



A Review on Pharmacological Activities of *Citrullus colocynthis* (L.) Schrad

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

Editor(s):

(1) Dr. Eze Ejike Daniel, Kampala International University, Uganda.

Reviewers:

(1) Busari Musa Bola, Federal University of Technology, Nigeria.

(2) Alka Rani Goyal, Chitkara University, India.

(3) Ritika Gupta, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/57333>

Mini-review Article

Received 08 April 2020

Accepted 13 June 2020

Published 25 June 2020

ABSTRACT

Plants are seen generally as resources for food and medicines by humans. *Citrullus colocynthis* is a decorative European plant. It belongs to the Cucurbitaceae family and is also called bitter apple and bitter cucumber. This plant is mostly found in Africa, Asia and many regions of Iran. 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. It seems that more research is needed to evaluate these findings.

Keywords: *Citrullus colocynthis*; pharmacology; bitter apple; antidiabetic; herbal medicine.

ABBREVIATIONS

C. colocynthis, *Citrullus colocynthis*; HbA1c, Hemoglobin A1c; EAC, Ehrlich's ascites carcinoma; PCOS, polycystic ovarian syndrome; MOTT, Mycobacterium other than tuberculosis; DNA, Deoxyribonucleic acid; FBS, Fasting blood sugar.

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1. INTRODUCTION

In general, plants are recognized as the most vital resources for medicine and food of human beings [1] and Biological compounds originating from plants have less side effects than chemical drugs [2,3]. *Citrullus colocynthis* belongs to the squash or Cucurbitaceae family, Some of the local titles allocated to this plant include coloquinte (French), bitter gourd, bitter apple, bitter cucumber (English) and Koloquinthe (German) [4]. Its alternative names indicate the bitterness of this plant. Colocynthine as a main 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 in combination for medicinal purposes. The root, leaf, pulp and seed of the plant have medicinal applications. In this regard, the pulp of the fruit has the most use. *Citrullus colocynthis* grows in Africa and Asia, including the southeast, east, southwest and central area of Iran [6].

Due to the importance of nutritional and therapeutic properties of *Citrullus colocynthis*, this study was conducted to review new findings related to the pharmacological activities of *Citrullus colocynthis*.

1.1 Botanical Properties

Citrullus colocynthis is from the Cucurbitaceae family. Its family has a wide genetic diversity [7]. It grows well in desert regions, especially in alkaline soils, and shows high resistance to water stress and salinity [5]. Similar to watermelon, *Citrullus colocynthis* is a perennial plant with leafy and stiff-haired stems. In addition, the plant has alternate leaves (distributed, variously indented, pubescent, triangular and obtuse) on its lengthy petioles [8]. While the upper surface of the plant is delicate green, its lower surface is pale and uneven. Moreover, its yellow flowers individually grow on the leaf axils [9]. The fruit of this plant is smooth, extremely bitter, yellow and dry and has the size of an apple. After ripening, the plant's fruit has the coriaceous peel filled with a white spongy flesh containing several white or brownish ovate seeds. Oily, shiny and compressed without an edge, seeds of the fruit have the length and width of 0.75 and 0.5 cm, respectively [10].

1.2 Chemical Components

Determination of the quantitative elements in plants is essential for the suitable evaluation of

their effects on humans [11]. In *Citrullus colocynthis* (L.), the chemical ingredients are mostly contain glycosides, which can produce dihydroelatericin B (cucurbitacin L), elatericin B (cucurbitacin I) and elaterin (cucurbitacin E) through enzymatic hydrolysis [12]. In addition, these compounds encompass Caffeic acid derivatives, chlorogenic acid and cucurbitacin E-, J-, L-glucosides [10]. Another compound extracted from *Citrullus colocynthis* is quercetin [13]. Also, the presence of phenolic acids, flavonoids, fatty acids, tocopherols, and alkaloids in the *Citrullus colocynthis* was identified [7].

1.3 Therapeutic Features

With its bitterness, laxative, cooling, antipyretic, and anthelmintic properties, the fruit of this plant could treat ascites, ulcers, urinary discharges, joint pain, asthma, throat diseases, constipation, tuberculosis glands of the neck, bronchitis, anemia, tumors, enlargement of spleen, elephantiasis, jaundice, and dyspepsia. It is also used as a traditional treatment for diabetes [7, 14,15].

2. PHARMACOLOGICAL ACTIVITY

2.1 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 [16].

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 [17].

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* on 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* [18]. It may be able to directly decrease HbA1c [19].

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 [20].

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 [21].

The therapeutic effect of fruit extracts of *Citrullus colocynthis* in diabetic neuropathy has been recently confirmed in a research [22]. 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 [23].

2.2 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* [24].

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 [25].

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* [26]. In a similar study, the extract of

C. colocynthis pulp with seeds reduced the serum lipids levels in diabetic rats [27].

2.3 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 [28]. 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 [5], 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].

2.4 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 [32]. Moreover, there were considerable antioxidant and hepatoprotective activities of *Citrullus colocynthis* extract in rats [33,34]. Furthermore, antioxidant activities were detected in some *Citrullus colocynthis* extract [35,36].

2.5 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

Table 1. Summary of Pharmacological activities of *Citrullus colocynthis*

Part of the plant /extracts	Pharmacological activity	Results	References
hydro-alcoholic extract	antiplatelet	there is a profibrinolytic and antiplatelet activity	(Alhawiti, 2017)
Fruit extract	anticonvulsant	the influence of the compound on opioid and γ -aminobutyric acid-ergicsystem	(Mehrzadi, Shojaii et al., 2016)
Fruit powder	Hypolipidemic	significant decrease in triglyceride, cholesterol and blood sugar level	(Mahmoodi, Sayyadi et al., 2012)
Seed powder		significant reduction in the triglyceride and cholesterol concentration in non-diabetic hyperlipidemic patients	(Rahbar and Nabipour, 2010)
Aqueous ethanol extract		decreased levels of triglyceride and serum phospholipids in rabbits	(Daradka, Almasad et al., 2007)
extract of pulp with seeds	Antineoplastic	reduced the serum lipids levels in diabetic rats	(Ghauri, Ahmad et al., 2020)
Cucurbitacin I and Cucurbitacin E		prolonged lifespan and survival duration because of these elements	(Ayyad, Abdel-Lateff et al., 2012)
Cucurbitacin E		cytotoxic activity against certain types of refractory tumors	(Saeed, Boulos et al., 2019)
Fruit extract		cytotoxicity effect of the <i>Citrullus colocynthis</i> extract on colorectal cancer	(Abdulridha, Al-Marzoqi et al. 2020)
Fruit extract		cytotoxicity effect on human Caucasian larynx carcinoma cell line (Hep2)	(Tavakkol Afshari, Rakhshandeh et al., 2005)
Methanol extract	Antioxidant	radical scavenging activity was found against ascorbic acid	(Kumar, Kumar et al., 2008)
Seeds		antioxidant activity of this plant is due to containing flavonoids	(Benariba, Djaziri et al., 2013)
Fruit extract		antioxidant and hepatoprotective activities in rats	(Vakiloddin, Fuloria et al., 2015), (Adeyemi, Ishola et al., 2017)
Leaves extract		leaf extract showed highest antioxidant potency	(Nessa and Khan, 2014)
Extracts of <i>C. colocynthis</i> leaf, stem and root		There were higher bioactivity of <i>C. colocynthis</i> than that of <i>T. apollinea</i> in various antioxidant assays	(Rizvi, Khan et al., 2018)
Fruit extract	anti-inflammatory	the topical anti-inflammatory effect of the CC fruit extract cream (2–8%) and the tissue levels	(Pashmforosh, Rajabi Vardanjani et al., 2018)

Part of the plant /extracts	Pharmacological activity	Results	References
Fruit extract		of IL-6 and TNF- α were estimated After 6 h, 97.29% inhibition in swelling was observed	(Marzouk, Marzouk et al., 2010)
cucurbitacin E		Inflammatory diseases and oxidative liver damage were treated	(Hussein, El-Gizawy et al., 2017)
<i>Citrullus colocynthis</i> extract	Analgesic	the reduced level of pain in individuals with painful diabetic polyneuropathy	(Heydari, Homayouni et al., 2016)
cucurbitacin E	Antiallergic	49.7% inhibition in ear passive cutaneous anaphylaxis (PCA) reaction	(Yoshikawa, Morikawa et al., 2007)
Pulp extract	Fertility	had positive impacts on antioxidants and oxidants alternations in the reproductive system of samples	(Ostovan, Gol et al., 2017)
Pulp extract		It can be used to treat PCOS	(Barzegar, Khazali et al., 2017)
Aerial parts and ripe deseeded fruits extract	Antimicrobial	Effect on drug resistant and drug sensitive Koch's bacillus	(Mehta, Srivastva et al., 2013)
Aqueous extracts		reacted against <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i> , <i>Escherichia coli</i> and <i>Candida glabrata</i>	(Marzouk et al., 2009)
4-methylquinoline extracted from <i>C. colocynthis</i>	Larvicidal and Pesticidal	can be used to deal with stored grain weevils and spider mites as a natural pesticide	(Jeon and Lee, 2014)
Leaf extract	Larvicidal	the great larvicidal activities	(Rahuman, Venkatesan et al., 2008), (Chawech, Njeh et al., 2017)
Fruit	Antidiabetic	significant decrease in blood sugar level	(Li, Zheng et al., 2015)
Fruit/hydraulic extract		significant blood glucose level reduction	(Nikbakht and Gheatasi, 2006)
Fruit powder		significant decrease in HbA1c and FBS	(Huseini et al., 2009)
Fruit		significant decrease in HbA1c and fasting blood glucose levels	(Fallah Huseini, Zaree et al., 2006)
Fruit		significant decrease in HbA1c	(Karimabad, Niknia et al., 2020)
Seeds		treat samples with type 1 and 2 diabetes	(Benariba, Djaziri et al., 2012)
Aqueous extract		impact on intra-islet and beta cells vessel	(Amin, Tahir et al., 2017)

traditional therapeutic applications of the compound due to anti-inflammatory and analgesic ingredients, have been confirmed [37,38]. Inflammatory diseases and oxidative liver damage were treated with the extracts of cucurbitacin E glucoside [39]. 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 [40].

In addition, the essential cucurbitane-type triterpene glycoside and cucurbitacin E exhibited an antiallergic ability in a research [41].

2.6 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 [42]. It can be used to treat PCOS [43]. Nevertheless, exposing female rats to this compound for a long duration could be associated with negative impacts on fertility and the reproductive system [26].

2.7 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 [44]. 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* [45]. Moreover, pharmaceutical and food supplemental agents, which are eco-friendly, can be developed by applying *Citrullus colocynthis* extract [46].

2.8 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 [47]. Furthermore, the ingredients separated from

C. Colocynthis had the great larvicidal activities [48, 49].

2.9 Other Activities

The significant anticonvulsant impact of *Citrullus colocynthis* extract on mice, which had seizures induced by pentylenetetrazole, 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-ergicsystem [50]. Moreover, there is a profibrinolytic and antiplatelet activity in *C. colocynthis* hydro-alcoholic extract [51].

In addition, *C. colocynthis* petroleum extract was beneficial to the management of alopecia induced by androgen [52]. 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 [53].

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 [54].

3. CONCLUSIONS

In this review article, *Citrullus colocynthis* shows 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

There has been no financial support for this work that could have influenced its outcome.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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