

REVIEW ARTICLE

A Review on Phytochemical and Pharmacological Properties of *Citrus medica* Linn

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ABSTRACT

Citrus medica Linn., known as *bijapura* in Ayurvedic literature, is widely used in traditional system of medicine. Many pharmacological studies have been conducted to investigate the properties of *Citrus medica* L. in an attempt to authenticate its use as a multi-purpose medicinal agent. The objective of this paper is to review the literature regarding *Citrus medica* Linn., a commonly used herb in Ayurvedic medicine. Specifically, the literature was reviewed for articles pertaining to chemical properties and therapeutic benefits. This review is in a narrative format and consists of all publications relevant to *Citrus medica* Linn. that were identified by the authors through a google scholar search and books from library of Dravyaguna department of IPGT &RA, regarding Indian medicinal plants. Result shows that *Citrus medica* Linn. possesses analgesic, hypoglycaemic, anticholinesterase, anticancer, antidiabetic, hypocholesterolemic, hypolipidemic, insulin Secretagogue, anthelmintic, antimicrobial antiulcer and estrogenic properties. The mechanisms of action for these properties are not fully understood. Preliminary studies have found various constituents of *Citrus medica* exhibiting a variety of therapeutic effects. These results are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects. Clinical trials using *Citrus medica* for a variety of conditions should also be conducted.

Key words: *Citrus medica*, *bijapura*, phytochemical properties, pharmacological properties.

INTRODUCTION

Citrus medica Linn., commonly known as a Citron in English and *bijapura* in Ayurvedic literature is shrub or small tree. its leaflets are 3-6 inch long, elliptic-ovate or ovate-lanceolate with sort, wingless or nearly wingless petioles; flowers are 5-10 in a raceme, small or middle-sized; petals are generally more or less pink; fruit is globose ovoid or oblong often mamillate at the apex. This plant is found apparently wild in Kumaon, Pachamarhi, Sikkim, Khasia Hills, Garo hills, Chittagong, Upper Yunzalin valley, the Western Ghats and Satpura range in Central India^[1].

Various parts of *bijapura* are widely used in Indian traditional system of medicine. Ripe fruits are potent antiscorbutic, stomachic, cardiac tonic, stimulant, sedative, analgesic and used in dyspepsia, bilious vomiting, cold, fever, palpitation, sore throat, cough, asthma, thirst, hiccough and earache; root is analgesic, antispasmodic and used in diarrhea, piles and constipation; seeds are anthelmintic, stomachic,

sedative, cardiac tonic and useful in palpitation; flowers and buds are astringent and used in blood disorders and peels are anthelmintic^[2-9]. Leaves are useful to induce sleep^[10]. Fruit extracts have also shown good antioxidant activity^[11]. In ancient literature citron was mentioned as an antidote of every kind of poison^[12]. Both the leaves and juice of the citron are used by the people of South-Eastern Nigeria for febrile illness^[13].

Many pharmacological studies have been conducted to investigate the properties of *Citrus medica* L. in an attempt to authenticate its use as a multi-purpose medicinal agent. The purpose of this paper is to review the literature regarding *Citrus medica* L. and report on clinically relevant studies, in an attempt to establish a scientific basis for the therapeutic use of *Citrus medica* L.

This literature review was limited to published articles and books in the English language. Books from library of Dravyaguna department of IPGT

&RA, regarding Indian medicinal plants were reviewed for this work. Published research data of national and international journal available on internet regarding phytochemical and pharmacological properties of *Citrus medica* Linn. were also collected (using google scholar search engine). The following keywords were used for the search: Citrus medica, Citron, Citrus. Results of these searches were reviewed to identify relevant articles.

PHYTOCHEMICAL PROPERTIES

(Table 1) show Phytochemical properties of fruit decoction, peels (rind of fruit) and leaves of *Citrus medica* Linn. fruit decoction have alkaloids, flavonoids, phenols, carbohydrates and mucilage; peels have alkaloids, flavonoids, steroids, phenols and carbohydrates; leaves contain alkaloids, flavonoids, steroids and glycosides [14-16]. The flavonoids reported from the fruits are hesperidin:3,5,6-trihydroxy-4,7-dimethoxy flavone; 3,5,6-trihydroxy-3',4',7-trimethoxy flavones [17,18]. The peel is reported to contain coumarins, limettin, scoparone, scopoletin and umbelliferone, while seeds contain limonin, limonol and nomilinic acid [19,20]. Gurdip *et al.* reported that the major constituents in leaf oil are citronellal, citronellol, limonene, citronellyl acetate, isopulegol, and linalool [21].

Nineteen and forty three constituents have been identified in leaf and peels essential oil respectively. (Table 2 & 3) shows major essential oil of peels and leaf of *Citrus medica* Linn. The leaves and peels oils were a complex mixture of numerous compounds; many of which were present in trace amounts. It is worth mentioning here that there is a great variation in the chemical composition of the leaf and peel essential oil of *Citrus medica*. Erucylamide and isolimonene are the most important and main components in leaf and peel oil of Bangladesh variety but it is totally absent in all other reported oils. So, it indicates that erucylamide and isolimonene are the first reported component in *Citrus medica* leaf and peel oils. *Citrus medica*, growing widely in Bangladesh, may be utilized as a source for the isolation of natural erucylamide and isolimonene respectively [22]. The high concentration of erucylamide and isolimonene in leaf and peel oil make it potentially useful in the medicines because they exhibit fungitoxicity [23].

PHARMACOLOGICAL PROPERTIES

Analgesic activity:

In hot plate method all the three doses (1, 2 and 4ml/kg) of fruit decoction of *Citrus medica* Linn.

were found to be effective. However only two doses (2 and 4ml/kg) of decoction were found to be effective in tail immersion method; the 1ml/kg dose was found to be ineffective in this analgesic model for evaluating centrally acting drugs. The decoction of *C. medica* Linn. in a dose of 4ml/kg inhibited the pain produced by hot plate and tail immersion methods with potency comparable to diclofenac sodium injection. Hence, it can be concluded that this study validates the traditional use of decoction of *C. medica* Linn. as an analgesic. The analgesic activity of *C. medica* Linn. could be due to flavonoids and phenolic compounds as the analgesic effect of these compounds have been well documented [24].

Hypoglycaemic and anticholinesterase activity:

Oxidative damage, caused by the action of free radicals, may initiate and promote the progression of a number of chronic diseases, including diabetes and Alzheimer's disease. The *n*-hexane extract of Diamante citron (*Citrus medica* L. cv. Diamante) peel, which is characterized by the presence of monoterpenes and sesquiterpenes showed significant antioxidant activity that was carried out using different assays (DPPH test, β -carotene bleaching test and bovine brain peroxidation assay). Diamante citron peel extract showed hypoglycaemic activity and an anticholinesterase effect. So, these *in vitro* activities of Diamante citron suggest that it can be used in treatment of diabetes and Alzheimer's disease [25].

Anticancer activity:

Some of the fruits and vegetables are considered as the main anti-cancer foods, because of their abundant antioxidants such as phenols, vitamin C, vitamin E, beta-carotene and lipotene. Citrus is the most interesting one among these fruits. Vital capacity test and Ames test were used to consider anticancer of *Citrus medica* Linn. effect with special emphasises on application of *salmonella typhimurium* to identify antimutagenesis and anticancer level of chemicals. In this research, half-ripe and ripe fruit juice displayed anticancer and antimutagenesis effect and among them half-ripe fruit juice was more effective than ripe fruit juice [26].

Antidiabetic, hypocholesterolemic and hypolipidemic activity:

The petroleum ether extract of *C. medica* Linn. seeds (200 and 400 mg/kg) 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. Though 200 mg/kg/day seed extract for 15 days was not showing any change in HDL level, while 400 mg/kg/day dose significantly increased HDL level in diabetic rats. So it is concluded that *C. medica* Linn. seeds have significant antidiabetic, hypocholesterolemic and hypolipidemic activity^[27].

Citrus medica L. cv Diamante peel extract was also able to reduce plasma glucose concentration and lowered the levels of plasma cholesterol and triglycerides *in vivo* metabolic effects in mice. *Citrus medica* L. could be used as new potential source with functional properties for food or nutraceutical products^[28].

Insulin secretagogue activity:

In vivo the safety, hypoglycemic, and antidiabetic activity of *Citrus medica* L. var. *Sarcodactylis* (Finger citron) in Sprague-Dawley–SPF rats and Wistar DIO rats respectively were performed. By kinetic analysis on the hypoglycemic patterns of the intraperitoneal glucose tolerance and the insulin–glucose tolerance tests, its insulin secretagogue effect was confirmed. In conclusion, Finger citron fruits that concomitantly possess insulin secretagogue and slimming effects would be very beneficial to type 2 diabetes mellitus patients^[29].

Anthelmintic activity:

In-vitro study, petroleum ether extracts of *Citrus medica* L. leaves demonstrate to possess dose dependant anthelmintic activity when compared to Piperazine citrate. *Citrus medica* L. has been confirmed as anthelmintic against the Indian adult earthworms (*Pheretima posthumad*). The possible mechanism of the anthelmintics activity of *Citrus medica* L. cannot be explained. However, it may be due to its effect on inhibition of glucose uptake in the parasites and depletion of its glycogen synthesis. *Citrus medica* L. may also have activated nicotinic cholinergic receptor in the worms resulting in either persistent depolarization or hyperpolarization. There is a need for further studies to identify the active constituent responsible for anthelmintic activity^[30].

Alcoholic extracts of the rind of *Citrus medica* also showed moderate *in-vitro* anthelmintic activity against human *Ascaris lumbricoides*^[31].

Antimicrobial activity:

Plant based antimicrobials have enormous therapeutic potential as they can serve the purpose with lesser side effects that are often associated

with synthetic antimicrobials. Continued further exploration of plant- derived antimicrobials is needed today. *In vitro* antibacterial activity of ethanolic extract of the *Citrus medica* peels was performed by agar cup method. It was found that the extract of peels was effective against *Staphylococcus aureus*, *Proteus vulgaris*, *Klebsiella pneumonia*, *Escheria coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa*. Further research is necessary to determine the identity of the antibacterial compounds from the peels of *Citrus medica* L. and also to determine their full spectrum of efficacy. *Citrus medica* L. peel extract possess a broad spectrum of activity against a panel of bacteria responsible for the most common bacterial diseases. This extract opens the possibility of finding new clinically effective antibacterial compounds^[32].

Antiulcer activity:

Aqueous extract of the fruits of *C. medica* Linn. showed statistically significant decrease in the ulcer scores, % 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 pre-treated 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^[33].

Estrogenic activity:

Oral administration of petroleum ether extract of *Citrus medica* leaves at 400mg/kg b.wt 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^[34]. Estrogenic/anti-oestrogenic activities of petroleum ether extract of *Citrus medica* seeds was also studied in albino rats. Its Result strongly indicates the potent estrogenic nature of petroleum ether extract of *Citrus medica* seeds, which may be used as an antifertility agent^[35].

Table 1: Phytochemical properties of fruit decoction, peels (rind of fruit) and leaves of *Citrus medica* Linn

Phytochemicals	Fruit decoction*	Peels**	Leaves***
Alkaloids	+	+	+
Flavonoids	+	+	+
Tannins	-	-	-
Terpenoids	-	-	-
Steroids	-	+	+
Glycosides	-	-	+
Phenols	+	+	-
Carbohydrates	+	+	-
Mucilage	+	-	-

(+) = Present, (-) = Absent

*Archana Negi *et al* (2010), **Kabra AO *et al* (2012), ***Bairagi G.B. (2011)

Table 2: Major constituents of leaf essential oil from *Citrus medica* Linn

S. No	Name of components	%
1	Erucylamide	28.43
2	Limonene	18.36
3	citral	12.95
4	Mehp	8.96
5	2,6-Octadien-1-ol, 3,7-dimethyl-, acetate, (Z)-	5.23
6	6-Octenal, 3,7-dimethyl-	4.39
7	1,2-Cyclohexanediol, 1-methyl-4-(1-methylethenyl)-	3.98
8	Methoprene	3.51

Bhuiyan M.N. *et al* (2009)

Table 3: Major constituents of peel essential oil from *Citrus medica* L

S.No	Name of constituents	%
1	Isolimonene	39.37
2	citral	23.12
3	Limonene	21.78
4	β -Myrcene	2.70
5	Neryl acetate	2.51
6	Neryl Alcohol	2.25

Bhuiyan M.N. *et al* (2009)

CONCLUSION

As outlined above, results from various studies indicate (**Table 4**) *Citrus medica* leave possesses anthelmintic and estrogenic activities; fruit has analgesic, anticancer, insulin secretagogue and antiulcer activities; peel possesses many qualities including hypoglycaemic, anticholinesterase, hypocholesterolemic, hypolipidemic, antimicrobial and anthelmintic properties; seed has antidiabetic, hypocholesterolemic, hypolipidemic and estrogenic activities. Further clinical studies should be conducted, as well as studies in multiple animal-based models using a variety of suitable biochemical markers to understand its mechanism of action. As for its use in fighting cancer, confirmatory studies in several other animal tumor systems must be conducted for more definitive findings. So far the activities attributed to various parts of *bijapura* like analgesic, anthelmintic, antiulcer mentioned in Ayurvedic claims have been proved through research, but other activities like sedative, antipyretic, antitussive, bronchodilator, stomachic, laxative and cardio-tonic require further scientific validation. It is also important to recognize that *Citrus medica* may be effective not only in

isolation, but may actually have a potentiating effect when given in combination with other herbs or drugs.

Although the results from this review are quite promising for the use of *Citrus medica* L. as a multi-purpose medicinal agent, several limitations currently exist in the current literature. While *Citrus medica* has been used successfully in Ayurvedic medicine for centuries, more clinical trials should be conducted to support its therapeutic use.

Table 4: Reported activity of various parts of *Citrus medica* L

Part used of <i>Citrus medica</i> L.	Reported activity	Researcher
Leaf	Anthelmintic	Bairagi G.B. <i>et al.</i>
	Estrogenic	Taha S. <i>et al.</i>
Fruit	Analgesic	Archana Negi <i>et al.</i>
	Anticancer	Maliheh E. <i>et al.</i>
	Insulin secretagogue	Chiung-Huei Peng <i>et al.</i>
	Antiulcer	B. Nagaraju <i>et al.</i>
Peel	Hypoglycaemic	C. Filomena <i>et al.</i>
	Anticholinesterase	C. Filomena <i>et al.</i>
	Hypocholesterolemic	Federica Menichini <i>et al.</i>
	Hypolipidemic	Federica Menichini <i>et al.</i>
	Antimicrobial	Kabra AO <i>et al.</i>
	Anthelmintic	Raj RK <i>et al.</i>
Seed	Antidiabetic	Archana N. <i>et al.</i>
	Hypocholesterolemic	Archana N. <i>et al.</i>
	Hypolipidemic	Archana N. <i>et al.</i>
	Estrogenic	Sharangouda <i>et al.</i>

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