Rao and Poonia
*Food Production, Processing and Nutrition* (2023) 5:4
https://doi.org/10.1186/s43014-022-00118-9

Food Production, Processing and Nutrition

REVIEW

Open Access

# *Citrullus colocynthis* (bitter apple): bioactive compounds, nutritional profile, nutraceutical properties and potential food applications: a review

Vasundhara Rao and Amrita Poonia*

## Abstract

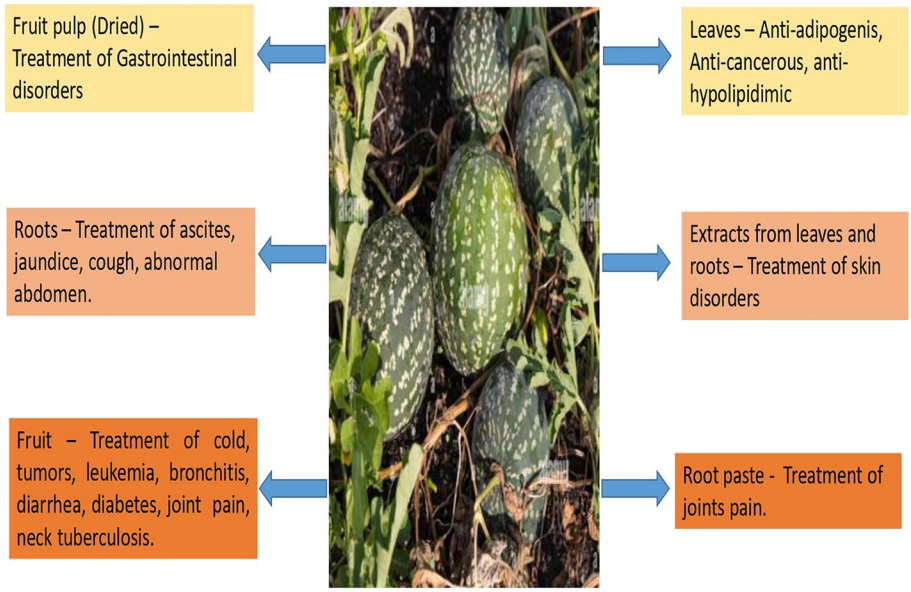
Herbal remedies and related foods provide healing properties for a range of diseases, resulting in a higher standard of living. Bitter apple is extremely beneficial due to its bioactive and nutraceutical compounds. Increasing awareness among consumers across the world about this unique fruit's properties may provide huge opportunities for the supplier of herbal products as well as their use in the food industry. It has significant applications in the field of food technology. This review focused on the important features of bitter apple mainly, bioactive compounds, their mode of action, medical applications, chemical characteristics, chemical compounds, and the latest research on the pharmacological interventions of bitter apple extracts. This review also highlights the potential use of bitter apples in the food industry as well as their application in nanotechnology for the formation of nanoparticles.

**Keywords:** Bioactive compounds, Bitter apple, *Citrullus colocynthis*, Medicinal properties, Nanoparticles, Food industry

*Correspondence: amrita12@bhu.ac.in

Department of Dairy Science and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India

**Graphical Abstract**




## Introduction

Bitter apple (*Citrullus colocynthis*) is a useful cucurbit plant that is extensively dispersed throughout the world's arid locations. These plants are mainly found in the deserts of Arabia and the Sahara and the southern part of Asia which mainly includes India, Pakistan, and southern islands (Coffey et al. 2015). Bitter apple fruit is commonly known as colocynth, bitter cucumber, bitter melon, egusi melon, *Citrullus colocynthis lanatus*, and the bitter vine of Sodom. It grows as a wild perennial in arid places across the world and has promising therapeutic, nutraceutical, and food uses (Asyaz et al. 2010). These plants are widely used in traditional medicines (Uma & Sekar 2014). Different parts of these plants serve as a therapy for diseases such as jaundice, diabetes, and asthma (Li et al. 2021). The fruit of *Citrullus colocynthis* is bitter in taste, spherical in shape, and has a smooth and fine texture. It is firm and has a crust around it and also consists of around 200-300 seeds per gourd (Uma & Sekar 2014). These plants are generally perennial vines that produce very small sized flowers which are aromatic in nature and have mesocarp thickness, density, and seed-fruit proportion. The physical attributes of bitter apple fruits include fruit mass, seed and pulp content, volume, epicarp, etc. The average mass of the fruit in grams is approximately 506 g. The mass content of the pulp accounts for about half of the fruit mass. About 75.1 g of the fruit's weight comprises of the seeds (Hussain et al. 2014). Mature fruits have tiny seeds and are about 6 mm long, oval in shape, compact in structure, brownish in color, and smooth in texture (Hussain et al. 2014). Kernels of egusi melon seed are said to be high in protein, essential minerals, and oil content. Egusi oil is a feasible alternative among most vegetable oils since melon farming is inexpensive and the plant is drought-tolerant when compared to most oil crops (Olubi et al. 2019). Certain essential amino acids such as methionine, tryptophan, arginine etc.; minerals such as zinc, iron, potassium, manganese, calcium, etc.; and vitamins are found in egusi seed kernels. These plants contain several bioactive compounds such as flavonoids and glycosides. Quercetin has been found as the most common bioactive flavonoid in the parts of the egusi plant such as the leaf, fruits, stem, and roots (Meena & Patni 2008). Bitter apple is used in the treatment of many diseases like joint pain, leprosy, bronchitis, cancer, and mastitis (Heydari et al. 2016). Along with this, these plants have medicinal uses which help in the prevention of gut-related disorders namely, dysentery and indigestion. It is often used as a traditional medicine for inflammation as it possesses anti-inflammatory properties (Kuralkar & Kuralkar 2021). A substantial majority of phytochemicals from different chemical classifications were shown to obstruct all pathogens (Li et al. 2021). Plant products are often used in medicinal herbs since the very beginning. Leaves of the plant, flower petals, root systems, fruits, and fruit extract, seed residue, and seed pods can be used to prepare medicines, and herbal products and it can also be used in the food industry. Medicinal plant treatment elements usually involve decoction, emulsion, liniments,

electroactive, and powder (Rashid et al. 2021). The components of such plants are also used in a variety of industries, which mainly includes, the cosmetic industry, fragrances, and food industry. Before actually being utilized in the development of pharmaceuticals and for making functional food products, the active compounds of bitter apple are extracted by different method (Mubeen et al. 2022). Many African countries have historically employed Egusi seed kernels in food compositions. These seed kernels are usually fermented, dry roasted, and ground before being used as a flavoring agent or thickener in stews and soups. Robo, origin, egusi soup, toasted egusi kernel beverages, and kernel pudding are some traditional products prepared using seed kernels.

## Nutritional profile and chemical composition

Although parts of *C. colocynthis* are widely incorporated in food as well as in the pharma industry, little nutritional information is publicly available for the global readers. A few variations in the attributes may be found due to differences in agricultural environmental conditions and farming techniques used in different countries (Berwal et al. 2022). The seed components are composed of approximately 23 - 25% oil (golden yellow colored), 70% unsaturated fatty acids as well as 51% polysaturated fatty acids (Berwal et al. 2022). The moisture content of the ripe fruit is very high, accounting for even more than 90% of the total weight (Hussain et al. 2014). According to another study, the moisture content of seeds was found to be 4.91 g/100 g, and protein and ash were 13.19 g /100 g and 2.00 g/ 100 g, respectively (Banjo et al. 2021). Nutritional profile, fatty acids content and the volatile components of different parts of bitter apple are shown in Table 1. *Citrullus colocynthis* is high in amino acids such as methionine, arginine, and tryptophan. The primary amino acids which were found are glutamic acid and arginine, recognized with concentrations of 19.8 g/100 g and 15.9 g/100 g of protein, respectively. Aspartic acid, serine, glycine, and glutamic acid were among the other amino acids found in protein (Hussain et al. 2014). Minerals are important micronutrients that the body requires to function ordinarily. Each one of the minerals is very well recognized for its advantageous properties in sustaining electrolytic fluid balance and also contributing to the alkalization of the body (Banjo et al. 2021). *C. colocynthis* fruits and seeds contain a wide variety of micronutrients that may be beneficial to the consumers. The major minerals found in the seeds are potassium and calcium, which have concentration levels of 569 mg/100 g and 465 mg/100 g of seeds, respectively (Hussain et al. 2014). The seeds are also high in magnesium and phosphorus. Iron and zinc levels are low in comparison to the other micronutrients.

## Functional and bioactive compounds in *C. colocynthis*

### Phenolic acids and flavonoids

Phenolic compounds constitute one of the most numerous and ubiquitous groups of plant metabolites. These compounds possess biological properties which mainly include anti-aging, anti-atherosclerosis, cardio-vascular safeguards, vascular endothelium function improvement, angiogenesis inhibition, and cell proliferation (Kim et al. 2022). Flavonoids are phenolic compounds (typically hydroxylated) that are produced by plants in reaction to infection by microbes. They have been reported to have in-vitro anti-microbial properties against a variety of microorganisms (Omojate Godstime et al. 2014). They are also potent antioxidants with cytotoxic activity. Such compounds tend to play critical roles in infectious agent as well as in predator defense, and also in physiological mechanisms such as seed development and stunted growth. Flavonoids are beneficial to humans because of their antioxidant properties and radical scavenging properties, and they also have potential anticancer properties. These compounds have the potential to be beneficial in disease resistance (Karak 2019). These substances have the potential to be beneficial in resistance to different diseases (Ahmed et al. 2019).

### Cucurbitacin

Natural antioxidants are triterpenoid chemicals that are well-known for their bitter flavor and toxic effects (Hussain et al. 2014). Cucurbitacins play an essential part in drug development, particularly in the development of chemotherapeutic agents, due to their anti-cancerous properties. The studies conducted on *Citrullus colocynthis* shows the presence of Cucurbitacin L, Colocynthosides A, and Cucurbitacin B. They were found in different part such as seeds and fruits (Rezai et al. 2017). The primary Cucurbitane type demonstrates anti-allergic properties. Different studies reveals the configuration relationship of cucurbitacin and its derivatives, which have been proficient in electrochemical reactions on cell materials or gene products (Rezai et al. 2017).

### Alkaloids

Alkaloids have always been recognized to play functions such as biochemical and structural in biological organisms. This substance has a defensive function in living creatures and has been used in healthcare, particularly steroidal alkaloids, which also make up the majority of beneficial substances (Saxena et al. 2013). Furthermore, phyto-constituents with effective trypanocidal interaction were reported to produce active ingredients, flavonoids, phenolics, etc. Satyavani et al. (2011) reported that *C. colocynthis* contains a high concentration of alkaloids. A study reported presence of secluded choline and a total

**Table 1** Nutritional and fatty acid composition of different parts of bitter apple

| Name of Constituents | Parts of plant | Amount | References |
|---|---|---|---|
| **Proximate composition** | | | |
| Ash (%) | Seed | 2.00 | Banjo et al. 2021 |
| | Seed | 2.23 | Riaz et al. 2015 |
| | Fruit | 3.08 | Ogundele et al. 2012 |
| | Fruit | 4.00 | National Research Council 2006 |
| Moisture (%) | Seed | 4.91 | Banjo et al. 2021 |
| | Seed | 6.43 | Riaz et al. 2015 |
| | Fruit (Mature) | 90.00 | National Research Council 2006 |
| Oil content (%) | Seed | 28.50 | Riaz et al. 2015 |
| | Seed | 26.60 | Banjo et al. 2021 |
| Fat (%) | Seed | 18.59 | Banjo et al. 2021 |
| | Fruit | 3.15 | Ogundele et al. 2012 |
| Protein (%) | Seed | 13.19 | Banjo et al. 2021 |
| | Seed | 13.99 | Riaz et al. 2015 |
| | Fruit | 24.37 | Ogundele et al. 2012 |
| | Fruit (Mature) | 30.00 | National Research Council 2006 |
| Crude fibers (%) | Seed | 46.73 | Riaz et al. 2015 |
| Starch (%) | Seed | 1.33 | Riaz et al. 2015 |
| Carbohydrate (%) | Fruit | 10.88 | Ogundele et al. 2012 |
| | Fruit | 10.00 | National Research Council 2006 |
| **Fatty acid and Amino acid profile** | | | |
| Oleic acid (by wt.% of seed) | Seed oil | 18.02 | Berwal et al. 2022 |
| | Seed oil | 33.66 | Riaz et al. 2015 |
| Linoleic acid (by wt.% of seed) | Seed oil | 50.31 | Berwal et al. 2022 |
| | Seed oil | 50.60-60.10 | Bhasin et al. 2020 |
| | Seed oil | 54.70 | Riaz et al. 2015 |
| Glutamic acid (% of protein) | Seed oil | 19.80 | Bhasin et al. 2020 |
| Arginin (% of protein) | Seed oil | 15.90 | Bhasin et al. 2020 |
| Palmitic acid (by wt.% of seed) | Seed oil | 8.1-17.30 | Bhasin et al. 2020 |
| | Seed oil | 4.30 | Riaz et al. 2015 |
| | Seed oil | 12.41 | Berwal et al. 2022 |
| Stearic acid (by wt.% of seed) | Seed oil | 6.10-10.50 | Bhasin et al. 2020 |
| | Seed oil | 15.15 | Berwal et al. 2022 |
| | Seed oil | 1.83 | Riaz et al. 2015 |
| Lignans (%) | Seed oil | 0.012 | Berwal et al. 2022 |
| Linolenic acid (%) | Seed oil | 2.15 | Riaz et al. 2015 |
| **Minerals** | | | |
| Calcium (%) | Seed | 0.057 | Bhasin et al. 2020; Banjo et al. 2021 |
| | Seed residue | 0.013 | Riaz et al. 2015 |
| Potassium (%) | Seed | 0.047 | Bhasin et al. 2020 |
| | | | Banjo et al. 2021 |
| | Seed residue | 0.012 | 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 | 0.012 | Banjo et al. 2021 |
| | Seed residue | 0.004 | Riaz et al. 2015 |
| Oryzanol (%) | Seed oil | 0.066 | Berwal et al. 2022 |

**Table 1** (continued)

| Name of Constituents | Parts of plant | Amount | References |
|---|---|---|---|
| **Bioactive compounds and Antioxidant activity** | | | |
| Total Phenolic Content (mg/100 g of oil gallic acid Eq.) | Seed oil | 5.39- 6.12 | Berwal et al. 2022 |
| Total Flavonoids Content (mg/100 g of oil catechin Eq.) | Seed oil | 938.0- 956.0 | Berwal et al. 2022 |
| Oryzanol (%) | Seed oil | 0.066 -0.069 | Berwal et al. 2022 |
| Lignans (%) | Seed oil | 0.012-0.014 | Berwal et al. 2022 |
| Carotenoids (%) | Seed oil | 0.008-0.01 | Berwal et al. 2022 |

of two un-identified naturally occurring substances from bitter apple fruit pulp. Alkaloids are supposed to play metabolic and developmental functions in life processes. These substance seems to have a defensive function in animals and has been utilized in medical science, example steroidal alkaloids (Saxena et al. 2013).

### Saponins

The extracts of the plant were found to have saponins that are recognized to provide an anti-inflammatory effect. They consists of triterpene and sterol glycosides which are utilized as expectorants and emulsifiers. As a result, saponin, like a carbohydrate derivative, could be steroids or tri-terpenoids (Khan et al. 2012). They are produced by combining phenylpropanoids as well as precursors of acetate-derivatives. Innumerable studies have highlighted the effectiveness and participation of steroidal saponins in community pharmacies (Egbuna et al. 2020). The application of different parts of the bitter apple plants, their bioactive compounds, and the mode of action are mentioned in Table 2. Furthermore, saponin is utilized in the pharmaceutical industries as well as in medicines due to its frothing capacity and foamy impact. Saponin has been used in medicine since ancient times and is one of the widely accepted bioactive components in cytotoxicity (Abdulridha et al. 2020).

**Table 2** List of different bioactive compounds present in different parts of bitter apple and their mode of action

| Bioactive compounds | Specific constituents | Activity | Mode of action | References |
|---|---|---|---|---|
| Flavonoids | Iso-vitexin, iso-orientin, iso-orientin 3′-methylether | Anti-tumor, Anti- inflammatory, Anti-diarrheal | Prevents the production of autacoids as well as prostaglandins. Enhances the regularization of abnormal transport of water all over intestinal mucosa. | Hussain et al. 2014 |
| Cucurbitacin | Colocynthosides A, Curcubitacin B | Anti-cancer, Antimicrobial | Membrane compression attributes are present<br>Disruption of membrane | Ali et al. 2012 |
| Glycosides | Cucurbitacin E 2-O-D-glucopyranoside, cucurbitacin E | Anti-diarrheal, Anti-allergic | Prevents the production of autacoids as well as prostaglandins. | Hussain et al. 2014 |
| Steroids | Not specified | Anti-diarrheal | Improve Na + and water holding capacity in the intestine | Uma & Sekar 2014 |
| Saponins | Not specified | Anti-cancerous | Membrane compression attributes. | Uma & Sekar 2014 |
| Alkaloids | Choline | Antimicrobial, Anthelmintic | Nitrate production is reduced, which is beneficial to protein biosynthesis | Ali et al. 2012 |
| Terpenes and Terpenoids | Thymol, linalool, geraniol, linalyl acetate, carvacrol and menthol | Antimicrobial | Disrupt the membranes of microorganisms thereby affecting the permeability of the microbial cell. Alteration of their ability to carry out osmoregulation | Banjo et al. 2021 |
| Phenols | Not specified | Antimicrobial | Inhibits adhesion in some pathogens.<br>Also disintegrate the cell membrane of the microbes which resulted in the porosity of the cell and thus affects the functionality of the cell | Banjo et al. 2021 |

## Biological activities of various constituents of *C. colocynthis*

### Antimicrobial property

Chawech et al. (2015) reported the impact of the ethanolic extract of the bitter apple fruit which was investigated utilizing the simple diffusion technique as well as the disc diffusion technique. The results showed that it does have antimicrobial effects on *Staphylococcus aureus*, *Bacillus subtilis,* and *Klebsiella pneumonia*. The results also showed that the ethanolic extract taken from the pulp was more active against specific strains of gram-positive bacteria. The seed extract showed slightly low activity against gram-positive and gram-negative bacteria. In-vitro testing revealed that diluted acetone extracts and aqueous extract had antimicrobial action against gram-negative as well as gram-positive bacteria. Better outcomes were reported from soluble fruit extract when compared with root extracts. Khatibi and Teymorri (2011) reported a high antimicrobial effect in fully matured bitter apple seeds and fruits. Extracts of *C. colocynthis* prepared in different solvents were tested for antimicrobial effects against, *Salmonella, Staphylococcus aureus, Bacillus* spp., *Proteus vulgaris, and Pseudomonas* spp. Other experiments reported that the majority of the extracts had MICs in the 20 to 100 g/mL range against all the other pathogenic bacteria.

### Anti-inflammatory property

*C. colocynthis* is a popular plant in folk medicine owing to its anti-inflammatory capabilities (Marzouk et al. 2011). Bitter apples seemed to disrupt histamine, serotonin mechanisms, prostaglandin as well as kinin pathways (Marzouk et al. 2013). The isolation and characterization of glycoside 11-deoxycucurbitacinI-2-O-b-D at concentrations of 0.5 to 1.0 mg/kg body composition in different animal studies yielded the principal potent bioactive constituents within the chloroform component of CCS extracts (Marzouk et al. 2013). In multiple animal studies, these substances were tested positive for anti-inflammatory properties (Marzouk et al. 2011). Bitter apple is generally known to have high anti-ulcerogenic properties (Zaidi et al. 2012). It is conceivable because, it is devoid of ulcerogenic effect and delivers a better and more efficient anti-inflammatory solution (Bernard & Olayinka 2010).

### Anti-diabetic property

Diabetes is among the most rapidly developing metabolic illnesses. The therapy is symptomatic and needs the use of pharmacological medications for the rest of one's life. In addition to being expensive; it has several adverse effects. Consequently, the hunt for some more effective alternative for anti-diabetic treatments persists (Rahimi et al. 2012). Bitter apple has been extensively used as an anti-diabetic in several nations and it has also provoked the interest of a huge amount of research on both animals as well as humans. The aqueous extract, when taken orally, may alleviate some of the deleterious effects of streptozotocin as well as it also lowers blood glucose level. *C. colocynthis* fruit is commonly used among herbalists in Iran to cure diabetes. Mariod and Jarret (2022) conducted a two-month clinical trial of the fruit on 50 diabetes mellitus patients to establish its effectiveness. Under regular anti-diabetic medication, two different groups of 25 consumers each were given 100 mg fruit tablets as well as placebo pills three times per day. At the commencement and then after 2 months of therapy, glycosylated hemoglobin, fasting sugar levels, lipid profile, low-density lipoproteins, high-density lipoprotein, cholesterol levels, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, etc. were determined. The authors reported a significant decrease in HbA1c and fasting blood glucose levels in bitter apple-treated patients.

### Antioxidant property

Cucurbitacin is an antioxidant and may destroy free radicals such as hydroxyl, superoxide radicals as well as oxygen singlets. It also prevents lipid peroxidation and degradation altogether (Bernard & Olayinka 2010). *C. colocynthi's* methanolic fruit extract were discovered to be an effective antioxidant. Because of the inclusion of gallic acid which is a phenolic molecule, it has significant free radical scavenging capability. The fruit extract's maximum antioxidants and radical scavenging capability were recorded at 2500 ml/ml (Kumar et al. 2008). Phytochemical analysis of bitter apple extracts demonstrated that the organic substances found in them provide as an effective antioxidant (Benariba et al. 2013). Polyphenolic chemicals are thought to be responsible for the therapeutic benefits of various nutraceutical and pharmaceutical plants used in traditional treatment. Marzouk et al. 2013 studied the DPPH free radical scavenging effect of an aqueous leaf extract of bitter apple produced in Tunisia. The authors reported an $IC_{50}$ value of 0.021 mg/mL. Cucurbitacin glycoside from bitter apple demonstrated ABTS radical scavenging capabilities ($IC_{50}$, 145 M), most likely as a result of direct scavenging impact on multiple free radicals (Hussain et al. 2014). Meybodi (2020) conducted an in-vitro investigation and found that *C. colocynthis* can reduce free radical damage to a person as it has a variety of biochemical that constitute to its effective antioxidant properties. *C. colocynthis* oil can improve antioxidant enzyme performance and safeguard the liver against damage (Amamou et al. 2015).

## Conventional uses *of C. colocynthis*

Bitter apples have been very useful in the treatment of many diseases for ages. Different parts of the plants have beneficial properties such as anti-diabetic, anti-inflammatory, and anti-cancerous (Drissi et al. 2021). The fruits and pulp of this plant have been used in medicine since ancient times. Traditionally it was mainly used as a source of medicine for the treatment of many diseases. Rahimi et al. (2012) reported that this plant is often used to treat diseases such as diabetes, liver diseases, digestive problems, intestine blockage, and even paralysis. Bitter apple leaf extracts reduces pain, improves nerves and muscles. It also improves health-related quality of people having uncomfortable diabetic neuropathy. *C. colocynthis* is used in the treatment of stomach problems as well as respiratory diseases, epidermis, infectious diseases, bowel problems, inflammation, leukemia, and kidney diseases (Hameed et al. 2020). It is also helpful in treating a variety of skin conditions such as scrapes, lesions, and blisters etc. Fruit Pulp has been used to treat pustules, clogged pores, breakouts etc. It is an effective herbal treatment for rheumatoid arthritis and inflammatory arthritis pain. It is a useful herb for pathological conditions such as jaundice. Analgesic properties of the fruit extracts were also reported (Rani et al. 2017). Many pharmacological studies have been influenced by *C. colocynthis* conventional medicinal applications. Many such extracts and active compounds have already been tested for bioactivity, particularly anti-carcinogenic and anti-hyperglycemic properties (Bhasin et al. 2020). The traditional uses of the bitter apple have been shown in Fig. 1 and Table 3. *C. colocynthis* appears to be of great interest for the development of new anti-carcinogenic drugs due to its high cucurbitacin composition (Kamalakar et al. 2015). Bitter apples can be used as a wound-healing substance. Gupta et al. (2018) reported that the methanolic extract from the fruit pulp at concentrations of 5 and 10% applied for 16 days, had a better pattern of healing when compared to control which did not contain the methanol.

## Potential uses of *C. colocynthis* in the food industry

### Significance of *C. colocynthis* in the flavor industry

Traditionally, spices and herbs are used to enhance the flavor of food and extend its shelf life. According to market research, customers are more interested in items that are 'organic' or feature 'innate taste,' which indicates that the components are derived from natural sources. The flavor industry producing different varieties of flavors such as vanilla, strawberry, etc., has always been in demand by consumers, especially by the younger generations (Mortzfeld et al. 2020). A wide range of volatile chemicals has been reported for usage in the food industry in recent years. Because of customer requirements as well as new legislative and food safety developments, the inclusion of these compounds in food applications is steadily rising (Wyrwa & Barska 2017). Terpenes, sulfur compounds, and aldehydes are examples of such substances. Because of their inherent antibacterial, antioxidant, insect-repellent, and other qualities, volatile chemicals such as aldehydes, terpenes, and sulfur compounds, among others, are

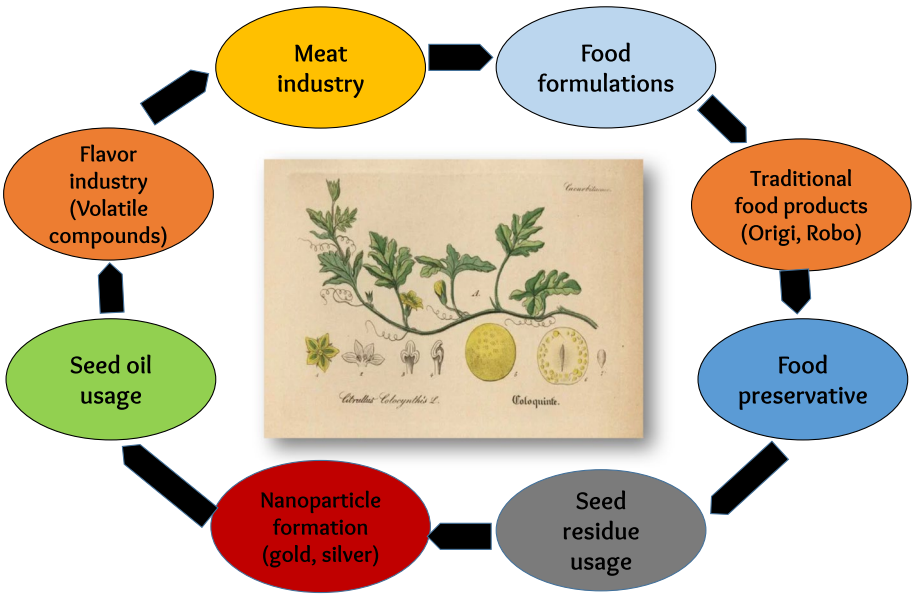



**Fig. 1** Application of Bitter Apple (*Citrullus colocynthis*) in food industry

**Table 3** Health benefits and traditional uses of the different parts of bitter apple

| Parts of bitter apple | Health benefits | References |
|---|---|---|
| Seeds | Antidiabetic properties | Pravin et al. 2013 |
| Leaves | These possess diuretic properties. Helps in treatment of diseases like asthma. It is also used in the treatment of cancer | Perveen et al. 2020 |
| Pulp | Helpful in treatment of throat diseases, tumor, anemia and tuberculosis | Hussain et al. 2014 |
| Roots | Helpful in the treatment of rheumatism | Pravin et al. 2013 |
| Fruit pulp (Dried) | Helpful in the treatment of gastrointestinal disorders. | Hussain et al. 2014 |
| Fruit extracts | Helps in relieving pain. Acts as an analgesic and also used for treatment of diabetics | Heydari et al. 2016 |
| Seed oil | Helpful in the treatment of constipation | Qureshi et al. 2010 |
| Root paste | Used in joint pain treatment | Benariba et al. 2013 |
| Fruit | Helpful in the treatment of diarrhea | Pravin et al. 2013 |

excellent active agents for a wide range of food applications (Baldim et al. 2021). Volatile organic compounds in food and beverages act as a taste imprint, assisting people and animals in identifying acceptable foodstuffs and avoiding bad or unsafe dietary choices. Polyphenolic substances found in nature are well-known for their therapeutic effects. Volatile molecules may be a viable potent antimicrobial preservative for food manufacturers searching to reduce chemical additions in functional or natural food items. Gurudeeban et al. (2011) reported that the bitter apples contained volatile compounds which were detected by using retention indices and GC-MS. The volatile compounds from bitter apple fruit pulp isolate were extracted by steam distillation and at the same time by using solvent distillation. About 17 components were isolated using different solvents such as dimethyl ether, petroleum ether as well as ethanol in the concentration of 75 ml, 25 ml, and 0.5 ml, respectively. These components were divided and classified into five groups namely ketones, alcohol, epoxy compounds, acids, and hydrocarbons. The experiment concluded that bitter apples may be used in the flavoring industry. Bitter apples can be utilized in different ways in the food industry which is demonstrated in Fig. 1.

### Significance of *C. colocynthis* nanoparticles in food packaging

Nanotechnology has assumed crucial importance in the present period due to its wide range of applications in all fields. Plant-based biologically produced nanoparticles offer an alternative to traditional approaches (Peralta-Videa et al. 2016). Nanotechnology is being widely used in all disciplines of medicine such as in the treatment of infectious diseases, food intolerances, diabetes, inflammatory disorders, and cancer treatment, due to the uniqueness of engineered nanoparticles. Nanoparticles are widely used in the field of food technology and have their application in food packaging due to their antibacterial and antifungal properties. Different parts of the plants such as stem, leaf, and roots are mainly used for the formulation of eco-friendly nanoparticles (Hernández-Díaz et al. 2021). Mubeen et al. (2022) studied in vivo development of gold nanoparticles (AuNPs) from the phytochemical extracts of bitter apples. The characterization of the developed nanoparticles included SEM (Scanning electron microscopy), FTIR (Fourier transform infrared spectroscopy), XRD (X-ray diffraction analysis), and UV-Vis spectroscopy. The authors reported a characteristic peak for UV-Vis in the range of 531.5 nm to 541.5 nm. The SEM results showed the spherical gold nanoparticles in the range of 7 nm to 33 nm. The crystalline structure of the product was shown by XRD. At planes 111, 200, 220, and 311 a peak was observed at 2θ equals 38 °C, 44 °C, 64 °C, and 77 °C, respectively. Bitter apple was used in the development of silver nanoparticles (AgNPs) using fresh leaves of the *C. colocynthis*. Silver nanoparticles have a broad range of pharmacological effects, and their cost-effectiveness makes them a viable option for local medicines. Satyavani et al. (2011) used the aqueous silver ions reduced by the callus extract of the fresh leaves of bitter apples, thus leading to the formation of eco-friendly AgNPs. The results were confirmed when the extract incubated with silver nitrate changed its color from green to reddish brown. By using Atomic Force Microscopy (AFM) it was seen that the nanoparticles formed were spherical and the size was 75 nm. The best report against the biofilm bacteria was observed by the antibacterial functions of the silver nanoparticles. A sustainable approach was applied for the development of the photoactive carbon dots from the bitter apple peels using the single-step carbonization method. In the development process, the peels were simply charred. The activity of the photodegradation of a dye (crystal blue) was observed under sunlight illumination (Aggarwal et al. 2020).

### Significance of *Citrullus colocynthis* in the meat industry

Consumers typically demonstrate a clear choice of foods generally viewed as healthy, owing to the influence of food and specific dietary patterns on the start of chronic illnesses, and in this respect, plants and vegetables have gained great attention (Estévez 2021). Meat products are part of a nutrient-dense food product matrix with a high-energy composition. Meat is also regarded as a substantial source of a variety of B vitamins, proteins, and other nutrients. The proteins have high energy and biological value. Significant higher lysine content in meat and its products is substantial when designing a diet to provide a balanced consumption (Zinina et al. 2019). *C. colocynthus* (Bitter apple) is a potential therapeutic fruit that contains a high concentration of natural components. Hassan and Sreea (2019) studied the impact of various extraction times of aqueous *C. colocynthus* extract on antioxidants, antibacterial, and cytotoxicity substances and employed it in beef luncheon rolls. The results indicate that aqueous *C. colocynthus* extract is high in phenols, flavonoids, as well as tannins, has potent antioxidant activity, and may be effective towards pathogenic microbes as well as oxidative stress. The authors concluded that *C. colocynthus* extract can be used in the food industry as a food preservative and food supplement.

### Significance of *C. colocynthis* in food formulations

Plant proteins are important in human nutrition. They are extremely crucial in poor nations where the average protein consumption is less than ideal (Hertzler et al. 2020). Akobundu et al. (1982) reported that egusi seeds flour can be prepared by dehulling the whole seed. Two samples were prepared and analyzed, one without a hull that is hull-free egusi full fat and hexane-defatted flour and one having 10% hull intact egusi full fat and hexane-defatted flour. A proximate analysis of the flour containing 10% hull was done and reported moisture (5.03%), protein (28.25%), carbohydrates (8.22%), ash (3.60%), and lipids (51.80%). The sample which was hulled and defatted contained moisture (4.97%), protein (25.44%), lipids (52%), ash (3.58%), and carbohydrates (8.21%). The authors concluded that egusi seed flour contains a variety of micronutrients that may be beneficial to the diet. *C. colocynthis* may be used as a seed meal to make patties after partial removal of oil to serve as a meat substitute. This defatted meal is used in several dietary preparations that vary with the food habits of people. It may also serve as a source of calcium and niacin, mainly in the low milk-consuming areas of lower West Africa. These findings supported the idea of formulation of egusi seed components into a potential variety of food.

### *C. colocynthis* (L.) seeds oils and residues

Riaz et al. (2015) investigated the aspect of *C. colocynthis* seeds oil and seeds residue as a non-conventional oil source. Characterization of the seed's oil and the residue was carried out and proximate analysis of the experiment is mentioned in Table 1. A similar study was carried out by Sadou et al. (2007) in which the proximate analysis of the seeds was done and the fatty acid profile of the seed oil was also determined. The evaluation shows that it contains Lauric acid ($0.15 \pm 0.12$ g/100 g), Myristic acid ($17.3 \pm 9.5$ g/100 g), Palmitic acid ($9.04 \pm 2.18$ g/100 g), and Palmitoleic acid ($0.28 \pm 0.09$ g/100 g).

### Traditional food products of *C. colocynthis* (L.)

Conventionally egusi seeds are used in many dishes. Ogiri is a greasy paste produced from the kernels of melon seeds. It is well-known in West Africa, notably in Nigeria, as a low-cost fermented soup seasoning or taste enhancer. Ogiri has been made from a variety of seed kernels, but egusi melon kernels are the most common (Chukwu et al. 2018). Robo is particularly famous among Nigeria's Yoruba people. Robo contains a lot of protein as it is produced from the defatted cake of the fruit. This helps to explain why certain Nigerians like Robo and corn cereal which is also called ogi cereal. Robo is quite comparable to the groundnut cake known as 'kuli kuli' in Northern Nigeria (Akinoso & Are 2018). Egusi pudding is popular among Cameroonians residing in West Africa. It is typically offered during social gatherings. The ingredients used to make egusi pudding differs, but the most common include beef, chicken, eggs, and other seasonings (Giwa & Akanbi 2020).

## Application of *C. colocynthis* as animal feed

Several studies have reported that some products as well as by-products of bitter apple fruit and other parts of the plants can be used as a source of feed for poultry animals. As reported in a study *C. colocynthis* fruit powder was supplied to about a hundred chickens (Broiler), with 100 chicks receiving it on the sixth day after inoculation of *Eimeria tenella*. The powder was gradually increased in fodder and fed at a percentage of 0.00, 0.05, 0.01, and 0.15. The 0.15% fruit powder substitute was found to be the most effective to prevent coccidiosis (Alagawany et al. 2021). Four hundred days old Ross broiler chickens were fed bitter apple fruit pulp to substitute antibiotic growth promoters. The fruit pulp of bitter apple was supplied at a rate of 1 gram per kilogram of the feed and 1.5 g per kilogram. The findings demonstrated that supplementing bitter apple fruit pulp towards the latter percentage might substitute antibiotic growth promoters (Kamran et al., 2021).

## Future concerns and perspective

Bitter apple is considered beneficial in multiple gut abnormalities which include indigestion, gastroenteritis, bowel problems, and colic pain (Dhakad 2017). There are enough possibilities to investigate this plant for the existence of such unique combinations of actions. Because it is traditionally used in gastroenteritis, the plant were shown to have anti-inflammatory action, but unlike NSAIDs, this might not potentially trigger gastric ulcers (Graham et al. 1988). Consequently, if anti-ulcerogenic properties are demonstrated, this could provide a safer route for inflammatory disorders. *C. colocynthis* has long been used to treat conditions such as diabetes and high blood pressure, both of which are on the rise around the world (Sharma et al., 2020). While there are studies that indicate its effectiveness in hyperglycemia, the plant has still not been researched for its usefulness in cardiovascular conditions, except for a handful of initial reports showing an antilipidemic impact (Afshari et al. 2021). Hyperglycemia, hyperlipidemia, and high blood pressure are prevalent in many patient populations, and diagnosis in medical technology is complicated, mandating the existence of the use of different medications, which also leads to multiple adverse effects as well as high cost. As a consequence, this plant with possible treatment applications in cardiometabolic disorders merits urgent attention for clinical and preclinical research. A few conventional uses have already been substantiated by phytoconstituents and contemporary pharmacological activities, but many more still have to be affirmed. Extracts and pure compounds have indeed been discovered to have a wide range of biological actions, particularly anti-diabetic, anti-carcinogenic, anti-inflammatory, anti-oxidative, fungicidal, and antimicrobial properties. Intriguingly, the plant was shown to have great nutritive content as a high source of protein, appetizing quality of seed oil, as well as some essential minerals like calcium, magnesium, and potassium, all of which are recognized to have therapeutic benefits (Sarmah et al. 2021).

## Conclusions

This review certainly implies that *C. colocynthis* is a fruit crop with potential applications in the treatment of a variety of metabolic disorders. Although a bitter apple has a dietary supplementation significance, it's not universally acknowledged. Further research is necessary to highlight the functionality of these tropical fruits as nutritional supplements that can have a positive effect. This analysis shows that the bitter apple is a herbal medicine plant with a diverse variety of pharmacological activities that may make it worthwhile and efficient in a range of medical implementations. This review provided an in-depth look at its phyto-constituents, as well as the framework correlation of certain bioactive components, pharmaceutics, positive effects, constraints, nanoparticles, and treatment options. *C. colocynthis* has several fundamental effects such as physiological, and biological capabilities; however, the mode of action underlying these characteristics in different living things is un-identified and must be explored. This review describes all the necessary phytochemicals, bioactive compounds, and their mode of action for the treatment of various diseases such as cancer, inflammation, diarrhea, and many more.

#### Abbreviations

UHT: Ultra Heat Treatment; AgNPs: Silver nanoparticles; AFM: Atomic Force Microscopy; GC-MS: Gas chromatography-mass spectrometry.

#### Acknowledgments

The authors would like to thank the Journal Editor and reviewers for their thoughtful reading of the manuscript and constructive comments.

#### Authors' contributions

Vasundhara Rao contributed to all sections and writing of the article. AP contributed to all sections of the article, extracted data, and reviewed the literature. The author(s) read and approved the final manuscript.

#### Funding

Sincere thanks are extended to Institutions of Eminence (IoE) scheme, Banaras Hindu University, Varanasi (Uttar Pradesh) India, for financial support under Incentive to Senior Faculties under IoE.

#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

## Declarations

#### Ethics approval and consent to participate

Not required.

#### Consent for publication

Not applicable.

#### Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Received: 24 July 2022 Accepted: 30 November 2022
Published online: 01 February 2023

#### References

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.

Afshari, A., Salimi, F., Nowrouzi, A., Khalili, M. B., Bakhtiyari, S., Hassanzadeh, G., & Farhadiannezhad, M. (2021). Differential expression of gluconeogenic enzymes in early-and late-stage diabetes: The effect of Citrullus colocynthis (L.) Schrad. Seed extract on hyperglycemia and hyperlipidemia in Wistar-Albino rats model. *Clinical Phytoscience*, *7*(1), 1–22.

Aggarwal, R., Saini, D., Singh, B., Kaushik, J., Garg, A. K., & Sonkar, S. K. (2020). Bitter apple peel derived photoactive carbon dots for the sunlight induced photocatalytic degradation of crystal violet dye. *Solar Energy*, *197*, 326–331.

Ahmed, M., Ji, M., Qin, P., Gu, Z., Liu, Y., Sikandar, A., & Javeed, A. (2019). Phytochemical screening, total phenolic and flavonoids contents and antioxidant activities of Citrullus colocynthis L. and Cannabis sativa L. *Applied Ecology and Environmental Research*, *17*, 6961–6979.

Akinoso, R., & Are, O. T. (2018). Elucidating energy requirements in alternative methods of robo production. *Journal of Biosystems Engineering*, *43*(2), 128–137.

Akobundu, E. N. T., Cherry, J. P., & Simmons, J. G. (1982). Chemical, functional and nutritional properties of egusi (Colocynthis citrullus L.) Seed protein products. *Journal of Food Science*, (47), 829-835.

Alagawany, M., Elnesr, S. S., Farag, M. R., Tiwari, R., Yatoo, M. I., Karthik, K., & Dhama, K. (2021). Nutritional significance of amino acids, vitamins and minerals as nutraceuticals in poultry production and health–a comprehensive review. *Veterinary Quarterly*, *41*(1), 1–29.

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.

Amamou, F., Nemmiche, S., kaouthar Meziane, R., Didi, A., Yazit, S. M., & Chabane-Sari, D. (2015). Protective effect of olive oil and colocynth oil against cadmium-induced oxidative stress in the liver of Wistar rats. *Food and Chemical Toxicology*, *78*, 177–184.

Asyaz, S., Khan, F. U., Hussain, I., Khan, M. A., & Khan, I. U. (2010). Evaluation of chemical analysis profile of Citrullus colocynthis growing in Southern area of Khyber Pukhtunkhwa, Pakistan. *Journal of World Applied Sciences*, (10), 402-405.

Baldim, I., Souza, C. R. F., & Oliveira, W. P. (2021). Encapsulation of essential oils in lipid-based nanosystems. In *Phytotechnology*, (pp. 197–230). CRC Press.

Banjo, T. T., Aina, Y. O., & Falade, F. A. (2021). Phytopharmacotherapeutic and antimicrobial attributes of bitter apple (Citrullus colocynthis)-A review. *Covenant Journal of Physical and Life Sciences*, *9*(1), 1–9.

Benariba, N., Djaziri, R., Bellakhdar, W., Belkacem, N., Kadiata, M., Malaisse, W. J., & Sener, A. (2013). Phytochemical screening and free radical scavenging activity of Citrullus colocynthis seeds extracts. *Asian Pacific Journal of Tropical Biomedicine*, *3*(1), 35–40.

Bernard, S. A., & Olayinka, O. A. (2010). Search for a novel antioxidant, anti-inflammatory/analgesic or anti-proliferative drug: Cucurbitacins hold the ace. *Journal of Medicinal Plants Research*, *4*(25), 2821–2826.

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.

Bhasin, A., Singh, S., & Garg, R. (2020). Nutritional and medical importance of Citrullus colocynthis-A review. *Plant Archives*, *20*(2), 3400–3406.

Chawech, R., Jarraya, R., Girardi, C., Vansteelandt, M., Marti, G., Nasri, I., & Fabre, N. (2015). Cucurbitacins from the leaves of Citrullus colocynthis (L.) Schrad. *Molecules*, *20*(10), 18001–18015.

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.

Coffey, J. L., Simmons, A. M., Shepard, B. M., Tadmor, Y., & Levi, A. (2015). Potential sources of whitefly (Hemiptera: Aleyrodidae) resistance in desert watermelon (Citrullus colocynthis) germplasm. *Horti Science*, *50*(1), 13–17.

Dhakad, P. K. (2017). Phytochemical investigation and anti-diarrheal activit y of hydroalcoholic extract of fruits of Citrullus colocynthis (L.) Schrad. (Cucurbitaceae). *Journal of Molecular and Genetic Medicine*, *11*(305), 1747–0862.

Drissi, F., Lahfa, F., Gonzalez, T., Peiretti, F., Tanti, J. F., Haddad, M., … Govers, R. (2021). A Citrullus colocynthis fruit extract acutely enhances insulin-induced GLUT4 translocation and glucose uptake in adipocytes by increasing PKB phosphorylation. *Journal of Ethnopharmacology*, *270*, 113772.

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.

Estévez, M. (2021). Critical overview of the use of plant antioxidants in the meat industry: Opportunities, innovative applications and future perspectives. *Meat Science*, *181*, 108610.

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.

Graham, D., Agrawal, N., & Roth, S. (1988). Prevention of NSAID-induced gastric ulcer with misoprostol: Multicentre, double-blind, placebo-controlled trial. *The Lancet*, *332*(8623), 1277–1280.

Gupta, S. C., Tripathi, T., Paswan, S. K., Agarwal, A. G., Rao, C. V., & Sidhu, O. P. (2018). Phytochemical investigation, antioxidant and wound healing activities of Citrullus colocynthis (bitter apple). *Asian Pacific Journal of Tropical Biomedicine*, *8*(8), 418.

Gurudeeban, S., Ramanathan, T., & Satyavani, K. (2011). Characterization of volatile compounds from bitter apple (Citrullus colocynthis) using GC-MS. *International Journal of Chemical and Analytical Science*, *2*, 108–110.

Hameed, B., Ali, Q., Hafeez, M. M., & Malik, A. (2020). Antibacterial and antifungal activity of fruit, seed and root extracts of Citrullus colocynthis plant. *Biological and Clinical Sciences Research Journal*, *2020*(1). https://doi.org/10.54112/bcsrj.v2020i1.33.

Hassan, S. A., & Sreea, M. A. (2019). Utilization of Citrullus colocynthis as antibacterial activity, antioxidant and food preservation in beef luncheon roll. *Middle East Journal of Applied Sciences*, *9*(4), 1190–1197.

Hernández-Díaz, J. A., Garza-García, J. J., León-Morales, J. M., Zamudio-Ojeda, A., Arratia-Quijada, J., Velázquez-Juárez, G., … García-Morales, S. (2021). Antibacterial activity of biosynthesized selenium nanoparticles using extracts of Calendula officinalis against potentially clinical bacterial strains. *Molecules*, *26*(19), 5929.

Hertzler, S. R., Lieblein-Boff, J. C., Weiler, M., & Allgeier, C. (2020). Plant proteins: Assessing their nutritional quality and effects on health and physical function. *Nutrients*, *12*(12), 3704.

Heydari, M., Homayouni, K., Hashempur, M. H., & Shams, M. (2016). Topical Citrullus colocynthis (bitter apple) extract oil in painful diabetic neuropathy: A double-blind randomized placebo-controlled clinical trial. *Journal of Diabetes*, *8*(2), 246–252. https://doi.org/10.1111/1753-0407.12287 PMID: 25800045.

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.

Kamalakar, K., Manoj, G. S., Prasad, R. B. N., & Karuna, M. S. L. (2015). Thumba (Citrullus colocynthis L.) seed oil: A potential bio-lubricant base-stock. *Grasas y Aceites*, *66*(1), e055.

Kamran, Z., Ruby, T., Hussain, M., Ali, S., Ahmad, S., Abdullah, M. & Afzal, G. (2021). Comparative Efficacy of Citrullus Colocynthis Fruit Powder and Popular Antibiotic Growth Promoters in Broiler Diet. *Animal Nutrition and Feed Technology*, (21), 421-428.

Karak, P. (2019). Biological activities of flavonoids: An overview. *International Journal of Pharmaceutical Sciences and Research*, *10*(4), 1567–1574.

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.

Khatibi, R., & Teymorri, J. (2011). Anticandidal screening and antibacterial of Citrullus colocynthis in south east of Iran. *Journal of Horticulture and Forestry*, *3*(13), 392–398.

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.

Kumar, S., Kumar, D., Saroha, K., Singh, N., & Vashishta, B. (2008). Antioxidant and free radical scavenging potential of Citrullus colocynthis (L.) Schrad. methanolic fruit extract. *Acta Pharmaceutica*, *58*(2), 215–220.

Kuralkar, P., & Kuralkar, S. V. (2021). Role of herbal products in animal production–An updated review. *Journal of Ethnopharmacology*, *278*, 114246.

Li, Q. Y., Munawar, M., Saeed, M., Shen, J. Q., Khan, M. S., Noreen, S., … Li, C. X. (2021). Citrullus colocynthis (L.) Schrad (bitter apple fruit): Promising traditional uses, pharmacological effects, aspects, and potential applications. *Frontiers in Pharmacology*, *12*, 791049.

Mariod, A. A., & Jarret, R. L. (2022). Antioxidant, antimicrobial, and antidiabetic activities of Citrullus colocynthis seed oil. In *Multiple biological activities of unconventional seed oils*, (pp. 139–146). Academic.

Marzouk, B., Mahjoub, M. A., Bouraoui, A., Fenina, N., Aouni, M., & Marzouk, Z. (2013). Anti-inflammatory and analgesic activities of a new cucurbitacin isolated from Citrullus colocynthis seeds. *Medicinal Chemistry Research*, *22*(8), 3984–3990.

Marzouk, B., Marzouk, Z., Fenina, N., Bouraoui, A., & Aouni, M. (2011). Anti-inflammatory and analgesic activities of Tunisian Citrullus colocynthis Schrad. Immature fruit and seed organic extracts. *European Review for Medical and Pharmacological Sciences*, *15*(6), 665–672.

Meena, M. C., & Patni, V. (2008). Isolation and identification of flavonoid "quercetin" from Citrullus colocynthis (Linn.) Schrad. *Asian Journal of Experimental Sciences*, *22*(1), 137–142.

Meybodi, M. S. K. (2020). A review on pharmacological activities of Citrullus colocynthis (L.) Schrad. *Asian Journal of Research and Reports in Endocrinology*, *3*(1), 25–34.
Mortzfeld, F. B., Hashem, C., Vranková, K., Winkler, M., & Rudroff, F. (2020). Pyrazines: Synthesis and industrial application of these valuable flavor and fragrance compounds. *Biotechnology Journal*, *15*(11), 2000064.
Mubeen, B., Rasool, M. G., Ullah, I., Rasool, R., Imam, S. S., Alshehri, S., & Kazmi, I. (2022). Phytochemicals mediated synthesis of AuNPs from Citrullus colocynthis and their characterization. *Molecules*, *27*(4), 1300.
National Research Council (2006). *Lost crops of Africa*. National Academies Press (ISBN 978-0-309–10333-6).
Ogundele, J. O., Oshodi, A. A., & Amoo, I. A. (2012). Comparative Study of Amino Acid and Proximate Composition of Citurllus colocynthis and Citrullus vulgaris Seeds. *Pakistan Journal of Nutrition*, (11), 247-251.
Olubi, O., Felix-Minnaar, J. V., & Jideani, V. A. (2019). Physicochemical and fatty acid profile of egusi oil from supercritical carbon dioxide extraction. *Heliyon*, *5*(1), e01083.
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.
Peralta-Videa, J. R., Huang, Y., Parsons, J. G., Zhao, L., Lopez-Moreno, L., Hernandez-Viezcas, J. A., & Gardea-Torresdey, J. L. (2016). Plant-based green synthesis of metallic nanoparticles: Scientific curiosity or a realistic alternative to chemical synthesis. *Nanotechnology for Environmental Engineering*, *1*(1), 1–29.
Perveen, S., Ashfaq, H., Shahjahan, M., Manzoor, A., & Tayyeb, A. (2020). Citrullus colocynthis regulates de novo lipid biosynthesis in human breast cancer cells. *Journal of Cancer Research and Therapeutics*, *16*(6), 1294.
Pravin, B., Tushar, D., Vijay, P., & Kishanchnad, K. (2013). Review on Citrullus colocynthis. *International Journal of Research in Pharmacy and Chemistry*, *3*(1), 46–53.
Qureshi, R., Bhatti, G. R., & Memon, R. A. (2010). Ethnomedicinal uses of herbs from northern part of Nara desert, Pakistan. *Pakistan Journal of Botany*, *42*(2), 839–851.
Rahimi, R., Amin, G., & Ardekani, M. R. S. (2012). A review on Citrullus colocynthis Schrad.: From traditional Iranian medicine to modern phytotherapy. *The Journal of Alternative and Complementary Medicine*, *18*(6), 551–554.
Rani, A., Goyal, A., & Arora, S. (2017). A brief review on Citrullus colocynthis-bitter apple. *Archives of Current Research International*, *8*(4), 1–9.
Rashid, S., Majeed, L. R., Nisar, B., Nisar, H., Bhat, A. A., & Ganai, B. A. (2021). Phytomedicines: Diversity, extraction, and conservation strategies. In *Phytomedicine*, (pp. 1–33). Academic.
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.
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.
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.
Sarmah, P., Neog, M., Bhuyan, M. K., & Basumatary, P. (2021) Ethnomedicinal Plants and their Traditional use for Treatment of Diabetes in Kokrajhar District of Assam. *International Journal of Current Microbiology and Applied Sciences*, *10*(01), 1-14.
Satyavani, K., Ramanathan, T., & Gurudeeban, S. (2011). Green synthesis of silver nanoparticles by using stem derived callus extract of bitter apple (Citrullus colocynthis). *Digest Journal of Nanomaterials and Biostructures*, *6*(3), 1019–1024.
Saxena, M., Saxena, J., Nema, R., Singh, D., & Gupta, A. (2013). Phytochemistry of medicinal plants. *Journal of Pharmacognosy and Phytochemistry*, *1*(6), 168-182.
Sharma, M. K., Sharma, P. K. & Sharma, J. (2020). Therapeutic Potential of Citrullus Colocynthis in Diabetes and its Complications. *European Journal of Molecular & Clinical Medicine*, *7*(1), 4674-4681.
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.
Wyrwa, J., & Barska, A. (2017). Innovations in the food packaging market: Active packaging. *European Food Research and Technology*, *243*(10), 1681–1692.
Zaidi, S. F., Muhammad, J. S., Shahryar, S., Usmanghani, K., Gilani, A. H., Jafri, W., & Sugiyama, T. (2012). Anti-inflammatory and cytoprotective effects of selected Pakistani medicinal plants in helicobacter pylori-infected gastric epithelial cells. *Journal of Ethnopharmacology*, *141*(1), 403–410.
Zinina, O., Merenkova, S., Rebezov, M., Tazeddinova, D., Yessimbekov, Z., & Vietoris, V. (2019). Optimization of cattle by-products amino acid composition formula. *Agronomy Research*, *17*(5), 2127–2138.

## Publisher's Note