

Chemical, Pharmacological and Medicinal properties of euphorbious plants *Codiaeum variegatum*: A Review

Ram P. Yadav* and Ajay Singh

Natural Products Laboratory
Department of Zoology
DDU, Gorakhpur University
Gorakhpur-273009 (U.P.)
INDIA

*Corresponding Author: **Ram P. Yadav**

E-mail: rampratapy@rediffmail.com or rampratapy123@gmail.com

Abstract: The genus *Euphorbia* (spurges) is one of the largest most widely distributed genera of plants. *Codiaeum variegatum* (Blume) is a commonly occurring plant in the garden of North-Eastern, U.P, India belonging to the family Euphorbiaceae. A some of compounds in the plant *Codiaeum variegatum* are found such as alkaloids, anthocyanins, anthraquinones, cardiac glycosides, cyanogenic glycosides, flavonoids, glucosilicates, phenols, saponins and tannins are mainly found. An attempt has been made in this review to assemble all the known information of common plants *Codiaeuma variegatum* of eastern Uttar Pradesh, India which might be useful for the living system.

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Introduction

The plant belongs to the family Euphorbiaceae is polyphyletic in origin, and cosmopolitan in distribution. It has about 8000 species in 300 genera, is of the largest and most diversified family of angiosperms. There is great diversity in form and the plants range from tall rain forest trees to lianas, shrubs, perennial and annual herbs, geophytes, succulents, and floating aquatics; only the epiphytic habit is lacking amongst the major 'niches' of vegetative adaptation [1].

Several species of the family Euphorbiaceae, which contain diterpenes show pharmacological properties. Those with known pharmacological properties are *Euphorbia royleana*, *E. antisiphilitica*, *E. lacteal acristata*, *E. pulcherima*, *E. neutral*, *Jatropha gossypifolia*, *Croton tiglium*, and *Codiaeum variegatum* shows piscicidal and molluscicidal properties [2,3,4,5,6,7,8,9,10,11,12,13,14,15].

Fourteen different phorbol diesters are known from *Croton tiglium*. The use of phorbol diesters as a tool in pharmacological studies represents an example of a valuable application of a toxic substance from a species employed for a very different purpose in primitive societies. Recent work has demonstrated that the toxicological actions of the latex can be attributed to

a new class of diterpenes, which are esters of phorbol (12-deoxyphorbol, 12-deoxy-16-hydroxy-phorbol, ingenol, 5-deoxy-ingenol, resiniferotoxin and tinyatoxin [16]. It has been reported that phorbol esters interact with and activate the recently discovered protein kinase-C [17].

Croton spp ethnobotanically, *Croton* is one of the fascinating genera of Euphorbiaceae. It contains 750 tropical and sub-tropical species distributed over both hemispheres. Several species of *Croton* have become important economic plants in advanced societies; the bark of *Croton cascarilla* and *Croton cluteria*, found of the West Indies, yields a tonic; the Asiatic *Croton tiglium* is one of the strongest known purgatives and a source of *Croton* oil; the seeds of *Croton lacciferus*, found in Sri Lanka, are used for making varnish [16, 18]. More than 70% of the global population uses medicinal plants to cure different diseases. For the majority of the world population medicinal plants represent the primary source of health care. As it was reported by the World Health Organization (WHO), about 80% of people in peripheral communities use only medicinal herbs for the treatment of many diseases [19].

Material and Methods

General Information

Codiaeum variegatum ("garden Croton" or "variegated Croton"; syn. *Croton variegatum* L.) is a species of plant in the genus *Codiaeum*, which is a member of the family Euphorbiaceae. It is native to India, Sri Lanka, Indonesia, Malaysia, and the western Pacific Ocean islands, growing in open forests and scrub. It is an evergreen shrub growing to 3 m tall and has large, thick, leathery, shiny evergreen leaves, *Codiaeum variegatum* is an evergreen shrub or a small tree branching from low down; it can grow up to 3 meters tall but is usually smaller in cultivation. The plant is sometimes harvested from the wild for local medicinal use. It is often grown as an ornamental in gardens, being especially valued for its vast range of variegated-leaf cultivars.

The inflorescences are long racemes 8–30 cm long, with male and female flowers on separate inflorescences; the male flowers are white with five small petals and 20–30 stamens, the female flowers yellowish, with no petals. The fruit is a capsule of 9 mm diameter, containing three 6 mm seeds. The stems contain a milky sap that bleeds from cut stems.

Botanical name: *Croton tiglium* Linn.

Family: Euphorbiaceae

Vernacular names [20] English – *Croton*, Hindi – Jamalgota, Malayalam – Neervalam, Tamil – nervalam, Kannada - Nepal, Japalbeej, Japala, Telungu–Nepalamu.



Fig: Plant *Codiaeum variegatum*

Habitat

An understory plant in well-developed lowland and upland rain forest but tends to be more common at the drier end of the rain forest types and is most abundant on soils derived from recent basalt flows; at elevations

up to 800 meters. The garden Croton *Codiaeum variegatum* (L) Blume is a group of beautifully variegated leafy perennial, tropical ornamental herbs, shrubs or trees with glabrous branches and prominent leaf scars [21].

They have glossy leathery leaves that are variable in shape, colour, and variegation. The leaves are alternate, non-serrated but sometimes lobed. The shape varies from linear-lanceolate, oblong, elliptic, lanceolate, ovate, spatulate, fiddle-shaped to broad, and ovate. Sometimes the leaf blade is interrupted along the midrib and becomes divided into an upper and lower parts. The leaf is probably green in its original natural state, but in cultivated forms, it is variously marked, streaked, blotched, or banded with green, white, reds (orange, purple, pink, indigo, violet), yellow, crimson, scarlet, brown or cream colour when grown in appropriate light conditions [22].

The latex produced from the bark, root, and leaves is poisonous. It contains the toxin 5-deoxyingenol. The bark and roots can cause burns of the mouth while the latex causes eczema in gardeners after repeated exposure. The exudates irritate the skin and are used as purgative by humans and in domestic animals [23].

Collection of samples

Plants of *Codiaeum variegatum* were collected from the D.D.U Gorakhpur University Gorakhpur Identification was carried out from the compiled checklist maintained on the stock and verified by the Department of Botany, Faculty of Science, D.D.U Gorakhpur University Gorakhpur (U.P), India.

Codiaeum variegatum belonging to the family Euphorbiaceae is one of the common medicinal plants grown in the Indian subcontinent. Different parts of this plant have been used in traditional medicines. *C. variegatum*, commonly known as *Croton* is one of the most popular ornamental plants because of vivid foliage colors and varied leaf shapes.

Plant Constituents:

Physiologically active plant constituents are usually classified by their chemical structure rather than specific actions. The plant constituents enumerate as alkaloids, anthocyanins, anthraquinones, cardiac glycosides, cyanogenic glycosides, flavonoids, glucosilicates, phenols, saponins and tannins are mainly found.

Terpenoid

Terpenoids are the predominant secondary metabolite constituents in the genus, chiefly diterpenoids, which may belong to the cembranoid, clerodane, neoclerodane, halimane, isopimarane, kaurane, secokaurane, labdane, phorbol and

trachylobane skeletal types. Triterpenoids, either pentacyclic or steroidal, have frequently been reported for *Croton* species. Volatile oils containing mono and sesquiterpenoids, and sometimes also Shikimate-derived compounds are not rare in the genus. Several species have been reported as sources of different classes of alkaloids, a fact that enhances considerably the importance of genus from the medicinal point of view. Phenolic substances have frequently been reported, among which flavonoids, lignoids, and proanthocyanidins predominate [24].

Phorbol esters are produced by species of Euphorbiaceae and Thymelaeaceae [25]. Among *Croton* species, only *Croton tiglium*, native and cultivated in India, has been extensively studied as a source of Phorbol derivatives, having been shown to contain tiglic phorbol esters. The main irritant component of *C. tiglium* seeds is 12-O-tetradecanoylphorbol-13-acetate, a tumor promoter used in experimental mice cancer research [26].

Alkaloids

The most frequent *Croton* alkaloids are compounds identical or similar to substances found in *Ranunculales*, i.e., alkaloids biogenetically related to benzyl isoquinolines, such as morphin andienones and tetra hydroproto berberine alkaloids. Glutarimide alkaloids and a new class of sesquiterpene guaiane type alkaloids have recently been obtained from *Croton* species [24].

Proanthocyanin

Tannins are polyphenols virtually ubiquitous in plants. They are medicinally important if occurring in high proportions in the plants. They may be formed by the combination of catechin monomers (the so-called or pro anthocyanidins), or by ester bounded units of glucose, gallic, and/or ellagic acid (hydrolysable tannins). So far, only proanthocyanidins have been characterized in *Croton* species [24].

Flavonoids

The available data suggest a common presence of flavonols and flavones as free as methoxylated aglycones. It is important to note, however, that no investigation directed specifically to flavonoids, which are currently made in hydro-alcoholic extracts, has been carried out with *Croton* species. Hence it is quite possible that flavonols and/or flavones glycosides (present in green tissues of most angiosperm species), have not been detected in the so far reported *Croton* chemical analyses.

Lignoids are common in plant groups bearing benzyl isoquinolines and related alkaloids (derived biosynthetically from tyrosine), such as *Ranunculales* and *Magnoliales*. However, only one lignoid has so far been found in *Croton*, the dihydro-benzofuran lignin 3,4-O-dimethylcedrusin. It is interesting to note that this lignin co-occur with taspine, having been found in *C. lechleri* and *C. palanostigma*, both species with red latex.

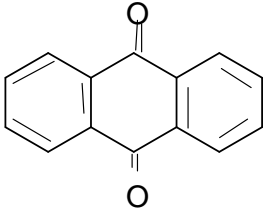


Fig. Structure of 9,10 anthraquinone (Anthraquinone)

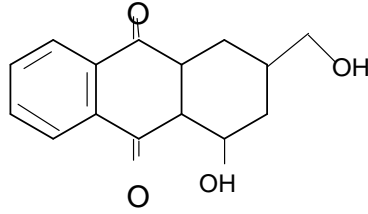


Fig. Aloe emodin (Anthraquinone)

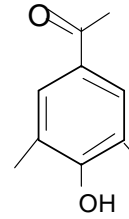


Fig. Gallic acid (Flavonoid)

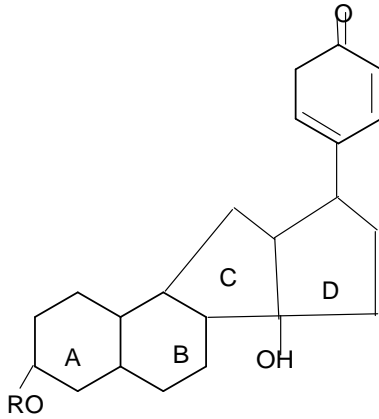


Fig. Bufadienolides (Cardiac glycosides)

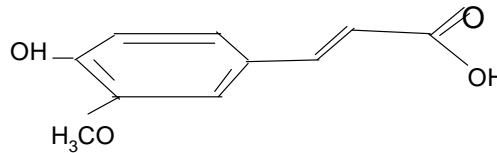


Fig. Ferulic acid (Flavonoid)

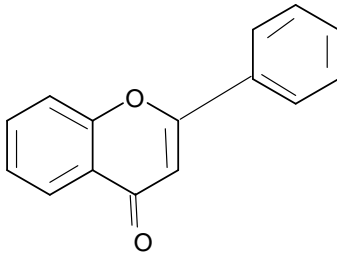


Fig. Flavone (Tannin)

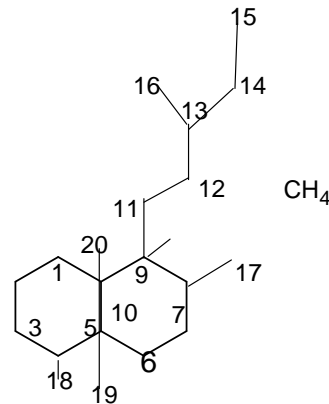


Fig. Clerodane diterpenoid

Sesquiterpenes

Sesquiterpenes are also constituents of essential oils of many plants, e.g. bisabolol, humulene and caryophyllene. Sesquiterpenes lactones are well known as bitter principles and occur in families like the Asteraceae. These compounds possess a broad range of activities due to the α -methylene- γ -lactone moiety and

epoxides. Their pharmacological activities are antibacterial, antifungal, antihelminthic, antimalarial and molluscicidal.

Phenolic Compounds

All phenolic compounds have an aromatic ring that contains various attached substitute groups such as hydroxyl, and methoxy ($-O-CH_3$) groups, and often other nonaromatic ring structures. They range from

simple structures with one aromatic ring to complex polymers such as tannins and lignins. Phenolics differ from lipids in being more soluble in water and less soluble in non-polar organic solvents. Some phenolics however, are rather soluble in ether, especially when the pH is low enough to prevent ionization of any carboxyl and hydroxyl group present.

Nitrogen containing compound

A large variety of plant secondary metabolites has nitrogen in their structures. Included in this category are well known anti herbivore compounds such as alkaloids and cyanogenic glycosides, which are of considerable interest because of their toxicity to humans and their medicinal properties. Most nitrogenous secondary metabolites are biosynthesized from common amino acids.

Cyanogenic glycosides

Perhaps the most obvious defense-related secondary metabolites cyanogenic glucosides. They are not in themselves toxic but are readily broken down to give off volatile poisons when the plant is crushed. Cyanogenic glycosides release the well known respiratory poisonous gas, hydrogen cyanide.

Saponins

Saponins are natural high-molecular weight glycosides of triterpenes or steroids with a very wide distribution in the plant kingdom, as well as lower marine animals. Saponins are glucosides with foaming characteristics. Saponins consist of a polycyclic glycone attached to one or more sugar side chains. The aglycone part, which is also called sapogenin is either steroid or a triterpene [27]. Saponins exhibited a range of biological activities, on the other hand, saponins also have beneficial pharmacological effects. They are anticholesterolemic due to the formation of a complex with cholesterol in gastrointestinal tract thus preventing absorption.

Discussion

Pharmacological Effects of Plant Parts and Crude Extracts

Larvicidal Effects

The most important insects in terms of public health importance are undoubtedly mosquitoes. They transmit various infectious diseases, causing millions of deaths annually [28]. Most of the mosquito control programs are now targeting the larval stage in breeding sites since control of adults may only reduce the adult population temporarily [29]. The studies evaluate the larvicidal activities of Croton (*Codiaeum variegatum*) leaf extracts on the larvae of *Culex* mosquitoes under ambient laboratory conditions.

Cytotoxic effects

Cancer is a term used to describe a large group of diseases characterized by the uncontrolled proliferation and spread of abnormal cells [30]. The recently evolving paradigm of drug resistance to

chemotherapeutic agents is also posing a great barrier to reducing the incidence and mortality of cancer [31]. Hence there is the need to exploit other remedies with possibly less known adverse effects and from readily accessible sources like plants. Plants could serve as a major source of bioactive compounds with potential efficacy against cancers [32].

Antidiarrhoeal Activity

Ethanol extract of *Codiaeum variegatum* leaves contains tannins and other pharmacologically active substance (s) possessing significant antidiarrhoeal activity. The antidiarrhoeal activity and determine the total tannin content of the ethanolic extract of the leaves of *Codiaeum variegatum*. The antidiarrhoeal activity was evaluated in castor oil induced diarrhoea in mice and the total tannin content was determined by using the Folin-Coicalteu phenol reagent. The ethanolic extract of leaves of *Codiaeum variegatum* showed a positive effect on castor oil induced diarrhoea in mice [33].

In vitro Anti-oxidant Activity

Euphorbiaceae plant family possesses strong antioxidant activities which are greatly associated with the presence of phenolic compounds [34]. *Codiaeum variegatum* also possesses alkaloids, anthraquinones, flavanoids, terpenes, steroid, phenol, saponins, tannins, phlobatannin and cardenolide [35] and showed potent cytotoxicities in brian shrimp lethality bioassays [36]. Phytochemical components, especially polyphenols (such as flavonoids, tannins, phenylpropanoids, phenolic acids, etc) are known to be responsible for the free radical scavenging and antioxidant activities. *In vitro* studies also suggested that polyphenols may exert their inhibitory effects by acting as prooxidants on cancer cells or may inhibit the formation and growth of tumors by induction of cell cycle arrest and apoptosis [37]. Phenolic compounds and flavonoids were reported to be associated with antioxidant properties, acting as scavengers of singlet oxygen and free radicals [38].

Antibacterial Activity

The increasing resistance of microorganisms to available antimicrobial agents is one of the major concerns for scientists and clinicians worldwide and has become a global problem in the last years [39]. Over the past decade, interest in the search for antimicrobial natural products has risen [40]. From all possible sources of natural products, plants are considered the most promising product [41]. Infectious diseases caused by pathogenic bacteria affect many communities and the treatment was made difficult partly because of antibiotic-resistant strains. Phytochemicals isolated from medicinal plants are known to be effective in treating bacterial infections. Antibacterial effects of crude extracts were performed using a modified Kirby-Bauer disc diffusion technique to determine the zone of inhibition. The extracts were tested for the antibacterial

activities against Gram-positive bacteria (*Bacillus subtilis*) and Gram-negative bacteria (*Serratia marcescens*). The results demonstrated that both ethanol and waterleaf crude extracts of *Codiaeum variegatum* have shown a strong zone of inhibition against *Serratia marcescens* (20 mm) and *Bacillus subtilis* (12 mm) compared to control [42].

In vitro Antilithiatic Effects

Renal lithiasis is one of the oldest diseases known to human beings and has been documented in ancient Greek. Urinary stones have been found in the remains of Egyptian mummies dating back as far as 7000 years [43]. Renal lithiasis is defined as the consequence of an alteration of the normal crystallization conditions of urine in the urinary tract [44]. Stone disease is common with the lifetime risk of stone formation exceeding 6-9% in men and 3-4% in women [45]. However, crystalluria alone is not a risk factor for lithiasis because it is common in healthy subjects and stone-formers [46, 47]. The limiting factors in stone formation could be those processes that affect the size of the particles formed, because particles may become large enough to occlude the urinary tract, leading to stone formation.

The extracts of medicinal plants induced more crystals in whole urine, thereby reducing super saturation and the particles' size. Therefore, this property of the extracts is advantageous, preventing urinary stone formation by inducing the excretion of small particles from the kidney and reducing the chance of retention in the urinary tract. *Codiaeum variegatum* caused the dissolution of CaOx crystal nucleation these results could be considered positives because the herb extract inhibits crystallization and prevents stone formation, revealing that the *Codiaeum variegatum* extract could reduce the size of the crystals formed indicative of antilithiatic activity [48].

Histological effects

Traditionally, the leaf concoction of *Codiaeum variegatum* is used to treat epilepsy, which is a chronic neurological disorder characterized by uncontrolled or excessive neuronal discharge in any part of the brain or all of the central nervous system (CNS) [49]. The major part of the brain affected by epilepsy is the cerebral cortex, an aspect of the brain that coordinates behavioral, motivational, consciousness, memory storage, communication, and control of motor activities across the entire vertebrates' species.

Molluscicidal activity

Molluscicides of plant origin have gained greater importance since it is believed that natural products are ecologically sound and culturally than synthetic ones. A large number of plant family euphorbiaceae which possess natural molluscicidal activity have been identified. The plant phytochemical

derived from plant resources can be used as an alternative to the synthetic molluscicides [50].

Antifertility activity

Antifertility activity of ses observed in the uterus at 15 days gestation. This is supported by the average number of corpus luteum were also found very little, so the suspected the folliculogenesis not occurred, although ovulation occurs, the ovum cell quality is not perfect. *Croton tiglium* contains steroids and terpenoids which could be developed into medicine to help people achieve the goal of the national family planning program [51].

Conclusion

The area of medicinal plant research is fast developing. Both preclinical and clinical testing are integral components of medicinal plant research. Preclinical testing of plants for medicinal properties is of vital importance to provide a scientific basis for their usage and validate their historical utilization by traditional healers and herbalists. Thus, it provides society with new, effective, and safe sources of drugs. With the opening of newer vistas in medicine, including the modern molecular biology tools, high output automated bioassays, and newer technologies for rapid structure determination in medicinal plant research, the field of preclinical testing seems to have a bright future.

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