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Chemical constituents and pharmacological effects of *Citrullus colocynthis* - A review

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Abstract: *Citrullus colocynthis* contained carbohydrate, protein, separated amino acid, tannins, saponins, phenolics, flavanoids, flavone glucosides, terpenoids, alkaloids, anthranol, steroids, cucurbitacins, saponarin, cardic glycoloids, trace elements and many other chemical groups. It possessed antioxidant, Antidiabetic, antimicrobial, anticancer, anti-inflamatory, analgesic, gastrointestinal, reproductive, protective and many other pharmacological effects. This paper will highlight the chemical constituents and pharmacological effects of *Citrullus colocynthis*.

Keywords*: Citrullus colocynthis, pharmacology, constituent, pharmacognosy*

I. INTRODUCTION

World Health Organization survey indicated that about 70-80% of the world's population rely on nonconventional medicine, mainly of herbal sources, in their primary healthcare. This is especially the case in developing countries where the cost of consulting a western style doctor and the price of medication are beyond the means of most people[1-2]. There are hundreds of significant drugs and biologically active compounds developed from the traditional medicinal plants. Plant showed wide range of pharmacological activities including antimicrobial, antioxidant, anticancer, hypolipidemic, cardio-vascular, central nervous, respiratory, immunological, anti-inflammatory, analgesic antipyretic and many other pharmacological effects[3-40].

Citrullus colocynthis contained carbohydrate, protein, separated amino acid, tannins, saponins, phenolics, flavanoids, flavone glucosides, terpenoids, alkaloids, anthranol, steroids, cucurbitacins, saponarin, cardic glycoloids, trace elements and many other chemical groups. It possessed antioxidant, Antidiabetic, antimicrobial, anticancer, anti-inflamatory, analgesic, gastrointestinal, reproductive, protective and many other pharmacological effects. This paper will highlight the chemical constituents and pharmacological effects of *Citrullus colocynthis*.

Plant profile:

Synonyms:

Colocynthis vulgaris Schrad., *Cucumis colocynthis* L. (basionym), *Citrullus pseudocolocynthis* M.Roem. and *Colocynthis officinalis* Schrad[414-2].

Common names:

Arabic: handhal, **English:** bitter-apple, bitter-cucumber, colocynth, vine-of-Sodom, wild gourd, **French:** coloquinte, coloquinte, **German:** bitter-melone, koloquinte**, India:** tumba, **Portuguese**: colocíntida, **Spanish:** alhandal**,** coloquíntida, **Swidish:** kolokvint[41].

Distribution:

It was native to dry areas of North Africa and it has been known in the Mediterranean region since Biblical times. The plant now is found in **Northern Africa:** Algeria, Egypt; Libya, Morocco, Tunisia; **Northeast Tropical Africa:** Chad, Ethiopia, Somalia; **East Tropical Africa**: Kenya; **West Tropical Africa**: Mali; **Asia:** Kuwait, Saudi Arabia, Iraq, Jordan, Lebanon, Syria, Yemen, Afghanistan, Iran, Turkey**,** India, Pakistan, Sri Lanka; **Europe:** Greece, Italy, Spain; and **Australia**[41,43].

Description:

Annual or perennial (in wild) herbaceous vine; stems angular and rough; leaves rough, 3- to 7-lobed, 5-10 cm long, middle lobe sometimes ovate, sinuses open; flowers monoecious, solitary, peduncled, axillary, corollas 5-lobed; ovary villous; fruit a pepo, nearly globular, 4-10 cm in diameter with somewhat elliptical fissures, about size of small orange, green and yellow variegated becoming yellow when ripe, with hard rind, pulp light in weight, spongy, easily broken, light yellowish-orange to pale yellow; intensely bitter; seeds numerous, ovoid, compressed, smooth, dark brown to light yellowish-orange, borne on parietal placenta[43].

Traditional uses:

The root was used in inflammation of the breasts, joints pain; externally it was used in ophthalmia and in uterine pains. The fruit and root were rubbed with water and applied to boils and pimples. A paste of the root is applied to the enlarged abdomen of children[44].

The fruit was also used in ascites, biliousness, jaundice, cerebral congestion, colic, constipation dropsy, fever, worms and sciatica. Root was also given in cases of abdominal enlargement, cough, asthma, inflammation of the breast, ulcers, urinary diseases and rheumatism. Oil from seeds is used for poisonous bites, bowel complaints, epilepsy and also for blackening the hair[45-46].

Citrullus colocynthis fruits were also traditionally used as an abortifacient and to treat constipation, oedema, bacterial infections, cancer and diabetes[47].

Part used: Dried fruit pulps, roots and leaves[44-47].

Chemical constituents:

Phytochemical analysis of plant extracts revealed the presence of carbohydrate, protein, separated amino acid, tannins, saponins, phenolic, flavanoids, terpenoids, alkaloids, anthranol, steroids, Cucurbitacin A, B, C, D, E (α-elaterin), J, L, caffeic acid and cardic glycoloids[47-53].

The seeds of *Citrullus colocynthis* contained proteins 13.99 ± 0.06%, crude fibers 46.73 ± 0.15%, moisture 6.43 ± 0.15%, α-tocopherol 1.90 ± 0.020 g/100g, δ-tocopherol 0.32 ± 0.020 g/100g and fixed oil 17-28.5 % with high proportion of unsaturated fatty acids (79.80%), mainly linoleic acid, oleic acid, low percentage of saturated, total saturated 20.20% and a very low n-3 poly-unsaturated FA level (0.5%). However, the seed fat of *Citrullus colocynthis* consisted of palmitic 10.40%; stearic 6.52%; arachidic 1.70%; oleic 11.7-20.92%; linoleic 58.81-70%; and linolenic 1.65%[54-57].

Physicochemical properties of *Citrullus colocynthis* seed oil: iodine value :114.46 g I_2/100g, density at 15 °C 905.3: Kg/m^3, kinematic viscosity at 40 °C: 31.52 mm^2/s, saponification value : 204.44 mg KOH/g, acid value: 0.98 mg KOH/g, free fatty acid: 0.49%, caloric value: 39.37 MJ/kg, colour: 5Y + 0.4R and average molecular weight: 874g[54].

Phytochemical screening showed that it contained 0.74% (*m/m*) phenolics (calculated as gallic acid) and 0.13% (*m/m*) flavonoids (calculated as catechin equivalents per 100 g of fresh mass)[58].

The phenolic contents 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. Catechic tannins and flavonoids were abundant in E1, HM and EA, whilst terpenoids were abundantly present in E1 and *n*-B but with low concentration in HM. Coumarins were found in E2, EA and *n*-B. Polyphenols (expressed as gallic acid equivalent, amounted, per 100 g plant matter), were 329, 1002 and 150 mg in EA, HM an E1 respectively. Flavonoids (expressed as catechin equivalent, amounted, per 100 g plant matter) were 620, 241 and 94 mg in EA, HM and E1 respectively. Comparable values were found in *n*-B and E1, with lower values in E2. Quercetin, myricetin and gallic acid were found in the EA and HM extracts[59].

Three flavone glucosides, isosaponarin, isovitexin and isoorientin 3'-*O*-methyl ether and two cucurbitacin glucosides, 2-*O*-β-D-glucopyranosylcucurbitacin I and 2-*O*-β-D-glucopyranosylcucurbitacin L were isolated from the fruits of *Citrullus colocynthis*[60].

Mineral contents of the unfermented *Citrullus colocynthis* were: Ca 0.250 ± 0.04, Mg 0.139 ± 0.041, K 0.244 ± 0.04 , Na 0.36 ± 0.02 and P 0.176 ± 0.022 mg/kg, while, mineral contents of the fermented *Citrullus colocynthis* were: Ca 0.341 ± 0.18, Mg 0.167 ± 0.12, K 0.327 ± 0.10, Na 0.034 ± 0.16 and P 0.097 ± 0.14 mg/kg [61].

Pharmacological effects:

Antimicrobial effect:

Inhibitory and 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* has shown good activity (MIC ≤ 62.5 µg/ml), one of the bioactive fractions demonstrated the best activity (MIC 31.2 µg/ml) against *Mycobacterium tuberculosis* H37Rv. However 3 bioactive fractions also inhibited 16 clinical isolates of *Mycobacterium tuberculosis* consisting of seven non-multidrug resistants, eight multidrug resistants, one extensively drug resistant and two of Mycobacterium other than tuberculosis (MOTT) bacilli with MICs in the range of 50-125, 31.2-125 and 62.5-125 µg/ml, respectively. Ursolic acid and cucurbitacin E 2-0-β-d-glucopyranoside were identified as the main biomarkers active against Mycobacterium tuberculosis H37Rv (MICs 50 and 25 µg/ml respectively), as well as against the 18 clinical isolates [62].

The maximum antimicrobial activity was exhibited by acetone, ethanol, methanol and distilled water extract of the fruits against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Shigella shigella* and *Candida albicans.* Whereas petroleum ether extract is less effective against test strains[48].

The ethanolic extract showed dose dependent inhibitory activity against *Staphylococcus aureus* more than water extract. 5 mg/ml fruits ethanolic extract possessed a similar inhibitory effect to novobiocin against standard *Staphylococcus aureus* strain[50].

MIC and MBC/MFC were determined for plant organs at different maturation stages. Aqueous and diluted acetone extracts (from the plant's roots, stems, leaves and three maturation stages of its fruit and seeds) were screened for activity 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*). All extracts showed activity against all strains. The highest MICs and MBCs/MFCs were obtained from the fruit aqueous extracts (MIC 0.10 mg/ml against *C. albicans* and *C. glabrata*, 0.20 mg/ml against *E. coli* and *P. aeruginosa*), the lowest antibacterial and anticandidal activity was recorded for the root extracts of *Citrullus colocynthis* Schrad[63].

The antimicrobial activity of alkaloid extracted from *Citrullus colocynthis* were examined against five local bacterial isolates (*Escherichia coli*, *Staphylococcus aureus*, *Streptococcus* sp., *Bacillus subtilis*, and *Klipsella* sp.) using agar disc diffusion method. The most active antimicrobial activity of extracted alkaloid were shown against *Streptococcus* Sp. Broth dilution methods were used to determine the minimum inhibitory concentration (MIC) for the extracted alkaloid. The study showed that MIC values of 600 µg/ ml, 3000 µg/ ml, were recorded against *Staph. aureus*, and *E.coli* isolates respectively[64].

The antifungal and antimycotoxigenic power of methanolic and aqueous extracts of *Citrullus colocynthis* seeds were studied *in vitro*. The antifungal and antimycotoxigenic activity of methanolic and aqueous extracts were screened against *Aspergillus ochraceus* and *Aspergillus flavus.* The results suggest that the extracts showed a very good antifungal activity against *A. ochraceus*, but not against *A. flavus.* The extracts have good antiochratoxigenic power in liquid medium[65].

Antiparasitic insecticidal and antiscorpion effects:

Albino mice were intraperitionally infected with 100 X 10^6 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 histopathologcal results in the positive control included scattered necrosis, lymphatic infiltration, proliferation of macrophages and a variable number of leishman bodies were observed. 80-100 mg/kg of *Citrullus colocynthis* return liver section to normal histology[66].

Larvicidal activity of crude hexane, ethyl acetate, petroleum ether, acetone, and methanol extracts of the leaf of five species of cucurbitaceous plants, *Citrullus colocynthis*, *Coccinia indica*, *Cucumis sativus*, *Momordica charantia*, and *Trichosanthes anguina*, were tested against the early fourth instar larvae of *Aedes aegypti* L. and *Culex quinquefasciatus* (Say) (Diptera: Culicidae). The larval mortality was observed after 24 h of exposure. All extracts showed moderate larvicidal effects; however, a high larval mortality was found in petroleum ether extract of *Citrullus colocynthis* against the larvae of *A. aegypti* (LC_{50}=74.57 ppm) and against lymphatic filariasis vector, *C. quinquefasciatus* (LC_{50}=88.24ppm)[67].

The larvicidal activity of crude acetone, hexane, ethyl acetate, methanol, and petroleum ether extracts of the leaf of *Citrullus colocynthis* (Linn.) Schrad were assayed for their toxicity against the early fourth instar larvae of *Culex quinquefasciatus* (Diptera: Culicidae). The larval mortality was observed after 24 h exposure. The highest larval mortality was found in whole plant petroleum ether extract of *Citrullus colocynthis*. Bioassay-guided fractionation of petroleum ether extract led to the separation and identification of fatty acids; oleic acid and linoleic acid were isolated and identified as mosquito larvicidal compounds. Oleic and linoleic acids were quite potent against fourth instar larvae of *Aedes aegypti* L. (their LC_{50} were 8.80, 18.20 and LC_{90} 35.39, 96.33 ppm respectively), *Anopheles stephensi* Liston (LC_{50} 9.79, 11.49 and LC_{90} 37.42, 47.35 ppm respectively), and *Culex quinquefasciatus* Say (LC_{50} 7.66, 27.24 and LC_{90} 30.71, 70.38 ppm respectively)[68].

Methylene chloride, n-hexane, chloroform and ethanol extracts of *Citrullus colocynthis* fruits were tested against *Aphis craccivora*. The highest insecticidal effect (LC_{50}: 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-glucopyranosylcucurbitacin E[69].

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 is able to protect animals against the toxicity of the venom. It significantly reduced paw edema, cell migration, exudation, hyperglycemia, and MDA. *Citrullus colocynthis* decreased also some inflammatory markers (MPO and EPO activities, CRP and C3) and maintain the level of CPK, ASAT and ALAT. *Citrullus colocynthis* appeared to be a potential tool that can reduce pathophysiological effects induced after envenomation (inflammation and oxidative stress)[70].

Antioxidant effects:

Flavonoids, isosaponarin, isovitexin and isoorientin 3'-*O*-methyl ether, isolated from the fruits of *Citrullus colocynthis* showed significant antioxidant properties[60].

The methanolic fruit extract of *Citrullus colocynthis* was screened to evaluate its free-radical scavenging effect. The highest antioxidant and free radical scavenging ability of the fruit extract was observed at a concentration of 2500 mg/ml[58].

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, a reducing percentage of 88.8% with EA, 74.5% with HM and 66.2% with E1 were recorded, with a corresponding IC_{50} of 350, 580 and 500 µg/ml respectively as compared to 1.1 µg/ml for ascorbic acid[59].

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[49].

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 is about 56% at 800µg/ml, MECC demonstrated dose dependent antioxidant activity comparable with Ascorbic acid[47].

Antidiabetic effect:

The efficacy of *Citrullus colocynthis* (L.) Schrad fruit in 2 months clinical trial was conducted in 50 type II diabetic patients. Two groups of 25 each under standard antidiabetic therapy, received 100 mg *Citrullus colocynthis* fruit capsules or placebos three times a day, respectively. The patients were visited monthly and glycosylated hemoglobin (HbA1c), fasting blood glucose, total cholesterol, LDL, HDL, triglyceride, aspartate transaminase, alanine transaminase, alkaline phosphatase, urea and creatinine levels were determined at the beginning and after 2 months. The results showed a significant decrease in HbA1c and fasting blood glucose levels in *C. colocynthis* treated patients. Other serological parameters levels in both groups did not change significantly. No notable gastrointestinal side effect was observed in either group[71].

The direct *in vitro* effects of several distinct *Citrullus colocynthis* seed extracts was evaluated in glucose-stimulated insulin release from pancreatic islets isolated from rats. Six extracts were tested, a crude aqueous, defatted aqueous, ethyl acetate, H_2O-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 H_2O-methanol extracts. The majority of extracts exhibited a positive insulinotropic action when tested in the presence of 8.3 mM D-glucose[72].

Citrullus colocynthis possessed antidiabetic effect in rats at the dose of 50 and 100mg/kg bw for 28 days. Haematological and biochemical estimations were done at the end of experiment. Rats were then sacrificed and histopathological examinations were carried out . The results obtained showed that *Citrullus colocynthis* is safe for use as an antidiabetic remedy[73].

The effect of root of *Citrullus colocynthis* on the biochemical parameters of normal and alloxan-induced diabetic was investigated in rats. 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%) ($p<0.01$). 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 total and conjugated bilirubin, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transminase and alkaline phosphatase [74].

The antidiabetic effect of *Citrullus colocynthis* on liver hexokinase and gluconeogenic enzymes such as glucose-6-phosphatase and fructose 1, 6-bisphosphatase was investigated in control and alloxan-diabetic rats. Oral administration of leaf suspension of *Citrullus colocynthis* (250 and 500mg /kg body weight) for 60 days resulted in momentous reduction in blood glucose (from 381 ± 34 to 105 ± 35 mg/ dl), glycosylated hemoglobin, a decrease in the activities of glucose-6 phosphatase and fructose 1, 6-bisphosphatase, and an increase in the activity of liver hexokinase. These findings further support the antidiabetic effect of *Citrullus colocynthis*[75].

A double-blind randomized placebo-controlled clinical trial using a parallel design was carried out to examine the safety and efficacy of *Citrullus colocynthis* topical formulation in patients with painful diabetic neuropathy. Sixty patients with painful diabetic polyneuropathy (PDPN) were randomly allocated to receive the topical formulation of *Citrullus colocynthis* (1:1 allocation ratio) or placebo for three months. The patients were evaluated before and after the intervention in terms of Neuropathic Pain Scale, electrodiagnostic findings, World Health Organization BREF quality of life scores and reported adverse events. The mean change in pain score was significantly higher in the *Citrullus colocynthis* group 3.89 than in the placebo group 2.28 ($P<0.001$). The mean changes in nerve conduction velocity of the tibial nerve, distal latency of the superficial peroneal

nerve and sural nerve, as well as sensory amplitude of the sural nerve in the intervention group were significantly higher than in the placebo group (P<0.001). No significant differences were observed between the mean changes in other nerve conduction values. World Health Organization BREF quality of life scores, only showed significant improvement of the physical domain[76].

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[77].

Anticancer effect:

The antiproliferative effect of cucurbitacin glycosides extracted from *Citrullus colocynthis* leaves was studied in human breast cancer cell growth. Leaves were extracted and cucurbitacin B/E glycosides were isolated from the extract. 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 G2/M phase of the cell cycle. Treated cells showed rapid reduction in the level of the key protein complex necessary to the regulation of G2 exit and initiation of mitosis, namely the p34CDC2/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 might also influence intracellular signaling by molecules such as protein kinase B (PKB), resulting in inhibition in the transmission of survival signals. Reduction in PKB phosphorylation and inhibition of survivin, an antiapoptosis family member, was observed. The treatment caused elevation in p-STAT3 and in p21WAF, 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 (DC) using a fluorescent dye, JC-1. The results revealed that cucurbitacin glycosides exhibit pleiotropic effects on cells, causing both cell cycle arrest and apoptosis. These results suggest that cucurbitacin glycosides might have therapeutic value against breast cancer cells[78].

Antiinflammatory and analgesic effects:

The analgesic and anti-inflammatory activities of Tunisian *Citrullus colocynthis* immature fruit and seed organic extracts (petroleum ether, chloroform, ethyl acetate, acetone and methanol extract) were assessed *in vivo*. The acetic acid writhing test in mice and the carrageenan- induced paw edema assay in rats were used for evaluation. All extracts displayed an important analgesic and anti-inflammatory activities at different doses (0.5 and 1 mg/kg for anti-inflammatory and 0.05 and 1 mg/kg for analgesic effect) without inducing any side effects[79].

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[80].

Gastrointestinal effect:

The *Citrullus colocynthis* seed methanolic extract was evaluated for anti-ulcerogenic activity by pyloric ligation induced ulcers model in Wistar albino rats. *Citrullus colocynthis* (200 mg/kg) showed maximum inhibition of gastric volume 1.68±0.18, free acid 39.86±3.86 and total acidity 61.23±1.87 at dose of 200 mg/kg. The maximum percentage inhibition of ulcerogenicity by the extract in pyloric ligation model was 71.57% at a dose of 200 mg/kg[49].

Hypolipidemic and anti-obesity effect:

The hypolipidemic effect of *Citrullus colocynthis* was studied clinically. One hundred dislipidemic patients were randomly divided into two treated and placebo groups. They were treated daily with powdered seeds of *Citrullus colocynthis* (300 mg) and placebo for 6 weeks. Lipid profile, SGOT and SGPT were measured at the beginning and the end of the treatment period. Significant differences within and between treated and placebo groups was recorded in TG and cholesterol (p<0.05). A daily intake of 300 mg/ day of powdered seeds of *Citrullus colocynthis* can lower the triglyceride and cholesterol concentration significantly in nondiabetic hyperlipidemic patients[81].

The effects of the fixed oil extracted from the seeds of *Citrullus colocynthis* on blood homeostasis and body weight were studied in rats. Animals were given daily 4% of dietary regimen of the *Citrullus colocynthis* oil for 8 weeks, they showed significant slowdown of the body weight evolution comparatively to the animal in control group received 4% of sunflower oil. Furthermore, Colocynth oil treatment had a tendency to increase

food intake feces output, and lipid in feces significantly. In parallel, the serum cholesterol, triglycerides, ALP levels and the count of erythrocytes and haematocrit level decreased significantly by 15.38, 22.22,46.29, 14.97 and 14.17%, respectively compared to control values; while AST level increased significantly by 21.71%. These results support the suggestion of using *Citrullus colocynthis* oil as a treatment for dyslipidemia and hyperglycemia, and related abnormalities[82].

The inhibitory effect of *Citrullus colocynthis* (CCT) on inflammatory cytokines secreted in obesity conditions was studied in mice. Control group was fed with normal diet (N-D) for 42 days alone or plus 50 mg/kg hydro-alcoholic (H-A) extract of CCT. The obese mice were given high fat diet (H-F-D) for 42 days alone or plus CCT extract. Food intake and body weight were recorded each week and expression of TNF-α, IL-6 and IL-10 in serum were assayed after every two weeks. CCT extract reduced body weight by 4.02% ($p > 0.05$) and food intake by 3.52% ($p>0.05$), but dramatically decreased expression of TNF-α 44.83($p< 0.001$), IL-6 30.23($p< 0.001$) and marginally increased IL-10 5.31 ($p> 0.05$) in obese mice. Accordingly, CCT extract did not show anti-obesity effects, it could have an anti-inflammatory effect through down regulation of obesity-associated pro-inflammatory cytokines[83].

Protective effects:

The protective effect of methanolic extract of *Citrullus colocynthis* fruits (MECC) was studied in nitrosodiethylamine induced hepatic damage in male rats. Rats received DEN/PB showed elevated levels of cholesterol ($p<0.05$), triglycerides (TG, $p<0.01$), free fatty acids (FFA, $p<0.01$), low density lipoprotein (LDL, $p<0.01$), very low density lipoprotein (VLDL, $p<0.05$) and decreased level of high density lipoprotein (HDL), urea and creatinine. Administration of MECC 200,400 mg/kg to rats orally for 28 days significantly reduced the biochemical alterations induced by DEN/PB[47].

The nephropathy protective effect of *Citrullus colocynthis* fruits extract was studied in streptozotocin induced diabetes in rats. The extract of *Citrullus colocynthis* fruit was given as (50mg/kg/day) orally for 50 days. *Citrullus colocynthis* fruits extract caused significant decrease in blood glucose, urea, creatinine, microalbuminuria and uric acid, while, GSH, GPx and SOD were significantly increased in comparison with diabetic untreated group. The histopathological findings were coincided with biochemical findings in both diabetic and treated groups. Diabetic kidney showed atrophy of renal curpusle, shrinkage of capillary within increase Bowman's space while, diabetic rat received *Citrullus colocynthis* fruit extract showed partial protection of glumeruli and appeared nearly normal. The study clearly demonstrated that *Citrullus colocynthis* fruit exerted protective effects on the kidney functions and tissues. So it may play a role in prevent nephropathy as one of microvascular complications of diabetes mellitus[84].

The protective potentials of *Citrullus colocynthis* was evaluated against gentamicin induced nephrotoxicity. Toxic doses of gentamicin (80 mg/kg/day, i.m.) were administered alone and as co-therapy with the extract of *Citrullus colocynthis* (25 mg/kg/day, po). Physiological, biochemical and histological examinations were performed to compare the experimental and toxic groups with control group animals. Co-therapy of *Citrullus colocynthis* with gentamicin protected changes in the body weight, blood urea nitrogen, creatinine clearance, proteins and lactate dehydrogenase excretions. However, a significant rise in serum creatinine and serum uric acid with fall in serum calcium and serum potassium was observed, which were significantly different from control group animals. Necrotic and ruptured tubules were also found abundantly. This study revealed that co-theapy of *Citrullus colocynthis* with gentamicin for twenty one days, failed to protect renal injury associated by gentamicin in spite of its strong antioxidant properties[85].

Effect on hair growth:

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[86].

Reproductive effect:

A crude 50% ethanol extract of *Citrullus colocynthis* Schrad was administered orally to male albino rats for evaluation of antifertility effects. The animals were divided into five groups: group A was a vehicle-treated control group; treatment groups B, C, and D received 100 mg/kg/day *Citrullus colocynthis* extract for periods of 20, 40, and 60 days, respectively, and group E animals received the extract at dose of 100 mg/kg/day for 60 days followed by 60 days of recovery. For androgenicity evaluation of the extract, the animals were divided into four groups: group F animals were castrated 30 days before the experiment to serve as controls, and group G, H, and I were subjected to castration 30 days before the experiments, followed by administration of fruit extract (100

mg/kg/day po), testosterone propionate (0.01 mg/rat/alternate day sc), and fruit extract along with testosterone propionate, respectively, for 30 days. Significant reduction of cauda epididymis sperm motility and density, number of pups, fertility, and circulatory levels of testosterone were observed in all treatment groups. The weights of testes, epididymis, seminal vesicle, and prostate were significantly decreased in groups B, C, and D. The weights of all organs in the different groups of the androgenicity study were markedly decreased in group F when compared with group A, in group G when compared with group F, and in group I when compared with group H, and increased in group H when compared with group F. The serum testosterone levels also showed a similar pattern. The concentration of testicular cholesterol was significantly elevated, while protein, sialic acid, acid and alkaline phosphatase concentrations were decreased. The histoarchitecture of the testes showed degenerative changes in the seminiferous epithelium, arrest of spermatogenesis at the secondary spermatocyte stage, cytolysis, and the lumen filled with eosinophilic material. Histometric parameters (except Sertoli cell) revealed that the nuclear area and the number of round spermatids were markedly altered. All altered parameters restored to normal in group E. No changes were observed in body weight, litter size, hematology, and serum biochemistry. The authors concluded that 50% ethanol extract of *Citrullus colocynthis* showed an antiandrogenic nature, thereby reduced infertility in male albino rats[87].

The toxic effects of *Citrullus colocynthis* was studied on the female reproductive system. After administration of 400 mg/kg/body weight to female rats for two time periods 4 and 12 weeks, females were allowed mating with males after 10 days prior to the last administration dose. Then females were autopsied under light anesthesia and several parameters were determined including: number of pregnant rats, body and reproductive organ weight, number of implantation sites, viable fetuses and resorption sites. Exposure to *Citrullus colocynthis* for 4 weeks did not have much effect on fertility. Significant decrease in the relative ovarian weights and embryo weights in female rats exposed to *Citrullus colocynthis* were observed. Exposure to *Citrullus colocynthis* for a 12 weeks resulted in a reduction in the percentage of pregnancies and in the number of implantation sites when compared with controls in both treatment periods. Rats receiving 12 weeks treatment showed a decrease in ovarian weights and a decrease in viable fetus's number. These results indicate that long-term exposure of female rats to *Citrullus colocynthis* causes adverse effects on the reproductive system and fertility[88].

Side effects and toxicity:

The teratogenicity of fruit pulp extract of *Citrullus colocynthis* was studied in rats at a dose of 40.6 mg/kg body weight that is equivalent to one fourth of the LD_{50} of the extract. Gross anatomical observation on the 20th day of gestation revealed a high percentage of resorbed fetuses, smaller size and weight fetuses as well as absence of coccygeal vertebrae, metacarpal and metatarsal bones, and carpal and tarsal bones. It could be concluded that the extract of fruit pulp of *Citrullus colocynthis* may cause teratogenic effects if given during the early stage of pregnancy[51].

Rabbits were treated with 100 or 200 mg/kg/day of either pulp or seed extract. One month later, surviving animals were sacrificed and specimens of small intestine, kidney, and liver were prepared for morphological evaluation. No animals treated with 200 mg/kg/day of pulp extract survived. Animals treated with 100 mg/kg/day of pulp extract displayed sever lesions in the small intestine, kidney, and liver. Interestingly, animals treated with either 100 or 200 mg/kg/day of seed extract displayed only minor intestinal insult. In contrast to seed extract, pulp extract of *Citrullus colocynthis* can be fatal to rabbits[89].

Four patients with colocynth intoxication were presented with acute rectorrhagia preceeded by mucosal diarrhea with tenesmus, which gradually progressed to bloody diarrhea and overt rectorrhagia within 3 to 4 hours. The only colonoscopic observation was mucosal erosion which was completely resolved in follow-up colonoscopy after 14 days. The membranolytic activity of some *Citrullus colocynthis* ingredients is responsible for the intestinal damage[90].

The drug is severely poisonous. It has a strongly irritating (and painful) effect on mucous membranes due to its cucurbitacin glycoside content. Overdose usually associated with vomiting, bloody diarrhea, colic, and kidney irritation, follow the intake of toxic dosages (0.6 to 1 g), and then increased diuresis which progressed to anuria. Lethal dosages (starting at 2 g) lead to convulsions, paralysis and, if untreated, to death through circulatory collapse. The treatment for poisonings should proceed symptomatically following gastric lavage[91].

II. CONCLUSION

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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