDICA*

Parts of *Citrus medica*	**Mechanism**	**Reference**
LEAF	Anthelmintic (decreases glucose uptake and exaggerate glycogen synthesis, activation of nicotinic receptors leads to constant depolarization).	[45]
	Estrogenic (increases concentration of mRNA by transcriptional regulation).	[43]
FRUIT	Analgesic (reduced pain and inflammation).	[44]
	Anticancer (by acting as antioxidant and radical scavenging activity).	[23]
	Ulcerprotective (exhibit gastro-protective effect by virtue because of antioxidant property).	[16]
	Antioxidant and free radical scavenging activity (multiple mechanisms but mainly due to presence of phenolic compounds and Vitamin C).	[7]
	Cardiotonic activity (potentiation of myocardium activity and potential diuretic effect).	[22]
	Analgesic and anti-inflammatory (might be due to its antioxidant activity).	[4]
	Hypoglycaemic and anticholinesterase activity (antioxidant and free radical scavenging activity).	[25]
	Anti–implantation (interfer in the preparation of uterus for implantation to occur).	[21]
	Antioxidant, antidiabetic and antilipidaemic activity (decrease DPPH and NO synthase, lower blood glucose level by increasing insulin secreation, inhibit HMG coenzyme reductase enzyme).	[26]
SEED	Estrogenic effect by increasing uterine weight and veginal cornification.	[24]

CONCLUSION

Citrus medica constituted many phytochemicals. It has number of traditional uses and medicinal properties too. Although *Citrus medica* widely used in Ayurvedic/Unani system since many years. *Citrus medica* may give significant synergestic effect in combination with other herbs or drugs.Various research reports that antioxidant effect of *Citrus medica* is due to presence of ascorbic acid. Many marketed formulation of citron and Vitamin C are available in the market which have many health benefits. further clinical study should be conducted to facilitate its therapeutic use in other disease problems.

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CONFLICT OF INTERESTS
There is no conflict of interests related to this manuscript.

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ETHICS STATEMENT
The authors will be responsible for all the technical content mentioned in this manuscript. Journal and publishers will not be responsible for any copyright issues.

ABBREVIATION
MIC- Minimum inhibitory concentration
MIB- Minimum inhibitory bactericidal concentration
T3- Triiodothyronine
T4- Thyroxine
HMG-CoA- Hydroxymethylglutaryl-coenzyme A
DMEM- Dulbecco‘s modified eagle medium

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