

AN OVERVIEW OF CITRULLUS COLOCYNTHIS

Abstract

Citrullus colocynthis (L.) Schrad (C. Colocynthis), often known as Colocynthis. [FAMILY : Cucurbitaceae]. It is commonly found wild in the sandy lands of North West, Punjab and central and Southern India and Coromandal coast. Fruit is Bitter, Pungent and the Fruit are used as a Purgative, anthelmintic, leucoderma, ulcers, asthma etc. Root is useful in Jaundice, ascites, urinary disease, rheumatism. The Pharmacological effects of Root, Fruits, Seeds, Leaves, and the whole *Citrullus Colocynthis* have been practiced for the treatment of disease. The aim of the study: The present research was undertaken to investigate the Pharmacological activities, Botanical description, Biological sources, Geographical sources, Taxonomic classification, characteristics, Morphological, Nutritional value, Ayurveda and Siddha action. *Citrullus colocynthis* fruits contain glycosides, flavanoids, fatty acids.

Keywords: *Citrullus Colocynthis*, Colocynthis, Cucurbitacins, Pharmacological activities, Bitter apple.

Authors

Dr.B.Prathap
Vice Principal And Professor
Department Of Pharmaceutical Analysis
Dhanalakshmi Srinivasan College Of
Pharmacy
Perambalur, Tamil Nadu.

Devika.M
Students, Dhanalakshmi Srinivasan
College Of Pharmacy
Perambalur, Tamil Nadu.

Christina Selvi.P
Students, Dhanalakshmi Srinivasan
College Of Pharmacy
Perambalur, Tamil Nadu.

Dharani.C
Students, Dhanalakshmi Srinivasan
College Of Pharmacy
Perambalur, Tamil Nadu.

Dinesh.K
Students, Dhanalakshmi Srinivasan
College Of Pharmacy
Perambalur, Tamil Nadu.

Divya.R
Students, Dhanalakshmi Srinivasan
College Of Pharmacy
Perambalur, Tamil Nadu.

I. INTRODUCTION

Citrullus Colocynthis, commonly known as Bitter apple, is a valuable cucurbit plant widely distributed in arid regions across the world. It belongs to the Cucurbitaceae family. It is often found in its wild form in sandy areas of Punjab, southern India, North West, and the Coromandel coast. This plant is primarily native to desert regions like Arabia, the Sahara, and parts of Southern Asia, including India, Pakistan, and Southern Islands. Initially, it was classified under the scientific name *Colocynthis Citrullus*.

Citrullus Colocynthis exhibits both male and female flowers. The mature fruits produced by this plant are small, approximately 6mm in length, oval-shaped, tightly structured, brownish in color, and possess a smooth texture.

Male flowers have long villous peduncles, a broadly campanulate calyx tube that is pale yellow, and obovate segments with apiculate tips. They have three short stamens that are free, with anthers that cohere, one-celled, while the other two are two-celled.

Female flowers share similarities with male flowers in terms of their calyx and corolla. They have three legulate stamens, an ovoid ovary with three placentiferous compartments, and numerous compressed ovules present within. Traditional medicine has historically used items obtained from plants. A wide range of plant components have been used in the food business, herbal medicine, and medicine, including leaves, flowers, petals, roots, fruit extracts, seed leftovers, and seed pods. The leaves of the plant exhibit variability, with a pale green upper surface and an ashy underside. They typically have a deltoid shape, are three-lobed, and deeply pinnate, with variations in size. The plant's fruits are globular and initially green in color, turning white and glabrous when they ripen. These fruits contain a dry, spongy, and highly bitter pulp. They have been employed in the treatment of conditions such as diabetes. This plant produces seeds that are light brown in hue. In addition, this plant is used to treat intestinal parasites, gastroenteritis, and other gastrointestinal conditions. Various plant parts have been utilized to treat a variety of conditions, such as liver issues, diabetes, asthma, jaundice, and sluggish bowel motions.

BOTANICAL DESCRIPTION



Figure 1: (*Citrullus colocynthis*)

II. SYNONYMS

C.Colocynthis many common name including AbuJahl’sMelon, Colocynth, Bitter apple, Bitter cucumber, Egusi, vine of Sodom (or) wild gourd .

Colocynthis vulgaris schrad.
Cucumis colocynthis L.(basionym)
Citrullus pseudocolocynthis M. Roem.
Colocynthis officinalis schrad.

1. Biological sources: Dried pithy pulp of the ripe fruits of CitrulluscolocynthisSchrade[FAMILY ; Cucurbitaceae]

2. Common name of Citrullus colocynthis Root: Citrullus colocynthis root English name is Bitter Apple Root, in Hindi, it is Indrayan Mool, it has many common names like Biteer Cucumber, wild gourd, Tumba ki jad.

This desert Viney plant grows in sand, and Ayurveda uses its fruits and roots for therapeutic purposes.

3. Taxonomic classification:

Kingdom	-	Plantae
Sub kingdom	-	Tracheobionta
Super division	-	Spermatophyta
Division	-	Magnoliophyta
Class	-	Magnoliopsida
Sub class	-	Dilleniidea
Order	-	Cucurbitales
Family	-	Cucurbitaceae
Genus	-	Citrullus
Phylum	-	Embryophyta
Species	-	Colocynthis

III.MORPHOLOGICAL CHARACTERISTIC

Roots and Stem	Perennial roots, stems are angular, tough and rough vine-like that spread on the ground and may climb up.
Seeds	Yellow to brown in colour, smooth in texture and oval in shape.
Flowers	A single yellow colour flower at leaf axils. They are monoecious and have long peduncles.
Fruit	Angular and about 5-10cm long. They are triangular, rough and green.



Figure 2: (A) seeds (B) roots (C) plant (D) leaf (E) flower and (F) fruit of *Citrullus colocynthis*

- 1. Roots and Stem:** The bitter apple plant possesses substantial, fleshy roots with extended taproots that enhance its survival in challenging conditions. This plant's extensive perennial root system produces lengthy, slender, and somewhat rough-textured stems characterized by angularity. These tough, coarse stems resemble vines and typically sprawl along the ground. In instances where shrubs or herbs are in proximity, the plant may employ secondary branching vines to facilitate climbing.
- 2. Flowers :** The yellow flowers of this plant emerge individually at the leaf axils. It is simple to differentiate between male and female flowers based on distinct characteristics. Female flowers stand out due to their villous, or hairy, ovary. In contrast, male flowers possess a calyx shorter than the corolla and feature 5 stamens, with 4 of them fused together while the remaining one stands alone, accompanied by a segment of anther. The presence of a spherical, hairy lower ovary is a key feature for identifying female flowers.

Flowering period: May, June, July, August.



Figure 3: (Flower of citrullus colocynthis)

- 3. Fruits:** The fruits are smooth spheres 5-10 cm in diameter and have a very bitter taste. The calyx encloses the yellow-green fruit and becomes marbled with yellow stripes at maturity. Each Citrullus Colocynthis plant typically yields approximately 15 to 30 spherical fruits, each with a diameter ranging from 7 to 10 centimeters. These fruits are characterized by an outer skin that is green and adorned with yellow stripes, although the fruits themselves may also exhibit a yellow hue. There are six seeds in each of the three carpels. 15–30 fruits are produced by each plant. The seeds are encased in a soft, dry, spongy, white pulp that fills the mesocarp.



Figure 4: (Fruit of *Citrullus colocynthis*)

- 4. Leaf:** The leaves, arranged alternately on extended petioles, are angular in shape. They typically measure between 5 to 10 centimeters in length and are characterized by having 3 to 7 lobes, occasionally featuring an ovate structure in the middle lobe. These leaves have a triangular shape with multiple indentations, presenting a coarse, hairy texture and open sinuses. Their upper surface is a vibrant green, while the lower surface appears relatively pale in comparison.
- 5. Seeds:** It has an equally bitter nutty flavour and is rich in fat and protein. Seeds are grey, 5mm (1/4 inch) long and 3mm (1/8 inch) wide. On the parietal placenta, they are located. The colors of the seeds range from pale yellowish-orange to dark brown.

Similar Species: It resembles a watermelon of the same genus.

IV. VARIOUS SPECIES OF CITRULLUS

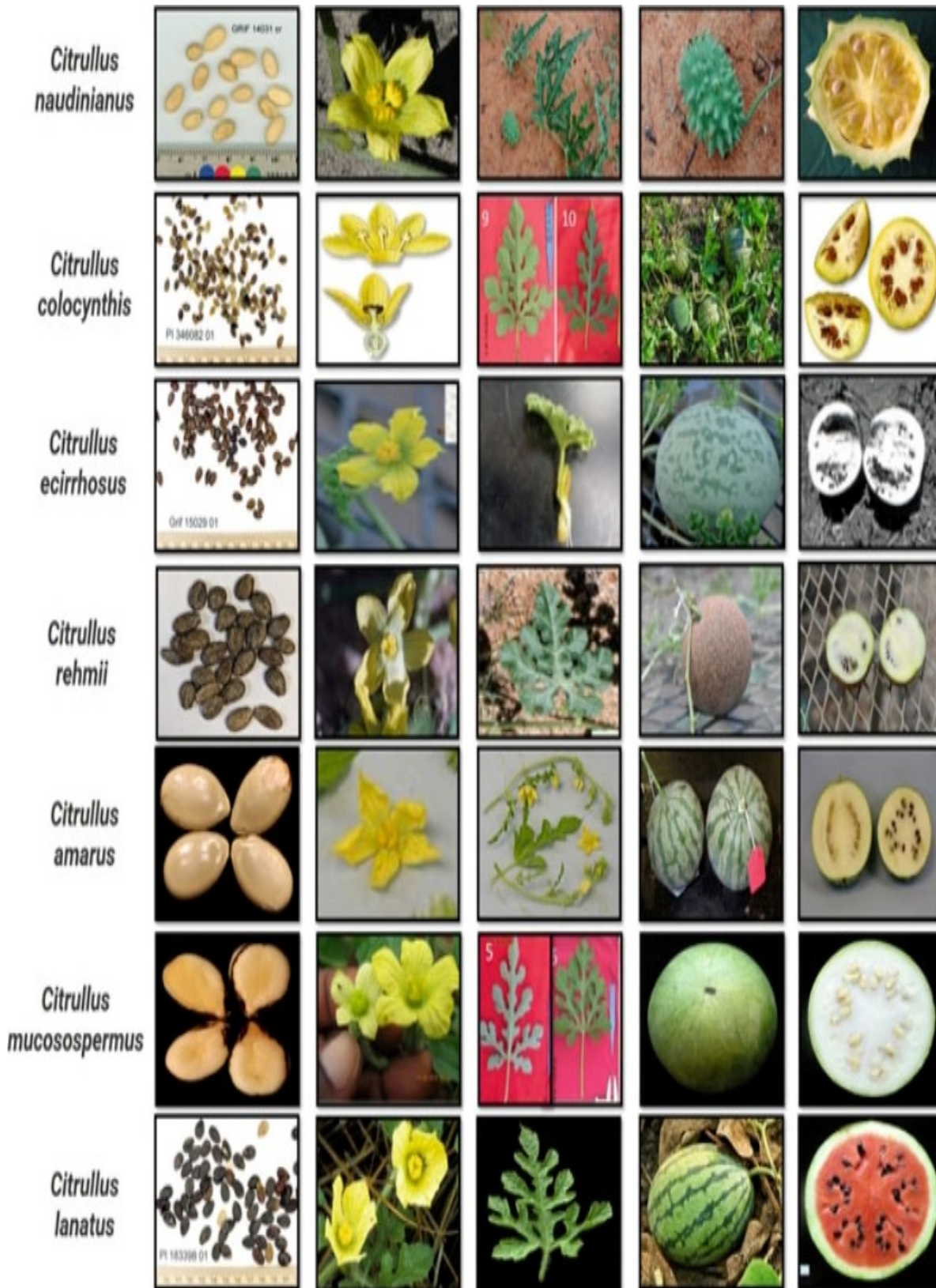


Figure 5: (Varies species in citrullus genus)

V. CULTIVATION

The perennial plant *Citrullus colocynthis* is propagable by both vegetative and sexual means. But in dry conditions, seed germination is noticeably low, which increases the prevalence and success of vegetative propagation. In the arid regions of India, growth primarily occurs from January to October, with summer being the optimal season for vegetative expansion. Growth tends to slow down with the onset of rains and cooler temperatures and nearly halts during the cold, dry months of December and January. This plant thrives in sandy soil and serves as a valuable model for studying effective water management in desert plants and their responses to water stress. Organic fertilizers can be applied to increase production colocynth is commonly grown (intercropped) with cassava in Nigeria. Cultivated colocynths like other crops suffer from climate stress and diseases such as cucumber mosaic virus, melon mosaic virus and fusarium wilt. To ameliorate that, relatively new regeneration protocols have been developed that aim to increase yield potential by incorporating resistance to disease and stress as well as safety by circumventing interspecific crossing barriers in rice field.

VI. NUTRITIONAL VALUE

The primary fatty acids in the oil are palmitic and stearic acids, with concentrations ranging from 8.1% to 17.3% and 6.1% to 10.5%, respectively. Notably, the oil contains a significant amount of the essential monounsaturated fatty acid linoleic acid, accounting for 50.6% to 60.1% of the composition, which plays a key role in its therapeutic properties. The unsaturated fatty acid profile reveals similarities between linoleic acid and certain other vegetable oils. Seeds contain 13.19g of protein, 18.59g of fat, 4.91g of moisture and 2mg of ash per 100g. Mineral present in the seeds contain 569mg Ca, 465mg of K, 210mg of Mg , 30.0mg of P, 11.9mg of Na, 11.6mg of Fe, 5.1mg of Cu and 1.1mg of Zn . [4][5]

VII. VERNACULAR NAMES IN INDIA

- | | | |
|--------------|---|------------------------------|
| 1. Tamil | - | Paedikari Attutummati |
| 2. English | - | Colocynth |
| 3. Sanskrit | - | Indravaruni |
| 4. Hindi | - | Indrayan , Badi indrayan |
| 5. Bengali | - | Makhal |
| 6. Gujarati | - | Indrayan |
| 7. Marathi | - | Kadu-indravani |
| 8. Telugu | - | Erri-Puchcha , Chittipaapara |
| 9. Malayalam | - | Paikummati , Kattuvellari |
| 10. Punjabi | - | Ghurunba |
| 11. Kannada | - | Daasamekke , Balibandrakshi |

VIII. NUTRITIONAL PROFILE AND CHEMICAL COMPOSITION

While various parts of *C. Colocynthis* are commonly used in both food and the pharmaceutical industry, there is limited publicly available nutritional information accessible to a global audience. Variations in farming practices and agricultural conditions across different countries might lead to discrepancies in qualities (Berwal et al., 2022). According to

Berwal et al. (2022)[14], the seeds have between 23-25% oil, which has a golden yellow color and is composed of 51% polysaturated fatty acids and 70% unsaturated fatty acids. Ripe fruits have a very high moisture content, exceeding 90% of the total composition at 4.91g/100g, while protein and ash content measure 13.19g/100g and 2.00g/100g, respectively (Banjo et al. 2021)[13]. Table 1 lists the volatile ingredients, fatty acid composition, and nutritional profile of the various bitter apple portions. Glutamic acid and arginine, which are found in *Citrullus colocynthis* in protein quantities of 19.8g/100g and 15.9g/100g, respectively, are two of the amino acids that are particularly abundant in this plant. Other amino acids detected in the protein include aspartic acid, serine, glycine, and glutamic acid (Hussain et al. 2014)[15]. Minerals are essential micronutrients necessary for normal bodily functions. According to Banjo et al. (2021)[13], each of these minerals is well known for its important function in preserving the electrolytic fluid balance and assisting in the body's alkalization. C. A wide variety of micronutrients found in *Colocynthis* fruits and seeds can benefit consumers. According to Hussain et al. (2014)[15], the two most abundant minerals in the seeds are calcium and potassium, which had concentrations of 465 mg and 569 mg/100 g, respectively. The seeds also show significant phosphorus and magnesium content. Nonetheless, iron and zinc levels are comparatively low in relation to other micronutrients[13–15].

Table: 1 Nutritional and Fatty Acid Composition of Different Parts of Bitter Apple

S.No	Name of Constituents	Parts of plant	Amount	References	
1	Proximate composition				
		Ash (%)	Seed	2.00	Banjo et al. 2021
			Seed	2.23	Riaz et al.2015
			Fruit	3.08	Ogundele et al. 2012
		Moisture (%)	Fruit	4.00	National research council 2006
			Seed	4.91	Banjo et al. 2021
			Seed	6.43	Riaz et al. 2015
		Oil content(%)	Fruit (mature)	90.00	National research council 2006
			Seed	28.50	Riaz et al 2015
			Seed	26.60	Banjo et al . 2021
		Fat (%)	Seed	18.59	Banjo et al . 2021
			Seed	3.15	Banjo et al. 2021
			Fruit	13.19	Banjo et al. 2021
		Protein (%)	Seed	13.99	Ogundele et al. 2012
			Seed	24.37	Banjo et al . 2021
			Fruit	30.00	Riaz et al. 2015
		Crude fibres (%)	Fruit	46.73	Ogundele et al. 2012
(mature)	1.33		National research council 2006		
Seed	10.88		Riaz et al.2015		
Starch (%)	Seed	10.00	Riaz et al.2015		
	Fruit		Riaz et al.2015		
	Fruit		Ogundele et al. 2012		
Carbohydrate (%)			National research council 2006		

2	Fatty acids and amino acid profile			
	Oleic acid (by wt.% of seed)	Seed oil Seed oil Seed oil	18.02 33.66 50.31	Berwal et al.2022 Riaz et al. 2015 Berwal et al.2022
	Linoleic acid (by wt.% of seed)	Seed oil Seed oil Seed oil Seed oil Seed oil	50.60- 60.10 54.70 19.80	Bhasin et al. 2020 Riaz et al.2015 Bhasin et al. 2020 Bhasin et al. 2020
	Glutamic acid (% of protein)	Seed oil Seed oil	15.90 8.1-	Bhasin et al. 2020 Riaz et al. 2015
	Arginin (% of protein)	Seed oil	17.30	Berwal et al. 2022
	Palmitic acid (by wt.% of seed)	Seed oil Seed oil Seed oil Seed oil	4.30 12.41 6.10- 10.50	Bhasin et al. 2020 Berwal et al. 2022 Riaz et al.2015 Berwal et al.2022
	Stearic acid (by wt.%of seed)	Seed oil	15.15 1.83 0.012 2.15	Riaz et al.2015
	Lignans (%)			
	Linolenic acid (%)			
3	Minerals			
	Calcium (%)	Seed Seed residue	0.057 0.013	Bhasin et al.2020 Riaz et al.2015
	Potassium (%)	Seed Seed residue	0.047 0.012	Bhasin et al.2020 Riaz et al.2015
	Magnesium (%)	Seed	0.210	Sadou et al.2007
	Copper (%)	Seed	0.005	Sadou et al.2007
	Sodium (%)	Seed	0.012	Sadou et al.2007
	Zinc (%)	Seed	0.001	Sadou et al.2007
	Iron (%)	Seed Seed residue	0.012 0.004	Banjo et al.2021 Riaz et al.2015
	Oryzanol (%)	Seed oil	0.066	Berwal et al.2022
4	Bioactive compounds and antioxidant activity			
	Total phenolic content (mg/100g of oil gallic acid Eq.)	Seed oil Seed oil	5.39- 6.12 938.0-	Berwal et al.2022 Berwal et al.2022
	Total flavonoids content (mg/100g of oil catechin Eq.)	Seed oil Seed oil Seed oil	956.0 0.066-	Berwal et al.2022 Berwal et al.2022 Berwal et
	Oryzanol (%)		0.069	al.2022[6,7,8,9,13,14]
	Lignans (%)		0.012-	

	Carotenoids (%)		0.014 0.008- 0.01	
--	-----------------	--	-------------------------	--

IX. AYURVEDA AND SIDDHA ACTION

As per Ayurveda and Siddha system of medicine Citrullus Colocynthis is

1. Tikta-rasam
2. Ushna veerayam
3. Katu vipakam
4. Purgative
5. Diuretics
6. Lagu
7. Kaphaharam
8. Puerperal disorder
9. Abortifacient
10. Ascites
11. Dropsy oil from seed used in hair growth and maladu.

X. CHEMICAL CONSTITUENTS

Numerous bioactive compounds found in the fruit have been extensively described in the literature. These compounds encompass alkaloids, flavonoids, carbohydrates, glycosides, fatty acids, and essential oils. Citrullus colocynthis fruits have been identified as containing cucurbitacins as their primary constituents[16].

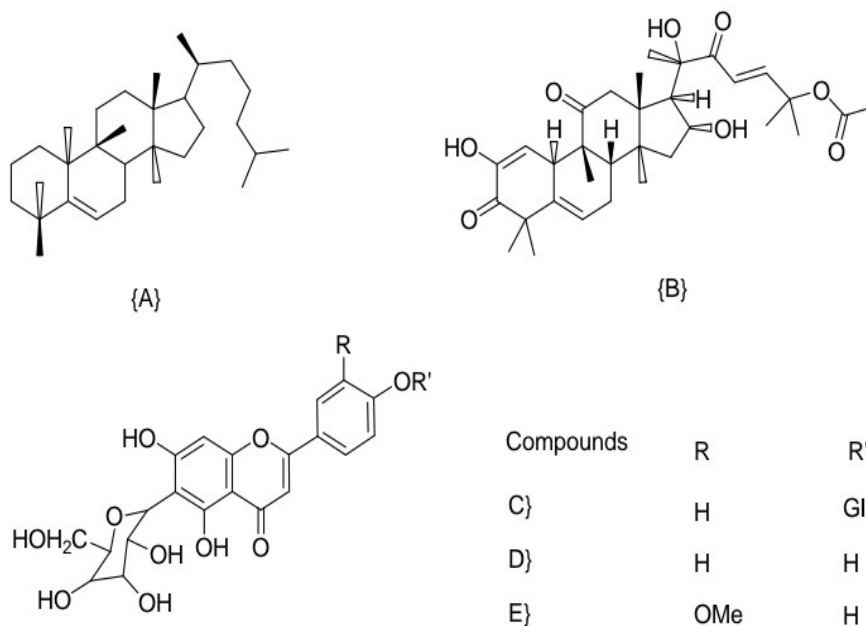


Figure 6: (Chemical constituents present in citrullus colocynthis)

1. **Cucurbitacins:** Cucurbitacins are a collection of highly oxygenated, predominantly tetracyclic and triterpenic plant compounds originating from the cucurbitane structure.

Because of the methyl group's transfer from C-10 to C-9, they are not categorized as steroidal compounds (Fig. A & B). These substances belong to the cucurbitaceae family[17].

2. **Glycosides, Polyphenols and Flavonoids:** Three flavonoid glycosides, including isosaponarin (Fig. C) and isovitexin (Fig. E), as well as two cucurbitacin glycosides, 2-O- β -D-glucopyranosyl cucurbitacin I and 2-O- β -D-glucopyranosyl cucurbitacin L, were isolated from *Citrullus colocynthis* fruits. A class of naturally occurring substances called polyphenols is well-known for its antioxidant and free-radical-scavenger qualities. As secondary metabolites, flavonoids have the ability to scavenge radicals and act as antioxidants[18, 19].

XI. BITTER CUCUMBER USES

The bitter apple root is used for diabetes, high cholesterol, constipation and skin problems. This is ready to use powder pack and comes with 2-year expiry, take 1-3 grams twice a day with lukewarm water or as recommended or consult a doctor before use. Some other uses include:

1. **As a food ingredient:** *Citrulluscolocynthis* root powder is used in some culinary cultures as a food ingredient to add a bitter flavour to dishes.
2. **As a traditional remedy:** In traditional medicine, the root powder is used as a natural remedy, the root powder is used as a natural remedy for digestive and parasitic issues.

XII. BITTER APPLE HEALTH BENEFITS

Citrullus colocynthis root has anti-diabetic, anti-oxidant, anti-inflammatory and anti-bacterial properties. It controls blood sugar and intestinal parasites and gives relief from constipation and stomachache.

1. **Digestive support:** *Citrulluscolocynthis* root powder is commonly used as a natural remedy for digestive issues, such as constipation, indigestion and diarrhea.
2. **Anti-inflammatory properties:** The root powder has been shown to have anti-inflammatory properties, which may help reduce swelling and pain in condition like rheumatoid arthritis.
3. **Anti-parasitic:** The root powder has been used traditionally as a natural remedy to treat parasitic infections, including tapeworms and other intestinal parasites.

XIII. TRADITIONAL FOOD PRODUCTS OF C.COLOCYNTHIS (L.)

Traditionally, egusi seeds find application in various dishes. Ogiri, a fatty paste derived from melon seed kernels, is a well-recognized ingredient in West Africa, particularly in Nigeria, where it serves as an affordable fermented soup seasoning and flavor enhancer. Egusi melon kernels are the most widely used seed kernel for making ogiri, though they may be prepared with any kind of kernel (Chukwu et al. 2018)[20]. The Yoruba people of Nigeria love robo, which is made from the fruit's defatted cake and is hence strong in protein. This explains why some Nigerians like Robo, which is frequently eaten with ogiri porridge, a type

of maize cereal. Robo has a striking resemblance to the groundnut cake called "kuli kuli" from Northern Nigeria (Akinoso & Are 2018)[21]. Egusi pudding is a favorite dish in West Africa, particularly among Cameroonians at social events. Egusi pudding's contents might vary, although they frequently consist of eggs, beef, poultry, and other seasonings (Giwa & Akanbi 2020)[22].

XIV. FUNCTIONAL AND BIOACTIVE COMPOUNDS

- 1. Phenolic acids and flavonoids:** Phenolic compounds represent a widely distributed and abundant category of plant metabolites. These compounds are characterized by their biological properties, which primarily encompass anti-aging effects, protection against atherosclerosis, cardiovascular benefits, enhancement of vascular endothelial function, inhibition of angiogenesis, and regulation of cell proliferation (Kim et al. 2022)[23]. Among phenolic compounds, flavonoids, which typically feature hydroxyl groups, are synthesized by plants in response to microbial infections. According to Omojate Godstime et al. (2014), in vitro research has shown that flavonoids have antibacterial qualities against a variety of microbes[24]. They have cytotoxic effects and are strong antioxidants as well. These substances play crucial roles in physiological processes such as seed development and growth regulation, as well as defense against pathogens and predators. Because flavonoids are antioxidants and scavenge free radicals, they are beneficial to humans and may even have anti-cancer benefits. These compounds have the ability to strengthen immunity against a range of diseases (Ahmed et al. 2019)[26] and show promise for improving disease resistance (Karak 2019)[25].
- 2. Cucurbitacin:** Natural antioxidants encompass triterpenoid compounds recognized for their bitter taste and potential toxicity (Hussain et al. 2014)[15]. Cucurbitacins are integral in drug development, especially for the creation of chemotherapeutic agents, owing to their anti-cancer properties. Research on agents derived from *Citrullus colocynthis* has identified the presence of compounds like Cucurbitacin L, Colocynthosides A, and cucurbitacin B in various parts such as seeds and fruits (Rezai et al. 2017)[27]. The primary type of cucurbitacin exhibits anti-allergic effects. Various studies have elucidated the structural relationships of cucurbitacin and its derivatives, which have shown efficacy in electrochemical reactions within cellular materials or gene products (Rezai et al. 2017)[27].
- 3. Alkaloids:** Alkaloids have long been recognized for their various roles, including biochemical and structural functions within biological organisms. These substances serve defensive roles in living organisms and have found applications in the field of medicine, particularly steroidal alkaloids, which constitute a significant portion of beneficial compounds (Saxena et al. 2013)[28]. Additionally, phyto-constituents with potent trypanocidal interactions have been reported to contain active ingredients like flavonoids, phenolics, and others. Satyavani et al. (2011) documented a high concentration of alkaloids in *C. colocynthis*. Furthermore, a study revealed the presence of isolated choline and two unidentified naturally occurring substances in the pulp of bitter apple fruit. Alkaloids are believed to play essential roles in metabolic and developmental processes, and they also serve protective functions in animals. Examples of such alkaloids include steroidal alkaloids (Saxena et al. 2013)[28].

- 4. Saponins:** It was discovered that the plant extracts contained saponins, which are sterol glycosides and triterpenes utilized as emulsifiers and expectorants and are well-known for their anti-inflammatory properties. Since saponins are derivatives of carbohydrates, they can resemble steroids or triterpenoids (Khan et al. 2012)[29]. Precursors derived from acetate and phenylpropanoids are combined to create them. The usefulness and function of steroidal saponins in community pharmacy have been the subject of numerous investigations (Egbuna et al. 2020)[30]. The paragraph goes over the uses of different bitter apple plant sections, their bioactive components, and how they work. Additionally, saponin is employed in the pharmaceutical industry and medicines due to its foaming capacity and frothy effect. Saponin has a long history of use in medicine and is widely recognized as a bioactive component in cytotoxicity (Abdulridha et al. 2020)[31].

XV. ETHNOBOTANICAL IMPORTANCES

The whole plant is used in many rural and tribal groups; the seeds are used to treat malaria, black hair, and digestive issues. Fruits are used to treat hepatitis, counteract snake poison, facilitate prompt and easy delivery, ease dropsy, and ease stomach aches. Paste-based applications of roots are used to relieve enlarged abdomens and rheumatism-related problems. A deeper understanding of the ethnobotanical significance of different plant parts has been acquired through various sources [32-42].

DISTRIBUTION OF CITRULLUS COLOCYNTHIS

Citrullus colocynthis is naturally occurring in India and Ceylon, both in the wild and cultivated forms. It is also indigenous to regions such as Arabia, tropical Africa, the Mediterranean region, and West Asia.

XVI. PHYTOCHEMICAL STUDIES

Numerous significant chemical constituents have been identified throughout the entire *Citrullus colocynthis* plant, including its roots, stems, leaves, fruits, and seeds. These constituents, as documented in the literature, contribute to the plant's medicinal properties and encompass carbohydrates, proteins, amino acids, alkaloids, flavonoids, and terpenoids. The fruits are particularly rich in bioactive compounds, with examples such as colocynthin, colocynthetin, cucurbitacins, á-elaterin, cucurbitacines, cucurbitacin glycosides, flavonoids, and flavone glycosides. Among these, cucurbitacins, specifically cucurbitacin E (abundant in the pulp), stand out. Additionally, phenolics, flavonoids, fatty acids, and various alcoholic and ketonic alkyl chains are noteworthy metabolites present in the fruit. These compounds, including phenols, tannins, and flavonoids, are crucial in the plant's defense mechanisms against diseases caused by a range of bacteria and fungi.

Citrullus colocynthis's medicinal properties are primarily attributed to a group of compounds known as cucurbitacins, which include cucurbitacin (A, B, C, D, E, J, and L). Additional compounds that contribute to this effect include terpenoids, tannins, saponins, anthranol, caffeic acid, and cardiac glycoloids. The leaves, fruits, and roots of plants have been shown to contain these active components, which also include flavonoids, tannins, alkaloids, terpenes, sterols, and steroids. While flavonoids were only reported to be present in the seeds, alkaloids were present throughout the plant, with the exception of the roots. All plant sections

included steroids, but only the leaves contained gallic acid, tannins, and coumarins. It was discovered that seeds included flavonoids, glycosides, steroids, and alkaloids.

Cucurbitacins, which are the active compounds found in this plant family, have been categorized into 12 different classes. Cucurbitacin E was notably abundant in the fruit pulp, whereas colocynthoside A and colocynthoside B were isolated from the fruit. These colocynthoside compounds were obtained from the methanolic extract of the fruits. Various cucurbitacin compounds, including d, e, f, g, and certain flavonoid glucosides like isovitixin, isorintin, and isosapanarin, were identified in the fruit extracts (butanol fraction). Among all the compounds extracted from the fruits, cucurbitacin and its glycosides were extensively studied, with nearly 20 of them being highly oxygenated triterpenoids. The hydromethanolic extract also revealed the presence of alkaloids, tannins, saponins, flavonoids, unsaturated sterols, terpenes, sterols, and steroids from various plant parts, including fruits, leaves, and roots. However, leaves were found to contain minimal quantities of alkaloids, tannins, saponins, and flavonoids.

Alkaloids, glycosides, terpenoids, tannins, and anthraquinol were detected in hexane, ethanol, and methanol solvents, whereas reducing sugars were found exclusively in hexane and ethanol. Flavonoids, on the other hand, were only identified in the ethanol extracts. Methanolic extracts of the fruits yielded compounds such as ursolic acid, cucurbitacin E, 2-O- β -D-glycopyranoside, and 4-methylquinoline. The hydromethanolic extracts, ether extract, chloroform-methanol (1:1) extract, and butanol extract from the fruits were reported to contain compounds like 3'O methyl ether, cucurbitacin glycoside, elatericin B, tetrahydroelatericin B, elaterin, del cucurbitacin E, I, and E. Additionally, the chloroform extracts from the whole plant contained cucurbitacin E, cucurbitacin I, and cucurbitacin L. Various researchers have extensively investigated the presence of phytochemicals such as carbohydrates, alkaloids, fatty acids, glycosides, flavonoids, and essential oils in the fruit of *Citrullus colocynthis*.

Cucurbitacins are the most frequently reported phytochemicals within the Cucurbitaceae family. These compounds, known for their cytotoxic properties, play a crucial role in drug discovery, particularly in the development of anti-cancer drugs. Among the various cucurbitacins, Cucurbitacin E (compound a) was found in abundance in fruit pulp extracts, while other significant compounds like Colocynthoside A (compound b) and Colocynthoside B (compound c) were identified in methanol fruit extracts. Butanolic extracts revealed the isolation of several other Cucurbitacin compounds, including Cucurbitacin L 2-O- β -D-glucopyranoside (compound d), hexanocucurbitacin I 2-O- β -D-glucopyranoside (compound e), cucurbitacin K 2-O- β -D-glucopyranoside (compound f), khekadaengoside E (compound g), cucurbitacin J 2-O- β -D-glucopyranoside (compound h), and cucurbitacin I 2-O- β -D-glucopyranoside (compound i).

The butanol fractions of the whole plant extracts in methanol showed the presence of two Cucurbitacin glycoside compounds, 2-O- β -D-glucopyranosyl cucurbitacin L and 2-O- β -D-glucopyranosyl cucurbitacin L, as well as flavonoid glycosides like isoorientin 3'-O-methyl ether (compound j), isovitixin (compound k), and isosaponarin (compound l). Similarly, compounds of flavone glucosides and Cucurbitacin glucosides were obtained from fruit extracts. Numerous prior investigations have provided significant documentation of these findings [43–58].

XVII. MEDICINAL PLANT CITRULLUS COLOCYNTHIS

Perennial *Citrullus colocynthis* grows wild in sandy areas in several parts of India, including Central and Southern India, North West India, Punjab, Sind, and Rajasthan. In addition, it is native to various regions of the world, including as the Mediterranean, West Asia, Arabia, and Tropical Africa. It was formerly categorized as *Colocynthis Citrullus* in science, but *Citrullus colocynthis* is the current official name.

The plant's characteristics include simple tendrils, which are about 2-3 feet long and covered in fine hairs. The leaves of *C. colocynthis* are quite variable in size, typically measuring between 3.8 to 6.3 cm in length and 2.5 cm in width. These leaves are pale green on the upper side and ashy in color on the lower side, with a deltoid shape and a slightly rough texture on both surfaces. They typically feature 5-7 lobes.

Citrullus colocynthis exhibits both male and female flowers. The fruit is bulbous with a slight depression, reaching a size of 5-7.5 cm in diameter. While initially green, the fruit turns white and smooth when it ripens. The fruit contains a dry, spongy, and bitter pulp. The seeds are relatively small, measuring about 4-6 mm in length and having a pale brown color.

XVIII. PHARMACOLOGICAL ACTIVITIES

- 1. Anti-inflammatory Activity:** A study by Belsem Marzouk et al. used the carrageenan-induced paw edema experiment in rats to test the anti-inflammatory properties of aqueous extracts of immature *C. colocynthis* fruit and seeds. Harvested from South Tunisia, the young fruits showed the most promising anti-inflammatory benefits. These results imply that these young fruit extracts may be worth investigating further for the purpose of treating inflammatory illnesses[59].
- 2. Anti-oxidant Activity:** Flavonoids including isovitexin, isosaponarin, and isoorientin 3'-O-methyl ether that are extracted from *Citrullus colocynthis* fruits have shown strong antioxidant capabilities. The methanolic fruit extract of *Citrullus colocynthis* was evaluated for its antioxidant and free radical scavenging properties; the maximum activity was noted at a concentration of 2500 mg/ml. A 1,1-diphenyl-2-picrylhydrazyl assay was used to analyze several *Citrullus colocynthis* seed extracts, including a defatted aqueous extract (E20), a crude aqueous extract (E1), an ethyl acetate extract (EA), a hydromethanolic extract (HM), and an n-butanol extract (n-B), at a concentration of 2000 µg/ml. Interestingly, the EA extract showed an 88.8% reduction percentage, HM came in second with 74.5%, and E1 came in third with 66.2%. Their corresponding IC₅₀ values were 350, 580, and 500 µg/ml, while ascorbic acid's was 1.1 µg/ml. *Citrullus colocynthis* methanolic seed extract was subjected to spectrophotometric evaluation of its antioxidant activity utilizing the 1,1-diphenyl-2-picryl hydrazyl and H₂O₂ free radical scavenging techniques. The extract showed the maximum inhibition percentages of 72.4% and 79.4% for the 1,1-diphenyl-2-picryl hydrazyl and H₂O₂ techniques, respectively, at a concentration of 300 µg/ml. Additionally, the methanolic extract of *Citrullus colocynthis* fruits (MECC) demonstrated substantial inhibition percentages of DPPH radicals and nitric oxide radical scavenging models in in vitro antioxidant studies, specifically 62%

and 56% at 800 µg/ml. These findings highlight the dose-dependent antioxidant activity of the extract compared to ascorbic acid[60-64].

- 3. Anti-microbial Activity:** The antimicrobial properties of silver nanoparticles (SNPs) against a range of bacterial species, such as *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas*, *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Streptococcus pyogenes*, were investigated using *Citullus colocynthis* aqueous extracts (AEs). Furthermore, these SNPs' antifungal activity was evaluated against *Trichophyton mentagrophytes*, *Aspergillus fumigatus*, *Candida albicans*, and *Geotricum candidum*; the results showed inhibition zones that ranged from 15.1±0.44 to 25.2±0.37 mm, respectively. The most powerful antibacterial activity was demonstrated by SNPs obtained from *Citullus colocynthis* roots AEs, which resulted in a reduction of 70%, 73%, and 75% in the Cytopathic effect (CPE).

Furthermore, the antibacterial potential of crude ethanolic extracts from *Citrullus colocynthis* was assessed against both Gram-positive and Gram-negative bacilli. The ethanolic extracts from fruits, leaves, stems, and roots displayed activity against Gram-positive bacilli, specifically *Bacillus pumilus* and *Staphylococcus aureus*. However, fruit and root extracts exhibited higher potency against Gram-positive bacilli, while no reactivity was observed against *Escherichia coli* and *Pseudomonas aeruginosa*. The research postulated that the observed antibacterial responses against various bacterial strains could be attributed to the presence of flavonoids, carbohydrates, tannins, and glycosides.

The study also looked at the antibacterial and anticandidal properties of *Citrullus colocynthis* schard's aqueous and diluted acetone extracts against both Gram-positive and Gram-negative bacteria, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Candida glabrata*, and *Candida kreusii*. Minimum Inhibitory Concentrations (MICs) and Minimum Bactericidal/Fungicidal Concentrations (MBC/MFCs) were determined for different plant organs at various maturation stages. The results revealed the highest MICs and MBCs/MFCs for the fruit aqueous extracts against *Escherichia coli* and *Pseudomonas aeruginosa*, while the root extracts displayed the lowest activity [65-67].

- 4. Anti-cancer Activity:** The purpose of the study was to look into how cucurbitacin glycosides, which are extracted from *Citrullus colocynthis* leaves, inhibit the growth of human breast cancer cells. From the leaf extract, cucurbitacin B/E glycosides were particularly isolated[68].
- 5. Anti-oxidant, Anti-inflammatory / Analgesic or Anti-proliferative:** Saba AB et al. successfully isolated cucurbitacins, which are triterpenoid steroids. These compounds exhibit efficient antioxidant properties attributed to their ability to effectively neutralize various free radicals, including hydroxyl radicals, superoxide anions, and singlet oxygen. Their ability to scavenge radicals across a broad spectrum is greater than that of other natural antioxidants including ginkgo biloba, wheat, alfalfa, and grape-seed extract. Furthermore, studies show that cucurbitacins are quite successful in blocking the oxidation and lipid peroxidation processes[69].

- 6. Anti-diabetic activity:** *Citrullus colocynthis* was administered at doses of 50mg/kg and 100mg/kg to evaluate its potential anti-diabetic effects over a 28-day period in a study. Hematological and biochemical assessments were conducted on the 29th day using standard kits. The findings demonstrated that *Citrullus colocynthis* could serve as a safe anti-diabetic remedy.

In a different study, the effects of *Citrullus colocynthis* fruit petroleum ether extract on thiobarbituric acid reactive substances (TBARS) and blood glucose reduction in Streptozotocin-induced diabetic albino rats were examined. When compared to Glibenclamide (0.5 mg/kg), the extract considerably lowered TBARS levels and significantly reduced blood glucose levels in diabetic rats.

Furthermore, in a clinical study involving patients with type II diabetes, After two months of *Citrullus colocynthis* (L.) Schrad fruit treatment, the HbA1c and fasting blood glucose levels significantly decreased. LDL, HDL, triglycerides, total cholesterol, aspartate transaminase, urea, creatinine, and fasting blood glucose were all measured at regular intervals during the trial.

The study involved the examination of various extracts, including crude aqueous, ethyl acetate, defatted aqueous, H₂O-methanol, n-butanol extracts, and H₂O-methanol extracts obtained from *Citrullus colocynthis* seeds, for their ability to stimulate insulin secretion from pancreatic islets in rats in response to glucose stimulation. Several of these extracts demonstrated a positive insulinotropic response when compared to a glucose concentration of 8.3mm D-glucose.

Additionally, hematological and biochemical assessments were conducted on rats treated with *Citrullus colocynthis* at doses of 50 and 100 mg/kg for a duration of 28 days. The results of this study confirmed the safety and potential efficacy of *Citrullus colocynthis* as a treatment for diabetes, particularly when utilizing the root extract, as evaluated in the rat model.

The aqueous extract demonstrated a significant reduction in blood sugar levels (58.70%) compared to the chloroform (34.72%) and ethanol extracts (36.60%) ($p < 0.01$). In this study, the leaf suspension of *Citrullus colocynthis* was used to treat the liver enzymes hexokinase, glucose-6-phosphatase, and fructose 1,6-bisphosphatase in both control and alloxan-diabetic rats. The findings revealed a significant decrease in blood glucose levels (from 381 ± 34 to 105 ± 35 mg/dl), a decrease in the activities of glucose-6-phosphatase, glycosylated hemoglobin, and fructose 1,6-bisphosphatase, and an increase in liver hexokinase activity. These results provide further evidence of the anti-diabetic effects of *Citrullus colocynthis*[70-75].

- 7. Anti-bacterial and Anti-candidal:** The antibacterial and anticandidal effects of aqueous and diluted acetone extracts derived from *Citrullus colocynthis* Schrad were assessed in vitro by Marzouk B and associates. Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal/Fungicidal Concentrations (MBC/MFC) were determined for various plant organs at different stages of maturation. The screening involved the assessment of aqueous and diluted acetone extracts from the plant's root, stem, leaves, as well as three different stages of fruit and seed maturation against Gram-negative and

Gram-positive bacteria, including *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, and various *Candida krusei* strains.

With MIC values of 0.10 mg/ml against *Candida albicans* and *Candida glabrata* and 0.20 mg/ml against *Escherichia coli* and *Pseudomonas aeruginosa*, the results demonstrated the extracts' uniform activity. Notably, out of all the extracts studied, the root extracts had the least activity[76].

8. **Effect of Hair Grow:** *Citrullus colocynthis* extracts were evaluated for their effectiveness in the treatment of hair growth in comparison to minoxidil in a rat model. These plant extracts were incorporated into an oily ointment base, and a 2% minoxidil solution was applied topically to shaved and exposed skin. The study recorded the time required for the initiation of hair growth and the completion of the hair growth cycle. The results demonstrated a positive outcome, as the treatment with *Citrullus colocynthis* extracts led to a higher percentage (>70%) of follicles transitioning to the anagenic stage compared to minoxidil (67%)[77].
9. **Anti-fertility:** Chaturvedi M and their team conducted a study in male albino rats to assess the anti-fertility effects of a 50% ethanol extract obtained from *Citrullus colocynthis* Schrad. The rats were categorized into five groups for the evaluation: Group A served as the control group and received a vehicle treatment. Groups B, C, and D were subjected to 100mg/kg/day of *C. Colocynthis* extract for durations of 20, 40, and 60 days, respectively. Group E animals were administered the extract at 100mg/kg/day for 60 days, followed by a 60-day recovery period.

Four groups of animals were separated into another set in order to evaluate the androgenicity of the extract: Group F received fruit extract (100 mg/kg/day p.o.), testosterone propionate (0.01 mg/rat/alternate day s.c.), and a combination of fruit extract and testosterone propionate, respectively, for 30 days after being castrated 30 days before the experiment.

The cauda epididymis sperm motility and density, pup count, fertility, and circulating testosterone levels all significantly decreased in all treatment groups, according to the results. In addition, there was a noticeable decrease in the weights of the prostate, seminal vesicle, testes, and epididymis in groups B, C, and D. Group A showed significantly lower organ weights than group F, group G showed lower organ weights than group F, and group I showed lower organ weights than group H in the androgenicity study. On the other hand, group F's organ weights were higher than those of the other groups [technical facts and observations remain unchanged].78].

The serum testosterone levels exhibited a similar pattern in their changes. The quantities of protein, sialic acid, and alkaline phosphatase declined, although the concentration of testicular cholesterol increased significantly. The testes' histological structure showed cytolysis, the presence of eosinophilic material in the lumen, degenerative changes in the seminiferous epithelium, and termination of spermatogenesis at the secondary spermatocyte stage. With the exception of the frequency of spherical spermatids and the nuclear area of the Sertoli cell, several histometric measures showed notable variations. Notably, group E saw a return to the original states of all these

changed parameters. Body weight, litter size, hematological parameters, and serum biochemistry did not alter. In summary, male albino rats displayed a reduction in reversible infertility when exposed to a 50% ethanol extract of *C. colocynthis*, owing to its anti-androgenic properties[78].

Table 2: Chemical Content of Citrullus Colocynthis

S.No	Part	Chemical content (reported/investigated)
1	Seed	<ol style="list-style-type: none"> 1. Fatty acid like stearic, Myristic, Palmitic, Oleic, Linoleic, Linolenic acid. 2. Protein 8.25% and rich content rich in lysine, leucin and sulfo amino acid like methionine 3. Vitamin B1, B2 and Niacin 4. Mineral like Ca, Mg, K, Mn, Fe, P and Zn
2	Aerial part and fruit	Flavonoid glycoside quercetin, Flavone-3-glycoside viz isovitexin, iso-orientin and iso-orientin-3-methyl ether.
3	Fruit	<ol style="list-style-type: none"> 1. Cucurbitacin type triterpen glycoside viz colocynthoside A & B. 2. Cucurbitane type triterpen glycoside viz cucurbitacin E 2-O-beta-D-glycoside and its aglycone Cucurbitacin E. 3. 2-O-beta-D-glycopyransoyl-16alpha-20R-dihydroxy-cucurbita-1,5,23E,25(26)-teraeen-3,11,22-trione. 4. 2-O-beta-D-glcopyranosyl-cucurbitacin B and 2, 25-di-O-beta-D-glycopyranosyl cucurbitacin L.

10. Hypolipidemic: Rahbar AR and colleagues conducted an investigation into the hypolipidemic effects of *Citrullus colocynthis* in addition to its hypoglycemic impact on humans. One hundred patients with dyslipidemia were randomly allocated into two groups, namely the treatment group (n=50). These individuals received daily doses of powdered *Citrullus colocynthis* seeds (300mg), while the placebo group received a placebo for a period of 6 weeks. Serum levels of triglycerides (TG), cholesterol (Chol), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) were measured using enzymatic methods at the beginning and end of the study. The statistical significance of differences within and between these groups was assessed using paired T-tests and analysis of covariance.

The results revealed significant differences both within the treatment and placebo groups during the intervention period, particularly in TG and cholesterol levels ($p < 0.05$). The daily intake of 300mg/day (-1) of powdered *Citrullus colocynthis* seeds led to a significant reduction in triglyceride and cholesterol concentrations in nondiabetic hyperlipidemic patients[79].

11. Growth inhibitory activity on breast cancer cells: The effect of Cucurbitacin glycosides isolated from *Citrullus colocynthis* leaves on the proliferation of human breast cancer cells was studied by Grossman S. and colleagues. Following the extraction of the leaves, cucurbitacin B/E glycosides were identified. The ER(-) MDA-MB-231 human

breast cancer cell lines were successfully inhibited from growing by the combination of cucurbitacin glycosides (in a 1:1 ratio). Treatment with the separated cucurbitacin glycoside mixture caused cells to accumulate in the G(2)/M phase of the cell cycle, according to cell-cycle analyses. Moreover, treated cells showed a fast decrease in the amounts of a critical protein complex, the p34 (CDC2)/cyclin B1 complex, which is required to control G(2) exit and the start of mitosis. The entire morphology of the cells changed as a result of the Cucurbitacin glycoside treatment, going from an elongated to a more rounded appearance. The morphological change indicates that the actin filament arrangement within the cells was disrupted by the cucurbitacin treatment [Observations and technical details are unchanged].

This significant morphological transformation may also impact intracellular signaling pathways involving molecules like PKB, leading to the inhibition of survival signals. Consequently, it was noted that survivin, a member of the anti-apoptosis family, was inhibited and that PKB phosphorylation decreased. In the absence of survival signals, the therapy also increased the expression of p21(WAF), a proven STAT3 positive target, and p-STAT3 levels. Cucurbitacin glycoside treatment also caused apoptosis, as demonstrated by changes in mitochondrial membrane potential ($\Delta\Psi$) using the fluorescent dye JC-1 and Annexin V/propidium iodide labeling. All of these results point to the possibility that cucurbitacin glycosides cause apoptosis and cell cycle arrest in cells through pleiotropic actions. These findings suggest that cucurbitacin glycosides may have therapeutic benefit against breast cancer cells[80].

12. Side Effects and Toxicity: A study was conducted to evaluate the toxicity of the fruit pulp extract of *Citrullus colocynthis*. Notably, significant and striking observations were made on the 20th day of conception. These included a high incidence of resorbed embryos characterized by smaller size and reduced weight, as well as the absence of a coccygeal vertebral column and bones. Based on these findings, it can be inferred that the administration of the fruit pulp extract of *Citrullus colocynthis* during the early stages of pregnancy can potentially induce teratogenic effects.

Another study, involving rabbits, aimed to assess the toxic effects of both seed and pulp extracts of *Citrullus colocynthis*. In this study, the animals were administered daily doses of either pulp or seed extract ranging from 100-200mg/kg. After one month, it was observed that none of the animals treated with 200mg/kg/day of pulp extract survived. In contrast, animals treated with lower doses of pulp extract exhibited severe lesions in the liver, small intestine, and kidney. Conversely, animals treated with seed extracts displayed only minor intestinal effects. As a result, it can be concluded that, in comparison to seed extracts, pulp extracts from the plant material can be lethal[81,82].

13. Hypoglycemic: Agarwal V and their team conducted a study to investigate the impact of *Citrullus colocynthis* root on the biochemical parameters of both normal and alloxan-induced diabetic rats. Diabetes mellitus was induced in the rats through intraperitoneal injection of alloxan at a dose of 120mg/kg body weight, leading to elevated blood glucose levels. Blood glucose concentrations were monitored on the 3rd, 5th, and 7th days following the start of the experiment. On the 7th day, blood samples were collected via cardiac puncture under mild ether anesthesia.

The aqueous extracts of *Citrullus colocynthis* roots exhibited a significant reduction in blood sugar levels (58.70%) compared to chloroform (34.72%) and ethanol extracts (36.60%) ($p < 0.01$). Serum levels of total bilirubin, conjugated bilirubin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), and alkaline phosphatase (ALP) were also restored by the aqueous extracts, along with improvements in a number of other parameters such as body weight, serum creatinine, serum urea, serum protein, and lipid profile[83].

14. Mosquito larvicidal Activity: *Citrullus colocynthis* (Linn.) Schrad was tested by Rahuman AA and associates for its toxicity against *Culex quinquefasciatus* (Diptera: Culicidae) larvae in their early fourth instar. The observation of larval mortality transpired after a 24-hour exposure period. While the larvicidal effects of all studied extracts were moderate, the petroleum ether extract that was made from the whole *C. colocynthis* plant showed the highest larval mortality.

The present investigation involved the separation and identification of fatty acids, specifically oleic and linoleic acid, as the mosquito larvicidal chemicals by a petroleum ether extract fractionation process guided by a bioassay. The fourth instar larvae of *Aedes aegypti* L. (LC₅₀ 8.80, 18.20 and LC₉₀ 35.39, 96.33 ppm), *Anopheles stephensi* Liston (LC₅₀ 9.79, 11.49 and LC₉₀ 37.42, 47.35 ppm), and *Culex quinquefasciatus* Say (LC₅₀ 7.66, 27.24 and LC₉₀ 30.71, 70.38 ppm) were all demonstrated to be highly effective against oleic and linoleic acids. Through the study of infrared, ultraviolet, ¹H-nuclear magnetic resonance, ¹³C-NMR, and mass spectral data, these compounds' structures were clarified[84].

15. Larvicidal: An evaluation of the larvicidal activity of crude extracts made from the leaves of five distinct cucurbitaceous plant species was carried out by Rahuman AA and associates. Hexane, ethyl acetate, petroleum ether, acetone, and methanol extracts were among these extracts. The impact they had on *Aedes aegypti* L. and *Culex quinquefasciatus* (Say) early fourth instar larvae (Diptera: Culicidae) was the main focus of the investigation. The mortality rate of larvae was documented after a 24-hour exposure period.

Every extract that was examined showed a moderate level of larvicidal activity. However, the highest rates of larval mortality against *A. aegypti* (LC₅₀=74.57, 309.46, 492.73, 199.14, and 554.20 ppm, respectively) and *C. quinquefasciatus* (LC₅₀=88.24, 377.69, 207.61, and 842.34 ppm, respectively) were found in the petroleum ether extract from *C. colocynthis*, the methanol extracts from *C. indica*, *C. sativus*, and *M. charantia*, as well as the acetone extract from *T. angunia*. Notably, when compared to the other extracts, the methanol extract of *M. charantia* and the petroleum ether extract of *C. colocynthis* shown higher effectiveness[85].

XIX. CONCLUSION

This review strongly suggests that *Citrullus colocynthis* is a fruit crop with promising potential for the treatment of a range of metabolic disorders. While bitter apple holds dietary supplementation significance, its acceptance is not universal. Notably, *Citrullus colocynthis* has been reported to possess significant therapeutic properties, including anti-diabetic, anti-

inflammatory, anti-microbial, analgesic, anti-oxidant, anti-cancer, and anti-fertility activities. However, it's important to note that the fruit extract of *C. colocynthis* has demonstrated hepatotoxicity and toxic effects on the kidneys. Therefore, it is crucial to make concerted efforts to identify plants used in folk medicine with narrow therapeutic indices, as their use can be hazardous and requires careful research, especially when used by diabetic patients. This comprehensive review provides insights into the various phytochemicals, bioactive compounds, and their mechanisms of action for treating a wide array of diseases, including cancer, inflammatory conditions, and many others.

REFERENCES

- [1] Databases GR. USDA, ARS, National Genetic resources program. Germplasm Resources information Network-(GRIN) [Online Database], National Germplasm Resources Laboratory, Beltsville, Maryland.
- [2] Chopra R. Chopra's indigenous drugs of India, UN Dhur & Sons Pvt. Ltd, Calcutta. 1958;12:495.
- [3] Upadhyay B, Roy S, Kumar A. Traditional uses of medicinal plants among the rural communities of churu district in the Thar Desert, India. *Journal of Ethnopharmacology*. 2007;113(3):387-99.
- [4] Dhakad PK, Sharma PK, Kumar S. A Review on phytochemical studies and Biological Potential of *Citrullus colocynthis* (L.) Schrad (Cucurbitaceae). *J Bioeng Biosci*. 2017;5(4):55-64.
- [5] Hussain AI, Rathore HA, Sattar MZ, Chatha SA, Sarker SD, Gilani AH. *Citrullus colocynthis* (L.) Schard (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. *Journal Ethanopharmacology*. 2014;155(1):54-66
- [6] National Research Council (2006). *Lost crops of Africa*. National Academies Press (ISBN 978-0-309-10333-6).
- [7] Riaz, H., Chatha, S. A. S., Hussain, A. I., Bukhari, S. A., Hussain, S. M., & Zafar, K. (2015). Physico-chemical characterization of bitter apple (*Citrullus colosynthis*) seed oil and seed residue. *International Journal of Biosciences*, 6(1), 283–292.
- [8] Ogundele, J. O., Oshodi, A. A., & Amoo, I. A. (2012). Comparative Study of Amino Acid and Proximate Composition of *Citullus colocynthis* and *Citrullus vulgaris* Seeds. *Pakistan Journal of Nutrition*, (11), 247-251.
- [9] Bhasin, A., Singh, S., & Garg, R. (2020). Nutritional and medical importance of *Citrullus colocynthis*-A review. *Plant Archives*, 20(2), 3400–3406.
- [10] Sadou, H., Sabo, H., Alma, M. M., Saadou, M., & Leger, C. L. (2007). Chemical content of the seeds and physico-chemical characteristic of the seed oils from *Citrullus colocynthis*, *Coccinia grandis*, *Cucumis metuliferus* and *Cucumis prophetarum* of Niger. *Bulletin of the Chemical Society of Ethiopia*, 21(3), 323–330.
- [11] Ali, S. A., Abdalla, H. O., & Elamin, M. A. (2012). *Citrullus colocynthis* (Handal) seed meal as a natural feed supplementation in broiler chickens' diets. *Egyptian Poultry Science Journal*, 32(2), 237–246.
- [12] Uma, C., & Sekar, K. G. (2014). Phytochemical analysis of a folklore medicinal plant *Citrullus colocynthis* L (bitter apple). *Journal of Pharmacognosy and Phytochemistry*, 2(6), 195-202.
- [13] Banjo, T. T., Aina, Y. O., & Falade, F. A. (2021). Phytopharmaceutical and antimicrobial attributes of bitter apple (*Citrullus colocynthis*)-A review. *Covenant Journal of Physical and Life Sciences*, 9(1), 1–9.
- [14] Berwal, M. K., Ram, C., Gurjar, P. S., Gora, J. S., Kumar, R., Verma, A. K., ... Kumar, P. (2022). The bioactive compounds and fatty acid profile of bitter apple seed oil obtained in hot, arid environments. *Horticulturae*, 8(3), 259.
- [15] Hussain, A. I., Rathore, H. A., Sattar, M. Z., Chatha, S. A., Sarker, S. D., & Gilani, A. H. (2014). *Citrullus colocynthis* (L.) Schrad (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. *Journal of Ethnopharmacology*, 155(1), 54–66.
- [16] Wasylikowa K, Van der Veen M. An archaeobotanical contribution to the history of watermelon, *Citrullus lanatus* (Thunb.) Matsum. & Nakai (syn. *C. vulgaris* Schrad.). *Vegetation History and Archaeobotany*. 2004;13(4):213-7.
- [17] Shaik RS, Gopurenko D, Burrows GE, Urwin NA, Lepschi BJ, Hildebrand SM, et al., editors. Identification of the invasive weeds, camel melon, prickly paddy melon and colocynth in Australia, a morphological and molecular approach. 18th Australasian weeds conference, The Sebel and Citigate Albert Park, Melbourne, Victoria, Australia; 2012.

- [18] Tannin-Spitz T, Grossman S, Dovrat S, Gottlieb HE, Bergman M. Growth inhibitory activity of cucurbitacin glucosides isolated from *Citrullus colocynthis* on human breast cancer cells. *Biochem Pharmacol.* 2007; 73(1):56-67.
- [19] Mukherjee A, Patil SD. Effects of alkaloid rich extract of *Citrullus colocynthis* fruits on *Artemia Salina* and Human Cancerous (MCF-7 AND HEPG-2) cells. *Journal of PharmaSciTEch.* 2012;1:15-9.
- [20] Chukwu, M., Nwakodo, C. S., Alozie, Q., & Ndulaka, J. C. (2018). Comparative studies on organoleptic properties of ogiri-ahuekere and ogiri-egusi condiments. *Research Journal of Food Science and Quality Control*, 4(1), 5–11.
- [21] Akinoso, R., & Are, O. T. (2018). Elucidating energy requirements in alternative methods of robo production. *Journal of Biosystems Engineering*, 43(2), 128–137.
- [22] Giwa, S. O., & Akanbi, T. O. (2020). A review on food uses and the prospect of Egusi melon for biodiesel production. *Bioenergy Research*, 13(4), 1031–1045.
- [23] Kim, E., Cui, J., Zhang, G., & Lee, Y. (2022). Physiological effects of green-colored food-derived bioactive compounds on cardiovascular and metabolic diseases. *Applied Sciences*, 12(4), 1879.
- [24] Omojate Godstime, C., Enwa Felix, O., Jewo Augustina, O., & Eze Christopher, O. (2014). Mechanisms of antimicrobial actions of phytochemicals against enteric pathogens—a review. *Journal of Pharmaceutical, Chemical and Biological Sciences*, 2(2), 77–85.
- [25] Karak, P. (2019). Biological activities of favonoids: An overview. *International Journal of Pharmaceutical Sciences and Research*, 10(4), 1567–1574.
- [26] Ahmed, M., Ji, M., Qin, P., Gu, Z., Liu, Y., Sikandar, A., & Javeed, A. (2019). Phytochemical screening, total phenolic and favonoids contents and antioxidant activities of *Citrullus colocynthis* L. and *Cannabis sativa* L. *Applied Ecology and Environmental Research*, 17, 6961–6979.
- [27] Rezai, M., Davoodi, A., Asori, M., & Azadbakht, M. (2017). Cytotoxic activity of *citrullus colocynthis* (L.) schrad fruit extract on gastric adenocarcinoma and breast cancer cell lines. *International Journal of Pharmaceutical Sciences Review and Research*, 45(1), 175-178.
- [28] Saxena, M., Saxena, J., Nema, R., Singh, D., & Gupta, A. (2013). Phytochemistry of medicinal plants. *Journal of Pharmacognosy and Phytochemistry*, 1(6), 168-182.
- [29] Khan, M., Khan, A. U., and Gilani, A. H. (2012). Gut and airways relaxant effects of *Carum roxburghianum*. *Journal of Ethnopharmacology*, 141(3), 938-946.
- [30] Egbuna, C., Mishra, A. P., & Goyal, M. R. (Eds.) (2020). Preparation of phytopharmaceuticals for the management of disorders: The development of nutraceuticals and traditional medicine. Academic press.
- [31] Abdulridha, M. K., Al-Marzoqi, A. H., & Ghasemian, A. (2020). The anticancer efficiency of *Citrullus colocynthis* toward the colorectal cancer therapy. *Journal of Gastrointestinal Cancer*, 51(2), 439–444.
- [32] .Nadkarni KM. *Indian materia medica*, popular Book Depot. Bombay. 1954;7:946- 8.
- [33] Mohammed S, Kasera PK, Shukla JK. Unexploited plants of potential medicinal value from the Indian Thar desert. *Natural Product Radiance*. 2004;3(2):69-74.
- [34] Joshi SG. *Medicinal plants*. Oxford and IBH Publishing. 2000.
- [35] Ali AA, Al-Rahwi K, Lindequist U. Some medicinal plants used in Yemeni Herbal Medicine to treat. *African Journal of Traditional, Complementary and Alternative Medicines*. 2004;1(1):72-6.
- [36] Singh V, Pandey RP. Economic and medicinal plants of Indian Desert. In *Desert Resources and Technology*. Scientific Publishers Jodhpur. 1983:307-68.
- [37] Nadkarni KM. *Indian Plants and Drugs with their medicinal properties and uses*. Asiatic Publishing House, New Delhi. 1998.
- [38] Sharma SC. *Indigenous Phytotherapy among Rural Women of Shahjahanpur District, Uttar Pradesh*. Ethnobotany. Aavishkar Publisher Jaipur, India. 2002;311-6.
- [39] Dafni A, Lev E. The doctrine of signatures in present-day Israel. *Economic Botany*. 2002;56(4):328.
- [40] Tiwari G, Srivastava DK, Gangrade SK. Status of Medicinal Plant Diversity of Kymore Plateau and Satpura Hill Region of Madhya Pradesh and Their Utilization. *Recent Progress in Medicinal Plants*. 2003;7:45-56.
- [41] Kirtikara KR, Basu BD, An IC, Blatter E, Caius JF, Mhaskar KS. *Indian medicinal plants, with illustrations*. 2001.
- [42] Adam SE, Al-Yahya MA, Al-Farhan AH. Response of Najdi sheep to oral administration of *Citrullus colocynthis* fruits, *Nerium oleander* leaves or their mixture. *Small Ruminant Research*. 2001;40(3):239-44.
- [43] Sturm S, Schneider P, Seger C, Stuppner H. Analysis of *Citrullus colocynthis* cucurbitacine derivatives with HPLC-SPE-NMR. *Scientia Pharmaceutica*. 2009;77(7):254.
- [44] Hatam NA, Whiting DA, Yousif NJ. Cucurbitacin glycosides from *Citrullus colocynthis*. *Phytochemistry*. 1989;28(4):1268-71.

- [45] Abbas DG, Simon R, Ali N, Hossein M, Masoud N, Lutfun N, et al. Flavone Cglycoside and cucurbitacin glycoside from *Citrullus colocynthis*. DARA. 2006;14(3):109-14.
- [46] Maatooq GT, El-Sharkawy SH, Afifi MS, Rosazza JP. Cp-hydroxybenzoyl glycoflavones from *Citrullus colocynthis*. Phytochemistry. 1997;44(1):187-90.
- [47] Priyavardhini S, Vasantha K, Umadevi M. Antibacterial activity on *Citrullus colocynthis* leaf extract. Ancient Science of Life. 2009;29(1):12.
- [48] Uma C, Sekar KG. Phytochemical analysis of a folklore medicinal plant *Citrullus colocynthis* L. (Bitter Apple). Journal of Pharmacognosy and Phytochemistry. 2014;2(6).
- [49] Nora NB, Hamid K, Snouci M, Boumediene M, Abdellah M. Phytochemical and antibacterial screening of *Citrullus colocynthis* of South-west Algeria. Journal of Chemical and Pharmaceutical Research. 2015;7(5):1344-8.
- [50] Ambi AA, Abdurrahman EM, Sule MI, Patch UU, Abdurrahman YR, Ibrahim NDJ. Phytochemical screening and histopathological studies on the seeds of *Colocynthis citrullus* in albino rats. Journal of Pharmaceutical Sciences. 2007;6(2):7-12.
- [51] Dhakad PK, Sharma PK, Kumar S. A Review on Phytochemical Studies and Biological Potential of *Citrullus colocynthis* (L.) Schrad (Cucurbitaceae). J Bioeng Biosci. 2017;5(4):55-64.
- [52] Hussain AI, Rathore HA, Sattar MZ, Chatha SA, Sarker SD, Gilani AH. *Citrullus colocynthis* (L.) Schrad (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. Journal of Ethnopharmacology. 2014;155(1):54-66.
- [53] Seger C, Sturm S, Mair ME, Ellmerer EP, Stuppner H. ¹H and ¹³C NMR signal assignment of cucurbitacin derivatives from *Citrullus colocynthis* (L.) Schrad and *Ecballium elaterium* L. (Cucurbitaceae). Magnetic Resonance in Chemistry. 2005;43(6):489-91.
- [54] Song F, Dai B, Zhang HY, Xie JW, Gu CZ, Zhang J. Two new cucurbitane-type triterpenoid saponins isolated from ethyl acetate extract of *Citrullus colocynthis* fruit. Journal of Asian Natural Products Research. 2015;17(8):813-8.
- [55] Jeon JH, Lee HS. Biofunctional constituent isolated from *Citrullus colocynthis* fruits and structure-activity relationships of its analogues show acaricidal and insecticidal efficacy. Journal of Agricultural and Food Chemistry. 2014;62(34):8663-7.
- [56] Delazar A, Gibbons S, Kosari AR, Nazemiyeh H, Modarresi M, Nahar L, et al. Flavone C-glycosides and cucurbitacin glycosides from *Citrullus colocynthis*. DARU Journal of Pharmaceutical Sciences. 2006;14(3):109-14.
- [57] Lavie D, Willner D, Merenlender Z. Constituents of *Citrullus colocynthis* (L.) Schrad. Phytochemistry. 1964;3(1):51-6.
- [58] Ayyad SE, Abdel-Lateff A, Alarif WM, Patacchioli FR, Badria FA, Ezmirly ST. In vitro and in vivo study of cucurbitacins-type triterpene glucoside from *Citrullus colocynthis* growing in Saudi Arabia against hepatocellular carcinoma. Environmental Toxicology and Pharmacology. 2012;33(2):245-51.
- [59] Belsem M, Zohra M, Ehsen H, Manel T, Abderrahman B, Mahjoub A and Nadia F. Anti-inflammatory evaluation of immature fruit and seed aqueous extracts from several populations of Tunisian *Citrullus colocynthis* Schrad. African Journal of Biotechnology. 2011; 10(20):4217-4225.
- [60] Kumar S, Kumar D, Jusha M, Saroha K, Singh N, Vashishta B. Antioxidant and free radical scavenging potential of *Citrullus colocynthis* (L.) Schrad. methanolic fruit extract. Acta Pharmaceutica. 2008;58(2): 215-20.
- [61] Benariba N, Djaziri R, Bellakhdar W, Belkacem N, Kadiata M, Malaisse WJ, Sener A. Phytochemical screening and free radical scavenging activity of *Citrullus colocynthis* seeds extracts. Asian Pacific Journal of Tropical Biomedicine. 2013; 3(1):35-40.
- [62] Gill N, Kaur S, Arora R, Bali M. Screening of antioxidant and antiulcer potential of *Citrullus colocynthis* methanolic seed extract. Res J Phytochem. 2011;5:98-106.
- [63] Eddouks M, Maghrani M, Lemhadri A, Ouahidi M-L, Jouad H. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). Journal of Ethnopharmacology. 2002;82(2):97-103.
- [64] Rajangam J, Christina AJ. Evaluation of *Citrullus colocynthis* fruits on in vitro antioxidant activity and in vivo DEN/PB induced hepatotoxicity. International Journal of Applied Research in Natural Products. 2013;6(1):10-5.
- [65] Memon U, Brohi AH, Ahmed SW, Azhar I, Bano H. Antibacterial screening of *Citrullus colocynthis*. Pak J Pharm Sci. 2003; 16(1):1-6.
- [66] Marzouk B, Marzouk Z, Decor R, Edziri H, Haloui E, Fenina N, Aouni M. Antibacterial and anticandidal screening of Tunisian *Citrullus colocynthis* Schrad. from Medenine. J Ethnopharmacol. 2009; 125(2):344-9.

- [67] Delazar A, Gibbons S, Kosari AR, Nazemiyeh H, Modarresi M, Nahar L, Sarker Sd. Flavone C-glycosides and cucurbitacin glycosides from *Citrullus colocynthis*. *DARU Journal of Pharmaceutical Sciences*. 2006;14(3):109-14.
- [68] Ali Esmail Al-Snaf, Chemical constituents and pharmacological effects of *Citrullus colocynthis* - A review, *Journal of IOSR Journal of Pharmacy*, 2016, 61-62.
- [69] Saba AB and Oridupa AO. Search for a novel antioxidant, anti-inflammatory/ analgesic or anti-proliferative drug: Cucurbitacins hold the ace. *Journal of Medicinal Plants Research*. 2010; 4(25): 2821-2826.
- [70] Atole S, Jangde C, Philip P, Rekhe D, Aghav D, Waghode H, Chougule A. Safety evaluation studies of *Citrullus colocynthis* for diabetes in rats. *Veterinary World*. 2009;2(11):423-5.
- [71] Jayaraman R, Shivakumar A, Anitha T, Joshi V, Palei N. Antidiabetic effect of petroleum ether extract of *Citrullus colocynthis* fruits against streptozotocin-induced hyperglycemic rats. *Rom J Biol Plant Biol*. 2009;4:127-34.
- [72] Huseini HF, Darvishzadeh F, Heshmat R, Jafariazar Z, Raza M, Larijani B. The clinical investigation of *Citrullus colocynthis* (L.) schrad fruit in treatment of Type II diabetic patients: A randomized, double blind, placebo-controlled clinical trial. *Phytotherapy Research*. 2009;23(8):1186-9.
- [73] Benariba N, Djaziri R, Hupkens E, Louchami K, Malaisse WJ, Sener A. Insulinotropic action of *Citrullus colocynthis* seed extracts in rat pancreatic islets. *Molecular Medicine Reports*. 2013; 7(1):233-6.
- [74] Agarwal V, Sharma AK, Upadhyay A, Singh G, Gupta R. Hypoglycemic effects of *Citrullus colocynthis* roots. *Acta Pol Pharm*. 2012;69(1):75-9.
- [75] Gurudeeban S, Ramanathan T. Antidiabetic effect of *Citrullus colocynthis* in alloxon-induced diabetic rats. *Inventi Rapid: Ethno Pharmacology*. 2010;1:112.
- [76] Marzouk B, Marzouk Z, Décor R, Edziri H, Haloui E, Fenina N and Aouni M. Antibacterial and Anticandidal screening of Tunisian *Citrullus colocynthis* Schrad. from Medenine. *J Ethnopharmacol*. 2009; 125(2):344-349.
- [77] Roy R, Thakur M, Dixit V. Effect of *Citrullus colocynthis*. On hair growth in albino rats. *Pharmaceutical Biology*. 2007;45(10):739-44.
- [78] Elgerwi AA, Benzekri Z, El-Magdoub A, ElMahmoudy A. Qualitative identification of the active principles in *Citrullus colocynthis* and evaluation of its teratogenic effects in albino rats. *International Journal of Basic & Clinical Pharmacology*. 2013;2(4):438-45.
- [79] Shafaei H, Esmaili A, Rad JS, Delazar A, Behjati M. *Citrullus colocynthis* as a medicinal or poisonous plant: A revised fact. *Journal of Medicinal Plants Research*. 2012;6(35):4922-7.
- [80] Chaturvedi M, Mali PC and Ansari AS. Induction of reversible antifertility with a crude ethanol extracts of *Citrullus colocynthis* Schrad fruit in male rats. *Pharmacology*. 2003; 68(1):38-48.
- [81] Rahbar AR and Nabipour I. The hypolipidemic effect of *Citrullus colocynthis* on patients with hyperlipidemia. *Pak J Biol Sci*. 2010; 13(24):1202-1207.
- [82] Grossman S, Dovrat S, Gottlieb HE and Bergman M. Growth inhibitory activity of cucurbitacin glucosides isolated from *Citrullus colocynthis* on human breast cancer cells. *TanninSpitz T, Biochem Pharmacol*. 2007; 73(1):56-67.
- [83] Agarwal V, Sharma AK, Upadhyay A, Singh G and Gupta R. Hypoglycemic effects of *Citrullus colocynthis* roots. *Acta Pol Pharm*. 2012;69(1):75-79.
- [84] Rahuman AA, Venkatesan P and Gopalakrishnan G. Mosquito larvicidal activity of oleic and linoleic acids isolated from *Citrullus colocynthis* (Linn.) Schrad. *Parasitol Res*. 2008 ;103(6):1383-1390.
- [85] Rahuman AA and Venkatesan P. Larvicidal efficacy of five cucurbitaceous plant leaf extracts against mosquito species. *Parasitol Res*. 2008;103(1):133-139.