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Phytopharmacotherapeutic and Antimicrobial Attributes of Bitter Apple (*Citrullus colocynthis*) - A Review

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***Abstract*:** Emergence of drug-resistant microorganisms over the past few decades has resulted in the search for bioactive compounds potent against these microorganisms. Phytochemicals derived from plants have shown positive curative properties and can be extracted from any part of the plant such as the roots, stem or flower. Bitter apple (*Citrullus colocynthis*) has been used traditionally for the treatment of infectious diseases and this has stimulated pharmacological interest in the active ingredients responsible for its medicinal properties. The plant also possesses several biological and pharmacological activities including anti-inflammatory, antidiabetic, antimicrobial, anticancer, and antioxidant. This review discussed the phytochemicals present in *C. colocynthis*, their mode of action and their antimicrobial attributes.
Keywords: Phytochemicals; *Citrullus colocynthis*; Pharmacological activities; Antimicrobial; Bioactive compounds.

1.0 Introduction

1.1 Bitter apple (*Citrullus colocynthis*)

Citrullus colocynthis is a member of the Cucurbitaceae family. Common names for this plant include colocynth, bitter gourd, bitter apple, and bitter cucumber [1]. However, It is popularly known as Tangiri in Nigeria. Several members are annual or perennial herbs with yellow or white flowers and climbing or trailing vines with characteristic tendrils. Some genera in this family include Cucurbita (pumpkin), Lagenaria, Citrullus (watermelon), Cucumis (cucumber), Momordica (bitter melon), and many others. Members of this family can be eaten raw or cooked, as ornamental plants and decorative items. *Citrullus colocynthis* is an annual or perennial (in wild) creeping herb found in sandy and arid soils. *C. colocynthis* is widely distributed around the world, throughout India, Arabia, west Asia, tropical Africa, and the Mediterranean region [2].

1.1.1 Description

The leaves are hairy and rough with open sinuses. Each leaf is about 5 to 10 cm long with about 3-7 lobes. Flowers are monoecious and yellow. They are solitary with yellow peduncles. The female flowers have villous hairy ovary and this can be used to differentiate the female from the male flowers. Fruits have a characteristic bitter taste, are fleshy and green in colour (with

yellow stripes), and turns yellow when ripe. Each fruit is nearly 4 to 10cm in diameter and filled with numerous compressed seeds. Its fruits resemble a watermelon. Seeds are numerous and oblong shaped. They are smooth and dark brown to light yellow in colour. They are around 6mm in size and located on the parietal placenta. Stems are angular, rough, long and slender, and vine-like which are usually spread on the ground and connected to the root [3]

Fig 1: The fruits of *Citrullus colocynthis*

1.1.2 Taxonomy
Kingdom Plantae -Plants
Subkingdom Tracheobionta -Vascular plants
Division Magnoliophyta -Flowering plants
Class Magnoliopsida - Dicotyledons
Order Violales
Family Cucurbitaceae -cucumber family
Genus Citrullus –watermelon
Species *Citrullus colocynthis*
Rani et al.[3]

2.1 Phytochemicals present in *Citrullus colocynthis*

The phytochemicals present in *Citrullus colocynthis* are broadly classified as Phenols, Alkaloids, Flavonoids, Terpenoids, Tannins and Terpenes [4;5].

2.1.1 Phenols

Phenols are bioactive phytochemicals with antimicrobial activities due to their unique ring structure. The hydroxyl groups in the structure of phenols have been reported to be responsible for their activity against microorganisms [6]. The action of this plant against microorganisms is also determined by the partially hydrophobic nature of the extracts [7].

2.1.1.1 Mode of action

Phenolics exhibit their antimicrobial activity against microorganisms by inhibiting adhesion in some pathogens. They also disintegrate the cell membrane of the microorganism and this resulted in the porosity of the cell which affects the functionality of the cell. This is brought about by forming bonds and leaching the cations from the cell membrane. Also, the integration of this bioactive compound into the cell membrane of the microorganism may be responsible for the replacement of the cations responsible for the functionality of the cell membrane leading to the disintegration of the bacterial cell membrane [6-7].

2.1.2 Flavonoids

Flavonoids are phenolic compounds present in the essential oils of plant. This bioactive compound is made up of some pigments whose chemical structure is responsible for their activities against microorganisms [8].

2.1.2.1 Mode of action of Flavonoids

The flavonoids and its derivatives are bioactive compounds with a carbonyl group in their structure. This group of phytochemical is active against a wide range of microorganisms in vitro [9]. The reaction

of flavonoids with the amino acids in the cell wall of microorganisms is solely responsible for their antimicrobial activity which results in the inactivation of bacterial enzymes [10].

2.1.3 Tannins

Tannins are astringent phenolic substances that bind and precipitate proteins. The solubility of tannins has been reported in certain solvents [11]. Tannins may be formed by polymerization of quinones and they are toxic to most microorganisms [12].

2.1.3.1 Mode of action

The mode of action of tannins against microorganisms operates on the principle of making microorganisms inaccessible to substrates necessary for their growth, resulting in the disruption of the respiratory process and also inhibiting the enzyme activity of the microorganisms [6]. Their antimicrobial activity is further enhanced by their ability to bind to and inactivate microbial proteins.

2.1.4 Terpenes

Terpenes and Terpenoids are hydrocarbons synthesized in the cytoplasm of plant cells using acetyl-CoA as a starting material in the pathway. The rearrangement of the carbon backbone of terpenes may give rise to a single or double cyclic structures [13]. The structures of the various examples and the different types of terpenes are shown in Figure 1.

Terpenoids on the other hand, are products of enzymatic and biochemical modifications of terpenes [13]. Members of this group of bioactive compounds are thymol, carvacrol, linalool, linalyl acetate, menthol, and geraniol. The functional group of the terpenoids has been reported to be responsible for their antimicrobial activity. Furthermore, studies have shown that the presence of delocalized electrons is important for antimicrobial activity [13].

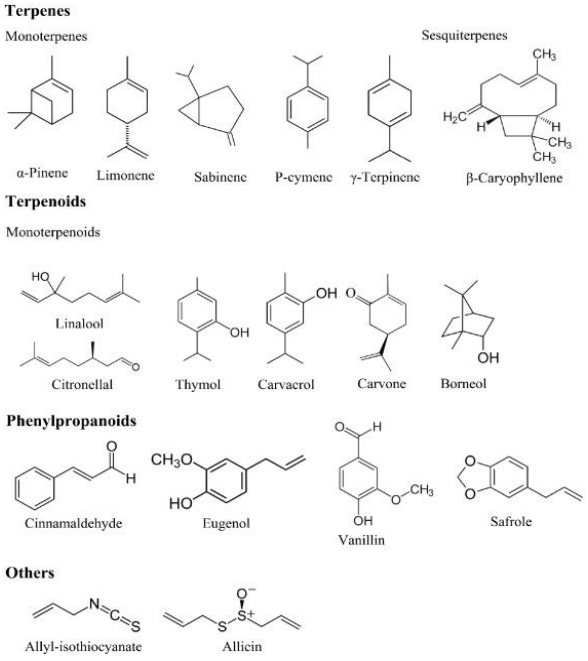

Figure 2: Chemical structure of some bioactive compounds [13]

2.1.4.1 Mode of action

Terpenes disrupt the membranes of microorganisms thereby affecting the permeability of the microbial cell and also altering their ability to carry out osmoregulation. Furthermore, terpenes alter the detoxification mechanism of the microorganisms through their outer membrane [14]. Terpenoids are absorbed by fungi from the environment which alters the physiological processes of this group of microorganisms [15].

2.1.5 Alkaloids

This group of bioactive compounds occurs in different concentrations in various parts of the plants and the different structural forms of these compounds are antimicrobial in action [16; 17].

2.1.5.1 Mode of action

Alkaloids and some of its derivatives operates on the principle of alteration of the

energy generation mechanism and the transport system of the microorganism [18;19].These compounds have been reported have also been found to form complexes with the DNA of the microorganism thereby altering their activities and ability to multiply [20].

2.2 Uses of *Citrullus colocynthis*

2.2.1 Edible uses

The fruit of *C. colocynthis* is also employed as food for animals and humans [21]. Hussain et al. [22] reported that *C. colocynthis* fruits and seeds contain several micronutrients (vitamins and minerals) that could significantly contribute to diet, however, despite the widespread importance of *Citrullus colocynthis* as food, little nutritional detail is readily available to an international readership. *C. colocynthis* may be used as a seed meal to make patties after partial removal of oil to serve as a meat substitute, this undefatted meal is used in several dietary preparations that vary with food habits of people. It may also serve as a source of calcium and niacin, especially to the low milk-consuming regions of lower West Africa [22]. Also, Sadou et al. [21] in their research found the moisture contents of bitter apple seeds to be 4.91 g/100 g and the amount of seed protein and ash were 13.19 and 2.00 g/100 g, respectively. They discovered that the yield of oil extracted from *C. colocynthis* was 26.60g/100g.

Table 1: Approximate composition and mineral contents of *Citrullus colocynthis* seeds.

Nutrient composition	g/100g
Moisture	4.91
Ash	2.00
Protein	13.19
Fat	18.59
Mineral composition	g/100g
Calcium	569
Copper	5.1
Iron	11.6
Magnesium	210
Phosphorus	30.0
Sodium	11.9
Zinc	1.1

Sadou et al. [21]

2.2.2 Medicinal uses.

Traditionally, *Citrullus colocynthis* has been used for many years in the treatment of infections and diseases. The medicinal use of different parts of this plant over the years has stimulated interest in researching its pharmacological activities and analysing its extracts and oils for the key active ingredients responsible for the medicinal properties of this plant. This has led to the use of this plant in the development of new drugs. Pravin et al. [1] reported that the fruits of *C. colocynthis* are bitter, pungent, cooling, purgative, anthelmintic, antipyretic, carminative and alleviate tumours, ascites, leukoderma, ulcers, asthma, bronchitis, urinary discharges, jaundice, enlargement of spleen, tuberculosis glands of the neck, dyspepsia, constipation, anaemia, throat diseases, elephantiasis and joints pain. The roots are useful in for the treatment of jaundice, ascites, urinary diseases, rheumatism, and given in abdominal enlargements and cough and asthmatic attacks of children. Also, the same authors indicated that there are several biological and pharmacological activities of this plant, including; anti-inflammatory, antidiabetic, antimicrobial, anticancer, antioxidant.

2.3 Pharmacological activity of *Citrullus colocynthis*

2.3.1 Anti-inflammatory and analgesic

The in vivo anti-inflammatory activity of the different types of *Citrullus colocynthis* extracts was reported in a study carried out by Aly et al. [23] by using the carrageenan-induced paw oedema model in albino rats. The pharmacological screening revealed that

the reduction of oedema produced by Colocynth extract was 45.39%, the hydrolysed extract produced 54.11% inhibition and the acetylated extract produced 64.95%. This result showed that acetylated colocynth extract can be used as an effective local anti-inflammatory agent. Similarly, another study carried out also showed that the extracts of the plant at different maturation stages displayed analgesic and anti-inflammatory activities at different doses without inducing acute toxicity, the stem and roots were shown to possess less significant inhibitory activity against analgesic and anti-inflammatory models [24].

2.3.2 Antidiabetic activity

The antidiabetic activity of *Citrullus colocynthis* was carried out by Huseini et al. [25]. Two groups of 25 each under standard antidiabetic therapy, received 100 mg *C. colocynthis* fruit capsules three times a day. Some parameters like glycosylated haemoglobin (HbA1c), fasting blood glucose were monitored in the patients on a monthly basis. The results showed a significant decrease in HbA1c and fasting blood glucose levels in *C. colocynthis* treated patients. The study showed that *C. colocynthis* fruit treatment reduced the glycaemic profile of type II diabetic patients. Furthermore, Al-Ghaithi et al. [26] carried out a study to determine the aqueous extract of the seed of *C. colocynthis* on the biochemical parameters of normal and Streptozotocin (STZ)-induced diabetic rats. Diabetes mellitus was induced by a single intraperitoneal (60 mg/kg body weight) injection of STZ. Normal and diabetic rats were fed with the plant extract daily by oral intubation for 2 weeks. Oral administration of the plant extract reduced the plasma level. This showed that *C. colocynthis* could be employed as a safe antidiabetic.

2.3.3 Antioxidant activity

Phytochemicals such as flavonoids and polyphenols possess antioxidant activity which protects the body cells from oxidative damage. Kumar et al. [27] investigated the antioxidant and free radical scavenging potential of *Citrullus colocynthis*, he reported that the phytochemical screening of the plant showed the presence of 0.74% (m/m) phenolics (Gallic acid) and 0.13% (m/m) flavonoids (Catechin) equivalents per 100g of fresh mass. The methanolic fruit extract of *C. colocynthis* was screened and results showed an increase in free radical scavenging effect with increasing concentration and maximum antioxidant activity was observed at 2500 mg ml^{-1}.

2.3.4 Anticancer activity

The potentials of *C. colocynthis* as an anticancer agent has been investigated and reported. The effect of Cucurbitacin glucosides extracted from *C. colocynthis* leaves on human breast cancer cell growth was studied by Tannin-Spitz et al. [28], the results showed that the Cucurbitacin glucosides inhibited the growth of ER + MCF-7 and ER-MDA-MB-231 human breast cancer cell lines. The treated cells showed a rapid reduction in the level of key protein complex necessary for the regulation of G_2 exit and initiation of mitosis. Cucurbitacin glucosides treatment also caused changes in the overall cell morphology from an elongated form to a round-shaped cell, which indicates that Cucurbitacin treatment caused impairment of actin filament organization. This profound morphological change might also influence intracellular signalling by molecules such as PKB, resulting in

inhibition in the transmission of survival signals.

2.3.5 Insecticidal/parasitic activity

The potentials of this bitter apple against insects and parasites have been reported by different researchers. In a study by Torkey et al. [29], the fruits of *Citrullus colocynthis* were extracted by different solvents (n-hexane, methylene chloride, Chloroform, and ethanol) and each extract was tested against *Aphis craccivora*. The highest insecticidal effect was obtained from the ethanol extract. In addition, a compound isolated from *Citrullus colocynthis* and identified by spectroscopy (2-O-â-D-glucopyranosylcucurbitacin E) was also reported to possess insecticidal activity against *Aphis craccivora*.

2.4 Antimicrobial attributes of *Citrullus colocynthis*

Due to the presence of different bioactive compounds in the leaf, seed and fruits of bitter apple plant, it exhibits varying degrees of antimicrobial activities against the different groups of microorganisms. This plant has been reported to be potent against; certain gram positive and gram-negative bacteria [30] and certain fungal strains [31].

2.4.1 Antimicrobial activities of Aqueous, hexane and ethanolic extracts of *Citrullus colocynthis*

The antimicrobial activity of *C. colocynthis* against some selected pathogenic microorganisms has been investigated and reported [32]. The pathogenic microorganisms include *Escherichia coli, Klebsiella pneumonia, Proteus mirabilis, Streptococcus pneumonia, Streptococcus agalactia, Streptococcus mutans, and Staphylococcus aureus.* The ethanolic extract showed inhibitory activity against *Escherichia coli, Proteus mirabilis, Staphylococcus aureus,* and *Streptococcus agalactia* while the water extract exhibited less or no activity. Moreover, Aljabry et al. [33] studied the potential antimicrobial and antifungal effects of *C. colocynthis* against some pathogens. Ethanol and hexane extracts of fruit and seeds of *C. colocynthis* were tested and proved effective against some bacteria and fungi. The results of the study showed obvious antimicrobial activity against tested microorganisms and can be a useful antimicrobial agents. In a related study, Gurudeeban et al. [31] reported a broad spectrum of antimicrobial activity against sixteen bacteria and six fungal strains. Qualitative phytochemical tests of extracts demonstrated the presence of phenols, tannins, and flavonoids as active constituents which possess antimicrobial activity. The results showed that *C. colocynthis* is potent against diseases caused by test organisms.

2.4.2 Antimicrobial activities of nanoparticles of *Citrullus colocynthis*

A study evaluated the effect of silver nanoparticles of *Citrullus colocynthis* against biofilm forming bacteria. It found that *C. colocynthis* exhibited tremendous antibacterial activity; it showed the maximum activity against biofilm bacteria such as *E. coli* (10.1 mm), *V. paraheamolyticus* (10.1 mm), *P. aeruginosa* (8 mm), *Proteus vulgaris* (9 mm) and *L. monocytogens* (8 mm) and also observed that it showed no activity against *Proteus mirabilis, Salmonella enteritidis,* and *Staphylococcus aureus* [34].

2.5 Conclusion

This review work discussed the pharmacological and antimicrobial attributes of *Citrullus colocynthis* since antimicrobials of plant origin have enormous therapeutic potential. [35]. One of the solutions to the

increase of emerging and resistant infectious disease will be the use of plants in the development of new drug as it ensures the infusion of novel compounds for healing disease [36]. The use of natural plants in pharmacological industry minimizes the hazards and allergies usually associated with chemicals. It is logical to consider the use of sustainable natural resources for medicinal purposes with the growing population of the World [33].

The different studies reported have shown that bitter apple (*Citrullus colocynthis*) is made up of bioactive compounds which can be a potential source of crude material for the pharmaceutical industry. This plant which can be easily grown and readily available can serve as a cheap natural source of raw material for the pharmaceutical industry [33].

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