



A Brief Review on *Citrullus colocynthis*- Bitter Apple

Alka Rani¹, Anju Goyal^{1*} and Sandeep Arora¹

¹Department of Pharmacy, Chitkara University, Rajpura-140104, Punjab, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author AR designed the study, wrote the protocol and wrote the first draft of the review manuscript. Author AG managed the literature searches with author AR. Authors SA and AR managed the process of review article and identified the plant species. All the authors read and approved the final manuscript for publication.

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ABSTRACT

Present review article reveals the importance of species *Citrullus colocynthis*, distributed in India and other parts of the world; this extensive research information on this species is highly significant for future researchers worldwide. In this article morphological and biological activity, inputs have been extensively recorded and discussed. As a part of our investigation on morphological and biological aspects of important medicinal plants from India, the aim of this pioneer attempt is to provide precise, truthful and detailed information of *C. colocynthis*.

Keywords: *Tumba; bitter apple; anticancer activity; antidiabetic; Egusi.*

1. INTRODUCTION

Recently there has been a change in universal thought from allopathy to herbal system, which can be pronounced as 'Go back to Nature'. Traditional plants have been recognized for millennia and are extremely honored all over the

world. Environment has presented our country with an vast prosperity of therapeutic vegetation; for that reason India has habitually been referred to as the Medicinal Garden of the humanity [1]. Ancient civilizations such as South America, China, India, Egypt, etc. are still using numerous plant therapies. In this regard, India has a

*Corresponding author: E-mail: alkagoyalph@gmail.com

exceptional place in the world, where numerous renowned native system of medicines have their own place viz., Ayurveda, Siddha, Unani, Homeopathy, Yoga and Naturopathy are frequently being utilized for the wellbeing of people [2].

Latest discoveries and development in therapeutic and aromatic plants have show the way to the improvement of health care of humanity [3]. A range of medicinal plants like *Panax quinquefolius*, *Salacia reticulata*, *Ocimum sanctum*, *Silybum marianum* and *Trigonella foenum-graecum*, *Aegle marmelos*, *Nigella sativa*, *Allium cepa*, *Ocimum sanctum*, *Gymnema sylvestre*, *Momordica charantia* etc. traditionally used for treating various problems.

Citrullus colocynthis (L.) Schrad is a valuable plants from Cucurbitaceae family, widely distributed in the barren region, is a non-hardy, herbaceous perennial vine, branched from the base [4]. *Citrullus colocynthis* fruits are generally documented for its broad range of pharmaceutical uses as well as medicinal and nutraceuticals potential. It a well recognized plant in the traditional medicine and was used by people in rural areas as a purgative, anti-diabetic, and insecticide [5].

1.1 Botanical Classification

Kingdom : Plantae
Subkingdom : Tracheobionta
Division : Magnoliophyta
Class : Mangnoliopsida
Order : Cucurbitales
Family : Cucurbitaceae
Genus : Citrullus Schrad.
Species : *Citrullus colocynthis* (L.) Schrad.

1.2 Vernacular Names

Bengali : Indrayan, Panjot, Indrabaruni
Hindi : Badi Indrayan, Ghorumba, Indarayan
Kannada : Hamekkae, Haremekkikayi
Malayalam: Kattuvellari
Marathi : Kaduindravani
Sanskrit : Atmaraksha, Brihadvani, Brihatphala
Tamil : Kumatti, Peykomatti
Telgu : Chittipapara
Urdu : Hanzal, Indyaran, Shahmehinzal

1.3 Common Name

Bitter Apple, Colocynth, Bitter Cucumber, Egusi, Vine of Sodom.

1.4 Geographical Distribution

C. colocynthis is widely distributed around the world from Mediterranean Europe, Cyprus, the Syrian Arab Republic, Lebanon, and Jordan to Egypt, Kuwait, Saudi Arabia, Turkey, the Islamic Republic of Iran, Pakistan, Afghanistan, India, North Africa, and Sahel.

2. CULTIVATION

C. colocynthis is a perennial plant (in wild) or an annual herb [6], that can be propagate both by vegetative and generative means. It's growth occurs during the season of summer in India, in between the period of January and October. Colocynth mostly grows in sandy soils.

3. MORPHOLOGICAL DESCRIPTION

An annual herb with lobular tendrils, obliqued branching stems and flocculent tender shoots [7-8].

Leaves: Acutely divided, lobes slender, thick and barren. The slanted leaves are alternately positioned on prolonged petioles. Leaves are almost 5- 10 cms in length and have approximately 3- 7 lobes.

Flowers: Mendacious, blonde, males and females both separate, corolla beige. The yellow-colored flowers emerge individually at leaf axioms.

Fruits: Bulbous or ovoid, corpulent, indehiscent berry, 5-7.5 cm in width and assorted with green and white. Each egusi harvest around 15- 30 globoid fruit having a diameter of almost 7- 10 cms. The outmost segment of the fruit is enclosed with a emerald coat having yellow bands.

Seeds: Around 6 mm in size, shaven, consolidate and compressed oblong-shaped. They are situated on the parietal placenta.

Root: large perpetual, long and delicate, bifurcate, tenacious and rocky vine-like. Stems: spread on the soil and have an affinity to mount over herbs and shrubs by their axillary branching tendrils.

4. ETHNOPHARMACOLOGICAL USES

Citrullus colocynthis is used generally in the cure of various diseases such as leprosy, diabetes,

constipation, asthma, bronchitis, jaundice, joint pain, cancer and mastitis [9-11]. The medicinal uses of this plant have been reported in the indigenous system of medicines of various countries, that include gut disorders include indigestion, colic, gastroenteritis and dysentery. In the equatorial and subequatorial countries, plant is used to cure diabetes traditionally [12-15]. In Morocco, it is also used to treat hypertension [16-17]. In India, Bangladesh, Nepal and Pakistan, the fruits are used for bacterial infections, intestinal disorders, diabetes and cancer [18-19]. In the UAE, it is one of the trendiest inhabitant medicines due to its anti-inflammatory action [20-21]. In Mediterranean countries, fruits and seeds of the plant, are potentially used to cure UTIs [22], as well as other diseases like, rheumatism, hypertension, pulmonary, dermatological problems and gynecological infections [22]. In Saudi Arabia and Israel, fruits are used as a anthelmintic, antirheumatic, purgative, carminative and laxative [23].

5. CHEMICAL CONSTITUENTS

Various bioactive compounds of fruit have been documented in the literature. They are arranged as alkaloids, flavonoids, carbohydrates,

glycosides, fatty acids and essential oils [24]. Cucurbitacins have been documented as the major constituent of *Citrullus colocynthis* fruits.

5.1 Cucurbitacins

These are a group of bitter tasting and extremely oxygenated, chiefly tetracyclic and triterpenic plant materials derived from the cucurbitane moiety. These are not expressed as steroidal due to the relocation of methyl group from C-10 to C-9 (Fig. A & B). The cucurbitacins are primarily belongs to the Cucurbitaceae family [24-25].

5.2 Glycosides, Polyphenols and Flavonoids

Two cucurbitacin glucosides i.e., 2-O- β -D-glucopyranosylcucurbitacin I and 2-O- β -D-glucopyranosylcucurbitacin L and three flavonoid glycosides i.e., isosaponarin (Fig. C), isovitexin (Fig. D) and isoorientin 30 -O-methyl ether (Fig. E) were extricated from *Citrullus colocynthis* fruits [26]. Polyphenols are a set of natural compounds that act as free-radical terminators and shows antioxidant activity. Flavonoids are the secondary metabolites that show antioxidant and radical-scavenging activities [27].

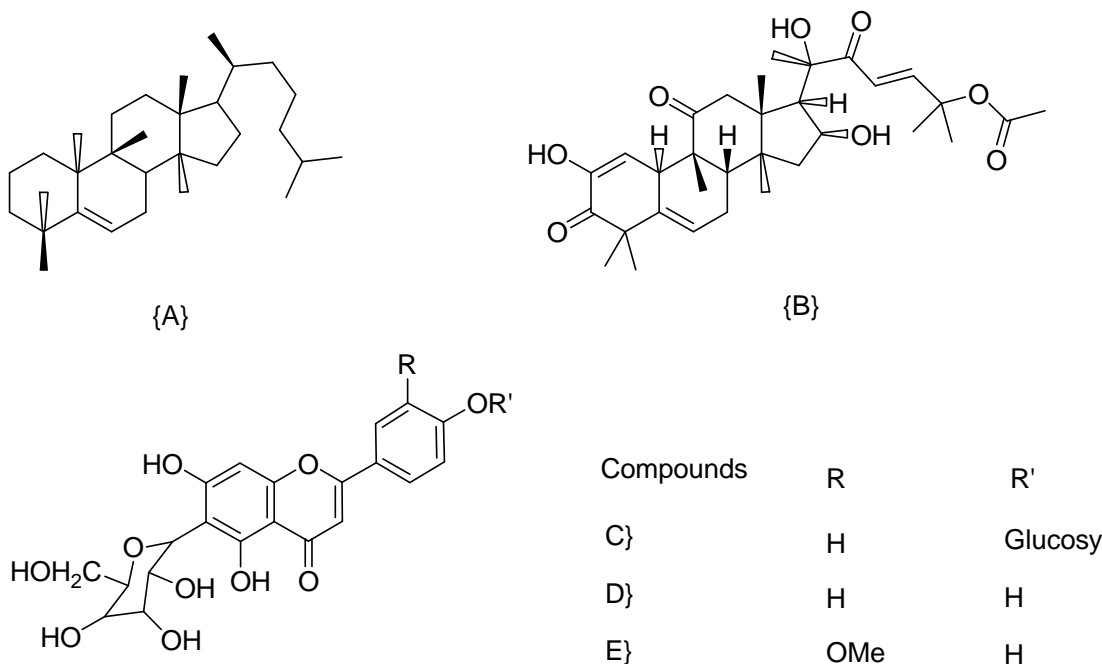


Fig. 1. Chemical constituents present in *Citrullus colocynthis*

6. PHARMACOLOGICAL AND BIOLOGICAL ACTIVITIES

6.1 Anticancer Activity

The cucurbitacin glycoside from *Citrullus colocynthis* leaves was examined for anticancerous effect in human breast cancer cell proliferation. The glycoside in the combination of 1:1 inhibited multiplication of ER- MDA-MB- 231 and ER+ MCF-7 human breast cancer cell lines. The cell-cycle study showed that therapy with screened cucurbitacin glycoside combination emerged in growth of cells at the G2/M stage of the cycle. Evaluated cells showed an accelerated decline in the production of the protein complex necessary to the management of G2 exit and beginning of mitosis, specifically the p34CDC2/cyclin B1 complex. This showed that cucurbitacin glycosides show signs of pleiotropic effects on cells, provoking both cell cycle arrest and apoptosis, it means cucurbitacin glycosides might have beneficial significance against cancer cells [28]. Anti-cancer effect of alkaloid rich extract of *Citrullus colocynthis* fruits was explored. The cytotoxic effect were evaluated on MCF-7 cells showed significant reduction in cell activity in dose dependant approach (LC50=17.2 µg/mL) at very small concentrations at 5, 10 and 20 µg/mL [29]. The cytotoxic effect of the crude extract of *Citrullus Colocynthis* and TiO₂ nanoparticles (NPs) was examined individually on cancer lines and recombinant mouse epithelial cell line on the surface of cells in comparison of the combination of both. The results revealed that the plant extract and the nanoparticles alone showed significant reduction in the growth of cell line instead of their combination, the combination exhibited antagonistic effect [8]. The cytotoxic study of four plants *Aristolochia longa* (L), *Citrullus colocynthis* (L), *Piper cubeba* (L) and *Delphinium Staphisagria* (L) was examined on five different cancer cell lines MCF7, HT29, N2A, H5-6 and VCREMS with 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay at a dose of 500 µg/ml. *P. cubeba* (L) concentrate showed the prohibition of 98.64 and 91.59% and *C. colocynthis* (L), 91.84 and 85.58% against MCF7 lines and HT29 cell lines, respectively. *C. colocynthis* (L) exhibited a dose-dependent effect on the respective cell lines with an IC₅₀ of 22.0 and 32.5 µg/ml [30].

6.2 Antimicrobial Activity

The Silver Nanoparticles (SNPs) using aqueous extracts (AEs) of *Citrullus colocynthis* were

investigated against different bacterial species; *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*; antifungal activity against *Geotricum candidum*, *Aspergillus fumigatus*, *Candida albicans* and *Trichophyton mentagrophytes*, with inhibition zones ranging from 15.1 ± 0.44 to 25.2 ± 0.37 mm respectively. The results showed that SNPs/ *C. colocynthis* roots AEs had strongest antimicrobial activity causing 70%, 73% and 75% reduction of the Cytopathic effect (CPE) [31]. The antibacterial potentialities of crude ethanolic extracts *Citrullus colocynthis* were examined for against Gram positive and Gram-negative bacilli. Ethanolic extracts of fruits, leaves, stems and roots were established active results against Gram-positive bacilli, viz., *Bacillus pumilus* and *Staphylococcus aureus*, whereas fruit and root extracts in higher potency gave positive results against Gram-positive bacillus (*Bacillus subtilis*). Some Gram-negative bacilli viz., *Escherichia coli* and *Pseudomonas aeruginosa* showed no reaction. The research concluded that active response against the various strains of bacteria may be because of flavonoid, carbohydrates, tannin and glycosides that are reported [32]. *In vitro* antibacterial and anticandidal activity of aqueous and diluted acetone extracts of *Citrullus colocynthis* Schrad had been examined against Gram-negative and Gram-positive bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis*)—and various *Candida* spp. (*Candida glabrata*, *Candida albicans*, *Candida parapsilosis* and *Candida kreusei*). MIC and MBC/MFC were determined for plant organs at different maturation stages. The results showed the highest MICs and MBCs/MFCs from the fruit aqueous extracts (MIC 0.10 mg/ml against *Candida albicans* and *Candida glabrata*, 0.20 mg/ml against *Escherichia coli* and *Pseudomonas aeruginosa*) and the lowest activity from the root extracts [33].

6.3 Antioxidant Activity

Extracts Isolated from the fruits of *Citrullus colocynthis* such as Flavonoids, isovitexin, isosaponarin and isoorientin 3'-O-methyl ether revealed as significant antioxidants [34]. The antioxidant and free radical scavenging ability of the methanolic extract of the fruit of *Citrullus colocynthis* was evaluated. The highest ability would be found at the concentration of 2500 mg/ml [35]. Various seed extracts of *Citrullus*

colocynthis such as a defatted aqueous extract (E2), a crude aqueous extract (E1), an ethyl acetate extract (EA), a hydromethanolic extract (HM) and a *n*-butanol extract (*n*-B) were examined in a 1,1-diphenyl-2-picrylhydrazyl assay at a concentration of 2000 µg/ml. The decreasing percentage of 88.8% with EA, 74.5% with HM and 66.2% with E1 were noted, with a parallel IC₅₀ of 350, 580 and 500 µg/ml subsequently as correlated to 1.1 µg/ml for ascorbic acid [36]. The methanolic seed extract of *Citrullus colocynthis* was studied for the antioxidant activity spectrophotometrically by using 1, 1-diphenyl-2-picryl hydrazyl and H₂O₂ free radical scavenging method. The extract exhibited highest percentage inhibition of 79.4 and 72.4% by 1, 1-diphenyl-2-picryl hydrazyl and H₂O₂ method subsequently at 300 µg /ml [16]. Methanolic extract of *Citrullus colocynthis* fruits (MECC) inhibited highest percentage of DPPH radicals and nitric oxide radical scavenging model in *In vitro* antioxidant studies, i.e., 62% and 56% at 800 µg/ml, extract showed the dose dependent antioxidant activity in comparison of ascorbic acid [37].

6.4 Antidiabetic Activity

Citrullus colocynthis was used to possess antidiabetic effect in rats at the rate of 50 mg/kg and 100mg/kg for 28 days. Haematological and Biochemical estimations were executed at the end of experiment i.e. on 29th day by means of standard kits. The results showed that *Citrullus colocynthis* could be used for safe an antidiabetic remedy [38]. The petroleum ether extract of *Citrullus colocynthis* fruits was used for the study on lowering the blood glucose levels and thiobarbituric acid reactive substances (TBARS) in Streptozotocin induced Diabetic albino rats. The extract showed a significant decrease in blood glucose level in diabetic rats as well as it significantly reduces TBARS levels when compared to Glibenclamide (0.5 mg/kg) [39]. A significant decrease in HbA1c and fasting blood glucose levels was found in the patients of type II diabetes when they were treated with *Citrullus colocynthis* (L.) Schrad fruit for 2 months. LDL, HDL, triglyceride, fasting blood glucose, HbA1c, total cholesterol, alkaline phosphatase, alanine transaminase, aspartate transaminase, urea and creatinine levels were checked at regular interval of time [40].

The crude aqueous, ethyl acetate, defatted aqueous, H₂O-methanol, *n*-butanol extract and H₂O-methanol extracts of the seeds of *Citrullus*

colocynthis had been examined in glucose-stimulated insulin discharge from pancreatic islets of rats. Out of these, various extracts exhibited a positive insulinotropic response as compared to 8.3 mM D-glucose [41]. Haematological and biochemical estimations were done on rats treated with *Citrullus colocynthis* at the dose of 50 and 100 mg/kg for 28 days and the results showed that the plant is safe as an antidiabetic remedy [38]. The biochemical parameters of normal and alloxan-induced diabetes using root of *Citrullus colocynthis* was evaluated in rats. Aqueous extract exhibited significant decrease in blood sugar level (58.70%) in comparison of chloroform (34.72%) and ethanol extracts (36.60%) ($p < 0.01$) [42]. The liver hexokinase and gluconeogenic enzymes such as glucose-6-phosphatase and fructose 1, 6-bisphosphatase of control and alloxan-diabetic rats was treated with the leaf suspension of *Citrullus colocynthis*. The study revealed in momentous decrease in blood glucose level (from 381±34 to 105±35 mg/dl), a reduction in the activities of glucose-6 phosphatase, glycosylated hemoglobin and fructose 1, 6-bisphosphatase, and a raise in the action of liver hexokinase. The research concluded another support to the antidiabetic effect exhibited by *Citrullus colocynthis* [43].

6.5 Antiinflammatory and Analgesic Effects

In vivo analgesic and anti-inflammatory activities of *Citrullus colocynthis* extracts were assessed. The carrageenan- induced paw edema assay in rats and the acetic acid writhing test in mice were used for valuation. All extracts displayed analgesic and anti-inflammatory activities at the dose of 0.5- 1 mg/kg and 0.05- 1 mg/kg with no side effects [44]. Carrageenan, serotonin and prostaglandin E1-induced paw edema assays were significantly inhibited by methanol extract of *Citrullus colocynthis*. Prostaglandin E1-induced paw edema showed excellent results. In carrageenan air-pouch model decreased the amount of exudates and relocation of monocytes and neutrophils [45]. Pro-inflammatory cytokine COX-2, INOS, IL-1β, TNF-α and NO, PGE2 on Inflammatory cells, similar osteoarthritis in chondrocyte cells and monocytes/macrophages were treated with the ethanol extract of *Colocynth* root. The three groups of normal and inflamed cells were treated with ethanol extract at a dose of 20 ng/ml LPS20, that showed the plant could reduce the pharsing of TNF-α in THP-1 monocytes / macrophages and

inflammatory cytokine, production of NO, PGE2 and pro-inflammatory cytokine COX-2, TNF- α , INOS in Chondrocyte cells [46]. The aqueous extract of different parts of *Citrullus colocynthis* had been used for the screening of analgesic and anti-inflammatory activities by using the acetic acid writhing test in mice and the carrageenan-induced paw edema assay in rats. The study evaluated that the plant parts induced analgesic and anti-inflammatory activities without assigning any of the side effects [47]. The study showed that *Citrullus colocynthis* (CCT) healed the obesity-related diabetes trouble by inhibiting inflammatory cytokines secreted in obesity. Food absorption and body weight were reported for 6 weeks and interpretation of TNF- α , IL-6 and IL-10 in serum were estimated by ELISA technique after every 14 days in mice. Extract decreased body weight by 4.02% (ns- $p > 0.05$) and food absorption by 3.52% (ns- $p > 0.05$), but effectively reduced the interpretation of TNF- α 44.83 (** $p < 0.001$), IL-6 30.23 (** $p < 0.001$) and lightly increased IL-10 5.31 (ns- $p > 0.05$). This study revealed that CCT extract could have an anti-inflammatory effect through down regulation of obesity-associated pro-inflammatory cytokines [48].

6.6 Effect on Hair Growth

Extracts of *Citrullus colocynthis* were tested for the treatment of alopecia in comparison of minoxidil in rats. The extracts of plant integrated into oily ointment base and 2% minoxidil, both were applied topically on shaved disrobed skin. The time period requisite for initiation of growth as well as completion of cycle was recorded. The treatment showed positive results as it brings a greater number of follicles (>70%) to anagenic stage than minoxidil (67%) [48].

6.7 Side Effect and Toxicity

The study for toxicity of fruit pulp extract of *Citrullus colocynthis* was performed. Gross phenomenal conclusion found on the 20th day of conception exposed that a high fraction of resorbed embryo, smaller in size and weight as well as lack of coccygeal vertebral column and bones. It could be concluded that the teratogenic effects may be caused by extract of fruit pulp of *Citrullus colocynthis* if given at the initial period of pregnancy [49]. A study had been performed on the rabbits to measure the toxic effect of seed extract and pulp extract of *Citrullus colocynthis*, all of them were served with 100-200 mg/kg/day of either pulp or seed extract. After one month,

no animals treated with 200 mg/kg/day of pulp extract sustained. Animals treated with less dose of pulp extract showed rigorous abrasions in the liver, small intestine, and kidney. However, animals treated with seed extract showed only minor intestinal effects. It could be concluded that in compare to seed extract, pulp extract of *plant material* can be lethal [50].

7. CONCLUSION

The paper reviewed *Citrullus colocynthis* as a great promise for development of novel drug with the wide range of pharmacological activities, which could be utilized for dreadful human disease, because of its effectiveness and safety.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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