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A Review of Biological Activities of Genus *Croton*

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Abstract:
Croton contains a wide range of constituents, including phorbol esters, alkaloids, di and triterpenoids such as clerodane, uphold derivatives, and flavonoids and their glycosides, all of which have medicinal value. In addition, several Croton species have a red sap, which contains proanthocyanins and/or alkaloids in some species. Some species are aromatic because they contain volatile oil. The current review summarizes the most important biological activities of Croton species for future research as potential medicines. It is important to note that the presence of secondary metabolite classes in Croton is a point worth considering because it could lead to the discovery of pharmacologically active substances.

INTRODUCTION

Herbal medicine is one in which the principal therapeutic effect is based on the presence of plant metabolites. Plant parts along with extracted and purified active ingredients used as medications are all examples of herbal drugs (Shahzad *et al.*, 2017; Zaynab *et al.*, 2018). The name "Croton" originates from the Greek word "kroton," meaning "thick," and denotes thick, smooth seeds found in many Croton species. Croton belongs to the Crotonoideae subfamily among the Euphorbiaceae family (Richardson and King, 2011). This genus is ranked the 11th largest angiosperm genus (Caruzo *et al.*, 2011).

Croton plants are utilized in folk medicine across the globe in a variety of ways. Studies have shown that cancer, diabetes, digestive disorders, external wounds, fever, inflammation, intestinal worms, hypertension, malaria, ulcers, and weight loss are some of the major ethnomedicinal applications of croton plants (Salatino *et al.*, 2007). Sangre de Drago sap derived from croton plants is used as a herbal medicine for diarrhea, irritation, insect bites, viral diseases, and wounds (Ndunda, 2014). The croton seed and oil have been utilized as Ayurvedic medicine to treat dropsy, cold, cough, constipation, asthma, and fevers (Dey *et al.*, 2015).

The croton genus is generally found in tropical regions around the world, although it also includes few members in subtropical and temperate zones. Brazil, the Antilles, and Mexico are the principal centers of diversity in the Neotropics (Caruzo *et al.*, 2011). It has been documented that 3 endemic croton species: *C. sulcifructus*, *C. socotranus,* and *C. sarcocarpus* are prevalent in Socotra Island, Yemen (Miller and Morris, 2004). The essential oil extracted from *C. nepetaefolius* has been described to show antiparasitic, intestinal myorelaxant, and antispasmodic effects (Magalhães *et al.*, 1998) and cardiovascular effects (Lahlou *et al.*, 2000).

Many species of the croton have been revealed to exhibit multiple other biological activities like anti-inflammatory, anti-convulsion, anti-nociceptive, and anxiolytic activities (Salatino *et al.*, 2007). In a study using hyperglycaemic rat models, the aqueous extract of the stem barks of *C. cuneatus* Klotz was found to exhibit anti-diabetic activity (Torrico *et al.*, 2007). The seeds of *C. tiglium* have been used in traditional medicine for many uses such as wound healing, constipation, traditional dyspepsia, and dysentery. The essential oil of *C. tiglium* has been documented to exhibit analgesic, antimicrobial, insecticidal, and inflammatory properties. The leaves of *C. tiglium* have been used to treat diarrhea, linea, pain, and hurt (Dey *et al.*, 2015).

Antibacterial activity

The hexane extract from *C. sonderianus* was tested against five bacterial isolates (*E. coli*, *B. subtilis*, *P. aeruginosa*, *M. smegmatis,* and *S. aureus*) to find its antimicrobial activity. Streptomycin sulfate, at a dosage of 1 mg/ml, was taken as a standard control. Extracts of hexane had no inhibitory effect against *E. coli*, but they had inhibitory activity against *B. subtilis*. This inhibitory activity was high (>13 mm). The hexane extract was tested against *M. smegmatis*, *P. aeruginosa*, and *S. aureus*, which had a moderate inhibitory activity (7-12 mm). Generally, the results were comparable to the standard streptomycin sulfate, and the most susceptible strain was *M. smegmatis* (McChesney *et al.*, 1991). *C. urucurana* extracts in ethanol, n-hexane, and n-hexane/ dichloromethane have greater antibacterial action against *S. aureus* than *S. typhimurium* (Peres *et al.*, 1997).

S. aureus, *S. epidermidis*, *B. subtilis*, *P. aeruginosa*, *S. settoubal*, *K. pneumoniae*, *S. cerevisiae*, *C. albicans*, and *Cryptococcus neoformans* have all been inhibited by the essential oil of *C. urucurana* (Simionatto *et al.*, 2007). The ethanol extract of *C. tiglium* seeds was found to inhibit *P. multocida* and *B. subtilis*. Ciprofloxacin was used as positive control and autoclaved water as negative control (Shahid *et al.*, 2008). The root methanolic extract of *C. membranaceus* demonstrated inhibitory activities against the tested microorganisms with a zone of inhibition values ranging from 1.0 ± 0.6 mm to 11.0 ± 1.6 mm (Bayor *et al.*, 2009).

It has been investigated that Plaunotol which is an acyclic diterpene obtained from the leaves of *C. sublyratus* was found to resist fourteen strains of methicillin-sensitive *S. aureus* and twenty strains of methicillin-resistant *S. aureus*. Ethanol extract of the leaves of *C. caudatus* Geisel has shown activity against *S. aureus* and *P. putida* demonstrating 12 mm inhibition zone. Chloroform and ethanol extract of *C. caudatus* Geisel leaves inhibited *Microphomina phaseolina* with inhibition zone of 10 mm and 12 mm respectively (Lokendrajit *et al.*, 2012).

Antifungal activity

Several studies have been conducted to evaluate the antifungal activity of various Croton species. In a study, the antifungal activity of the extract of *C. macrostachys* stem bark was tested against *C. albicans*, *C. krusei*, and *Cryptococcus neoformans*. The ethanol stem bark extract has the best antifungal efficacy against *C. albicans* (Tene *et al.*, 2009). *C. macrostachyus* extracts reduced the radial growth of *Colletotrichum kahawai* indicating the potential for *C. macrostachyus* extracts to be used as a treatment for coffee berry disease (Abera *et al.*, 2011). The ethyl acetate and dichloromethane extracts of Cronton polyandrous leaves showed antifungal activity against *C. albicans*. Furthermore, these extracts showed low antifungal activity against *C. krusei* (Biscaro *et al.*, 2013).

In studying the antifungal activity of *C. sparsiflorus* plant against *A. niger*, *C. albicans,* and *C. tropicalis*, the results confirmed that the antifungal activity increases with the concentration of the different organic extracts. The zone of inhibition was found to be closer to the standard Ketoconazole at the concentration of 10µl. The inhibition activity varied depending on the organic solvents and the activity of the extracts was in the order of Ethyl acetate > Chloroform > Hexane based on the polarity of the solvents. The activity of the methanolic extract was due to both phenolic and flavonoid content I and it can be suggested that extracts of selected plants would help in fungal diseases (Abi Beaulah *et al.*, 2013). The 4 triterpenoids products (lup-1, 2-and-3- one, lupeol, oleanolic acid, ursolic acid) isolated from toluene extract of the root of *C. bonplandianum* showed potent activity against the five tested fungal species (*Colletotrichum camellia*, *Fusarium exquisite*, *Alternaria alternate*, *Curvularia eragrostidis*, and *C. gloeosporioides*) versus Bavistan standard (Ghosh *et al.*, 2014). The leaves and seeds extracts (water, ethanol, methanol, and acetone) of *C. tiglium* were found to possess antifungal activity against *C. albicans*, *Trichophyton rubrum*, and *Microsporum canis*). The MIC range was 62.5-250µg/ml against the fungal strains vs standard. (Std=Nystatin for *C. albicans* and Ketoconazole for *T. rubrum* and *M. canis*) (Iraqui and Yadav, 2015). A study carried out by Rahim et al., 2016, to assess the antifungal activity of *C. zambesicus* extract showed that neither methanol nor chloroform extracts were active against standard fungi (*A. niger* and *C. albicans*) (Rahim *et al.*, 2016).

In investigating the antifungal activity of crude extracts (water, methanol, and ethanol) of *C. macrostachyus* against two fungal pathogenic species (*A. flavus* and *A. niger*). The alcoholic (methanol and ethanol) crude extracts had shown high antifungal activity against *A. niger* and *A. flavus* than water extract (Habtom and Gebrehiwot, 2019). The antifungal study of *C. tiglium* revealed that the methanolic extract had strong antifungal efficacy against two fungus strains (*A. niger* and *R. oryza*) as compared with different commercially available drugs (Zahid and Mughal, 2019).

Antioxidant Activity

Plants are a worthy source of exogenous antioxidants because they produce them as a protection against oxidative stress. Because of the direct effect of components on particular targets, such as cyclooxygenase, *C. celtidifolius* bark has been shown to have antioxidant potential (Nardi *et al.*, 2003). The essential oils of three Croton species found in northeastern Brazil, *C. zenthmeri*, *C. nepetaefolius*, and *C. argyrophylloides*, showed high antioxidant activity (Morais *et al.*, 2006). The crude essential oil extracted from the stem bark of *C. urucurana* showed antioxidant properties. The main antioxidant components were α-bisabolol, α-eudesmol and guaiol (Simionatto *et al.*, 2007).

The sap of *C. lechleri* protected *S. cerevisiae* against apomorphine-induced oxidative damage. Red latex from *C. urucurana* demonstrated antioxidant and free radical scavenging properties (Salatino *et al.*, 2007). Ethanolic extract of the *C. caudatus* leaves had revealed antioxidant activity, thus demonstrating that its leaves are a possible source of natural antioxidants (SL D *et al.*, 2009). The leaves extract of *C. argyratus* had the highest antioxidant activity, as well as the highest total phenolic and total flavonoid content, suggesting that *C. argyratus* plant extracts might be used as a natural source of antioxidants (Ali *et al.*, 2012).

Anticancer Activity

In 2008, approximately 12 million new cancer cases were recorded, with 7 million cancer deaths worldwide, 8 million deaths in 2012, and 13-17 million deaths projected by 2030 (Irfan *et al.*, 2016; Mulcahy, 2008). Mutations are contributing to the progression of various cancer types (Amjad *et al.*, 2020; Ashraf *et al.*, 2018). Several biochemical and physiological routes should be targeted in an integrative approach to cancer management to minimize normal-tissue toxicity (Din *et al.*, 2016; Iqbal, 2021a; Iqbal, 2021b). Both laboratory research and clinical trials have shown that combining chemotherapy with herbal medications can improve effectiveness while reducing side effects. The possibility of the use of herbal medicine to treat cancer was raised as a result of these findings (Ruan *et al.*, 2006). Many therapeutic compounds can be obtained from plants to treat various disorders (Ashraf *et al.*, 2020; Iqbal and Ashraf, 2018; Ullah *et al.*, 2018). Isoguanosine isolated from *C. tiglium* showed antitumor activity in mice (Kim *et al.*, 1994).

Three labdane diterpenoids, 2-acetoxy-3-hydroxy-lambda-8, 12(E)-14-triene, 3- acetoxy-2-hydroxy-lambda-8, 12(E)-14-triene, and 2,3-dihydroxy-lambda-8, 12(E),14-triene extracted from the *C. oblongifolius* stem bark revealed non-specific, modest cytotoxicity against human tumor cells (Roengsumran *et al.*, 2001). A new compound from the stem bark of *C. oblongifolius* exhibited significant cytotoxicity against various human tumor cell lines including HEP-G2 (human liver cancer), SW620(metastatic colon Cancer), CHAGO (bronchogenic Carcinoma), KATO3 (human gastric carcinoma), and BT474 (breast Cancer) (Roengsumran *et al.*, 2002). The anticancer effect of Sangre de Grado obtained from *C. palanostigma* on human cancer cells, like AGS (stomach cancer cells), HT29 (colorectal adenocarcinoma), and T84 (colon cancer cells) was observed. Sangre de Grado must be investigated further as a possible source of anti-cancer drugs due to the production of apoptosis and microtubule impairment in AGS, HT29, and T84 cells (Sandoval *et al.*, 2002).

CONCLUSION

Medicinal herbs have played an important role in our life. They are distributed worldwide but are most abundant in tropical countries. It has been estimated that about 25% of all new medicines are originated from natural sources. In the present review, we systematically summarized the pharmacological effects of the genus Croton. As antimicrobial, antioxidant, and anticancer activities, Croton species may be considered as future potential medicines for many illnesses.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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