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REVIEW ARTICLE

A comprehensive review on phytochemistry, folkloric uses and pharmacological including toxicity profiles of *Codiaeum variegatum* L.

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Abstract

A plant's ability to affect human physiological functions is attributed to the presence of a chemical compound. These substances fall into two groups: main and secondary metabolites. Metabolic processes produce secondary metabolites that are crucial to a plant's defence mechanism, whereas primary metabolites are required for a plant's growth and development. Alkaloids, carbohydrates, glycosides, steroids, flavonoids, coumarins, fatty acids, terpenoids and phenols are examples of secondary metabolites. *Codiaeum variegatum*, also known as the miracle shrub, is a plant that belongs to the family Euphorbiaceae. It is usually utilized as an interior plant for decorative purposes due to its beautiful, colourful and large leaves. This review aims to provide a concise summary of the most important and recent information available about *C. variegatum*. This plant is highly valued for its content of important secondary metabolites with various therapeutic activities, including antioxidant, Antidiarrheal, Anticonvulsant, Antiinflammatory, Antipyretic, antiamoebic, antimicrobial, antiviral and anticancer properties. Flavonoids, phenolic acids, stilbenes, alkaloids, sterols and fatty acids were the major secondary metabolites identified and isolated from C. *variegatum.* This study was chosen because *C. variegatum* is a rich plant with various secondary metabolites, serving as a reference for researchers interested in this plant. This review article examines the phytochemical composition, Folkloric uses, pharmacological activities versus toxic potential of *C. variegatum*. It is made by evaluation of publishing on *C. variegatum* listed in the online databases Web of Science, Springer Link, PubMed, Science Direct, Scopus and Google Scholar was run between 1980 and 2024 and interesting researches was founded related to the traditional uses, phytochemicals, profile of toxicity and pharmacological activity of *C. variegatum* and the essential and valued sections were chosen to be reviewed. The results suggest that the Iraqi *C. variegatum* plant is a promising natural source that can be utilized in nutrition and medicine, because of its safety and efficacy profile. It provides a basis for researchers and opens the door to studying, testing, evaluating and developing compounds of great value for human health.

Keywords: *Codiaeum variegatum*; Croton; Euphorbiaceae; secondary metabolites

Introduction

The most plentiful source of effective and safe treatments has been plants, which have been used for the benefit of humans and other creatures since the beginning of time. Medicinal plants are thought to be used in over 90 % of traditional medicine formulas (1). Medicinal plants have been a vital source of both curative and preventive medical therapy preparations for humans, which have also been used for the extraction of important bioactive compounds (2). Secondary metabolites in plants have been recognized as a novel basis of potential bio-pesticides, paving the way for their use in sustainable agriculture. Plant secondary metabolites have pivotal roles in plant-pathogen interactions. Some important secondary metabolites of plants, such as terpenoids, flavanols and flavones, are stress-inducible phytochemicals that play a crucial role in the development of the plant immune response (3). The presence of a chemical molecule in plants is believed to be responsible for their ability to influence human physiological processes. These substances can be separated into two categories: primary and secondary metabolites. While primary metabolites are necessary for a plant's growth and development, secondary metabolites are produced by metabolic processes and are essential to a plant's defence mechanisms. Secondary metabolites include substances such as alkaloids, Gums and mucilage, proteins and amino acids, terpenoids, anthraquinones, phenols, fatty acids, steroids, glycosides, flavonoids, coumarins and saponins, because these phytochemicals could be utilised to make novel drugs; therefore, research on them is essential (4). Often referred to as Croton and occasionally nicknamed Joseph's Coat, *Codiaeum variegatum* belongs to the Euphorbiaceae family and is a popular ornamental plant due to its vibrant colors of the foliage and variety of leaf shapes. *C. variegatum* is indigenous to Indonesia, Malaysia, the Philippines, India, Thailand and Sri Lanka. It is an evergreen shrub that thrives in humid climates and can reach a height of 6 m, although it is typically kept at a height

of 60 to 90 cm. Around the world, there are more than 200 different types of Croton, characterized by diverse leaf shapes, sizes and colours. Typically, young leaves are White, crimson, cream, pink, gold, maroon, purple, black, or brown. Later, they can be green, bronze, yellow or red (5). Crotons' leaves are likely green in their natural state, but when grown in the right light, they can have eye-catching variegations and be streaked, blotched, or banded in various hues. *C. variegatum* is therefore among the most intriguing ornamentals. It responds adaptably to different light levels, though. Different leaf hues are produced when plants are cultivated under various growing circumstances and light intensities. Compared to leaves in full sun, those in shade appear more greenish (6). Because of their therapeutic qualities, several *C. variegatum* cultivars are also used to cure a variety of illnesses. Filipinos drink a tea made from freeze-dried *C. variegatum* leaves and consuming crushed leaves helps treat diarrhoea. The bark and root are used to treat dysuria, syphilis, constipation, stomachaches and loss of appetite. The native people in Cameroon treat amoebic dysentery by decocting the leaves of *C. variegatum* (7). The plant's roots are used in the treatment of dysentery, its leaves serve as a tonic, its flowers are used to treat flatworms, its fruits are employed for the treatment of dysmenorrhea, its seeds have purgative properties and its bark is used to treat dyspepsia. The bark is also used to address repeated fever and persistent liver enlargement (8). Crotons are renowned for their therapeutic benefits in addition to their aesthetic appeal as an indoor plant. Croton leaf extracts are purported to offer a range of therapeutic benefits, including sedative, purgative, antifungal, antiamoebic and anticancer effects. Additionally, the plant is widely known for producing useful secondary metabolites, including terpenes, flavonoids and alkaloids, in nature (9). *Codiaeum variegatum*'s methanolic extract yielded the alkaloids glaucine, oxoglaucine and hemiargyrine (10). Through this review, we examine all the documented and isolated secondary metabolites of *C. variegatum*, as well as its studied and proven pharmacological activities, which make it essential in primary healthcare systems and drug manufacture worldwide.

Methodology

The basic information in this review article is derived from data collected from academic databases, including Scopus, Web of Science, Google Scholar and SpringerLink, using relevant keywords. The keywords used were: "*Codiaeum variegatum*,"" Croton,"" Euphorbiaceae," "secondary metabolites," “pharmacological activity,” “phytochemicals,” “antidiarrheal,” and “antioxidant”. The inclusion and exclusion criteria are based on the modernity and availability of full-text articles, ensuring that the last twenty-five years are covered. to compile all publications with pertinent details about the plant, taking into account that *C. variegatum* is also referred to as garden Croton or variegated Croton.

Phytochemicals

Codiaeum variegatum leaves and stems are a valuable source of a range of bioactive secondary metabolites, crude fibres, mineral elements, unsaturated fatty acids and sterols, as indicated by the results of qualitative phytochemical screening (11).

Polyphenols

Polyphenols are natural compounds synthesized exclusively by plants, with chemical features related to phenolic substances with reported bioactivities (12). There is growing evidence that polyphenols, which are abundant micronutrients in our diet, may help avoid degenerative illnesses. The prevalent polyphenols in our diet do not always result in the highest amounts of active metabolites in target tissues, as bioavailability varies widely among polyphenols (13). Chemically, they are compound with an aromatic ring linked to one or more hydroxyl groups (14). Despite their great structural diversity, phenolic compounds are generally characterized by the presence of one (for simple phenolics) or more (for polyphenols) hydroxyl substituents directly attached to one or more aromatic or benzene rings.

Although phenolic compounds can generally be found in plants in free forms, they are more frequently found with one or more sugar residues in conjugated forms connected to an aromatic ring carbon atom (C-glycosides) or a hydroxyl group (O-glycosides) by β-glycosidic bonds. Monosaccharides, disaccharides, or even oligosaccharides may be the related sugars (15). Frequent consumption of foods high in polyphenols may help lower the risk of liver problems, diabetes, obesity, colon cancer and cardiovascular diseases, among other conditions. Plants often produce these substances as a defensive mechanism against environmental and physiological stimuli (16). Although there is much disagreement on the precise quantity of polyphenols needed to have such a protective effect, there is mounting evidence linking polyphenol consumption to a lower risk of developing chronic illnesses (17). PCs' accessibility, specificity of reaction and low toxicity are among their benefits; however, their poor bioavailability and quick metabolism are their primary drawbacks (18).

Flavonoids

The flavonoids are the biggest and best-studied members of polyphenols (12). Flavonoids are low-molecular-weight polyphenolic secondary metabolic compounds that are found in cell vacuoles and are extensively dispersed across the kingdom of green plants. Flavonoids have a range of biological functions in microorganisms, plants and mammals (19). Flavonoids can exist as free a glycones or as glycosides that combine with sugar (glycone). Glycosylation reduces the flavonoid's reactivity, increases its polarity and makes it more soluble in water. This modification is a crucial defence mechanism for plants to prevent cytoplasmic damage and safely store flavonoids within plant cells (20, 21). Flavonoids chemically have the general structure of a 15-carbon skeleton arranged in structure can be abbreviated C6-C3-C6 in which both of the C6 are benzene rings named A and B while the C3 act as a bridge linked between A and B rings, this later bridge again can cyclize by oxygen and produce a new ring called C ring (oxygen containing pyrene ring) (22). The antioxidant properties of flavonoids are widely recognized. Antioxidants are substances that shield cells from the harmful effects of reactive oxygen species. Oxidative stress is caused by an imbalance between reactive oxygen species and antioxidants, which damages cells (23). Flavonoids have also been found to have antiallergic, antiinflammatory, anticancer and antiviral effects in several studies. Additionally, flavonoids can protect plants from ultraviolet rays and atmospheric exposure (24).

Flavonoids can be separated into different subgroups based on the degree of unsaturation and oxidation of the C ring, as well as the carbon of the C ring to which the B ring is attached. These, with the B ring attached to the C ring at position three are known as isoflavones. While those with the B ring attached at position 2 can be further divided into several subgroups based

on the structural properties of the C ring, neoflavonoids are characterized by the B ring being joined at position 4. Catechins, anthocyanins, chalcones, flavones, flavonols, flavanones and flavanonols are some of these subgroups (25).

Phenolic acids and their derivatives

Aromatic secondary metabolites found in many parts of the plant kingdom are called phenolic acids. Interest in the biological functions of phenolic acids as secondary metabolites, as well as their roles in determining food quality and organoleptic properties, has led to the development of current analytical techniques (26). All phenolic acids have a carboxyl group connected to or bonded to a benzene ring. The two types of phenolic acids can be identified by their structural differences: hydroxybenzoic acid derivatives (C6-C1) and hydroxycinnamic acid derivatives (C6-C3) (15). The main phenolic acids' structures in *Codiaeum variegatum* (Fig. 1).

The degree of biological activity exhibited by phenolic acids is primarily determined by their bioavailability, which considers the percentage of absorption, digestion and metabolism that occurs once they enter the bloodstream. Numerous experimental and epidemiological studies have demonstrated the protective effects of phenolic acids against degenerative diseases, including diabetes, cancer, heart disease and inflammation, among others (27). Under various abiotic stresses, phenolic acids of plants, which are potent antioxidants, can influence the scavenging of damaging reactive oxygen species (ROS) in plants. The quantity of hydroxyl groups in phenolic acids and their derivatives mostly determines their antioxidant potential (28, 29).

Alkaloids

One of the largest classes of natural products is plant alkaloids, a diverse class of chemical substances. The vast class of alkaloids includes almost 12000 natural compounds. The primary prerequisite for being categorized as an alkaloid is that the molecule must contain a basic nitrogen atom at any location; this excludes nitrogen in amide or peptide bonds. This comprehensive definition suggests that the alkaloids are a group of substances. with different structures and biogenetic unrelatedness. Numerous of these substances have strong pharmacological effects. The narcotic painkillers morphine and codeine, apomorphine (a morphine derivative used to treat Parkinson's disease), the muscle relaxant papaverine and the antibacterial agents sanguinarine and berberine are a few examples of well-known plant alkaloids. Also, several potent anticancer drugs have been developed from plant compounds (30).

Stilbenes

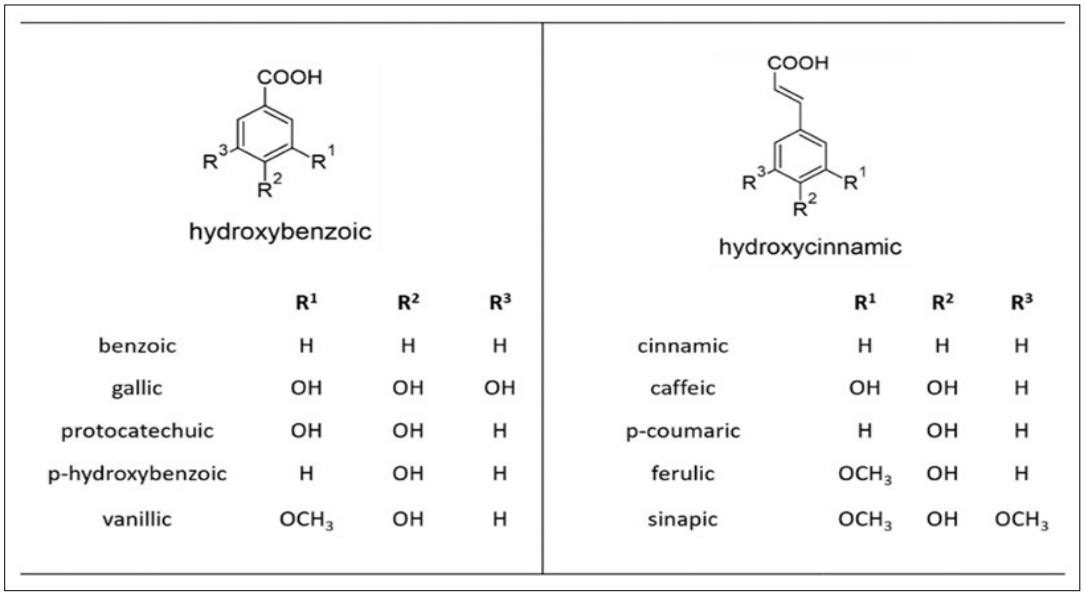
They are a tiny but crucial class of non-flavonoid polyphenols which consist of two benzene rings joined by an ethylene bridge to form a 14-carbon skeleton (31). Stilbenes have the skeleton of C6-C2-C6 carbon atoms in another word stilbenes contain two benzene rings joined by a molecule of ethanol or ethylene, chemically named (1, 2 diphenylethylene) (32). Stilbenes exist as two potential stereoisomers, cis and trans, due to the core ethylene molecule that sits between the aromatic rings. However, the trans form is typically found in naturally occurring stilbenes (33). The primary function of stilbenes is to protect plants both constitutively and inducibly from biotic (such as phytopathogenic bacteria and herbivores) and abiotic (such as UV radiation and tropospheric ozone) stressors (34).

Tannins

Tannins are a class of water-soluble polyphenols with molecular weights ranging from 500 to 3000. They are further classified as hydrolyzable and condensed tannins and they are frequently found complexed with proteins, polysaccharides and alkaloids, especially the latter. There are two categories of hydrolyzable tannins based on structural features: gallotannins and ellagitannins. The leaves of *Codiaeum variegatum* may have antidiarrheal properties due to tannins, steroids and alkaloids (35).

Coumarins

Numerous natural items contain the coumarin (also known as benzopyran-2-one or chromen-2-one) ring structure, which exhibits a variety of pharmacological characteristics. For many years, chemists and medicinal chemists have been interested in it. Using cutting-edge synthetic techniques, several compounds based on the coumarin ring system have been described. Interesting coumarin analogues with pharmacological activities, including anti-HIV, antibacterial, antiinflammatory, anticancer, anti-TB, anticonvulsant and MAO inhibitory properties, have been produced through these synthetic pathways (36). The most characterized coumarins in *Codiaeum variegatum* are Daphnetin and Esculin (37).



	R^1	R^2	R^3
benzoic	H	H	H
gallic	OH	OH	OH
protocatechuic	OH	OH	H
p-hydroxybenzoic	H	OH	H
vanillic	OCH_3	OH	H

	R^1	R^2	R^3
cinnamic	H	H	H
caffeic	OH	OH	H
p-coumaric	H	OH	H
ferulic	OCH_3	OH	H
sinapic	OCH_3	OH	OCH_3

Fig. 1. The structures of the major phenolic acids in *Codiaeum variegatum* (15).

Sterols

One type of plant metabolite, a member of the triterpene family, is called phytosterol. These substances must be obtained from the diet, as they are vital biomolecules essential for human health. The primary phytosterols present in plants are stigmasterol, campesterol and β-sitosterol. Because they can lower plasma cholesterol levels and possess antiinflammatory, antidiabetic and anticancer properties, phytosterols are beneficial for human health. However, since the amounts of these chemicals derived from plant raw materials are small and their chemical synthesis is not commercially viable for exploitation, obtaining them presents significant challenges (38). Because they stabilize the phospholipid bilayers in cell membranes, phytosterols are triterpenes that resemble cholesterol in both structure and function. They share a four-ring steroid nucleus, a 3β-hydroxyl group and frequently a 5,6-double bond (39). The cyclopentane-perhydrophenanthrene ring system, which is composed of four stiff rings and has a hydroxyl group at position C_3 along with a lateral chain of varying length (8-10 carbons) linked to carbon, is the basis for the common structure of sterols (40). It has been suggested that PSs have a variety of pharmacological effects, including as the ability to lower levels of total and low-density lipoprotein (LDL) cholesterol, which would lower the risk of cardiovascular illnesses. Plant sterols also have antiinflammatory, antimicrobial, antidiabetic, anti-obesity and immunomodulatory properties that promote health. Additionally, it has been strongly proposed that phytosterol-rich diets have anticancer effects, as they may cut the risk of cancer by 20 % (41).

Fatty acids

Fatty acids are monocarboxylic, aliphatic and often straight-chain compounds. Although all chain lengths are included in the broadest definition, the majority of naturally occurring fatty acids have even chain lengths between C_4 and C_{22}, with C_{18} being the most prevalent. There are more than 1000 known fatty acids with various chain lengths, locations, unsaturation types and configurations, as well as a variety of other substituents along the aliphatic chain (42). Fatty acids (FA), as part of molecules or acting individually, have diverse functions in cells that range from structural “building blocks” of cell membranes to suppliers of energy and signalling molecules (43). Dietary free fatty acids (FFAs), including ω-3 fatty acids, are known to control metabolic and antiinflammatory processes. Many of these effects are due to FFAs’ interaction with a group of G protein-coupled receptors. This evidence suggests that fatty acids may have a significant impact on diabetes management. *Codiaeum variegatum* (L.) is recognized for its diverse bioactive compounds, including fatty acid esters. Although specific research on the antidiabetic effects of these fatty acid esters in *C. variegatum* (L.) is sparse, studies have indicated that fatty acids can display antidiabetic properties (44).

Codiaeum vartiegatum Folkloric Uses

Codiaeum variegatum may be used as an alternative treatment for various illnesses due to its bioactive compounds. The medicinal benefits of plants vary depending on their category and geographic region (45). Diabetes, cancer, constipation, diarrhoea, external injuries, inflammation, fever, intestinal worms, elevated cholesterol levels, malaria, pain, weight loss and ulcers were all treated locally with the leaves of the *Codiaeum* species. The leaves of the *C. variegatum* plant are used as a tonic, while its fruits, seeds and flowers are used as purgatives to treat flatworms and dysmenorrhea, respectively. While the roots are used to treat diarrhea, the bark is utilized to relieve dyspepsia (46). To treat intestinal worms, diarrhoea, bacterial infections and stomachaches, for example, leaf decoctions are commonly used. Root infusions are used to heal stomach ulcers and bark infusions and sap are applied topically to cure skin infections or external ulcers. It is crucial to note that the plant's bark, roots and leaves produce a toxic latex that contains 5-deoxyingenol. Prolonged exposure to this latex can induce dermatitis and perhaps cause burns on the tongue (47-49). Additionally, this plant has been utilised in countries such as India, Malaysia, the Fiji Islands and Papua New Guinea to treat skin conditions, including bacterial and fungal infections, skin allergies and gastrointestinal discomfort. Ointments containing *C. variegatum* latex, leaf extract, or root extract were applied to the afflicted areas (50). The herb might be powdered and applied externally to treat skin conditions and leprosy (51). The leaves of *C. variegatum* are used by local populations in Cameroon to treat bloody diarrhea (52). The bark and root are used to treat dysuria, syphilis, constipation, stomachaches and loss of appetite. The native people in Cameroon use a decoction of *C. variegatum* (var. *mollucanum*) leaves to cure amoebic dysentery (53, 54).

Freeze-dried leaves of *C. variegatum* are taken as a decoction by Filipinos and eating crushed leaves is said to cure diarrhoea (55). The plant's roots are used in the treatment of dysentery, its leaves serve as a tonic, its flowers are used to treat flatworms, its fruits are used to treat dysmenorrhea, its seeds are used as a purgative and its bark is used to treat dyspepsia. Additionally, the bark is used to treat repeated fever and chronic liver enlargement (56).

Pharmacological activities

Antidiarrheal activity

Castor oil was used to induce diarrhoea in mice to investigate the antidiarrheal properties of *C. variegatum* leaf extract (9, 10). A total of twenty Swiss albino mice (n = 20) were randomly divided into four groups. The test groups were administered the extracts at doses of 250 and 500 mg/kg body weight. The positive control group received loperamide at 50 mg/kg body weight as a standard and the control group received distilled water (2 mL/mouse) only. Mice were kept in individual cages with paper underneath to collect their waste. Castor oil (1.0 mL/mouse) was administered orally to the mice to induce diarrhoea. One hour prior to the administration of castor oil, the extract and medications were administered orally. The animals' total faecal production and the time of their initial faecal expulsion were recorded and watery stool was noted.

These observations suggest that extracts at doses of 250 mg/kg & 500 mg/kg reduced diarrhoea by inhibiting castor oil-induced intestinal fluid accumulation. The plant extract's tannins and phenolics inhibit the release of prostaglandins and autacoids, which in turn prevent the motility and secretion induced by castor oil (57).

Antibacterial activity

Natural medicines derived from plants have long been used as treatments for various illnesses, including infections, in traditional African medicine. Many communities have been affected by the prevalence of infectious diseases caused by

virulent bacteria and in some instances, treatment has been complicated by the presence of antibiotic-resistant strains. It is widely known that phytochemicals derived from medicinal plants have therapeutic promise in treating bacterial infections. Ethanol and water leaf extracts of *Codiaeum variegatum* have been thoroughly studied for their antibacterial properties. The modified Kirby-Bauer disc diffusion method was used to analyze the antibacterial properties of these crude extracts and the resulting zone of inhibition was evaluated. The possible antibacterial action of extracts was tested using both Gram-positive (*Bacillus subtilis*) and Gram-negative (*Serratia marcescens*) bacteria. Crude extracts of *C. variegatum* leaves, in both ethanol and water, demonstrated notable inhibitory zones of 20 mm and 12 mm against *Bacillus subtilis* and *Serratia marcescens,* respectively, compared to the control group.

This suggests that the therapeutic qualities of plants could lead to the development of safe, standardized and affordable herbal medicines. Additionally, these extracts might contain novel chemical components that could be used to create broad-spectrum antibacterial medications (58).

Antiinflammatory activity

The effects of *Codiaeum variegatum* extracts and fractions on macrophages were examined, with a particular emphasis on blocking 5-lipoxygenase activity, Tumour Necrosis Factor α and NO (nitric oxide). At the measured concentrations, no discernible effect on cell viability was seen during the incubation period, despite the administration of various dosages (0.1, 1, 10 and 100 g/mL). As a result of fractionation, the extracts and fractions showed improved antiinflammatory activity and a concentration-dependent decrease in 5-lipoxygenase activity, as well as the production of TNF α and NO by live primary murine macrophages. Among the fractions, HEF2 (human oesophagal tissue), HEF3, HEF5, EEF1 (fibroblast cell line), EEF3 and EEF5 exhibited the most antiinflammatory effects. Both *C. variegatum* extracts and fractions exhibited significantly greater antiinflammatory activity, primarily by inhibiting proinflammatory mediators such as 5-lipoxygenase, TNF-α (tumour necrosis factor) and NO (59).

Antifungal activity

The disc diffusion method on SDA medium was used to determine the antifungal activity of AgNPs extracted from leaves. The petri dish is filled with the aforementioned SDA medium. The solid plates were covered with the inoculums using a sterile swab saturated with the fungus suspension shortly after the medium had solidified. The present experiment involved using four fungal strains: *Aspergillus flavus*, *Aspergillus niger*, *Candida albicans* and *Penicillium chrysogenum*. The activity varied was determined by comparing Amphotericin-B and fluconazole (Diflucan) as controls. Sterile discs were filled with 20 µL samples and controls and then placed in SDA plates. The plates were incubated at 37 °C for 24 hr in an auto incubator. The diameter of the zone of inhibition was measured to determine the antifungal activity of the sample. Furthermore, different concentrations of AgNPs were tested for antifungal properties to pinpoint the minimum inhibitory concentration (MIC) (60). The effect of leaf extract of *Codiaeum variegatum* on the growth of fungi (*Alternaria* and *Fusarium*) measured as the diameter of the culture is shown in Table 1.

Antioxidant activity

Lipid LPO inhibitory assays, ferric iron-reducing antioxidant power and DPPH (2,2-diphenyl-1-picrylhydrazyl) assays were used to assess the antioxidant activity of *Codiaeum variegatum* aqueous, hydroethanolic 70/30 (v/v) and ethanolic extracts. The highest antioxidant activity was demonstrated by the ethanolic extract against DPPH (IC 50, 50 % lethal concentration 00.77 g/mL of DPPH), fluorescently-labeled mole cules (FRAP) (EC 50 (50 % efficient concentration) 00.543.6 g/mL) and lipid peroxidation prevention (IC 50 00.21.52 g/mL). It's essential to note that this activity was still significantly less than that of ascorbic acid. A statistically significant difference ($p < 0.05$) was found between the extracts and ascorbic acid by statistical analysis. Phenolic molecules were identified in these extracts through phytochemical investigation and they may be responsible for the reported antioxidant properties (61).

Anticonvulsant activity

The origins of the medication and known therapeutic compounds include medicinal plants like *Codiaeum variegatum*. The impact of an ethanol extract of *C. variegatum* for anticonvulsant has been examined. The stroma of the brain was shown to have alterations in necrosis and cellular adaptation, characterized by a sparse cellular population, inflammation, hypertrophy and neurosis. When comparing the treatment groups receiving doses of 200 mg/kg, 400 mg/kg and 600 mg/kg to the control group administered with 0.1 mL of normal saline, notable effects were observed in some regions of these groups. It has been well recognised that glial cells, particularly astrocytes, support neurons, the specialised and fundamental building blocks of the central nervous system (52).

Anticancer

It was discovered that the methanol extracts and isolated alkaloids of *Codiaeum variagatum* cv. Petra leaves exhibited active cytotoxicity, with an activity range of 17.3 % to 98 %, when tested against the hepatocellular carcinoma cell line (HepG2), human Caucasian breast adenocarcinoma (MCF-7), colon cell line (HCT116) and lung carcinoma cell line (A549) (51).

Antidiabetic activity

Croton species may be utilized in diabetes management. This motivates further exploration of the inhibitory effects of an n-hexane extract from *Codiaeum variegatum* (L.) and acarbose on

Table 1. Effect of leaf extract of *Codiaeum variegatum* on the growth of fungi (*Alternaria* and *Fusarium*) measured as the diameter of the culture (65)

Fungal culture	control	10 %	25 %	50 %	10 %	25 %	50 %
Alternaria alternata	24.7 ± 0.88	15.7 ± 0.42	12.6 ± 0.82	9.7 ± 0.81	16.8 ± 0.81	14.3 ± 0.62	10.3 ± 0.61
Fusarium oxysporum	54.7 ± 1.21	35.0 ± 0.57	31.0 ± 0.52	19.3 ± 0.33	32.33 ± 0.20	27.66 ± 0.42	14.3 ± 0.45

Each value represents the mean of 3 replications ± SE

two key enzymes: α-glucosidase and α-amylase. These enzymes play a crucial role in breaking down carbohydrates into glucose. By inhibiting these enzymes, the digestion of carbohydrates is slowed, which subsequently reduces the rise in blood sugar levels post-meal. This mechanism is particularly beneficial in managing certain types of diabetes. The n-hexane extract and acarbose inhibit the activities of α-glucosidase and α-amylase. As their concentrations decrease, so does their inhibitory effect due to less availability of the inhibitor. The IC50 value measures an inhibitor's potency, with a lower value indicating a stronger inhibitor. Acarbose has lower IC50 values (2.11 µg/mL for α-glucosidase and 12.29 µg/mL for α-amylase) than the n-hexane extract (27.40 µg/mL for α-glucosidase and 24.43 µg/mL for α-amylase), making it a stronger inhibitor. Thus, more n-hexane extract is needed to achieve the same inhibition level as acarbose. This comparison clearly indicates the superior inhibitory potency of acarbose over the n-hexane extract. These findings provide valuable insights into the potential use of these substances in managing blood sugar levels, particularly in the context of diabetes. However, it's essential to note that further studies are needed to fully understand their therapeutic effects, safety profiles and potential side effects (44).

Antiamoebic activity

The following are the results of an assessment of *Codiaeum variegatum's* antiamoebic action on axenic cultures of trophozoites: The incubation period and the requirements for collecting leaves for extract preparation significantly influenced the mortality rate and the presence of the plant aqueous extract promotes the growth inhibition or mortality of *Entamoeba histolytica* in a concentration-dependent manner. We found that the extracts' antiamoebic effectiveness increased with incubation time and is dependent on the leaf harvest criteria. There was no discernible difference between the extracts from the various plant collection locations; however, the extract from plants harvested at midnight (E6) exhibited noticeably more antiamoebic activity than extracts from plants picked at other times of the day. With an EC50 of 120.00 µg/mL after 48 hr of incubation and 60.54 µg/mL after 72 hr, the extract made from old leaves and collected in the morning (E8) showed the strongest significant antiamoebic activity of all the samples examined (62).

Toxicity profile of *Codiaeum variegatum*

Aqueous extract of *Codiaeum variegatum* leaves administered orally at levels up to 24 g/kg did not cause any appreciable aberrant toxicity symptoms. Actually, at doses higher than 16 g/kg, all animals exhibited similar behaviour 4 hr after administration. No mortality was noted 48 hr after treatment, except for the decrease in aggression, locomotion and response to stimuli that was seen right after the administration of the special dose of aqueous extract of *C. variegatum* leaves (AECVL). Similarly, there were no appreciable changes in the weight of the organs under study (spleen, liver, kidneys, heart and lung) after taking AECVL orally for 28 days. Indeed, alterations in blood aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels may be noted following medication delivery, However, the AST/ALT ratio should be less than 2 and should not fluctuate much; in this instance, the liver is not harmed (63).

Furthermore, at concentrations up to 2000 µg/mL, no discernible DNA damage or induction of micronucleus production was found. Furthermore, no discernible induction of gene mutationswas found in the mutagenic potential of these extracts following short-term (4 hr) and long-term (24 hr) treatment. Because neither the amoebicidal fraction SF9B nor the aqueous extract of *C. variegatum* is mutagenic in the mouse lymphoma mutation assay nor genotoxic on non-competent or metabolically competent cell lines, they may be used safely in medicine at lower dosages (64).

Conclusion

According to this assessment, *Codiaeum variegatum* is not only a lovely outdoor plant but has also been utilized by various populations for its traditional medicinal properties. Actually, this plant contains flavonoids, alkaloids, phenolic acids, stilbenes, sterols and fatty acids that have been identified; however, other phytochemicals require further research. Despite the many studies on the plant, we were unable to access the full text for many of them. *C. variegatum* is probably ideal for the creation of pharmaceutical goods because of its efficacy and safety, which will undoubtedly set the stage for clinical research.

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Authors' contributions

IAG planned the research and conducted the search and collection of all relevant information from various academic databases, including Scopus, Web of Science, Google Scholar and SpringerLink, using appropriate keywords. They also wrote the manuscript. DAAA proofreads, reviews and supervises all information in the manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflicts of interest to declare.

Ethical issues: None

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