



**A REVIEW ON DIFFERENT PARTS OF THE PLANT *CITRULLUS
COLOCYNTHIS SCHRAD* AND THEIR ANTIDIABETIC POTENTIAL**

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ABSTRACT

Diabetes is a major evildoer behind the mortality in the world. Worldwide data on mortality, Prevalence, and Incidence demand the humankind to take genuine endeavors on this issue, Current investigations and statics have expounded diabetes as one of the most prevalent endocrine disorder throughout the world. *Citrullus colocynthis Schrad (CCS)* is one of the most widely recognized conventional plants utilized as a remedy against diabetes. It is well recognized by its hypoglycaemic effect, which is substantiated. This plant, the fruit is usually recognized for its wide scope of anti-diabetic uses as well as pharmaceutical and nutraceutical potential. A genuine effort without any bias and interest has been taken in this article which provides the clear and cosine worldwide clinical and regulatory data of *CCS*. This review also sums up the various proven antidiabetic potential of *CCS* along with the granted patents. The only objective behind this article is to provide a thought process and to give a new vision to present and future scientists, researchers, industries, and regulatory bodies on the potential of *CCS* in diabetes for the betterment of society by highlighting clinical and pre-clinical studies which contributed to support the concept. This paper concludes that *CCS* possesses a wide range of medicinal uses and has been well studied for its antidiabetic potential.

**Keywords: *Citrullus colocynthis Schrad*, Clinical Trials, Diabetes, Medicinal Parts, Patents,
Herbal**

1. INTRODUCTION

Out of many endocrinal diseases, diabetes is one of the most commonly prevalent metabolic disorders which distresses over one billion population of the world and cause extensive deaths. Various factors causing this disease have been observed, including diet and age [1]. World Health Organization (WHO) has revealed that three billion diabetic cases would be observed by the year 2025 [2]. As per WHO diabetes is one of the main culprits of death in the world and around 422 million individuals worldwide have diabetes, especially in low-and center

pay nations [3, 4]. The American Diabetes Association gave insights about diabetes and proposed to make a move against prediabetes few changes in diet and exercise that can have a major effect with prediabetes [5, 6]. Centre for disease control and prevention, 2020 national report estimated excess of 88 million US grown-ups—over a third—have prediabetes, and over 80% of them don't realize they have it and diabetes is the seventh driving reason for death in the United States [7-9].

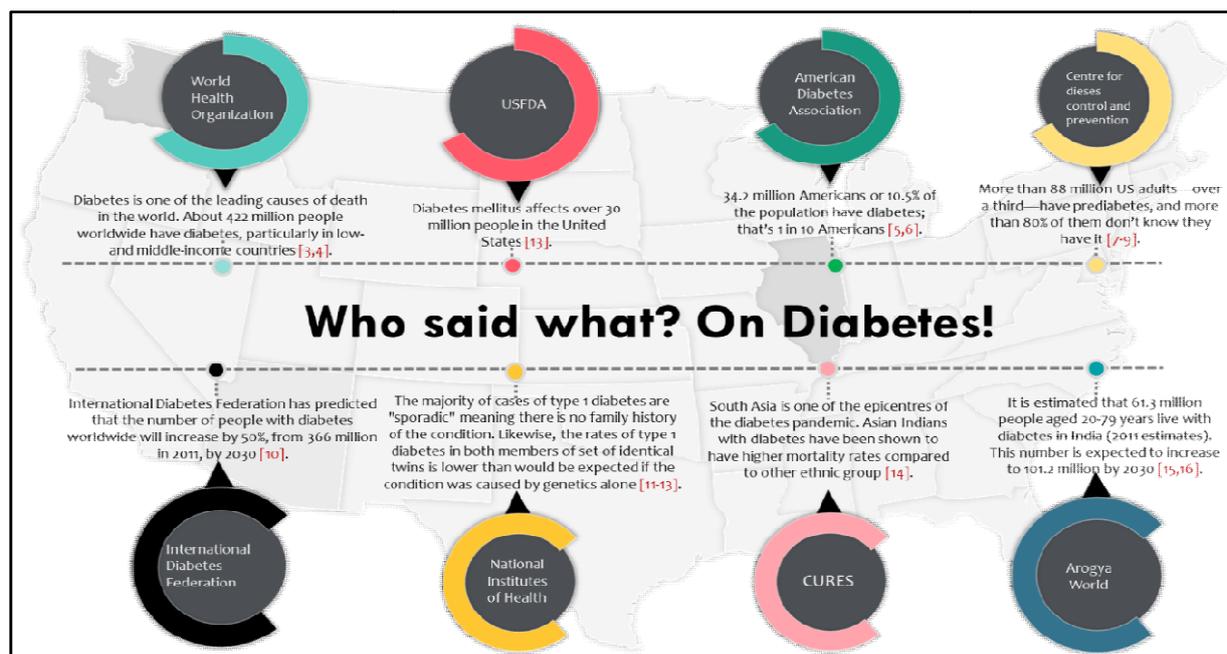


Figure 1: worldwide regulatory and non-regulatory statics on diabetes Source [3-16]

Arogya world predicted that diabetes cases figure is predicted to increase to 101.2 million by 2030 [15, 16]. The rest of the regulatory and non-regulatory institutions discussion on diabetes if listed in figure-1 above. Irregular carbohydrate metabolism leads to higher

blood glucose level than normal, that may be a root of numerous complications like nephrotoxicity and retinopathy and finally death of a diabetic person [17]. In the case of Chronic illness due to diabetes instabilities of metabolism of proteins, lipids [18] occur that

and promotes peroxidation of lipids of membrane resulting in trouble in cell function. Hyperglycemia also promotes nonenzymatic glycation of proteins promoting an increase in the development of reactive oxygen species [19].

There is a long history of herbal use as antidiabetic therapy. In the future also there is need for herbal antidiabetic therapy and the validated antidiabetic potential of many plant remedies that are available in the literature showing controlled analyses in healthy and diseased animals as well as humans in the last ten years. The mode of the antidiabetic effect of herbal remedies involves the modulation of carbohydrate metabolism by restoring the integrity and function of the β cells [20, 21]. In this regard *Citrullus colocynthis* Schrad is a proven anti-diabetic plant for many years, it

belongs to the *Cucurbitaceae* family and is an annual plant that grows in native to North Africa, the Middle East and South Asia Southern Europe, [22]. It is a perennial herb usually dragging. It is commonly found wild in the sandy lands; it's extremely bitter tastes and violent purgative properties are well known [23]. Hence, its popular common names in English are bitter apple, bitter cucumber, colocynth, and bitter gourd [24]. The appearance of CCS (Figure 2 A) resembles that of watermelon, possessing herbaceous stems, triangular and hairy leaves, yellow flowers, and globular bitter fruit. Its fruit consists of an outer hard rind and an inner white spongy pulp. A large number of seeds are embedded in its pulp [25]. Further fruit is yellow and smooth [26].

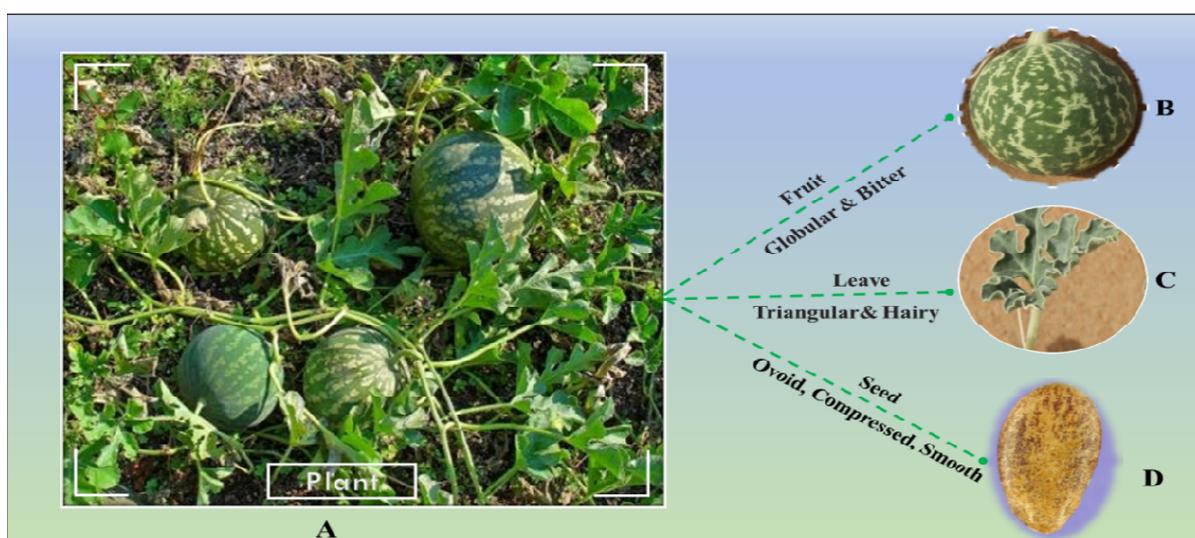


Figure 2 A: *Citrullus colocynthis* Schrad whole plant, B= Fruit, C= Leaf, and D= Seed

The main medicinal fragment of the plant is the fruit pulp, and other medicinal parts of the plant are the seed, leaf, and root [28, 29]. The

objective of this review is to collect and summarize under one roof of all such data, which involve the study of the antidiabetic

effect of parts of CCS. The detailed-on fruit and other medicinal parts along with their past proven activities are discussed in the below section:

1.1 Fruits of CCS:

As discussed above, the fruit of this plant (**Figure 2 B**) is globular, yellow, and smooth, which when ripe contains within it a hard-coriaceous rind, and a white spongy pulp enclosing many ovate compressed white or brownish seeds [26, 30]. It is hard having skin around it and contains 200–300 seeds/gourd [31]. The fruit is also slightly depressed, 5–7.5 cm in diameter, and gets white glabrous when ripe. The fruit is loaded up with a dry, elastic exceptionally harsh mash. Each unpleasant apple plant delivers around 15–30 globular fruits having a diameter of almost 7–10 cm. The external segment of the organic product is secured with green skin having yellow stripes [32]. A few bioactive chemical constituents of fruits are recorded, such as glycosides, alkaloids, fatty acids, flavonoids, and essential oils. The isolation and identification of a valuable constituent of fruit *Cucurbitacins* A, B, C, D, E, I, J, K, and L and *colocynthosides* A and B are also reported [33]. Traditionally and Ethnomedicinally CCS fruit is used for numerous treatments like:

➤ **Diabetes:** Pulp of ripe CCS fruits is trampled by naked feet till feeling of bitter taste appears in the mouth for 15 days and root powder is also used in

diabetic patients in some areas of Haryana and Rajasthan.

- **Constipation:** Decoction of fresh fruits of “CCS” is prepared in water in ratio of 1: 6. Five ml decoction is administered orally at bed time for three days.
- **Deafness:** Ripe whole fruits or pericarp of “CCS” is boiled in *Sarson/Mustard Oil* (*Brassica campestris* L., Family-*Brassicaceae*) in a ratio of 1: 7. Three to four drops of this oil are dropped in the affected ear two times in a day till ailment is cured completely.
- **Flatulence:** Ripe “CCS” fruits are stuffed with black pepper (*Piper nigrum* L., Family-*Piperaceae*) through a hole made in the pericarp. Each fruit is shielded with mud and baked in the cow-dung fire till it becomes red. The ash of “CCS” fruit and black-pepper are collected and stored. Half gm ash is given after each meal for 15 days.
- **To promote lactation:** Decoction of fresh fruit of “CCS” is prepared in water in ratio of 1: 6. Two ml decoction is administered orally twice daily for seven days.
- **Pimples:** The fruit and roots with or without *Nux-vomica*, is rubbed into a paste with water. The paste is applied externally on pimples, till a complete cure is achieved.
- **Stomach ache:** Small fruits of ‘CCS’ are collected and stuffed with salt and

'Ajwain'. The fruits are dried and ground to make powder. Two g powder is given orally twice in a day for 2 days.

- **Jaundice:** Fresh fruit pulp of 'CCS' is mixed with 'Ajwain' seeds and this mixture is kept for seven days and then dried in shade, grind to powder. 2 g powder is given orally twice in a day for 3 days.
- **Piles:** Dry fruit pulp is kept in water overnight in the earthen pots. Regular washing of anal part after nature's call in the morning [34].

Bande and Co-workers determined basic dimensions and mass of CCS fruit with a digital gauge that aimed to give information on the loading capacity in transportation and storage of the harvested fruit before processing; they reported scale with accuracy 0.01 mm and 0.01 g, respectively. Maximum length, width, thickness, and mass of 100 samples were 12.86 cm, 12.53 cm, 15.52 cm, and 1031.5 g, respectively. Arithmetic and geometric mean diameters were between 5.68 and 13.63 and 5.58 and 13.22 cm while mean bulk and true densities were 404.98 and 1074.6 kg/m³ on 3 and 6 runs, respectively. The sphericity and aspect ratio were about 1, with an average packaging coefficient, on five separate runs, of 33.49. The average vertical and horizontal weight to break the fruit was 121.23 and 74.09 kg, respectively [35]. Generally, the average mass of CCS fruit is 506 g, and the mass of pulp is almost

50% of the mass of fruit, while the seed content is 71.8 g [36]. Marzouk *et al.*, 2011 examined the anti-inflammatory activity of aqueous extracts of CCS fruit at a juvenile phase utilizing the carrageenan-induced paw edema assay in rats. The best anti-inflammatory activities were gotten with immature fruits from south Tunisia. Consequently, CCS could be a valuable item appropriate for additional assessment of inflammatory diseases [37]. Bactericidal exercises of unrefined concentrates, divisions and mixes of CCS plant flying parts and ready deseeded natural products were performed against the medication touchy standard strain of *Mycobacterium tuberculosis* H37Rv (ATCC 27294), 16 medication safe strains of *Mycobacterium tuberculosis* and two *Mycobacterium* other than tuberculosis (MOTT) strains, utilizing radiometric BACTEC framework. Methanolic concentrate of a ready deseeded product of CCS indicated great movement (MIC = 62.5 µg/ml) and one of the bioactive parts exhibited the best action (MIC 31.2 µg/ml) against *Mycobacterium tuberculosis* H37Rv [38].

1.2 Leaves of CCS:

The leaves (**Figure. 2 C**) stand alternately on long petioles. They are triangular, many cleft, variously sinuated, obtuse, hairy, a fine green on the upper surface, also rough and pale underneath [30] they are 2-4 inches long, with 3-7 profound lobes; and solitary light-yellow blossoms are found [39]. Sometimes leaves

are very variable in size. The wild leaf is 3.8–6.3 cm in length and 2.5 cm in width while cultivated leaves are large. The leaf shows deltoid margin, the pale green color above and ashy color beneath, scabrid on both surfaces, 5–7 lobed. The angular leaves are alternately situated on long petioles. Each leaf is about 5–10 cm long and has around 3–7 lobes. Some of the time the center flap may have an applaud structure. The leaves have an unpleasant, shaggy surface with open sinuses [32]. *Cucurbitacin* is a major chemical constituent of leaves of *CCS* [40] apart from this Quercetin [41] alkaloids, flavonoids, and glycosides are possible constituents responsible for various activities [42]. Traditionally and Ethnomedicinally leaves of *CCS* is used for numerous treatments like:

- **Leukoderma:** Fresh leaf extract, obtained by squeezing pounded leaves in a muslin cloth, is put on affected areas of skin twice or thrice a day. Seed oil is kept to depigmented areas every third day. The therapy is continued until the pigments reappear and become stable. This is a reputed therapy for leukoderma in the study area.
- **Skin lice infection:** Leaf juice, boiled with pure mustard oil, filtered and massaged all over the body before bath.

In a study conducted by Sagar et al., 2018 various extracts viz alcoholic, acetone, chloroform of the leaves of *CCS* were assessed for antibacterial activity against

Staphylococcus aureus and *E.coli* and it was observed that none of the extracts displayed antibacterial activity against both the bacteria when compared to standard antibiotic [43]. *Cucurbitacin* glucosides extracted from *CCS* leaves have shown growth-inhibitory activity on human breast cancer cells [44].

1.3 Seeds of *CCS*:

The seeds are small (6mm in length), ovoid (**Figure 2 D**), compressed, smooth, and brownish when ripe. Seeds constitute about 75% of the weight of the fruit of *CCS* [31] While growing on marginal lands, about 6,500 kg ha⁻¹ seed yield is possible with little effort since this plant seed has high oil contents of up to 53% [45]. The seeds contain flavonoids and polyphenolics [46], Fatty acids like palmitic acid, stearic acid, linoleic acid, oleic acid [47, 48] and tocopherols and carotenes like α -tocopherol, β -tocopherol, β -carotene Fruitseed oil [49]. Traditionally and Ethnomedicinally seeds of *CCS* is used for numerous treatments like:

- **Premature greying of hairs:** Mature “*CCS*” seeds are compressed to extract the oil. Regular application of this oil is claimed to impart natural black color to the grey hair.
- **Malaria:** Pulp of seeds eaten twice a day for 2 days.
- **Scarcity:** Seeds of ‘*CCS*’ are beneficial in scarcity. Bitter seeds buried in common salt to wash-off their bitter principles,

dried and mixed with *Bajra* seeds and the mixed flour is taken [34].

The seeds of *CCS* are known to possess: 567.32 kcal/100 g dry weight, 17%–23% fatty acids, of which a low amount of free fatty acids (1.57% total seed weight and 7% total oil) and both triglycerides and free fatty acids comprise mostly linoleic acid (66%–76.4%), palmitic acid (6.3%–8.1%), oleic acid (7.8%–14.2%), and stearic acid (6.1%–7.3%); proteins at 11.7% of total weight; nonfibrous carbohydrates at 29.5% total weight; dietary fiber at 5.51% total weight; $7.51 \pm 0.53\%$ moisture content; 2.9%–3.2% ash content (dry weight); vitamin E at 121.85 mg/100 g with a high α -tocopherol content (116.36 ± 0.15 mg/100 g; 95% total vitamin E) and lower α (0.72 ± 0.06 mg/100 g), β (0.57 ± 0.03 mg/100 g), and δ (4.19 ± 0.12 mg/100 g) content [48]. Mariod *et al.* (2009) investigated the fruit characteristics of *CCS*; they reported 14.8 g dry fruit weight, 13.0 cm fruit length, and 13.0 cm fruit diameter. They found that the weight of dried seeds was 4.6 g, while the weight of dried pulp was 10.2 g. These authors reported that the dried pulp of *CCS* represented more than 68.9% of dry fruit weight. The *CCS* seeds showed 15.75% protein content, carbohydrates as 17.01 and ash as 4.62 g/100 g, respectively. The oil content of *CCS* is 27.10% of the seed weight. The oil obtained from the seed of *CCS* showed good physicochemical properties like the refractive index ($40 \pm 1^\circ\text{C}$) is 1.429, the

relative density ($30 \pm 1^\circ\text{C}$) is 0.886, the unsaponifiable matter is 0.8%, and iodine value is 112.7. Arbi Nehdi *et al* and co-workers' research work gave new data to the world where, they evaluated the physicochemical properties, fatty acid, tocopherol, thermal properties, ^1H NMR, FTIR and profiles of non-conventional oil extracted from *CCS*. Seeds were evaluated and compared with conventional sunflower seed oil. Besides, the antioxidant properties of *CCS* seed oil were also evaluated. The oil content of the *CCS* seeds was 23.16%. The main fatty acids in the oil were linoleic acid (66.73%) followed by oleic acid (14.78%), palmitic acid (9.74%), and stearic acid (7.37%). The tocopherol content was 121.85 mg/100 g with α -tocopherol as the major one (95.49%). The thermogravimetric analysis showed that the oil was thermally stable up to 286.57°C , and then began to decompose in four stages namely at 377.4°C , 408.4°C , 434.9°C , and 559.2°C . The present study showed that this non-conventional *CCS* seed oil may be utilized for food and non-food applications to supplement or replace a few of the conventional oils. *CCS* seeds showed significant antihyperlipidemic results on New Zealand rabbits. The hypercholesterolemic control rabbits remained hypercholesterolemic throughout the experimental time but serum cholesterol and triglyceride in the groups administered with both seeds and pulps extracts of *CCS* were

reduced ($p < 0.05$). The reduction of LDL-C in the groups treated with the pulp extracts and 100 mg/kg seed extract was significant ($p < 0.05$). The impact of CCS on the blood lipid profile in rabbits might be because of high measures of saponins in CCS which diminished cholesterol levels by lessening the ingestion of cholesterol, expanding the repulse of feces estriol and looseness of the bowels because of expanded peristalsis.

2. DIVERSE PARTS OF *CITRULLUS COLOCYNTHIS SCHRAD* AND THEIR CHEMICAL CONSTITUENTS

A few bioactive compounds of CCS plant have been verified in the literature. They are assembled as carbohydrates, flavonoids, alkaloids, glycosides, fatty acids, and essential oils; however, there are just a couple of reports on the isolation and identification of individual chemical constituents [42]. **Table 1** represents the summary of various chemical constituents of different parts of CCS.

Cucurbitacins have been reported as the main components of CCS fruits. Numerous investigations announced the presence of alkaloids in the CCS fruit, however, just a couple of reports are accessible on the isolation and identification of individual alkaloids [42]. Gurudeeban et al., identified 17 volatile compounds from the fruit pulp, ranging from 0.51% to 48.0% of peak area the alcohols identified were 4-(1-methyl)ethoxy-1-butanol; 5-methoxy, 2-

methyl 1,2-pentanol; 1-cyclopentyl, 2-propene-1-ol and 2-furanm ethanol, tetrahydro 5-methyl-cis and trans-isomers. The ketones characterized were 3,4-dimethyl, 2-hexanone; 2-methyl, 4-heptanone and 3-methyl, 2-heptanone. Two epoxy compounds (1-propoxy pentane and 2,3-epoxy methyl propionate) were identified. The seed kernels contain about 50% oil, 30% protein, 10% carbohydrate, 4% ash, and 3% fiber. CCS is also an excellent source of different amino acids as arginine, methionine, and tryptophan. In another report, the key mineral component from CCS was found to be phosphorus, potassium, magnesium, manganese, sulfur, calcium, iron, and zinc.

3. ANTI-DIABETIC POTENTIAL OF *CITRULLUS COLOCYNTHIS SCHRAD*:

Diabetes is one of the fastest-growing metabolic diseases. The treatment is symptomatic and requires life-long use of chemical drugs, which produce numerous adverse actions in addition to high cost, hence, the search for more effective and safer anti-diabetic continues. CCS has been broadly utilized as anti-diabetic in various nations and interestingly attracted an enormous number of studies both on animals and humans. Few in-vivo studies are discussed below and listed in **Table 2**. Recently, the impact of the aqueous extracts from the seeds on the biochemical parameters of normal and streptozotocin (STZ) induced diabetic rats was determined by a researcher. Diabetes was instigated by a

single intraperitoneal (60 mg/kg body wt) injection of *STZ*. Oral administration of the plant extract (300 mg/kg, daily for 2 weeks) diminished the plasma level of AST and LDH significantly, while it failed to reduce the raised blood level of GGT and ALP in diabetic rats.

CCS has been traditionally utilized as a medicinal plant for diabetes; since it induces insulin secretion from the pancreas after supplementation, while reducing blood glucose and improving lipid levels. Oral ingestion of the fruit at doses lower than (300–800 mg daily) tends to be prescribed in some Middle Eastern locations for the treatment of diabetes to avoid the intestinal side effects. There is one such study in the literature, which involved the use of leaf extract of *CCS*. Where researchers investigated the hypoglycemic influence of *CCS* on hepatic hexokinase and gluconeogenic enzymes like glucose-6-phosphatase and fructose 1,6-bisphosphatase of control and AID rats after oral intake of its leaf suspension in the doses of 250 mg/kg and 500 mg/kg of body weight for sixty days and found a significant fall in blood glucose level from 381 + 34 to 105 + 35 mg/dL. There was a reduction in the activities of glucose-6-phosphatase and fructose 1,6- bisphosphatase, and an enhancement in liver hexokinase activity supporting the hypoglycemic importance of this medicinal plant. Tannin-Spitz et al, studies the differential impacts of

diets supplemented with *CCS*, sunflower, or olive oils on the pancreatic M-cell mass in streptozotocin (*STZ*)-induced diabetes in rats. *STZ* injection-induced rapid hyperglycemia in all animals. However, after 2 months, hyperglycemia was significantly less pronounced in the rats fed a *CCS* oil-enriched diet compared with other rat groups. Evaluation of insulin sensitivity using the homeostasis model assessment technique also showed less insulin resistance in the rats fed on a *CCS* oil-enriched diet than the other rats. Two months after *STZ* injection, the pancreatic M-cell mass was similar in both *STZ*-treated rats fed the colocynth oil-enriched diet and their controls fed the same diet.

Antidiabetic action of petroleum ether fruits extract of *CCS* against Streptozotocin initiated hyperglycemic rats was assessed after oral administration of two distinct doses (300 and 500 mg/ kg) of *CCS*. Phytochemical investigations revealed the following chemical constituents like alkaloids, terpenes, saponins, and glycosides. Administration of petroleum ether extract of *CCS* fundamentally enhanced the bodyweight of diabetic rats in a dose and time-dependent manner. *CCS* showed antidiabetic action through stimulation of β -cells of islets of Langerhans by releasing more insulin and this effect was brought about by constituents like glycosides, saponins, flavonoids [48]. Salami et al. also observed significant hypoglycemic effects of

suspensions of *CCS* fruit pulp in normal 12 h fasting rats after a single dose of 30 mg/kg, while suspensions of *CCS* fruit pulp in the doses of 10 mg/kg and 90 mg/kg exhibited non-significant hypoglycemic effects. The effect of hydro-ethanolic extract of *CCS* pulp was studied on alloxan-induced hyperlipidemia in diabetic rats and the results predicted noticeable decrease in the of total cholesterol levels, free fatty acids, triglycerides, and phospholipids in serum and liver of diabetic rats treated with *CCS* when compared to diabetic untreated rats. Agarwal *et al.*, 2012 examined the effect of the root of *CCS* 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 presenting blood glucose level in the range of 175-300 mg/dL were included for study. The blood glucose concentrations of the animals were estimated at the start of the examination and the estimations were rehashed on the third, fifth, and seventh day after the beginning of the analysis. Aqueous extract of roots of *CCS* indicated a noticeable change in blood sugar level (58.70%) when compared with chloroform (34.72%) and ethanol extracts (36.60%). The aqueous extracts demonstrated improvement in parameters like body weight, serum urea, serum creatinine, 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) [46]. The effect of *CCS* pulp extract on the structure of the liver was tested in diabetic rats at both light and scanning electron microscopic levels. Diabetes produces degenerative changes in the form of disorganization of the hepatic cords, cytoplasmic vacuolization, and pyknosis of the nuclei of hepatocytes and inflammatory cell infiltration. The SEM examination of these livers exposed various lipid droplets within hepatocytes, damaged blood sinusoids, and haemorrhage of erythrocytes between hepatocytes and inside Disse's spaces. The liver of *CCS*-treated rats revealed slight histological alterations versus the control animals. All these reports supported the potential of *CCS* as a traditional medicine in diabetes and suggested it to be a safe modern antidiabetic agent.

4. CLINICAL TRIALS CONDUCTED ON *CITRULLUS COLOCYNTHIS* SCHRAD PLANT:

Human trials always provided an evidence for the efficacy and safety of a drug when conducted ethically for the advantage of society, some clinical studies performed worldwide on *Citrullus colocynthis* Schrad plant are summarized below:

4.1 Study title:

Evaluation of topical *Citrullus colocynthis* schrad fruit oil efficacy in treatment of painful peripheral diabetic neuropathy.**Study details:**

Study / Registration number: NCT02155361,
Sponsor: Shiraz University of Medical Sciences.

Brief summary:

This research was intended to assess the topical CCS fruit oil efficacy in the treatment of painful peripheral diabetic neuropathy (PDN) in a randomized double-blind placebo-controlled clinical trial design. This study included 60 patients with painful conditions other than PDN like radiculopathies were excluded. After giving the Informed consent the patients were undergone NCS (Nerve Conduction Study) before recruitment. Study arms of this study were topical CCS fruit oil (1%) for Phase 1 and Topical vehicle oil for Phase 2. Study primary outcome measure was Pain Scores on the Neuropathic Pain Scale (NPS) [Time Frame: 12 weeks]. Participants were from 18 Years to 70 Years (Adult, Older Adult) of both the Sexes. Inclusion criteria for this trial were Patients having Controlled type 1 or 2 diabetes mellitus. Painful Peripheral diabetic neuropathy for more than 3 months and Patients consent on enrolling study and admitting study protocol. This trial was conducted in Iran under the investigation and Study Chair of Mesbah Shams, M.D. Research Center for Traditional Medicine &

History of Medicine. The study is completed but no official results are posted yet.

4.2: Study title:

The clinical investigation of *Citrullus colocynthis* Schrad fruit in treatment of type II diabetic patients: a randomized, double blind, placebo-controlled clinical trial.

Study details:

Study / Registration number: 207-Q-1/8/1383., **Sponsor:** Endocrinology and Metabolism Research Centre, Tehran University of Medical Sciences, Tehran, Iran.

Brief summary:

A total of 50 of type II diabetic patients (aged 40–65 years), registered at the Diabetic Clinic registry of Shariati Hospital, were selected and enrolled in this study. Written informed consent was obtained from each patient. All the patients who participated (12 males and 38 females) had a confirmed diabetes type II diagnosis with Inclusion criteria type II diabetes with a fasting blood glucose of less than 200 mg/ dL and with a disease duration of 2–8 years, body weight between 55 and 75 kg, normal blood pressure and lipid levels. The selected 300 mg (5 mg/kg for an average of 60 kg body weight/day) dried fruit powder in 3 separate doses was the lowest of doses of CCS prescribed by 10 herbalists (range of doses 300–800 mg/day) with no gastrointestinal disturbance. Fasting glucose levels were accessed by the glucose-oxidase technique using a Beckman Glucose-2

Analyzer immediately after blood sampling. All the patients completed 2 months of therapy. The demographic and paraclinical characteristics of two groups at the start of the trial were significant. The results predicted that CCS fruit treatment has a beneficial effect on lowering the glycemetic state in type II diabetic patients. The use of this herbal medicine at a dose of 300 mg/day in 3 divided doses showed no adverse gastrointestinal symptoms or liver and kidney abnormalities during 2 months of therapy.

4.3: Study title:

The effect of *Citrullus colocynthis* Schrad fruit extract on blood sugar in type II diabetic patients: a double-blind clinical trial.

Study details:

Study / Registration number: RCT2013010211984N1. **Sponsor:** Vice chancellor for research, Zahedan University of Medical Sciences, Karaj, Iran.

Brief summary:

In the present clinical study, 80 patients were enrolled with type II diabetic patients aged between 30 to 60 years, with fasting blood glucose between 150-220 mg/dl and HbA1c 7.5-10% taking two metformin 500 mg or two glibenclamide 5 mg tablets daily, with a minimum two-year history of diabetes that not changed the antidiabetic regimen before 3 months. This was an inclusion criterion; patients were of both the genders for Phase 2-3. The patients signed the written informed

consent and randomly allocated into CCS and placebo groups. The patients were allowed to continue their standard anti-diabetic therapy without any change during the study. The patients in the CCS group were treated by CCS capsules of 100 mg three times in a day and other groups with a placebo capsule in the same manner for 4 months. At close of the trial the fasting blood glucose, glycosylated hemoglobin, cholesterol, LDL, HDL, triglyceride, aspartate aminotransferase, alanine aminotransferase, and creatinine levels were measured in both groups. Mr. Hasan Fallah Huseini is investigating the trails in Iran, no results are published yet.

4.4: Study title:

The efficacy of *Citrullus colocynthis* Schrad fruit on fasting blood glucose and glycosylated haemoglobin as well as its possible side effects among the patients with type II diabetes.

Study details:

Study / Registration number: EC/92/H/187. **Sponsor:** Faculty of Medicine, Ilam university of Medical Sciences, Ilam, Iran.

Brief summary:

In another clinical investigation in Iran, 70 patients having diabetes were investigated by dividing them into two groups of intervention and placebo randomly and were studied for 2 months. The mean serum level of FBS and HbA1c was compared within and between groups at the end of the trial. Data were analyzed using student and paired t-tests via

SPSS software version 16. The trial outcomes were noticed as an important variation was between before and after intervention for HbA1c and FBS levels in the intervention group ($P = 0.01$ and $P = 0.04$, respectively). The difference between before and after intervention for FBS and HbA1c levels in the placebo group was not significant ($P = 0.8$, $P = 0.68$ respectively). This trial displayed a negative relationship between either the mean \pm standard deviation serum level of FBS or HbA1c and body mass index in the treatment group significantly ($P = 0.03$, 0.008 , respectively). This study did not identify any side effects during the trial period among the treatment group. As per the discoveries of this research, the application of 125 mg CCS once in a day for two months may lead to a significant reduction in the mean levels of HbA1c and FBS among the patients with type II diabetes without any adverse event.

4.5: Study title: “Effectiveness of bitter apple oil (*Citrullus colocynthis*) versus coconut oil foot massage on neuropathic pain, among patients with diabetes mellitus at selected rural area, Puducherry”.

Brief summary:

A clinical study was done with the primary objective to evaluate the existing level of Neuropathic pain among patients with diabetes mellitus in Group-I and Group-II. And to assess the viability of bitter apple oil (Group-I) and coconut oil (Group-II) foot massage on neuropathic pain among patients

with diabetes mellitus. Where a Randomized controlled trial design was implemented. 90 samples were assigned utilizing a Simple random sampling method. Group I received bitter apple oil foot massage and Group II received coconut oil foot massage for a month. Data were examined by clear and inferential insights, results indicated that. The examination discoveries revealed that bitter apple oil foot massage was effective to reduce neuropathic pain ($p < 0.001$) than coconut oil foot massage. This trial concluded that diabetic neuropathy pain is the important need of patients with Diabetes Mellitus which should be intervened by a nurse. The bitter apple oil foot massage is a boon to alleviate the pain of the suffering diabetic population. This investigation demonstrates that bitter apple oil foot massage was effective than coconut oil on reducing neuropathic pain.

5. PATENTS FILED ON *CITRULLUS COLOCYNTHIS* SCHRAD PLANT:

Filing and approval of a patent is a final confirmation about a commercial interest of a particular article. In this regard, various patents have been granted to the researcher for their innovation and research work on *Citrullus colocynthis* Schrad. The patents offer an owner the exclusive rights to an invention and prevent others to misuse it. A few of the patents which are granted to the researcher for their novel work on CCS are discussed below in **Table 3**.

Table 1: Medicinal part and chemical constituents of different parts of *Citrullus colocynthis* Schrad

Sr. No	Medicinal Part	Chemical constituents	Phytoconstituents responsible for activity
1	Fruits	<i>In methanolic extract</i>	<i>In methanolic extract</i>
		Ursolic Acid and Cucurbitacin E 2-O-β-D-glucopyranoside.	Phenolic compounds.
2	Fruits	<i>In Butanol fraction hydro-methanolic extract</i>	<i>In Hydroalcoholic extract</i>
		3'-O-methyl ether and two Cucurbitacin glycosides, 2-O-β-D-glucopyranosyl-Cucurbitacin L & 2-O-β-D-gluco-pyranosyl-Cucurbitacin.	Glycosides and resins, colocynthin and colocynthin alkaloids.
3	Fruits	<i>In Ether extract</i>	<i>In Petroleum ether</i>
		elatericin B (II)(Cucurbitacin I) dihydroelatericin B (III) and tetrahydroelatericin B (IV), elaterinidell.	Saponins, flavonoids, and glycosides.
4	Fruits	<i>In Chloroform: Methanol (1:1) ratio</i>	<i>In Aqueous extract</i>
		Cucurbitacin E and Cucurbitacin I glycosides.	Alkaloids, iridoids, flavonoids, steroids.
5	Fruits	<i>In Butanol extract</i>	<i>In Ethanolic extract</i>
		2-O-D-glucopyranosyl-Cucurbitacin E	Alkaloids, flavonoids, & glycosides.
6	Fruits	<i>In Fruit extract</i>	<i>In Aqueous extract</i>
		2-O-β-D- glucopyranosyl Cucurbitacins I, J, K, and L.	Saponin, glycosides.
7	Whole Plant	<i>In Methanolic extract</i>	<i>In Ethanolic & aqueous extracts</i>
		colocynthins A, B & C along with β-sitosterol, 3-O-β-D-glucopyranoside, elaterinide, and bryoamaride.	Flavanoids, saponins, alkaloids, and tannins.
8	Whole Plant	<i>In Chloroform extract</i>	<i>In Butanolic extract</i>
		2-O-β-D-glucopyranosyl-Cucurbitacin E, 2-O-β-D-glucopyranosyl-Cucurbitacin I, 2-O-β-D- glucopyranosyl-Cucurbitacin L and 2-O-β-D-glucopyranosyl-(22-27)-hexanor-Cucurbitacin I.	Cucurbitacin E Glycoside.
9	Leaf	<i>In Ethyl acetate extract</i>	<i>In Aqueous & Methanolic extracts</i>
		25-p-coumaroyl-3'- acetyl-2-O-β-D-glucoCucurbitacin I & 6'-acetyl-2-O-β-D-gluco-Cucurbitacin.	Alkaloids, Tannins, Flavonoids.
10	Leaf, Stem, Fruit, and Root	<i>In Soxhlet extraction of 80% methanol and then re-extracted with petroleum ether, diethyl ether, and ethyl acetate</i>	<i>In Aqueous and diluted acetone</i>
		Quercetin.	Tannins, steroids, pigments and flavonoids, alkaloids, iridoids.

Table 2: In-vivo anti-diabetic potential of *Citrullus colocynthis* Schrad

Plant Part	Extract	Dose	In-Vivo Tested Sample	Outcomes and Reference
Seeds	Aqueous Extracts.	300 mg/kg, daily for 2 weeks.	Rats.	Reduced the plasma level of AST and LDH significantly[37].
Leaf	Leaf Extract.	250 mg/kg and 500 mg/kg of body weight for sixty days.	Rats.	Found a significant fall in blood glucose level from 381 ± 34 to 105 ± 35 mg/dL. There was a reduction in the activities of glucose-6 phosphatase and fructose 1,6-bisphosphatase, and an enhancement in liver hexokinase activity[46].
Fruit Pulp	Ethanollic Extract.	Oral dose of 300 mg/kg/mL of extract.	Rats.	A swift decrease in blood glucose level of normal fasting rats was observed[48].
Pulp	Ethanollic.	Oral ingestion of 300 mg/kg of the pulp.	Rats.	Reduced blood glucose and improved the lipid levels, increase serum insulin AUC by 59.5% alongside a reduction in glucose (33%) and elsewhere this extraction has been noted to increase insulin content of pancreatic β -cells [4].
Whole Plant	Aqueous Extract	300 mg/kg body weight for twenty-two days.	Rats.	Increased blood glucose, insulin, haemoglobin, HbA1C and glycogen levels in AID rats reverted back to normal level after treating with extract[40].
Fruit Pulp and Seed	Fruit pulp as well as seed Extract.	Oral administration of 100 mg per kilogram of rabbit weight.	New Zealand Rabbits.	Excellent antidiabetic results[41].
Fruits	Petroleum Ether Fruits Extract.	Two distinct doses (300 and 500 mg/kg) of body weight.	Rats.	antidiabetic action through stimulation of β -cells of islets of Langerhans by releasing more insulin and this effect were brought about by constituents like glycosides, saponins, flavonoids[45].
Root	Aqueous Extract.	orally at dose level 2000 mg/kg.	Rats.	Significant reduction in blood sugar level (58.70%) also 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)[46]
Fruit	Hydro-Ethanol extract of fruit.	300g/kg.	Rats.	Significant decrease in the levels of total cholesterol, Triglycerides, free fatty acids and phospholipids in serum [42].
Fruits	Aqueous Extract of Fruits.	300 mg/kg	Rabbits.	Decrease of blood glucose from 132 to 93 mg/100 mL after 24 h [35].

Table 3: Patents granted to the researcher on *Citrullus colocynthis* Schrad

Inventor	Patent /Application number	Summary of the invention & References	Date of patent/ Publication
Liu Chong, He Jiang, Yang Weijun, Dili Nour Turson River ManharHabaHerula	CN102144491A	A patent was granted to an inventor for his invention that discloses a method for cultivating CCS plants, comprising the following steps: 1,land selection: selecting inland desert or semi-desert soil or semi-sandy soil with dry climate, average temperature ranging from 20 DEG C to 30 DEG C In May to September, and pH value of the soil ranging from 5.0 to 7.8; 2, seed pretreatment; 3, cultivation of treated CCS seeds: opening holes on a film and directly sowing seeds, and finally reserving a strong seedling in each hole; watering for 3-6 tons per mu (Chinese area measurement unit) at the first time around the middle of June, then carrying out drip irrigation once every 7 to 15 days, and totally carrying out drip irrigation 5 to 12 times; and harvesting during the first ten-day to the middle of September. Due to the adoption of the method for cultivating CCS plants, disclosed by the invention, the artificial mass planting cultivation of the traditional wild CCS is achieved, the yield of the CCS is improved by a wide margin, and the ecological environments of desert or semi-desert soil or semi-sandy soil selected for the artificial planting cultivation of CCS are protected [43].	2011-08-10
Hari Mohan Behl, Uttar Pradesh (IN); Om Prakash Sidhu, Uttar Pradesh(IN); Shanta Mehrotra, Uttar Pradesh (IN); PalpuPushpangadan , Uttar Pradesh (IN); SaimbiCharanjit Singh, Uttar Pradesh (IN).	US7083779B2	Hari Mohan Behl from India was given an approval for the patent that relates to a synergistic herbal formulation comprising an active fraction from AzadirachtaIndica designated as Fraction A and a fraction from CCS designated as Fraction B, along with a fraction C containing an antioxidant from Cucumis sativus extract; and pharmaceutically accepted a carrier wherein the ratio of the components ranging between about 2 to 5.5% of fraction A; about 0.5 to 2.5% of fraction B; about 0.1–0.4% of extract of Cucumis sativus; and about 82–97% of carrier or additive [44].	2006-08-01
Yang Weijun Liu ChongmanHaba Dili Nuer Huang Hua.	CN102138957B	A chines scientist registered a patent on his name recently in 2013 for his invention relates to a colocynth extract, and a production method and application thereof. The production method comprises the following steps of: 1, crushing colocynth fruits, and crudely extracting by using water or ethanol to obtain extracting solution; 2, filtering and concentrating the extracting solution, adding absolute ethanol, placing for precipitating, and filtering precipitates to obtain ethanol solution; 3, concentrating the ethanol solution, regulating the pH value, loading the ethanol solution to a macroporous resin and/or polyamide resin layer chromatography column for absorption; and 4, concentrating the obtained solution, recovering the ethanol, and drying to obtain the colocynth extracts. The inventor concludes that the production method is simple and easy and has a reliable process, and the obtained extract has stable quality; and materials used in the production process can be recycled by ethanol recovery and resin regeneration, so the production cost is low, and the method is suitable for industrialization	2013-05-29

		[45].	
Dai Bin Miao Jing Zhang Jie Zhang Haiyan XieJianwei.	CN102659889A	Another approval for a patent was given to a research work "Preparation of 23, 24-dihydro-epi-iso- <i>Cucurbitacin</i> D and use in antitumor drug thereof. The invention belongs to a natural pharmaceutical chemistry field. The invention mainly discloses a preparation method of 23, 24-dihydro-epi-iso- <i>Cucurbitacin</i> D, and use in medicaments for treating tumor diseases thereof. The invention belongs to a natural pharmaceutical chemistry field. The invention mainly discloses a preparation method of 23, 24-dihydro-epi-iso- <i>Cucurbitacin</i> D and a use in medicaments for treating tumor diseases thereof. The preparation method is recrystallizing an extract of <i>CCS</i> in chloroform through a combination of silica gel column chromatography and Sephadex LH-20 column chromatography to prepare 23, 24-dihydro-epi iso- <i>Cucurbitacin</i> D. The 23, 24-dihydro-epi-iso- <i>Cucurbitacin</i> D can be used as a single preparation or a combination with medicinal dressing to prepare antitumor drugs for treating ovarian cancer, prostatic cancer, oral epidermoid cancer, and gastric cancer [46].	2012-09-12
LamazyanGayaneR achyivna ,Sereda Petro Ivanovych.	UA103897U	Recently on 12 January 2016, A method for the determination of amino acid composition of bitter apple fruits by investigation of metabolism disorder. Amino acid composition of bitter apple fruits was determined to utilize gas-liquid chromatography. Histidine, arginine, asparaginic acid, serine, glutamic acid, proline, amino acetic acid, alanine, cysteine, tyrosine, lysine, methionine, isoleucine, leucine, and phenylalanine content is determined and calculated in mg per 100 mg of sample. This method was approved for the patent [47].	2016-01-12
Dina Ahmed Hajjar, Stephan KREMB, Christian Voolstra, Timothy Ravasi.	US20190298786A1	Dina Ahmed, last year in 2019 got approval for his patent work of Cell-based phenotypic profiling and image based high-content screening are used to gain insight into the mode of action and potential cellular targets of plants historically used to determine anti-cancer activity of Saudi Arabian plants <i>Juniperus phoenicea</i> (Arar), <i>Anastatica hierochuntica</i> (Kaff Maryam), and <i>CCS</i> (Hanzal). The cytological profiles of fractions taken from the plants were compared with a set of reference compounds with known modes of action. Cluster analyses of the cytological profiles were performed, which revealed detailed information on the modes of action of the tested compounds as potential topoisomerase inhibitors. Cytological profiles showed that some of these compounds inhibited cell proliferation causing cell cycle disruption [48].	2019-10-03

6. CONCLUSION

Diabetes is one of the leading causes of mortality worldwide. The conventional therapies are associated with several adverse drug reactions and require repeated administration of the medicine. Generally,

natural agents, including *Citrullus* plants are considered to be safe while treating or preventing this disease. *CCS* and its different medicinal parts have potential antidiabetic activity. Some of the pharmacological properties pronounced for this plant and its

parts are confirmed by the various examinations done in modern physiotherapy which are expressed in this paper. Among all parts, the antidiabetic action of the fruit and seed of this plant is very popular, and some in vivo and clinical trials in modern *Phototherapy* confirm this action. This review, have recorded the current and conventional uses of the CCS plant and its parts and summed up ongoing exploration on the antidiabetic potential of the plant parts. In view of the previously mentioned realities, patents, clinical investigations, it is obvious that the plant CCS and its medicinal parts have an enormous potential for diabetes, which may reduce the mortality and prevalence rate in the world once taken into serious and novel considerations in the future.

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