

Review Article

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A Brief Review on Bitter Apple - Pharmacological Activities

Rashmi Sagar* and V.K. Dumka

Department of Veterinary Pharmacology and Toxicology, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana-141001, Punjab, India

*Corresponding author

ABSTRACT

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Present review article reveals the importance of Bitter Apple belonging to the 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. As per Ayurveda and Siddha system of medicine it is Tikta-rasam, ushna-veeryam and katuvipakam and used as purgative, diuretic, lagu, kapharam and abortifacient. Fruit is bitter, pungent and used as purgative, anthelmintic, antipyretic, carminative, cures tumors, leucoderma, ulcers, asthma, etc. Root is useful in jaundice, ascites, urinary disease, rheumatism. In this article pharmacological and biological activity, inputs have been extensively recorded and discussed.

Introduction

Bitter Apple also known as *Citrullus colocynthis* (L.) Schrad. (Cucurbitaceae) has medicinal and ornamental purposes, the former derived primarily from the fruit pulp (de Smet, 1997).

Common names for this plant include colocynth, bitter gourd, bitter apple, and bitter cucumber in English while it is known as Koloquinthe in German and coloquinte in French (de Smet, 1997). *C. colocynthis* has only one accepted name but six synonyms (The Plant List, 2017).

In India and Pakistan, it is known as tumba (Mahajan and Kumawat, 2013; Hussain *et al.*, 2014).

Importance and Uses

According to Hussain *et al.*, (2014), *C. colocynthis* has the following traditional medicinal uses: “diabetes, leprosy, common cold, cough, asthma, bronchitis, jaundice, joint pain, cancer, toothache, wound, mastitis, and in gastrointestinal disorders such as indigestion, constipation, dysentery, gastroenteritis, colic pain and different microbial infections.” Also, according to the same authors, who wrote a comprehensive review on several properties of *C. colocynthis*, indicated that there are multiple medicinal and biological activities, including antidiabetic, anticancer, cytotoxic, antioxidant, antilipidemic, insecticidal, antimicrobial and anti-inflammatory. De Smet (1997) also reviewed earlier literature on the

medicinal properties of *C. colocynthis*. Several accessions have shown resistance to several viruses and diseases (Dabauza *et al.*, 1997). Dabauza *et al.*, (1997) developed an *Agrobacterium tumefaciens*-mediated genetic transformation protocol in which 7-day-old seedling cotyledons were infected with strain LBA4404 carrying the binary vector pBI121, harboring the β -glucuronidase (*gus*; reporter) and the neomycin phosphotransferase (*nptII*; marker) genes. Based on GUS expression, 14% of explants were shown to be transformed. PCR confirmed the integration of the *gus* and *nptII* genes while Southern blot analysis conferred transmission of the *gus* gene to several transgenic plants obtained by selfing. *C. colocynthis* is able to withstand extreme desert temperatures through a high rate of transpiration to lower leaf temperatures below lethal temperatures (Althawadi and Grace, 1986)

Anti-inflammatory and analgesic activity

Marzouk *et al.*, 2011 studied aqueous extracts of *C. colocynthis* fruit and seed at an immature stage for anti-inflammatory activity using the carrageenan-induced paw edema assay in rats.

The best anti-inflammatory activities were obtained with immature fruits from south Tunisia. Therefore, *C. colocynthis* could be a useful product suitable for further evaluation for inflammatory diseases.

Methanol extract of *Citrullus colocynthis* significantly inhibited carrageenan, serotonin and prostaglandin E1-induced paw edema. Maximum inhibition was observed in prostaglandin E1-induced paw edema. In carrageenan air-pouch model, methanol extract of *Citrullus colocynthis* significantly reduced the volume of exudate and migration of neutrophils and monocytes. The extract significantly decreased formation of

granuloma tissue in chronic inflammation model. Hence, this investigation established some pharmacological evidences to support the use of *Citrullus colocynthis* as anti-inflammatory agent (Rajamanickam *et al.*, 2010).

Anticandidal and antibacterial activity

Bactericidal activities of crude extracts, fractions and compounds of *Citrullus colocynthis* plant aerial parts and ripe deseeded fruits were performed against the drug sensitive standard strain of *Mycobacterium tuberculosis* H37Rv (ATCC 27294), 16 drug resistant strains of *Mycobacterium tuberculosis* and two *Mycobacterium* other than tuberculosis (MOTT) strains, using radiometric BACTEC system. Methanolic extract of ripe deseeded fruit of *Citrullus colocynthis* showed good activity (MIC \leq 62.5 μ g/ml) and one of the bioactive fractions demonstrated the best activity (MIC 31.2 μ g/ml) against *Mycobacterium tuberculosis* H37Rv (Mehta *et al.*, 2013).

The maximum antimicrobial activity was exhibited by acetone, ethanol, methanol and distilled water extract of the fruits of *Citrullus colocynthis* against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Shigella shigellae* and *Candida albicans*. Whereas petroleum ether extract was found to be less effective against test strains (Rodge and Biradar 2013).

In the study conducted by Sagar *et al.*, 2018 various extracts viz alcoholic, acetone, chloroform of the leaves of *Citrullus colocynthis* were evaluated for antibacterial activity against *Staphylococcus aureus* and *E.coli* and it was observed that none of the extracts showed antibacterial activity against both the bacteria when compared to standard antibiotic.

Antioxidant potential

The antioxidant effects of *Citrullus colocynthis* seeds extracts [a crude aqueous extract (E1), a defatted aqueous extract (E2), a hydromethanolic extract (HM), an ethyl acetate extract (EA) and a *n*-butanol extract (*n*-B)] were studied at a concentration of 2 000 µg/ml in a 1,1-diphenyl-2-picrylhydrazyl assay, reducing percentage of 88.8% with EA, 74.5% with HM and 66.2% with E1 was recorded with a corresponding IC₅₀ of 350, 580 and 500 µg/ml respectively as compared to 1.1 µg/ml for ascorbic acid (Benariba *et al.*, 2013).

Antioxidant activity of *Citrullus colocynthis* seed methanolic extract was studied spectrophotometrically by 1, 1-diphenyl-2-picryl hydrazyl and hydrogen peroxide free radical scavenging method. The methanolic seed extract of *Citrullus colocynthis* showed maximum percentage inhibition of 79.4 and 72.4% by 1, 1-diphenyl-2-picryl hydrazyl and hydrogen peroxide method respectively at 300 µg /ml (Gill *et al.*, 2011).

In vitro antioxidant studies revealed that, maximum percentage inhibition of DPPH radicals by methanolic extract of *Citrullus colocynthis* fruits (MECC) was 62% at 800 µg/ml. In the nitric oxide radical scavenging model, the maximum percentage inhibition by MECC was about 56% at 800µg/ml. From the study, it was concluded that MECC demonstrated dose dependent antioxidant activity comparable with ascorbic acid (Jayaraman and Christina 2013).

Hypoglycemic activity

Agarwal *et al.*, 2012 examined the effect of root of *C. colocynthis* on the biochemical parameters of normal and alloxan-induced diabetic rats. Diabetes mellitus was induced by intraperitoneal (120 mg/kg b.wt.) injection

of alloxan monohydrate for three days and the animals showing blood glucose level in the range of 175-300 mg/dL were selected for study. The blood glucose concentrations of the animals were measured at the beginning of the study and the measurements were repeated on 3rd, 5th and 7th day after the start of the experiment. Aqueous extract of roots of *Citrullus colocynthis* showed significant reduction in blood sugar level (58.70%) when compared with chloroform (34.72%) and ethanol extracts (36.60%). The aqueous extracts showed improvement in parameters like body weight, serum creatinine, serum urea and serum protein as well as lipid profile and also restored the serum level of bilirubin total, conjugated bilirubin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase (ALP).

The direct *in vitro* effects of *Citrullus colocynthis* seed extracts were evaluated in glucose-stimulated insulin release from pancreatic islets isolated from rats. Six extracts were tested, a crude aqueous, defatted aqueous, ethyl acetate, H₂O-methanol, *n*-butanol extract and an extract containing a mixture of the major component (fraction A) (identified by gel chromatography in the ethyl acetate), *n*-butanol and H₂O-methanol extracts. The majority of extracts exhibited a positive insulinotropic action when tested in the presence of 8.3 mM D-glucose (Benariba *et al.*, 2013).

The effect of *Citrullus colocynthis* pulp extract on the structure of the liver was tested in diabetic rats at both light and scanning electron microscopic levels. Diabetes caused degenerative alterations in the form of disorganization of the hepatic cords, cytoplasmic vacuolization and pyknosis of the nuclei of hepatocytes and inflammatory cell infiltration. Scanning electron microscope examination of these livers revealed

numerous lipid droplets within hepatocytes, damaged blood sinusoids and hemorrhage of erythrocytes between hepatocytes and inside Disse's spaces. The liver of *Citrullus colocynthis* -treated rats revealed minor histological changes versus the control animals (Khalil *et al.*, 2010).

Anti – alopecia activity

Dhanotia *et al.*, 2011 evaluated *C. colocynthis* for hair growth activity in androgen-induced alopecia. Petroleum ether extract of *C. colocynthis* was applied topically for its hair growth-promoting activity. Alopecia was induced in albino mice by testosterone administration intramuscularly for 21 days. Its inhibition by simultaneous administration of extract was evaluated using follicular density, anagen/telogen (A/T) ratio and microscopic observation of skin sections. Finasteride (5 α -reductase inhibitor) solution was applied topically and served as positive control. Petroleum ether extract of *C. colocynthis* exhibited promising hair growth promoting activity, as reflected from follicular density, A/T ratio and skin sections. The treatment was also successful in bringing a greater number of hair follicles in anagenic phase than the standard finasteride. The result of treatment with 2 and 5% petroleum ether extracts were comparable to the positive control finasteride. The petroleum ether extract of *C. colocynthis* and its isolate was found useful in the treatment of androgen-induced alopecia.

Petroleum ether and ethanol extracts of *Citrullus colocynthis* were tested for their effect on hair growth in albino rats. The extracts incorporated into oleaginous ointment base were applied topically on shaved denuded skin of albino rats. The time required for initiation of hair growth as well as completion of hair growth cycle was recorded. Minoxidil 2% solution was applied

topically and served as the standard. Hair growth initiation time was significantly reduced to half on treatment with the petroleum ether extracts compared with untreated control animals. The time required for complete hair growth was also considerably reduced. The treatment was successful in bringing a greater number of hair follicles (>70%) to anagenic phase than standard minoxidil (67%). The result of treatment with 2 and 5% petroleum ether extracts were comparable with the standard minoxidil (Roy *et al.*, 2007).

Antiparasitic insecticidal and antiscorpion effects

Albino mice were intraperitoneally infected with promastigotes of *Leishmania donovani* (MHOM/ IQ/ 982/BRCI) strain. The inoculation of albino mice caused elevation of liver and spleen weight after 7-15 days. The mice treated with 20-100 mg/kg from *Citrullus colocynthis* showed decreased average liver and spleen weight in comparison to the positive control. The most important histopathological results in the positive control including scattered necrosis, lymphatic infiltration, proliferation of macrophages and a variable number of leishman bodies were observed and it was noted that 80-100 mg/kg of *Citrullus colocynthis* returned liver section to normal histology (Al-Harmni *et al.*, 2012).

Methylene chloride, n-hexane, chloroform and ethanol extracts of *Citrullus colocynthis* fruits were tested against *Aphis craccivora*. The highest insecticidal effect (LC50: 11003 ppm) was obtained from the ethanol extract. The residue remaining after evaporation of ethanol extract was re-extracted by different solvents with increasing polarity. Each fraction was tested against *Aphis craccivora*. The butanol extract showed the maximum insecticidal effect. The effective compound

was identified as 2-O-β-D-glucopyranosylcucurbitac in E (Torkey *et al.*, 2009).

Citrullus colocynthis was evaluated as new therapeutic approach for scorpion envenomation mainly *Androctonus australis* hector venom (Aah). Local action (paw edema) and systemic effects (inflammatory, metabolic parameters, oxidative stress and hyperglycemia) were studied in pretreated mice with *Citrullus colocynthis* (50 mg/kg); 30 min before injection of sublethal dose of *Androctonus australis* hector venom (10 µg/20 g). Results showed that injected *Citrullus colocynthis* extract before envenomation was able to protect animals against the toxicity of the venom. It significantly reduced paw edema, cell migration, exudation and hyperglycemia. *Citrullus colocynthis* decreased also some inflammatory markers (MPO and EPO activities, CRP and C3) and maintain the level of CPK, ASAT and ALAT. So, it was concluded that *Citrullus colocynthis* appeared to be a potential tool that can reduce pathophysiological effects induced after envenomation (inflammation and oxidative stress) (Fatima and Mohamed 2014).

Growth inhibitory activity on breast cancer cells

Grossman *et al.*, 2007 studied the effects of cucurbitacin glycosides extracted from *Citrullus colocynthis* leaves on human breast cancer cell growth. Leaves were extracted, resulting in the identification of cucurbitacin B/E glycosides. The cucurbitacin glycoside combination (1:1) inhibited growth of ER (+) MCF-7 and ER (-) MDA-MB-231 human breast cancer cell lines. Cell-cycle analysis showed that treatment with isolated cucurbitacin glycoside combination resulted in accumulation of cells at the G (2)/M phase of the cell cycle. Treated cells showed rapid

reduction in the level of the key protein complex necessary to the regulation of G (2) exit and initiation of mitosis, namely the p34 (CDC2)/cyclin B1 complex. Cucurbitacin glycoside treatment also caused changes in the overall cell morphology from an elongated form to a round-shaped cell, which indicates that cucurbitacin-treatment caused impairment of actin filament organization. This profound morphological change was thought to influence intracellular signaling by molecules such as PKB, resulting in inhibition in the transmission of survival signals. Reduction in PKB phosphorylation and inhibition of survivin, an anti-apoptosis family member, was observed. The treatment caused elevation in p-STAT3 and in p21 (WAF), proven to be a STAT3 positive target in absence of survival signals. Cucurbitacin glycoside treatment also induced apoptosis, as measured by Annexin V/propidium iodide staining and by changes in mitochondrial membrane potential (DeltaPsi) using a fluorescent dye, JC-1. It was suggested that cucurbitacin glycosides exhibit pleiotropic effects on cells causing both cell cycle arrest and apoptosis. These results indicated that cucurbitacin glycosides might have therapeutic value against breast cancer cells.

The paper reviewed *Citrullus colocynthis* as promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

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