

Review Article

Therapeutic Potential of Citrullus Colocynthis in Diabetes and Its Complications

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Abstract

Plants are generally viewed by humans as a source of food and medicine. Citrullus Colocynthis is an ornamental European plant. It belongs to the family Cucurbitaceae and is also called bitter apple and bitter cucumber. This plant is distributed in India and other parts of the world; this extensive research in formation on this species is highly significant for future researchers worldwide. Morphological and biological activity, inputs have been extensively recorded and discussed in this article. Citrullus colocynthis was found to have antidiabetic, hypolipidemic, antineoplastic, antioxidant, anti-inflammatory, profibrinolytic, analgesic, antiallergic, antimicrobial, pesticidal and immunostimulant activity. It also has an effect on the reproductive system and fertility. This review suggests that Citrullus colocynthis has a broad spectrum of pharmacological activity, in which antidiabetic activity is prominent.

Keywords: antioxidant, anti-inflammatory, profibrinolytic, analgesic

Introduction

Plants are recognized as the most important resource for medicine and human food [1] and plant-derived biological compounds have fewer side effects than chemical drugs [2]. Citrullus colocynthis belongs to the family Squash or Cucurbitaceae, some of the local titles assigned to this plant include coloquinte (French), bitter gourd, bitter gourd apple, bitter gourd (English) and Koloquinthe (German) [4]. Its alternate names indicate the bitterness of the plant. Colocynthis as an important ingredient causes the bitter taste of this plant [5]. Citrullus colocynthis is known in traditional medicine as a medicinal plant and is used alone or for medicinal purposes. Medicines are used in the root, leaf, pulp and seeds of the plant. Fruit pulp is most commonly used in this regard. Citrullus colocynthis grows in Africa and Asia, including the southeastern, eastern, southwestern, and central regions of Iran. [6] Was made for Citrullus colocynthis activities. Citrullus colocynthis fruit is commonly documented for its wide range of pharmaceutical uses, as well as medicinal and nutraceutical potential. It is a well-known plant in traditional medicine and was used by people in rural areas as a disinfectant, anti-diabetic and pesticide.

BOTANICAL CLASSIFICATION

Kingdom: Plantae

Subkingdom: Tracheobionta

Division: Magnoliophyta
Class: Mangnoliopsida
Order: Cucurbitales
Family: Cucurbitaceae
Genus: Citrullus Schrad.
Species: Citrullus colocynthis (L.) Schrad.

COMMON NAME

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

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.

CULTIVATION

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



Figure 1 *Citrullus colocynthis* plant with leaves and fruits in the desert region.

MORPHOLOGICAL DESCRIPTION

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

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 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.

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 [8-10]. 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 [11]. In Morocco, it is also used to treat hypertension [12-13]. In India, Bangladesh, Nepal and Pakistan, the fruits are used for bacterial infections, intestinal disorders, diabetes and cancer [14]. In the UAE, it is one of the trendiest inhabitant medicines due to its anti-inflammatory action [15]. In Mediterranean countries, fruits and seeds of the plant, are potently used to cure UTIs [16], as well as other diseases like, rheumatism, hypertension, pulmonary, dermatological problems and gynecological infections [22]. In Saudi Arabia and Israel, fruits are used as an anthelmintic, antirheumatic, purgative, carminative and laxative [17].

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 [18]. Cucurbitacins have been documented as the major constituent of *Citrullus colocynthis* fruits.

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. The cucurbitacins are primarily belongs to the Cucurbitaceae family [19-20].

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, isovitexin and isoorientin 30 -O-methyl ether were extricated from *Citrullus colocynthis* fruits. 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 [21].

PHARMACOLOGICAL ACTIVITY

1. Antidiabetic

The effect of *Citrullus colocynthis* hydraulic extract on rats, which had diabetes induced by streptozocin and normoglycemic rats was evaluated in a research, the results showed the alleviated blood glucose level of diabetic rats using a specific dose of the extract. However, the extract had no significant impact on blood glucose level in normoglycemic rats [22].The

literature review revealed that 50 patients with type 2 diabetes were evaluated for two months in a clinical trial. In this research, two groups of intervention (n=25) and control (n=25) received 100 mg capsules of *C. colocynthis* extract and placebo three times daily, respectively. According to the results, a significant reduction was observed in the level of fasting blood sugar and HbA1c of the subjects in the intervention group. In a research, 44 female and male patients with type two diabetes were selected and randomly assigned to two groups (22 cases per group) in order to assess the impact of *Citrullus colocynthis* reaction intermediates of oxidative stress. In addition to standard treatment of the ward, 100 mg capsule of *Citrullus colocynthis* and placebo was administered as three daily doses to the subjects of the intervention and control groups, respectively. According to the results, a significant reduction was observed in the fasting blood sugar level and HbA1c in patients administered with *Citrullus colocynthis* [23]. It may be able to directly decrease HbA1c. In another research conducted on rats, results revealed the ability of the components of *Citrullus colocynthis* L. Seeds (i.e., n-butanol and crude aqueous extracts) to treat samples with type 1 and 2 diabetes. Depending on time and dosage, hyperglycemia and weight of animals can be improved and stabilized by the aqueous extract of *Citrullus colocynthis*, respectively. The results also demonstrated that the main cause of this reduction could be attributed to the impact on intra-islet and beta cells vessel [24]. The therapeutic effect of fruit extracts of *Citrullus colocynthis* in diabetic neuropathy has been recently confirmed in a research. Moreover, patients with diabetes experienced a significant decrease in their blood sugar level due to the application of the capsule of *Citrullus colocynthis* within an interval of 30 days [25].

2. Hypolipidemic

In an experiment performed on 40 rats, there was a significant decrease in triglyceride, cholesterol and blood sugar range of the samples using various doses of the powder of *Citrullus colocynthis* [26]. In a research conducted on nondiabetic dislipidemic patients with hyperlipidemia, there was a significant reduction in the cholesterol and triglyceride levels of the subjects due to the consumption of powder of *Citrullus colocynthis* seeds on a daily basis [27]. Use of the extract of *Citrullus colocynthis* in another research led to decreased levels of triglyceride and serum phospholipids in rabbits. Similarly to the modifications in serum lipids, changes were observed in the profiles of tissue lipids found in the muscle of heart and liver. According to the literature, there are active hypolipidemic elements in *Citrullus colocynthis*. In a similar study, the extract of *C. colocynthis* pulp with seeds reduced the serum lipids levels in diabetic rats [28].

3. Antineoplastic

In a research on mice, activities against mice-bearing tumor of Ehrlich's ascites carcinoma (EAC) and Hepatoma Cell Line (HepG2) were detected in Cucurbitacin I glucoside (Cu I, 2) and Cucurbitacin E glucoside (Cu E, 1), which were extracted from *Citrullus colocynthis*. In addition, results were indicative of prolonged lifespan and survival duration because of these elements, which were also able to fix the biochemical parameters of mice infected with EAC at a normal range. Also, Cucurbitacin E had the cytotoxic activity against certain types of refractory tumors [29]. Literature review demonstrated the cytotoxicity effect of the *Citrullus colocynthis* extract on colorectal cancer, and Hep2 cell line, which depended on the dose of the compound. Human Caucasian larynx carcinoma cell line (Hep2) was applied in a research to assess the anti-tumoral impacts of *Citrullus colocynthis* extract in vitro [30].

4. Antioxidant

In a study, researchers monitored the *C. colocynthis* methanolic extract to assess the free-radical-scavenging ability of this compound. At a 2500 mg/ml concentration, *Citrullus*

colocynthis extract showed the maximum free-radical-scavenging and antioxidant abilities [31]. After phytochemical evaluation of extracts of *Citrullus colocynthis* seeds, it was concluded that the antioxidant activity of this plant is due to containing flavonoids, which is a chemical element. Moreover, there were considerable antioxidant and hepatoprotective activities of *Citrullus colocynthis* extract in rats [32]. Furthermore, antioxidant activities were detected in some *Citrullus colocynthis* extract [33].

5. Antiallergic, Anti-inflammatory and Analgesic

Citrullus colocynthis extracts showed anti-inflammatory and analgesic activities at various dosages. Subject findings were received with unripe fruits. According to this research, there is a potential in *Citrullus colocynthis* to be properly used for rheumatoid arthritis. In addition, the traditional therapeutic applications of the compound due to anti-inflammatory and analgesic ingredients, have been confirmed [34]. Inflammatory diseases and oxidative liver damage were treated with the extracts of cucurbitacin E glucoside. In Iran, 60 patients were evaluated in a research, and the results demonstrated the reduced level of pain in individuals with painful diabetic polyneuropathy due to the use of *Citrullus colocynthis* topical formulation [35]. In addition, the essential cucurbitane-type triterpene glycoside and cucurbitacin E exhibited an antiallergic ability in a research [36].

6. Fertility

In a research, the possible impact of *Citrullus colocynthis* on significant enhancement of histological and hormonal symptoms of polycystic ovarian syndrome (PCOS) was demonstrated. In a study conducted on rats, which were diabetes due to streptozotocin induction, the pulp extract of *Citrullus colocynthis* had positive impacts on antioxidants and oxidants alternations in the reproductive system of samples [37]. It can be used to treat PCOS. Nevertheless, exposing female rats to this compound for a long duration could be associated with negative impacts on fertility and the reproductive system.

7. Antimicrobial

Activities were observed by the elements extracted from *Citrullus colocynthis* against drug resistant and drug sensitive Koch's bacillus and two MOTT (mycobacteria other than tuberculosis) clinical isolates [38]. In addition to anticandidal and antibacterial characteristics of the extract of *Citrullus colocynthis*, aqueous extracts reacted against *Pseudomonas aeruginosa*, *Candida albicans*, *Escherichia coli* and *Candida glabrata* [39]. Moreover, pharmaceutical and food supplemental agents, which are eco-friendly, can be developed by applying *Citrullus colocynthis* extract.

8. Larvicidal and Pesticidal

Along with its structural analogues, 4-methylquinoline extracted from *C. colocynthis* can be used to deal with stored grain weevils and spider mites as a natural pesticide. Furthermore, the ingredients separated from *C. Colocynthis* had the great larvicidal activities [40].

9. Other Activities

The significant anticonvulsant impact of *Citrullus colocynthis* extract on mice, which had seizures induced by pentylene tetrazole, was confirmed in a research. It should be noted that these impacts might be due to the influence of the compound on opioid and γ -aminobutyric acid-ergic system. Moreover, there is a profibrinolytic and antiplatelet activity in *C. colocynthis* hydro-alcoholic extract. [41] In addition, *C. colocynthis* petroleum extract was beneficial to the management of alopecia induced by androgen [42]. In addition to its potential

use as a supplement for protecting patients experiencing chemotherapy, the extract of *C. Colocynthis* has implied an antigenotoxic activity in mice with oxidative DNA damage induced by cyclophosphamide. According to the results, there was a higher immunostimulant activity of *C. colocynthis* seed extract. Although, there was a higher toxicity in the pulp extract [43].

Conclusion

In the present review, *Citrullus colocynthis* shows a promising antidiabetic, hypolipidemic, antineoplastic, antioxidant, antiinflammatory, profibrinolytic, analgesic, antiallergic, antimicrobial, pesticidal and immunostimulant activity, but antidiabetic activity is prominent. Also, it can effect on the reproductive system and fertility. It seems more research is needed to evaluate the mechanism of this action.

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