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Antidiabetic Efficacy of *Citrullus colocynthis* and *Citrullus lanatus*: A Review

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ABSTRACT

The present review is focused on the anti-diabetic potential of Citrullus colocynthis and Citrullus lanatus, commonly referred to as bitter apple and watermelon, respectively. The plants have a history of being employed for therapeutic uses and recent investigation has revealed their potential as antidiabetic agents owing to the presence of bioactive compounds, including cucurbitacins, flavonoids, and alkaloids. The present study examines the therapeutic potential of the plants, highlighting their antidiabetic, anti-inflammatory, antioxidant, and hypoglycemic properties. Additionally, the mechanisms responsible for the antidiabetic effects of these substances, and their effectiveness in the treatment of diabetes in animal and human subject. In addition to safety and toxicity, potential adverse effects were also discussed. In conclusion, these plants possess considerable potential as alternative therapies for diabetes. However, additional investigation is required to extensively comprehend their therapeutic efficacy and establish appropriate and safe dosages for clinical application.

KEYWORDS: *Anti-inflammatory, Antioxidant, Hypoglycemic, Cucurbitacins, Flavonoids, Alkaloids*

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INTRODUCTION

Diabetes mellitus is a global disease that manifests when the body cannot control the amount of glucose (a type of sugar) in the blood and the kidneys produce a large amount of urine (Kumar, 2021). Diabetes mellitus is known to be a chronic metabolic disorder marked by hyperglycemia as a result of defects in secretion and action of insulin (Htwe, 2021; Tripathy & Chavez, 2010). Diabetes occurs when the body does not produce enough insulin or does not properly utilize insulin (Buryukova, Jabbar, & Elizarova, 2017). According to the World Health Organization (WHO), diabetes mellitus has been a global health concern with an increasing number from 108 million in 1980 to 422 million in 2014. It was also estimated that 463 million adults were affected worldwide and its prevalence projected to increase to 700 million by 2045(International Diabetes Federation, 2019). This disease's prevalence continues to increase rapidly in low- and middle-income countries, but not in high-income countries (Choukem & Dimala, 2021). Hyperglycemia was estimated to be the direct cause of 1.5 million deaths in 2019 and 2.2 million deaths in 2012 (American Diabetes Association, 2021). At present, treatments for the management of diabetes mellitus varying from oral hypoglycemic agents and insulin have shown diverse side effects and more so, not always effective of lowering the blood glucose level (Imamoğlu, 2021). Hence, the reason for the increased search for an alternative therapy with great effectiveness and reduced or no adverse effect.

Citrullus colocynthis is a perennial herb typically found commonly in the sandy soils of the Central and Southern India, West Asia, Tropical Africa and Mediterranean region (Burrows & Shaik, 2014). Its leaves vary greatly in size, with wild leaves measuring between 3.8 and 6.3 cm in length and 2.5 cm in width, and cultivated leaves being large (Chawech *et al*., 2015). The fruit is globular, slightly depressed, between 5 and 7.5 cm in diameter, green when unripe, turning white and glabrous when ripe, and with a dry, spongy, extremely bitter pulp (Burrows & Shaik, 2014). The seeds are between 4 and 6 mm long and pale brown.

Citrullus lanatus is popularly known as Egusi (Akpambang *et al*., 2008) in West Africa with other common names including Ibara, or wild watermelon (Awiligwe *et al*. 2021). The plant is a prostrate or climbing annual with several herbaceous, firm, and stout stems that can grow up to 3 metres in length (Agic, Bogoevska, & Ibusoska, 2013). The fruit is consumed all over the world for its sweet flavor and taste and has a thick rind, fleshy centre, and high-water content (Abu-Hiamed, 2017). Typically, the sugar content and sweetness are the most important determinants of watermelon variety quality (Mashilo, Shimelis, Ngwepe, & Thungo, 2022). In Africa, the juice of *Citrullus lanatus* is primarily fermented to create a mildly alcoholic beverage with a tasty flavor (Adedeji, 2017).

The aim of this review is to provide an overview of present understanding on the diabetic-related benefits of *Citrullus colocynthis* and *Citrullus lanatus*, focusing on the bioactive constituents, their mechanisms of action, as well as the safety profiles.

Botanical Description of *Citrullus colocynthis* and *Citrullus lanatus*

Taxonomy

Botanical name: *Citrullus colocynthis* (L.) Schrad
Kingdom: Plantae
Division: Magnoliophyta
Class Magnoliopsida
Order: Cucurbitales
Family: Cucurbitaceae
Genus: Citrullus
Botanical name: *Citrullus lanatus* (Thunb)
Kingdom: Plantae
Class: Equisetopsida
Order: Cucurbitales
Family: Cucurbitaceae
Genus: Citrullus
Common name: Watermelon, Wild Watermelon
Local name: Egusi, Ibara

Figure 1: *Citrullus colocynthis* plant

Figure 2: *Citrullus lanatus* plant

GEOGRAPHICAL AND MORPHOLOGICAL DISTRIBUTION OF *CITRULLUS COLOCYNTHIS* AND *CITRULLUS LANATUS*

Citrullus colocynthis is a Cucurbitaceae family with alternating angular leaves on the long petiole. It is indigenous to the sand-filled, arid regions of West Asia, Arabia, tropical Africa, and the Mediterranean (Burrows & Shaik, 2014). The triangular leaves have multiple clefts and a rough hairy texture with open sinuses. The leaves are fine green on their upper surfaces and rather pale green on their lower surfaces (Azizi, Mohamad, & Mahdavi Shahri, 2017). The globular fruit, often referred to as the bitter apple plant, has a diameter of roughly 7 to 10 cm and is coated in a green skin with yellow stripes (Burrows & Shaik, 2014). The fruits have a thin but tough shell and a delicate, white pulp loaded with many ovate compressed seeds (Kim, Lee, Yang, & Lee, 2014). The monoecious yellow flowers appear singly in leaf axils and have lengthy peduncles with a yellow campanulate (Sagar & Dumka, 2019). The seeds are around 6 mm in diameter, smooth, compressed, and oval in shape (Kostecka-Mądalska & Noculak, 2015). It has a big perennial root from which long and thin,

angular, tough, rough vine-like stems sprout (Burrows & Shaik, 2014). The corolla contains five lobes, while the calyx is divided into five sections (Faisal, Ali, & Ali, 2018). The villous, hairy ovary distinguishes female flowers from males. The seeds are smooth, compressed, and oval in shape, with a diameter of around 6 mm. They range in colour from pale yellowish-orange to dark brown (Kostecka-Mądalska & Noculak, 2015).

Citrullus lanatus, also a Cucurbitaceae family is a flowering vine-like plant that is often grown in tropical and subtropical areas (Wahyuni, 2019). For the past 4,000 years, it has been cultivated mostly for its fruit, particularly in Africa (Mashilo, Shimelis, Ngwepe, & Thungo, 2022). Its origins are based on two distinct theories, one of which suggests that it was developed from the perennial related *Citrullus colocynthis* found in wild archaeological sites, while the other believes that it was domesticated from wild species of *Citrullus lanatus* (Parihar, Vaja, Dhruve, Rukhsar, & Kumar, 2020). According to Erhirhie and Ekene (2013), it spread to Southeast Asia, Japan, Europe, and the United States from Africa in the late 1500. *Citrullus lanatus* is an annual with numerous herbaceous, robust, and sturdy stems up to 3 m long (Ogbuji *et al*., 2012). The young are thickly fuzzy and covered with hairs, while older parts become hairless. The leaves are 7-15 cm in diameter, alternating, simple, cordate with seven shallow lobes and variously serrated margins (Wahyuni, 2019). Both male and female flowers grow on the same plant, with yellow petals and sepals and a greenish hue (Levi, Thomas, Joobeur, Zhang, & Davis, 2002). The fruits range in size from 14 cm to 20 cm, with a spherical shape with shallow grooves and a greenish yellow skin. The smooth, tiny, light brown seeds have a length and width of 0.4 to 1.1 cm and 0.2 to 0.3 cm, respectively (Burrows & Shaik, 2014).

TRADITIONAL USES OF *CITRULLUS COLOCYNTHIS* AND *CITRULLUS LANATUS*

Plants have long been used in traditional medicine as a source of therapeutics for both the management and prevention of several ailments for many years. Despite significant advances in modern medicine, a large portion of the world's population, particularly those with poor incomes, continues to rely on natural product-based traditional methods of treatment (Li *et al*., 2022).

Citrullus colocynthis is a plant that is widely used in different parts of the world to treat a variety of diseases such as diabetes, constipation, leprosy, asthma, bronchitis, jaundice, joint pain, cancer, and mastitis (Sansri, Kalbaza, & Bairi, 2022). The indigenous medical systems of Pakistan, India, China, Africa, and Asia have reported the medicinal uses of this plant. It is traditionally employed as an anti-diabetic and antihypertensive medication in tropical and subtropical regions (Ghauri, Ahmad, & Rehman, 2020). Extracts from *Citrullus colocynthis* has also been found to possess a significant hepato protective properties by protecting the liver against damages resulting from toxins (Ellahi Elltayeib, 2020). The fruits are used to treat cancer, diabetes, bacterial infections, and intestinal disorders in Pakistan and India (Kim, Lee, Yang, & Lee, 2014). Its anti-inflammatory properties contribute to it being among the most prominent folk medicines some regions (Silva & Hussain, 2017). The fruit pulp has been reported to have an anti-inflammatory and analgesic properties. *Citrullus colocynthis* has been widely recognized for its usage as a purgative, antirheumatic, anthelmintic, carminative, and a treatment for skin infections and sore throats (Karunakaran & Hari, 2022; Kim, Lee, Yang, & Lee, 2014).

Traditionally, *Citrullus lanatus* has special importance as a plant having protective properties in kidney diseases and having the ability to clear urine (Adebayo, 2014). The fruit is eaten raw and roasted besides desserts, salad, snacks, watermelon cake, lemonade, and watermelon rind pickles (Erhirhie and Ekene, 2014; Khusnul Khotimah, 2019). The fruit is rich in antioxidants, including lycopene and vitamin C, which help to reduce the risk of chronic diseases such as cancer, cardiovascular diseases, and diabetes (Saeed *et al*., 2017). Drinks and juices made from fruits and seeds are used for freshness, chilling, and thirst-quenching in summer (Rahman *et al*., 2013). The traditional herbal practitioners use seeds to cure urinary complaints, hepatic congestion, intestinal

catarrh, and gastrointestinal disorders (Khare, 2007). The seeds of *Citrullus lanatus* have been found to have hypoglycemic, hypocholesterolemic, and hypotensive properties. They are also richin proteins, vitamins, and minerals, making them a valuable source of nutrition. The seeds and fruit have analgesic, anti-inflammatory (Wahid, Saqib, Qamar & Ziora, 2017), diuretic, anti-urolithiatic (Siddiqui *et al*., 2018), antioxidant (Gill *et al*., 2011), hypotensive, cardioprotective (Itoh *et al*. 2018), and antiulcerative activities (Gill *et al*., 2011).

BIOACTIVE COMPOUNDS IN *CITRULLUS COLOCYNTHIS* AND *CITRULLUS LANATUS*

Citrullus colocynthis (bitter cucumber) and *Citrullus lanatus* (watermelon) are not only a refreshing fruit but also known to be rich in bioactive compounds which have been studied for their various nutritional benefits and potential uses.

Citrullus lanatus is one of the richest dietary sources of lycopene, which is an antioxidant linked to a reduced risk of chronic diseases such as cardiovascular disease, cancer and age-related neurodegeneration (Oberoi, Singh, & Sogi, 2020). It has been reported that *Citrullus lanatus* contains a high concentration of citrulline, an amino acid essential in the urea cycle for removing toxic ammonia from the body (Della, Soetjipto, & Aminu, 2022). It has also been identified to enhance cardiovascular health and exercise performance (Duran Barón, *et al*. 2021).

Citrullus colocynthis contains glycosides including colocynthoside A, which has shown potential in various pharmacological activities such as antitumor, antioxidant, and antimicrobial effects (Kumar *et al*., 2008; Anis, 2012); and have been investigated for their potential use in the treatment of microbial infections and cancer (Kamboj & Dahiya, 2022). Colocynthoside is also a known alkaloid found in *Citrullus colocynthis* with other type of alkaloid, colocynthin, which have been investigated for their anti-inflammatory, analgesic and antimicrobial properties (Mehmood, Kousar, Arshad, Iqbal, & Zeshan, 2021). They have been reported for their potential application in the management of pain, inflammation and infections (Kamboj & Dahiya, 2022).

Citrullus colocynthis and *Citrullus lanatus* both possesses cucurbitacin, a triterpenoid compound recognized for its numerous pharmacological activities as anti-cancer, antidiabetic and anti-inflammatory agents (Karunakaran & Hari, 2022; Pathania, Chawla, Sharma, Kaushik, & Khan, 2022). *Citrullus colocynthis* has been found to contain Cucurbitacin L, Colocynthosides A, and Cucurbitacin B. These were discovered in several parts, including seeds and fruits (Marzouk *et al*., 2012). Cucurbitacins are integral to drug development, specifically in the creation of chemotherapeutic agents, because of to their anti-cancer properties (Hussain *et al*., 2019). According to Zhou *et al*. (2016) and Feng *et al*. (2019), cucurbitacin has shown an inhibitory potential for diabetes progression, cancer cell growth and inflammation related processes. Furthermore, they contain flavonoids such as luteolin, quercetin and kaempferol, which are known to possess an antioxidant, anticancer and anti-inflammatory properties. Flavonoids have been the subject of scientific inquiry due to their potential benefits when it comes to cardiovascular health, cancer prevention, and neuroprotection. Flavonoids possess antioxidant and radical scavenging properties, which render them advantageous to human health. Additionally, they exhibit potential anticancer properties. These compounds exhibit promising potential for enhancing disease resistance (Karak 2019). Phenolics such as caffeic acid, chlorogenic acid and gallic acid are also found in *Citrullus lanatus*. These compounds have shown significant antioxidant activity and have been associated with other health benefits including the neuroprotective and cardioprotective effect. They have been identified to possess in-vitro anti-microbial properties against a numerous microorganisms (Omojate Godstime *et al*. 2014)

PHARMACOLOGICAL PROFILE OF *CITRULLUS COLOCYNTHIS* AND *CITRULLUS LANATUS*

The numerous bioactive compounds found in *Citrullus colocynthis* and *Citrullus lanatus* gives

them a wide range of pharmacological profile. Below are some of their pharmacological profiles and their potential applications.

Antidiabetic Activity**:** *Citrullus colocynthis* and *Citrullus lanatus* have traditionally been utilized in folk medicine for their potential anti-diabetic properties. These extracts have been shown in scientific studies to reduce blood glucose levels and enhance insulin sensitivity (Omigie & Agoreyo, 2014; BENARIBA *et al*., 2012). Patel *et al*. (2012) examined the antidiabetic activity of *Citrullus colocynthis* extract in animal models of diabetes and found that the extract significantly lowered fasting blood glucose levels, improved glucose tolerance, and increased insulin sensitivity. The antidiabetic activity of *Citrullus lanatus* seed extract was also studied in diabetic animal models byAjiboye, Shonibare, & Oyinloye, (2020), who found that it significantly lowered blood glucose levels, improved lipid profile, and improved antioxidant defenses. In addition, several bioactive compounds found in both *Citrullus colocynthis* and *Citrullus lanatus*, including cucurbitacin compounds, citrulline, and polyphenols, have been shown to possess antidiabetic properties.

Antioxidant Activity: *Citrullus colocynthis* and *Citrullus lanatus*are two species of melon that possess antioxidant properties. Studies have shown that these melons contain various antioxidants, including phenolic compounds, flavonoids, and vitamin C, which contribute to their antioxidant activity (Al-Nablsi *et al*. 2022). Bourhia *et al*. (2018) found that *Citrullus colocynthis* extract exhibited strong antioxidant activity in vitro, as measured by various assays such as DPPH radical scavenging and reducing power. Neglo *et al*. (2021) investigated the antioxidant properties of *Citrullus lanatus,* and the study demonstrated that the extract possessed significant antioxidant activity, which was attributed to the presence of phenolic compounds. These findings suggest that these melons may have potential as natural sources of antioxidants for various applications in the food, pharmaceutical, and nutraceutical industries.

Anti-inflammatory Activity: *Citrullus colocynthis* and *Citrullus lanatus*, have been investigated for their potential anti-inflammatory properties. Several bioactive compounds present in the extracts of these melons are responsible for their anti-inflammatory properties, as shown by scientific research. Rajamanickam *et al*. (2010) investigated the anti-inflammatory activity of *Citrullus colocynthis* extract and found that it inhibited inflammatory mediators such as nitric oxide (NO), prostaglandin E2 (PGE2), and tumour necrosis factor-alpha (TNF-α) to a significant level. In an animal model of inflammation, El-Mahmood *et al*. (2018) investigated the anti-inflammatory potential of *Citrullus lanatus* extract and found a significant reduction in the levels of inflammatory markers, including interleukin-6 (IL-6) and C-reactive protein (CRP). Anti-inflammatory properties are attributed to flavonoids and phenolic compounds in the extracts (Bazabang *et al*. 2023). These results suggest that these melons have the potential to be used as natural anti-inflammatory agents in the development of novel therapeutics.

Anti-cancer Activity**:** *Citrullus colocynthis* extract and *Citrullus lanatus* extract have been shown to have anti-cancer properties in various cancer cell lines, as evidenced by their cytotoxic effects, induction of cell cycle arrest, and induction of apoptosis (Varela *et al*. 2022; Faisal, Ali, & Ali, 2018). These anti-cancer effects are aided by the presence of bioactive compounds such as cucurbitacin B and cucurbitacin E, as well as phenolic compounds, flavonoids, and cucurbitacin derivatives in the extract (Karakuş*,* Yılmaz*,* Eyol*,* & Ünüvar, 2019; Marzouk *et al*., 2012). These findings suggest that these melons have the potential to be natural sources of anti-cancer agents and require further research into their use in cancer prevention and treatment.

Anti-microbial Activity**:** Research studies have highlighted the antimicrobial effects of *Citrullus colocynthis* and *Citrullus lanatus*, which can be attributed to various bioactive compounds such as cucurbitacins and cucurbitacin glucosides, present in their extracts. A study conducted by Faisal, Ali, & Ali, (2018) revealed that the extract exhibited significant inhibitory effects against a range of pathogenic microorganisms, including bacteria and fungi. Additionally, a research article by Mohammed *et al*. (2020) investigated the antimicrobial potential of *Citrullus lanatus*

extract, which demonstrated that the extract exhibited antimicrobial activity against various pathogenic bacteria, including both Gram-positive and Gram-negative strains. These findings suggest the potential of these melons as natural antimicrobial agents and highlight their possible applications in the development of antimicrobial therapies and products.

***Analgesic Activity*:** *Citrullus colocynthis* and *Citrullus lanatus* have been the subject of limited scientific research regarding their analgesic properties. Traditionally, these melons have been used for their medicinal properties, which include pain relief, but there is a dearth of research on their analgesic effects (Shafaei, 2012). For this information, anecdotal evidence and traditional use are more important than scientific studies. *Citrullus colocynthis* has been traditionally employed in folk medicine for its potential analgesic properties (Karunakaran & Hari, 2022), whereas *Citrullus lanatus* has been utilized for a variety of purposes, including pain relief (Wahid, Saqib, Qamar & Ziora, 2017). Some anecdotal evidence suggests that citrulline and cucurbitacin, two compounds found in watermelon, may have analgesic properties (Burrows & Shaik, 2014). However, rigorous scientific studies are required to establish *Citrullus lanatus*' analgesic properties and identify the active compounds responsible for such effects. In order to evaluate and validate the analgesic properties of these melons and determine the active compounds responsible for their potential pain-relieving effects, additional research is required.

***Neuroprotective Activity*:** The ability of *Citrullus colocynthis* and *Citrullus lanatus* to protect and preserve the health of neuronal cells has shown promising results, which can be attributed to the bioactive compounds present in their extracts. Mohan *et al*. (2016) discovered that the extract exhibited significant neuroprotective activity against neuronal cell damage induced by oxidative stress. In addition, Sharma *et al*. (2017) investigated the neuroprotective potential of *Citrullus lanatus* extract, which was discovered to exhibit protective effects against neuronal cell death induced by neurotoxic agents. The authors concluded that the extract's phenolic compounds and flavonoids were responsible for its neuroprotective effects. Therefore, *Citrullus colocynthis* and *Citrullus lanatus* protect against neurotoxicity and reduce neuronal cell damage caused by oxidative stress.

***Cardioprotective Activity*:** *Citrullus colocynthis* extracts were found to have significant cardioprotective effects in animal models against myocardial injury induced by ischemia-reperfusion. The extract reduced cardiac injury, oxidative stress, and inflammatory markers. El-Sayed *et al*. (2020) also investigated the cardioprotective potential of *Citrullus lanatus* extract, which exerted protective effects against cardiac injury induced by doxorubicin, a known cardiotoxic chemotherapy drug. Researchers attributed the cardioprotective properties of the extract to the presence of phenolic compounds and flavonoids.

MECHANISM OF ACTION IN THE MANAGEMENT OF DIABETES MELLITUS

The potential of *Citrullus colocynthis* and *Citrullus lanatus* in the management of diabetes mellitus has been demonstrated, with their underlying mechanisms of action involving multiple pathways and processes. The antidiabetic effects of these melons are attributed to various mechanisms such as increased insulin secretion, enhanced insulin sensitivity, inhibition of carbohydrate digestion and absorption, and modulation of glucose metabolism.

The potential of *Citrullus colocynthis* and *Citrullus lanatus* to boost insulin secretion from pancreatic beta cells is considered responsible for their antidiabetic characteristics. The hormone insulin is of paramount importance in the regulation of blood glucose levels as it enables the transportation of glucose into cells. According to Omigie & Agoreyo, (2014), the stimulation of insulin secretion by *Citrullus colocynthis* and *Citrullus lanatus* has been demonstrated, resulting in heightened glucose uptake and decreased blood glucose levels.

Citrullus colocynthis and *Citrullus lanatus* have exhibited the capacity to enhance insulin sensitivity, apart from their insulin secretion promotion properties. Insulin sensitivity

pertains to the degree of cellular reactivity to insulin. The bioactive compounds present in melons, such as flavonoids and phenolic compounds, have been discovered to improve insulin sensitivity, thereby facilitating the efficient utilisation of glucose by cells (Patel *et al*., 2012; Abdel-Sattar *et al*., 2019). Enhanced insulin sensitivity is advantageous in mitigating insulin resistance, a defining characteristic of type 2 diabetes.

An additional mechanism of action involves the restraint of carbohydrate digestion and absorption. The plants *Citrullus colocynthis* and *Citrullus lanatus* possess certain compounds, specifically cucurbitacin, that have demonstrated the ability to impede the activity of enzymes that participate in the breakdown of carbohydrates, such as alpha-amylase and alpha-glucosidase, as evidenced by Ajiboye, Shonibare, & Oyinloye, (2020). The melons exhibit the ability to impede the activity of certain enzymes, thereby decelerating the pace of carbohydrate assimilation from the gastrointestinal tract. This, in turn, leads to enhanced regulation of blood glucose levels.

Furthermore, it has been suggested that *Citrullus colocynthis* and *Citrullus lanatus* have the potential to regulate glucose metabolism. It has been discovered that they are capable of inducing activation of AMP-activated protein kinase (AMPK), which is an enzyme that plays a crucial role in the regulation of cellular energy (Badmus *et al*., 2021; Obi & Offorha, 2015). The activation of AMPK through the consumption of melons results in an augmentation of cellular glucose uptake and an elevation in the translocation of glucose transporter 4 (GLUT4) to the cell membrane, as reported by Ajiboye, Shonibare, & Oyinloye, (2020). The aforementioned mechanism facilitates the utilization of glucose by cells, thereby augmenting glycemic control.

SAFETY, TOXICITY AND POTENTIAL SIDE EFFECTS OF *CITRULLUS COLOCYNTHIS* AND *CITRULLUS LANATUS*

Citrullus colocynthis and *Citrullus lanatus* are two species of melons that have been historically utilized for their medicinal properties. However, it is important to take into account the potential toxicity of these plants when evaluating their utilization. *Citrullus colocynthis* has been found to be associated with gastrointestinal, hepatic, and renal toxicities (Ishtiaq, 2020). Watermelon, scientifically known as *Citrullus lanatus*, is deemed safe for consumption due to its substantial hydration properties and nutritional benefits, but it may entail certain adverse effects; and exhibits a high glycemic index, which can lead to a rapid increase in blood glucose levels (Omigie & Agoreyo, 2014; Faisal, Ali, & Ali, 2018). Watermelon consumption should be regulated and blood glucose levels should be monitored by individuals with diabetes or those following a low-sugar diet. Although, it has been reported to be used in the management of diabetes, however, the antidiabetic activity is determined in some plants part and also at a particular dosage. Furthermore, excessive consumption of watermelon may result in frequent urination and potential electrolyte imbalances due to its high-water content (Artana, 2020). Hence, the need for moderate consumption of *Citrullus lanatus*. Certain individuals may encounter allergic responses to watermelon, which may present as swelling, hives, or itching. In the event of any manifestation of allergic symptoms, it is recommended to exercise caution and seek guidance from a medical professional prior to utilizing these plants for medicinal purposes, particularly if there are pre-existing health conditions or allergic reactions.

FUTURE DIRECTIONS AND CONCLUSION

In conclusion, *Citrullus colocynthis* and *Citrullus lanatus* exhibit promising characteristics as natural alternatives to antidiabetic therapies. Future directions may involve more research focusing on the identification of the bioactive constituents responsible for their effects, expounding upon the molecular mechanisms involved, and conducting clinical trials to validate their effectiveness and safety in individuals with diabetes. Through advancement of our understanding in these areas, we can effectively employ the therapeutic potential of these plants and create innovative interventions for diabetes.

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