

Citrullus colocynthis (L.) Schrad: A Promising Prospect Towards Pharmacology, Traditional Uses, and Potential Applications

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Abstract

Citrullus colocynthis (L.) Schrad is an ancient plant that grows in desert areas worldwide. Its fruit is known for its medicinal uses and potential applications in the pharmaceutical and nutraceutical industries. This narrative review aims to evaluate the published information on the ethnobotanical knowledge, phytochemistry, ethnopharmacology, nutraceutical potential, and toxicological studies of *C. colocynthis*, highlighting gaps and potential areas for future research. The present review extensively compiles, reviews, and analyzes the best available evidence from PubMed, Scopus (Embase), Web of Science (Web of Knowledge), Cochrane Library, Google Scholar, and other sources. Scientific literature shows that *C. colocynthis* contains bioactive compounds such as cucurbitacin, polyphenols, flavonoids, and other potent molecules that contribute to its antidiabetic, anticancer, antioxidant, antimicrobial, and anti-inflammatory properties. However, its potential therapeutic applications for digestive and respiratory systems, and cardiovascular disorders require further exploration. The present review reveals that the plant has significant potential for pharmaceutical and nutraceutical applications, with indications of synergistic effects and combinations that neutralize side effects.

Keywords: *Citrullus colocynthis*, Antitumor, Antidiabetics, Antioxidants, Bitter apple, Traditional medicine

Introduction

Medicinal plants have been used for thousands of years to treat a wide range of illnesses and health conditions. These plants contain various compounds that have pharmacological properties and can be used to alleviate symptoms, cure diseases, and promote overall well-being. The use of medicinal plants is still prevalent today, and many modern medicines are derived from plant sources.¹ The application of medicinal plants continues to be an area of research and exploration, with new discoveries and uses being uncovered all the time. From traditional remedies to modern medicine, medicinal plants play an essential role in healthcare and offer a natural and sustainable approach to healing.²

Cucurbitaceae, also known as the gourd family, is a plant family that includes over 900 species of plants. This family is widespread throughout the world and is found in tropical and subtropical regions. Plants of the Cucurbitaceae family are typically able to withstand drought conditions but are sensitive to wet and poorly drained soil and susceptible to frost damage. The Cucurbitaceae family includes many important crops such as pumpkins, cucumbers, watermelons, and squash.^{3,4}

Cucurbitaceae plants are important in many different

cultures and are used as food and medicine. In addition to their culinary uses, many species of Cucurbitaceae have been used in traditional medicine to treat a variety of ailments.⁴ For example, bitter melon (*Citrullus colocynthis* (L.) Schrad) has been used in traditional Persian medicine to treat diabetes.⁵

Citrullus colocynthis (L.) Schrad, also known as Bitter Apple or Colocynth, Handal in Arabic, Hendeveh-ye Aboujahl in Farsi, Acı kavun in Turkish, and Cocomero amaro in Italian, is a plant species that belongs to the family Cucurbitaceae. It is a perennial vine that is native to the Mediterranean region and parts of Asia, and it can also be found in North Africa and the Middle East. The plant is known for its unique appearance, with its fruit resembling a small yellow-green watermelon, but it is much smaller and has a more bitter taste.⁶

Citrullus colocynthis has been used for medicinal purposes for centuries, dating back to ancient Egyptian and Greek civilizations. It has traditionally been used to treat a variety of ailments, including constipation, digestive issues, fever, and skin conditions.⁷ The plant contains various active compounds, including cucurbitacins, flavonoids, and alkaloids, which are believed to be responsible for its medicinal properties.⁸



In Persian traditional medicine, the bitter apple is one of the most common plants used in the treatment of diabetes. Besides, the fruit, seeds, and leaves of the plant are used to treat a variety of ailments, including fever, inflammation, and digestive issues.^{5,9} The plant is also used topically to treat skin conditions like wounds and burns.¹⁰

In addition to its medicinal uses, *C. colocynthis* is also used in cuisine. The fruit is sometimes used to flavor stews and pickles.¹¹ In some parts of Iran, *C. colocynthis* is also used for pest control. The fruit is sometimes placed in grain stores to repel rodents and insects.¹²

In the light of the diverse applications of *C. colocynthis* fruit as a valuable source of nutrition, traditional medicine, and functional food ingredient, we have undertaken the task of compiling a comprehensive review of the latest and dispersed information available on this plant. This extensive review provides an extensive survey of the ethnobotanical uses of *C. colocynthis* fruit, as well as recent studies exploring its ethnopharmacology, phytochemistry, pharmacological activities, and toxicology.

Botanical Properties

Citrullus colocynthis (L.) Schrad is a member of the Cucurbitaceae family. The plant is indigenous to arid sandy regions in West Asia, Arabia, Iran, tropical Africa, and the Mediterranean, with a significant presence in the desert regions of Iran.¹³ *C. colocynthis* is believed to have originated from Asia and the Mediterranean Basin, specifically Turkey and Nubia, and spread westward to the coastal regions of Africa, including the Sahara and Egypt, as well as eastward to India and the northern coastal areas of the Caspian and Mediterranean seas.¹⁴ *C. colocynthis* is a perennial herbaceous vine that produces small flowers. The stems are angular and rough. The leaves are alternately arranged on the petioles and rough to touch, 5–10 cm in length, 1.5–2 cm in width, and deeply 3–7 lobed. It has solitary pale-yellow blooms.^{11,15} Flowers are yellow and seen on the axils of the leaves. It is monoecious, single, and pedunculated. Each plant produces 15–30 round fruits, about 7–10 cm in diameter, green with undulate yellow stripes, becoming yellow all over when dry.¹⁶ The fruit of *C. colocynthis* is bitter and globular with a smooth texture. It is hard and has a rind around it and contains 200–300 seeds/gourd. Seeds are small (6 mm in length), ovoid, compressed, smooth, and brownish when ripe. Seeds contain about 75% of the weight of fruit. Some physical properties of fruits such as the mass of fruit, seed, and pulp, volume, thickness of epicarp and mesocarp, seed-fruit ratio, and density are reported in the literature.¹⁷ Generally, the average mass of *C. colocynthis* fruit is 406 g, and the mass of pulp is approximately 50% of the mass of fruit, while the mass of the seeds is 71.8 g. Bitter apple was found to contain 24.37% protein, 1.91% fiber, 10.88% carbohydrate, 56.61% fat, 3.15% ash, and 3.08% moisture based on its proximate analysis.¹⁸

Phytochemistry

Numerous bioactive compounds have been identified in *C. colocynthis* fruit and classified into different categories such as glycosides, flavonoids, alkaloids, carbohydrates, fatty acids, and essential oils. However, only a few studies have reported the isolation and identification of individual chemical constituents. Among them, three flavone glucosides (isosaponarin, isovitexin, and isoorientin) and two cucurbitacin glucosides (2-glucopyranosyl-cucurbitacin L and glucopyranosyl cucurbitacin) were identified in the fruits of *C. colocynthis*.¹⁹ Cucurbitacins are the primary components of *C. colocynthis* fruits; however, flavonoids exhibit significant antioxidant effects, which make them valuable in treating various disorders since reactive oxygen species are implicated in inflammation, cancer, tissue damage, and other illnesses. Phytochemical screening of *C. colocynthis* has also revealed the presence of tannins, alkaloids, flavonoids, saponins, and glycosides.²⁰ Additionally, the ethanolic extract of *C. colocynthis* was shown to possess strong antibacterial properties due to its alkaloids, glycosides, and flavonoids.²¹ Crude extracts of *C. colocynthis* were found to contain terpenoids, steroids, alkaloids, flavonoids, glycosides, phenols, tannins, flavones, and saponins. Different preparations of *C. colocynthis* have also been shown to contain carbohydrates, proteins, tannins, distinct amino acids, steroids, phenolic compounds, alkaloids, glycosides, terpenoids, and several cucurbitacins (A, B, C, D, E, J, and L).²²

Nutrition

The *C. colocynthis* fruits ripen during the summer season and are typically gathered between May and October. However, in certain regions, these fruits are perennial, which could impact their carbohydrate, protein, fat, and fiber contents. While fruits of *C. colocynthis* are utilized in both food and pharmaceutical industries, there is a limited amount of nutritional information available.²³ This includes the proximate composition (such as moisture, ash, protein, and fat content) of both the seeds and fruits sourced from various countries. The seeds contain approximately 23%-25% golden-yellow colored oil, with 70% unsaturated fatty acids, and 51% polysaturated fatty acids.²⁴ The ripe fruit has a high moisture content, accounting for over 90% of the total weight. The seeds have a moisture content of 4.91 g/100 g, and protein and ash content of 13.19 g/100 g and 2.00 g/100 g, respectively.²⁵ *C. colocynthis* is rich in amino acids such as methionine, arginine, and tryptophan, with glutamic acid and arginine being the primary amino acids found with concentrations of 19.8 g/100 g and 15.9 g/100 g of protein, respectively.²⁶ Aspartic acid, serine, glycine, and glutamic acid were also found in the protein. Micronutrients are essential minerals required by the body to function normally. *C. colocynthis* fruits and seeds contain a diverse range of micronutrients that may be beneficial to consumers. Potassium and calcium are the major minerals found in the seeds, with concentrations of 569 mg/100 g and 465 mg/100 g of

seeds, respectively.²⁷ The seeds also contain high levels of magnesium and phosphorus, while iron and zinc levels are relatively low compared to other micronutrients.²⁸

The protein composition is unique due to the high concentration of essential amino acids. *C. colocynthis* may be used as a seed meal to make patties after partial removal of oil to serve as a meat alternative. The meal without any fat is utilized in various dietary preparations, which are influenced by the food habits of different populations. In addition, people enjoy consuming whole *C. colocynthis* seeds as a dry roasted snack.²⁹ *C. colocynthis* seed kernels have been traditionally used in various African countries as a key ingredient in food preparations. Typically, the kernels are fermented, dry roasted, and ground before being used as a thickener or flavoring agent in stews and soups. The plant fruit is commonly utilized in Iran to make stews and pickles, owing to its anti-diabetic and laxative characteristics, which hold a good position in Iranian cuisine.¹¹

Pharmacological Properties of *Citrullus colocynthis*

The utilization of *C. colocynthis* in traditional medicine has stimulated extensive pharmacological inquiries. Numerous extracts and isolated compounds have been subjected to evaluation for their biological properties, with particular focus on anticancer and antidiabetic activities. The substantial levels of cucurbitacins present in *C. colocynthis* have captured the attention of researchers seeking to develop novel anticancer and antitumor therapeutics. Its utility as a therapeutic agent is recognized in the domains of metabolic functions, as well as gastrointestinal and cardiovascular systems.³⁰

Anti-diabetic Properties

Citrullus colocynthis has been extensively studied for its potential as an anti-diabetic agent in both animals and humans, and its aqueous extract has shown promise in alleviating the deleterious effects of streptozotocin and lowering blood glucose levels. In Persian traditional medicine, herbalists commonly use *C. colocynthis* fruit to treat diabetes.³¹ The effects of various extracts of *C. colocynthis* peel, including aqueous, alkaloidal, saponin, and glycosidic, on plasma glucose levels in rabbits were investigated. The impact of saponin extract on fasting blood sugar levels in alloxan-induced diabetic rabbits was also examined. When the aqueous extract of *C. colocynthis* (300 mg/kg) was administered orally to normal rabbits, their plasma glucose levels significantly decreased after one hour, but they increased to high levels after 2, 3, and 6 hours. The saponin extract significantly reduced fasting glucose levels after 1 and 2 hours and considerably after 3 and 6 hours.³² The ethanol extract of *C. colocynthis* was found to have a significant anti-hyperglycemic effect in diabetic rats at a dose of 300 mg/kg by reducing blood glucose, triglyceride, and cholesterol levels. In vitro testing also demonstrated that *C. colocynthis* can inhibit glucosidase, which causes postprandial hyperglycemia,

suggesting its potential as a hyperglycemia treatment.³³

A two-month clinical trial on 50 diabetes mellitus patients who were also on regular anti-diabetic medication found that patients treated with *C. colocynthis* had a significant decrease in HbA1c and fasting blood glucose levels. Two groups of 25 patients were given either 100 mg fruit tablets or placebo pills three times a day, and their glycosylated hemoglobin, lipid profile, and liver function were evaluated before and after the trial. These results suggest that *C. colocynthis* may be a promising alternative treatment for diabetes.³⁴ The *C. colocynthis* fruit was found to possess insulin-enhancing activity, which may explain its antidiabetic effects in traditional medicine. The study identified *C. colocynthis* as a potential source of a novel insulin enhancer that could be useful in reducing hyperglycemia in type 2 diabetes. The ethyl acetate fractions of aqueous extracts of non-defatted seeds and pulps were used, and the pulp extract was found to increase glucose uptake by enhancing the insulin-induced translocation of glucose transporter (GLUT4) from intracellular storage sites to the plasma membrane. This effect was observed to act on the same intracellular signaling cascade employed by insulin.³⁵

Antioxidant Activity

The antioxidant properties of *C. colocynthis* were studied using its methanolic fruit extract. Gallic acid, a phenolic compound, was found to be responsible for its good free radical scavenging activity. The extract exhibited the highest antioxidant and free radical scavenging activities at a concentration of 2500 mg/mL.³⁶ Cucurbitacin, an antioxidant, was also found to be present in the extract, which can destroy free radicals such as hydroxyl, superoxide, and oxygen singlets and prevent lipid peroxidation and degradation. The bitter apple extracts were reported to contain organic substances that can act as effective antioxidants, as well as polyphenolic chemicals responsible for the therapeutic benefits of traditional nutraceutical and pharmaceutical plants.³⁷

The aqueous leaf extract of *C. colocynthis* was found to have a DPPH free radical scavenging effect, with an IC₅₀ value of 0.021 mg/mL. Cucurbitacin glycoside derived from bitter apple also demonstrated ABTS radical scavenging capabilities (IC₅₀, 145 M), likely due to its direct scavenging impact on multiple free radicals.³⁸

An in-vitro investigation revealed that *C. colocynthis* can reduce free radical damage to the body due to its various biochemical constituents with effective antioxidant properties. The oil derived from *C. colocynthis* was found to improve antioxidant enzyme performance and protect the liver against damage.³⁹ Overall, *C. colocynthis* is a good antioxidant due to the presence of gallic acid and cucurbitacin, as well as other biochemicals.

Anti-inflammatory Properties

Citrullus colocynthis is widely used in traditional medicine due to its anti-inflammatory capabilities. The

anti-inflammatory activity of the methanolic extract of *C. colocynthis* leaves was assessed using various in vivo screening models. The extract showed an inhibitory effect on paw edema caused by different inflammatory drugs at doses of 250 and 500 mg/kg, as well as on the infiltration of leukocytes and the formation of exudate caused by carrageenan. These results demonstrate the ability of the extract to have an anti-inflammatory effect during both the acute and subacute phases of inflammation.⁴⁰ *C. colocynthis* has been found to interfere with histamine, serotonin mechanisms, prostaglandin, and kinin pathways. Glycoside 11-deoxycucurbitacinI-2-O-b-D has been identified as the principal potent bioactive constituent within the chloroform component of CCS extracts in various animal studies, with concentrations of 0.5 to 1.0 mg/kg body weight. These substances have been shown to have positive anti-inflammatory properties in multiple animal studies.³⁸

Citrullus colocynthis is also known for its high anti-ulcerogenic properties, likely due to its lack of ulcerogenic effects and ability to provide a more effective anti-inflammatory solution that could be used in peptic ulcers caused by *Helicobacter pylori*.⁴¹

Antimicrobial Activity

Several previous studies have shown that extracts from various parts of the *C. colocynthis* plant are active against both gram-positive and gram-negative bacteria, including *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecalis*, with a stronger effect on newer bacteria. The minimal inhibitory concentration (MIC) of these extracts was determined using the broth dilution method, with concentrations ranging from 0.10 to 6.50 mg/mL. The aqueous extracts obtained from immature fruits exhibited an MIC of 0.20 mg/mL for *Escherichia coli* and *P. aeruginosa*, depending on the strain, plant organ, stage of maturity, and type of extraction used.⁴²

Furthermore, the ethanolic extract of the *C. colocynthis* fruit was found to have a standard antibacterial effect on both gram-positive (*S. aureus* and *Bacillus subtilis*) and gram-negative bacteria (*Klebsiella pneumoniae*), with the pulp extract showing greater activity against Gram-positive bacteria and the seed extract being slightly less effective against both types of bacteria.⁴³ Additionally, Khatibi and Teymorri reported that seeds and fruits of bitter apple showed a strong antimicrobial effect. Various extracts of *C. colocynthis* prepared using different solvents were tested for their antimicrobial effects against several pathogenic bacteria, including *Salmonella*, *S. aureus*, *Bacillus* spp., *Proteus vulgaris*, and *Pseudomonas* spp. The results showed that most of the extracts had MICs ranging from 20 to 100 g/mL against all tested bacteria.⁴⁴

Finally, Chawech et al showed the impact of the ethyl acetate extract of the leaves against various bacteria, including *Salmonella enteritidis*, *B. cereus*, *E. coli*, *S. aureus*, *E. faecalis*, and *P. aeruginosa*, with MIC values

against *B. cereus* at 0.625 mg/mL using the agar disc well-diffusion method.⁴⁵

Anticancer Properties

Citrullus colocynthis exhibits anti-tumor properties through various mechanisms, such as apoptotic pathways, antioxidant and anti-inflammatory effects, inhibition of the Wnt/ β -catenin signaling pathway, and anti-metastatic effects. Its anti-cancerous properties are attributed to cucurbitic acid.⁴⁶ The methanolic extract of *C. colocynthis* leaves and its ethyl acetate and chloroform fractions have notable anti-cancerous effects on human breast cancer cell lines. The extract can reduce the multiplication and growth of cells and arrest human breast cancer cells by inhibiting cyclin-CDK inhibitors.⁴⁷ The pulp extracts of the fruit can also block the proliferation and metastatic activity of breast cancer cells, prevent cell migration, and inhibit cancer stemness properties. *C. colocynthis* leaves can modulate lipid metabolism and thus exhibit excellent potential as anti-cancer agents. Additionally, the extract of *C. colocynthis* fruit has been shown to exhibit anti-tumor activity on cancerous cell lines.^{48,49}

Neuroprotective Activity

Citrullus colocynthis has been found to exhibit neuroprotective properties in rats with rotenone-induced Parkinson's disease. This was evidenced by its positive impact on endogenous antioxidant molecules in brain samples, which lessened oxidative stress and inhibited apoptotic cell death.⁵⁰ Further, in both in-vitro and in-vivo models, *C. colocynthis* demonstrated an excellent neuroprotective impact. Additionally, the hydro-alcoholic extract of *C. colocynthis* pulp was found to have an anticonvulsant effect in rats. Injection of the extract at 25 and 50 mg/kg offered protection against seizures, significantly prolonged their onset, and decreased their duration.⁵¹ Further studies showed that *C. colocynthis* extract significantly enhanced cell viability under high glucose conditions in a dose- and time-dependent manner and exhibited a protective effect against high glucose-induced cytotoxicity in PC-12 cells.⁵² These findings indicate that *C. colocynthis* has potential therapeutic applications in the treatment of a range of health conditions such as stroke.

Toxic Potential

A study was conducted to assess the harmful effects of ingesting an extract containing 10% *C. colocynthis* fruits on rats. The results of treatment with *C. colocynthis* included depression, ruffled hair, reduced body weight, decreased feeding efficiency, and entero-hepato-nephropathy. Diarrhea was observed as a clear sign of *C. colocynthis* poisoning. In addition, lesions were found on the organs, and there were changes in serum enzyme levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP]), as well as alterations in the concentrations of whole protein, urea, bilirubin,

albumin, and other serum constituents. Leukopenia and anemia were also observed.⁵³

The toxicity of the methanolic extract of *C. colocynthis* fruit was assessed in male albino Wister rats. The acute median lethal dose of its extract was found to be 1311.45 mg/kg. The extract was found to be hepato-nephrotoxic, as evidenced by the notable effects on plasma AST, ALT, urea, and creatinine titers. These results confirm that the consumption of *C. colocynthis* fruit extract has toxic effects on the liver, kidney, and bone marrow of rats.⁵⁴

The subchronic hemotoxicity and cytotoxicity of *C. colocynthis* on albino rats were evaluated by Elgerwi et al. The LD50 of oral administration of the *C. colocynthis* flower extract was calculated to be 162.4 mg/kg of body weight. The study also documented pathological changes in the lungs, liver, kidneys, spleen, stomach, and intestines of the treated rats.⁵⁵

Rabbits that were treated with 100 mg/kg/d of *C. colocynthis* pulp extract showed severe lesions in their small intestine, kidneys, and liver. Surprisingly, animals treated with either 100 or 200 mg/kg/d of seed extract only experienced minor intestinal injuries. In contrast to the seed extract, the pulp extract of *C. colocynthis* was found to be fatal to rabbits.¹⁹ Another research was conducted on male rabbits, which found that all the rabbits that were treated with 200 mg/kg/d of *C. colocynthis* pulp extract died, whereas 46% of the rabbits that received 100 mg/kg/d of pulp extract also died. Additionally, the group that received 100 mg/kg/d of pulp extract exhibited an increase in the number of intestinal mucosal lymphocytes.⁵⁶

In a case report from Iran, a 48-year-old man ingested decoction of *C. colocynthis* fruit to self-treat his constipation and was admitted to the emergency department 10 hours later due to acute toxicity. He subsequently experienced hypotension, hypoglycemia, and watery diarrhea, as well as hepatic injury characterized by elevated levels of ALT and AST enzymes. The patient was managed with supportive care in the ICU. After 4 days, all his parameters returned to normal and he was discharged from the hospital with complete recovery.⁵⁷

Conclusion

This review evaluates the nutritional and medicinal applications of *C. colocynthis* based on previous studies, highlighting its potential to treat various diseases. Despite its high dietary value, *C. colocynthis* is not widely recognized, and further investigations are needed to determine its usefulness as a dietary supplement for enhancing fitness. The review also emphasizes pharmacological properties of *C. colocynthis*, indicating its potential for medical applications. By compiling the latest data, the present review aims to provide comprehensive information on the benefits of *C. colocynthis*. However, more precise information on inclusion levels, usage, and possible side effects must be validated by pharmacological investigations in vivo. Although *C. colocynthis* has various health-promoting effects, its mechanism of action remains

unclear and requires further exploration.

Authors' Contribution

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Competing Interests

The authors declare no competing interests for this manuscript.

Ethical Approval

Not applicable.

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