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Flavonoid and alkaloid constituents from *Croton* genus: chemical structures and biological activities

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Abstract. The *Croton* genus (Euphorbiaceae) comprises more than 1,300 species distributed worldwide, especially in tropical and subtropical regions. These species are rich in secondary metabolites, notably flavonoids and alkaloids, which contribute significantly to their wide range of traditional medicinal uses. This review aims to provide a comprehensive overview of *Croton* species in terms of their botanical characteristics, traditional uses, phytochemical diversity, and pharmacological potential. The review focuses on the structural diversity and biological activities of flavonoids and alkaloids, highlighting their role in anti-inflammatory, antioxidant, antimicrobial, anticancer, and neuroprotective effects. Furthermore, the review outlines the current preclinical research status and emphasizes the need for further investigations into the pharmacokinetics, toxicity, and mechanisms of action of these promising natural compounds.

Keywords: Croton, flavonoid, alkaloid, traditional use, pharmacological activity

Classification numbers: 1.1.1.

1. INTRODUCTION

The Euphorbiaceae family, commonly known as the spurge family, is one of the largest plant families, comprising 300 genera with approximately 8,000 species. These are grouped into 47 tribes in seven subfamilies: the biovulate Phyllanthoideae and Oldfieldioideae, and the uniovulate Peroideae, Cheilosoideae, Acalyphoideae, Crotonoideae, and Euphorbioideae. Species within this family are primarily distributed in subtropical and tropical regions such as Africa, Asia, and South America, with a few species inhabiting temperate zones. The Crotonoideae subfamily contains around 1,300 species; it is the second most diverse genus of plants in the family, distributed mainly across tropical and subtropical regions worldwide [1].

The species belonging to this genus exhibit considerable morphological diversity, encompassing small herbs, large shrubs, and trees. Common botanical features of *Croton* species include simple, alternate leaves that are often covered with stellate hairs or scales, and a distinctive spicy or aromatic odor when crushed. The inflorescences are typically terminal or axillary racemes or panicles with unisexual flowers where male and female flowers often occur

on the same plant (monoecious) or on separate plants (dioecious). The flowers lack petals and are generally small, with the male flowers possessing numerous stamens, while the female flowers typically have a trilocular ovary [1, 2]. Representative species of the genus are illustrated in *Figure 1*.

In terms of distribution, *Croton* species are widely spread across the Americas, Africa, Asia, and the Pacific Islands. A high diversity of species is found in South America. In Africa, some *Croton* species, such as *Croton macrostachyus* and *Croton megalocarpus* are commonly found in tropical forests and savanna ecosystems. Several species are also native to Southeast Asia. These plants are often collected from their natural habitats, either from the wild or cultivated areas, depending on their traditional or medicinal use. Collection is usually done during the flowering or fruiting seasons when the plant's bioactive compounds are at optimal levels for extraction and study.

Figure 1. Photographs of the *Croton* species. (The images were obtained from http://tropical.theferns.info)

Extensive research has revealed that *Croton* species possess a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antimicrobial, antiprotozoal, antimalarial, anticancer, hepatoprotective, cardiovascular, neuroprotective, and wound-healing properties [3]. Among the numerous compounds identified from *Croton* plants, flavonoids, alkaloids, terpenoids, lignans are known to be the main active constituents. Particularly, flavonoids and alkaloids isolated from *Croton* species have shown remarkable pharmacological potential, notably in modulating oxidative stress, inflammation, microbial infections, and tumor

progression. Some species also demonstrate notable immunomodulatory and enzyme-inhibitory effects, further supporting the genus relevance in drug discovery and therapeutic development [3].

2. TRADITIONAL USES OF *CROTON* SPECIES

2.1. Traditional uses in Viet Nam

In Viet Nam, there are about 45 species of the genus *Croton* [4], of which at least 17 species have been recorded to have applications in folk medicine. These species and their traditional uses are summarized in *Table 1*. These species are often used to treat various diseases such as abdominal pain, diarrhea, ulcers, fever, and skin diseases [5, 6]. The parts of the plant used include leaves, roots, stems, fruits, and seeds, depending on the treatment purpose. For example, *Croton argyratus* is used as a drink to treat diarrhea; *Croton crassifolius* has the effect of reducing stomach pain, reducing inflammation, and stopping bleeding from wounds; meanwhile, *Croton tiglium* is used to treat constipation, rheumatism, and even infections. The use is often done through drinking, applying externally, or bathing in medicinal water, reflecting the diversity in application and rich experience of traditional medicine.

Table 1. Traditional uses of *Croton* species in Viet Nam

No	Scientific name	Vietnamese name	Traditional uses	Part used	Ref.
1	*Croton argyratus* Blume	Cù đèn bạc, bạc lá	To treat diarrhea, ulcers, fever, and for medicinal baths after childbirth	leaves	[5]
			To treat ulcers	roots	
2	*Croton cascarilloides* Raeusch.	Cù đèn lá bạc- hoa răm, ba đậu lá nhót	To treat abdominal pain	leaves roots, wood	[5]
			To treat anemia, fatigue, and fever		
3	*Croton caudatus* Geiseler.	Cù đèn đuôi, ba đậu leo	To treat sprains and fever	leaves	[5]
			To treat constipation	roots	
4	*Croton crassifolius* Geisel.	Củ đèn lông, ba vỏ	To treat stomach pain, abdominal bloating, chronic hepatitis, rheumatic numbness, pain, injuries, wounds, abscesses, and snake bites	roots	[5]
5	*Croton delpyi* Gagnep.	Ba đậu delpy; cù đèn delpy	To treat back pain, bone pain, paralysis, and pruritic eruptions	branches, leaves, bark	[5]
6	*Croton glandulosus* L.	Cù đèn lông cứng	To treat allergies and rashes	whole plant	[5]
7	*Croton joufra* Roxb.	Cù đèn khai, vọng	To produce oil used in lamps and as a medicinal ingredient	seed	[5]
			To treat snake bites	leaves	
8	*Croton kongensis* Gagnep.	Cù đèn cửu long	To treat furuncles, impetigo, and stomach disorders	leaves	[5]
9	*Croton lachnocarpus* Benth.	Cù đèn nhiếm	To treat rheumatoid arthritis and postpartum paralysis	roots	[5]
10	*Croton maieuticus* Gagnep.	Cù đèn hộ sản	To treat postpartum conditions (medicinal baths)	leaves	[5]

11	*Croton phuquocensis* Croiz.	Cù đèn phú quốc	To treat headache	leaves	[5]
12	*Croton poilanei* Gagnep.	Cù đèn răng cưa	To treat allergic rash,	leaves	[5]
			To treat eye diseases and stomach ache	bark	
13	*Croton potabilis* Croiz.	Cù đèn trà, côn trà	To stimulate nerves	leaves	[5]
14	*Croton oblongifolius* Roxb.	Cù đèn, cù đèn roxburgh	To promote meridian circulation, treat urinary retention, aid digestion, relieve back pain, and alleviate bone aches	roots	[5]
			To treat constipation, inflammation, pain, oxidative stress, and bacterial infections	seed	
			To treat infections and bleeding	bark	
			To treat bacterial infections, inflammation, wounds, scabies, and pruritus	leaves	
15	*Croton thorelii* Gagnep.	Cù đèn thorel	To treat menstrual cramps	roots	[5]
			To treat scabies and eliminate insects	leaves	
16	*Croton tiglium* L.	Ba đậu	To treat cold stagnation, bloating, constipation, intestinal obstruction, phlegm, chest pain, diphtheria, and malaria	seed	[5]
			To treat gouty arthritis, hematomas, injuries from falls, and snake bites	roots	
			To treat chilblains externally and as an antiseptic	leaves	
17	*Croton tonkinensis* Gagnep.	Khổ sâm bắc bộ, cù đèn bắc	To treat dysentery, detoxification, ulcers, rhinitis, stomach ache, and duodenal ulcers	leaves	[5]

2.2. Traditional uses in the other countries

Worldwide, the *Croton* genus includes more than 1,300 species, dozens of which are widely used in folk medicine in many countries in Asia, Africa, and the Americas [2]. The *Croton* species have been recorded in folk medicine with diverse therapeutic effects such as anti-inflammatory, antibacterial, antimalarial, analgesic, laxative, menstrual regulation, and supporting the treatment of respiratory, digestive, dermatological and neurological diseases [7, 8]. For example, *Croton lechleri* in South America is notable for its hemostatic and wound-healing effects; *Croton dichogamus* in Africa is used to treat malaria, infections and body aches; *Croton bonplandianus* in Asia and South America has antibacterial, anticancer and dermatological improvement effects; *Croton tiglium* is a famous species in traditional Chinese medicine with laxative, purgative, and cold treatment effects; *Croton celtidifolius* from South America has anti-inflammatory, and antioxidant properties; *Croton gratissimus* from Africa is aromatic and used to treat coughs and sexually transmitted infections; *Croton urucurana* is noted for its hepatoprotective and anti-inflammatory properties; and *Croton schiedeanus* from the Americas is used to treat hypertension. A complete list of Croton species worldwide and their traditional uses is presented in *Table 2*. The preparation methods typically involve decoction, inhalation, or topical application, depending on the species and traditional practices of each region, demonstrating the wide range of potential uses and high biodiversity of this genus.

Table 2. Traditional uses of *Croton* species in other countries

No	Scientific name	Countries	Traditional uses	Part used	Ref.
1	*Croton acutifolius*	Thailand	To treat open wounds	leaves	[9]
2	*Croton argyratus*	Asia	To treat malaria	leaves	[10]
3	*Croton argyrophyllus*	Southern America	To treat anxiety, flu, and headaches	leaves, flowers	[11]
4	*Croton aromaticus*	Asia	To treat insect infestation	roots	[12]
5	*Croton bonplandianus*	Southern America, Asia-Tropical	To treat wounds, arthritis, microbial infections, cancer, fever, and skin diseases	whole plant	[13], [14]
6	*Croton capitatus*	Northern America	To treat pain	leaves	[15]
7	*Croton caudatus*	Asia-Temperate-Tropical	To treat constipation	roots	[16]
			To treat stomach disorders	bark	[16]
			To treat malaria, ardent fever, convulsions, rheumatic arthritis, and numbness	stems, leaves	[17]
8	*Croton celtidifolius*	Southern America	To treat leukemia, ulcers, rheumatism, inflammation, and oxidative stress-related conditions	bark and leaves	[18]
			To induce abortion and to treat various diseases	resin	[19]
9	*Croton dichogamus*	Africa	To treat respiratory diseases, chest complaints, malaria, stomach disorders, arthritis, and gonorrhoea	leaves	[20]
			To treat tuberculosis, chest pain, and fever	roots	[21]
			To treat back pain, malaria, stomachache, chest problems, fever, oedema, and cough	bark	[21]
10	*Croton draco*	America	To treat wounds, inflammation, and infections	whole plant	[22]
11	*Croton echioides*	South America	To treat sexual dysfunction and weakness	bark	[23]
12	*Croton eluteri*	Mexico and South America	To treat sinus congestion	bark	[24]
			To treat cough, diarrhea, flu, indigestion, and stomach pain	leaves	
13	*Croton erythroxyloides*	Southern America	To treat asthma and cancer	bark, leaves	[25]
14	*Croton flavens*	Southern America	To treat mouth ulcers, menstrual pain, and as an abortion pill; also	leaves	[26, 27]

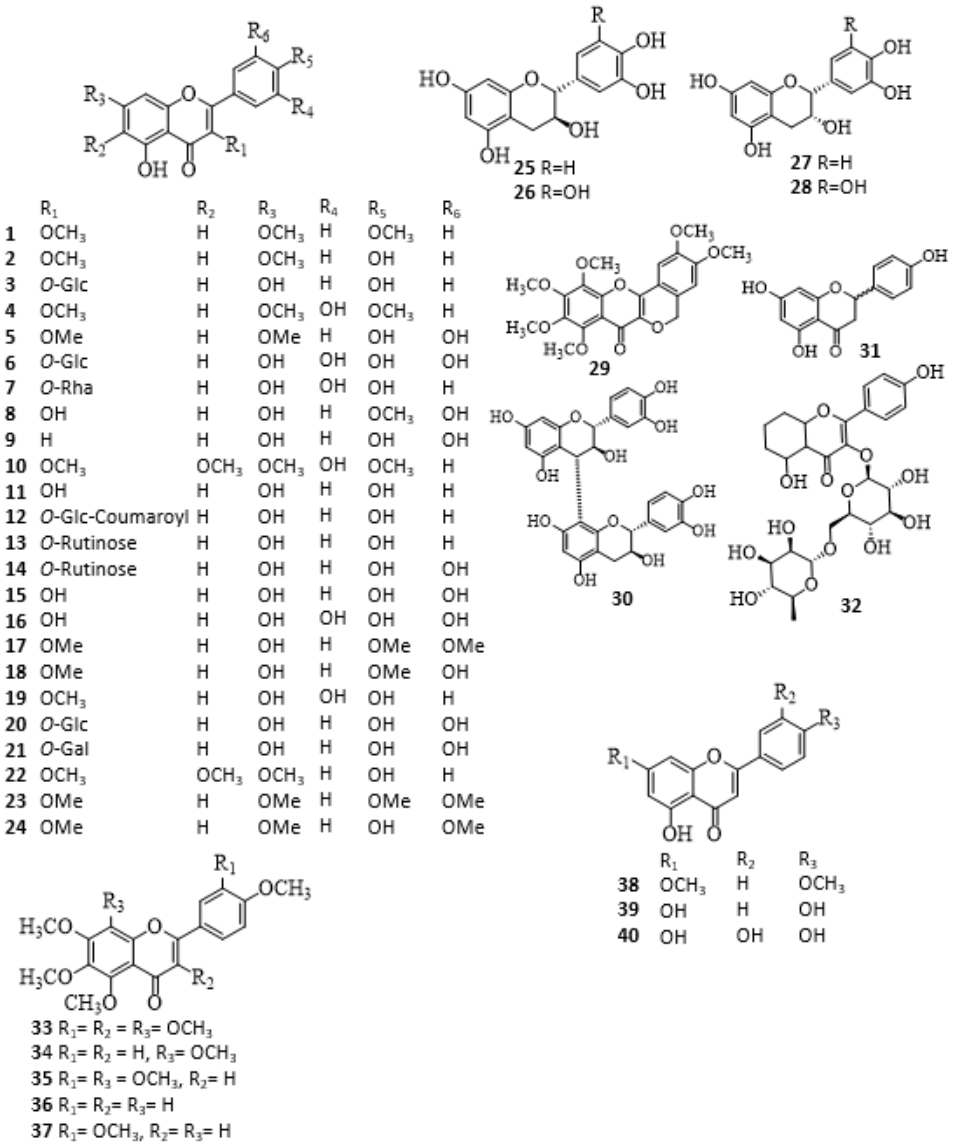
			used as a cleanser and insect repellent		
			To treat stomach ache and colds	roots	[28]
15	*Croton fruticulosus*	Northern America	To treat liver disorders	leaves	[8]
16	*Croton ferrugineus*	Southern America	To treat wounds, thornback ray bites, and infections	whole plant	[29]
17	*Croton glandulosus*	Tropical and subtropical regions	To treat allergies and rashes	whole plant	[5]
18	*Croton gratissimus*	Africa	To treat coughs	leaves	[30]
			To treat chest complaints, fever, and sexually transmitted diseases	roots	
			To treat bleeding gums, abdominal disorders, skin inflammation, earache, and respiratory disorders	bark	
			To treat uterine disorders	whole plant	
19	*Croton heliotropiifolius*	America	To treat infections, pain, and inflammation	roots, leaves	[31]
			To treat diabetes mellitus, Alzheimer's disease, Parkinson's disease, flu, skin diseases, back pain, cough, stomach pain, menstrual disorders, anemia, blood disorders, and parasitic diseases	whole plant	[32]
20	*Croton hirtus*	America, Africa, Asia-tropical	To treat insect infestation	essential oil	[33]
21	*Croton humilis*	Northern America, Southern America	To treat skin problems and urinary disorder	roots	[34]
22	*Croton insularis*	Australasia, Pacific	To treat skin problems and, aids digestion	leaves	[35]
23	*Croton jatrophoides*	Africa	To treat insect infestation	root bark	[36]
24	*Croton joufra*	India, Southeast Asia	To treat dysentery and peptic disorders	leaves, bark	[37]
			To treat helminth infections	flowers	
			To treat blood disorders and fever	heartwood, stems	
25	*Croton klotzschianus*	Asia-Tropical	To treat insect infestation, microbial infections, and oxidative stress-related	roots	[38]

			conditions		
26	*Croton kongensis*	Southeast Asia, Southern China	To treat dysmenorrhea, gastric ulcers, gastric cancers, and dysentery	whole plant	[39]
27	*Croton kilwae*	East Tropical Africa	To treat worm infections, colds, stoma chache, constipation, malaria, tuberculosis, ear infections	whole plant	[40]
28	*Croton laevigatus*	China	To treat injuries, malaria, and stomach ache	roots, leaves	[41, 42]
29	*Croton lechleri*	Southern America	To treat wounds, ulcers, toothaches, skin fungal infections, and rheumatism	resin	[43, 44]
30	*Croton macrostachyus*	Africa	To treat infections, digestive and respiratory disorders, reproductive diseases, skin conditions, wounds, and chronic illnesses	whole plant	[45, 46]
31	*Croton magdalenensis*	Africa	To treat sexually transmitted diseases, malaria, and fever	whole plant	[47]
			To treat skin infections, muscle aches, and for purgative purposes	fruit	[47]
32	*Croton niveus*	America	To treat certain sores	leaves	[48]
			To treat intermittent fevers	bark	
			To treat rheumatic ailments	whole plant	
33	*Croton oblongifolius*	Southeast Asia, India	To treat menstrual cramps, indigestion, dysentery, stomach ulcers, and stomach cancer	whole plant	[49]
34	*Croton ovalifolius*	America	To treat stomach ache, influenza	whole plant	[50]
			To treat respiratory problems	leaves, roots	[51]
35	*Croton palanostigma*	Southern America	To treat gastrointestinal ulcers, cancer, and wounds	resin	[52]
36	*Croton poilanei*	Southeast Asia	To treat stomach pain	bark	[9]
37	*Croton pseudopulchellus*	Africa	To treat insect infestation	essential oil	[53]
			To treat arthritis, cancer, and impaired wounds	whole plant	[54]
38	*Croton robustus*	Southeast Asia	To treat anemia	wood	[55]
			To treat skin diseases and stop bleeding	barks, leaves	[55]
39	*Croton ruizianus*	Southern America	To treat wounds and spasms	whole plant	[56]
40	*Croton roxburghii*	Southeast Asia, India	To treat infertility, fever and wounds	whole plant	[57]

41	*Croton schiedeanus*	America	To treat high blood pressure	leaves	[58]
42	*Croton sonderianus*	Southern America	To treat bacterial and fungal infections	roots	[59, 60]
			To treat gastrointestinal disturbances, rheumatism, and headache	leaves, bark	[60]
43	*Croton sparsiflorus*	Asia, South America	To treat hypertension	whole plant	[61]
			To treat high blood pressure, skin diseases, and wounds	whole plant	[62]
44	*Croton tiglium*	Asia	To treat stagnation and diarrhoea	barks	[6, 63]
			To treat stroke, pulmonary embolism, and jaw stiffness	oil	[64]
			To treat skin diseases	roots	[6]
			To treat stroke, apoplexy, phlegm, throat obstruction, and trismus	seeds	[6]
			To treat constipation, abdominal pain, peptic ulcers, and intestinal inflammation	fruit	[6, 64]
45	*Croton urucurana*	Southern America	To treat diarrhoea	resin	[65]
			To treat cancer, rheumatism, wounds, ulcers, diarrhoeal infections, and gastrointestinal ulcers	resin	[66, 67]
46	*Croton zambesicus*	Africa	To treat fever, dysentery, and convulsions	leaves	[68]
			To treat hypertension, urinary infections, malaria, and diabetes	roots	[69]

3. FLAVONOIDS ISOLATED FROM *CROTON* SPECIES

Approximately 40 flavonoid compounds have been isolated from the *Croton* genus, spanning over 20 species. These compounds belong to several major subclasses, including flavonols (e.g., kaempferol, quercetin), flavan-3-ols such as catechin and epicatechin, flavones such as apigenin and casticin, and methoxylated flavonoids such as ayanin, retusin, and pachypodol. The chemical structures of representative flavonoids from Croton are shown in *Figure 2*. The most common scaffolds include flavonol and flavan-3-ol, with quercetin derivatives being among the most frequently reported and biologically active. Notably, catechin, epigallocatechin, and quercetin are found in multiple species and often exhibit strong antioxidant or anti-inflammatory activity. A summary of flavonoid compounds, their sources, and plant parts is presented in *Table 3*.



	R_1	R_2	R_3	R_4	R_5	R_6
1	OCH_3	H	OCH_3	H	OCH_3	H
2	OCH_3	H	OCH_3	H	OH	H
3	*O*-Glc	H	OH	H	OH	H
4	OCH_3	H	OCH_3	OH	OCH_3	H
5	OMe	H	OMe	H	OH	OH
6	*O*-Glc	H	OH	OH	OH	OH
7	*O*-Rha	H	OH	OH	OH	H
8	OH	H	OH	H	OCH_3	OH
9	H	H	OH	H	OH	OH
10	OCH_3	OCH_3	OCH_3	OH	OCH_3	H
11	OH	H	OH	H	OH	H
12	*O*-Glc-Coumaroyl	H	OH	H	OH	H
13	*O*-Rutinose	H	OH	H	OH	H
14	*O*-Rutinose	H	OH	H	OH	OH
15	OH	H	OH	H	OH	OH
16	OH	H	OH	OH	OH	OH
17	OMe	H	OH	H	OMe	OMe
18	OMe	H	OH	H	OMe	OH
19	OCH_3	H	OH	OH	OH	H
20	*O*-Glc	H	OH	H	OH	OH
21	*O*-Gal	H	OH	H	OH	OH
22	OCH_3	OCH_3	OCH_3	H	OH	H
23	OMe	H	OMe	H	OMe	OMe
24	OMe	H	OMe	H	OH	OMe

	R_1	R_2	R_3
38	OCH_3	H	OCH_3
39	OH	H	OH
40	OH	OH	OH

Figure 2. The structures of flavonoids from *Croton* species

Table 3. Names of flavonoids from *Croton* species

No	Name	Sources	Plant parts	Ref.
1	Kaempferol 3,4',7-trimethyl ether	*C. cajucara*	leaves	[70]
2	Kaempferol 3,7-dimethyl ether	*C. cajucara*	leaves	[70]
3	Kaempferol 3-*O*-glucoside	*C. heliotropiifolius*	roots	[32, 71]
4	Ayanin	*C. gratissimus*, *C. schiedeanus*	fruits whole plant	[72-74]
5	Quercetin 3,7-dimethyl ether	*C. schiedeanus*	whole plant	[73, 75]
6	Myricitrin	*C. draco* *C. menyharthii*	bark leaves	[76, 77]
7	Quercitrin	*C. draco*	bark	[76]

8	Tamarixetin	*C. steenkampianus*	leaves	[78]
9	Eriodictyol	*C. steenkampianus*	not specified	[75]
10	Casticin	*C. betulaster*	aerial parts	[79, 80]
11	Kaempferol	*C. caudatus* *C. bonplandianus* *C. sylvaticus* *C. cajucara* *C. ehrenbergii*	stems whole plant not specified leaves bark	[17, 81-84]
12	Tiliroside	*C. caudatus* *C. ehrenbergii*	stems aerial parts	[17, 83]
13	Kaempferol-3-*O*-rutinoside	*C. caudatus*	stems	[17]
14	Rutin	*C. caudatus,* *C. bonplandianus* *C. betulaster* *C. sphaerogynus* *C. ehrenbergii*	stems whole plant aerial parts leaves aerial parts	[17, 80, 81, 83, 85]
15	Quercetin	*C. celtidifolius* *C. urucurana* *C. bonplandianus* *C. sylvaticus* *C. steenkampianus* *C. menyharthii* *C. blanchetianus* *C. cajucara* *C. sphaerogynus*	latex leaves whole plant whole plant leaves leaves leaves leaves leaves	[19, 77, 78, 81, 82, 84-87]
16	Myricetin	*C. celtidifolius*	latex	[19]
17	Quercetin-3,3',4'-trimethyl ether	*C. gratissimus*	fruits	[72]
18	Quercetin-3,4'-dimethyl ether	*C. gratissimus*	fruits	[72]
19	Quercetin 3-*O*-methyl ether	*C. sphaerogynus*	leaves	[85]
20	Quercetin 3-*O*-glucoside	*C. heliotropiifolius*	roots	[32]
21	Hyperoside	*C. blanchetianus*	leaves	[87]
22	Penduletin	*C. betulaster*	aerial parts	[80]
23	Retusin	*C. ciliatoglanduliferus* *C. gratissimus*	aerial parts fruits	[72, 88, 89]
24	Pachypodol	*C. ciliatoglanduliferus* *C. gratissimus*	aerial parts fruits	[88, 89]
25	Catechin	*C. lechleri* *C. draco* *C. celtidifolius* *C. urucurana*	latex latex leaves bark	[76, 90 - 92]
26	Gallocatechin	*C. lechleri* *C. draco* *C. urucurana*	latex latex bark	[76, 90, 91]
27	Epicatechin	*C. lechleri* *C. draco* *C. urucurana*	latex latex bark	[76, 90, 91]
28	Epigallocatechin	*C. lechleri* *C. draco* *C. celtidifolius*	latex latex leaves	[19, 76, 90]
29	Crotoncaudatin	*C. caudatus*	stems	[17]
30	Procyanidin B3	*C. urucurana*	bark	[91]

31	Naringenin	*C. gratissimus*	fruits	[72]
32	Nicotiflorine	*C. ehrenbergi*	aerial parts	[83]
33	3,5,6,7,8,3',4'-Heptamethoxyflavone	*C. caudatus*	aerial parts	[17]
34	Tangeretin	*C. caudatus*	aerial parts	[17]
35	Nobiletin	*C. caudatus*	aerial parts	[17]
36	5,6,7,4'-Tetramethoxyflavone	*C. caudatus*	aerial parts	[17]
37	Sinensetin	*C. caudatus*	aerial parts	[17]
38	5-Hydroxy-7,4'-dimethoxyflavone	*C. betulaster*	leaves	[80]
39	Apigenin	*C. betulaster*	leaves	[80]
40	Eriodictyol	*C. steenkampianus*	leaves	[78]

3.1. Antioxidant activity of *Croton* flavonoids

Several *Croton* species have demonstrated significant antioxidant potential through their crude extracts, particularly due to their high flavonoid content. The extract of *Croton cajucara* exhibits strong antioxidant activity in the DPPH assay (IC_{50} 63.34 μg/mL) and effectively reduces oxidative stress in streptozotocin-induced diabetic rats [93]. Similarly, the ethanol-soluble leaf extract of *Croton urucuran*a was found to possess antioxidant, lipid-lowering, renal, and cardioprotective effects in Wistar rats subjected to cigarette smoke and a high-cholesterol diet, significantly improving oxidative stress markers and biochemical parameters at a dose of 300 mg/kg [94]. Additionally, the methanolic root extract of *Croton macrostachyus*, which contains a high concentration of flavonoids, showed notable antioxidant activity with IC_{50} values ranging from 3.5 to 6.4 mg AAE/g, alongside moderate antibacterial effects against *Staphylococcus aureus, S. pneumoniae, Escherichia coli,* and *Klebsiella pneumoniae* [95].

At the compound scale, various flavonoids isolated from *Croton* species have been identified as key contributors to antioxidant activity. In the rubber latex of *Croton lechleri*, flavan-3-ol derivatives, including catechin, epicatechin, epigallocatechin, and gallocatechin, were predominant, with epigallocatechin exhibiting the strongest activity (IC_{50} 0.561 μM), followed by gallocatechin (IC_{50} 10.0 μM) and epicatechin (IC_{50} 19.3 μM) [90]. Flavonoids such as gallocatechin, procyanidin B3, catechin, and epicatechin isolated from *Croton urucurana* demonstrated dual antioxidant and anti-inflammatory properties, mediated through reactive oxygen species scavenging, suppression of pro-inflammatory cytokines, and COX-2 inhibition [91]. Among the flavonoids from the leaves of *Croton urucurana*, glycosylated compounds such as quercetin O-deoxyhexosyl-hexoside were identified. This quercetin derivative is known for its strong antioxidant capacity and its ability to induce vasodilation via the nitric oxide (NO)-dependent pathway [86]. Similarly, *Croton bonplandianus* is rich in flavonoids, such as rutin, quercetin, and kaempferol derivatives. It demonstrated notable free radical scavenging activity and reducing power, confirming its antioxidant properties [81]. Moreover, in *Croton sylvaticus*, quercetin and kaempferol were found to contribute significantly to antioxidant capacity (IC_{50} 11.28 ± 0.23 ppm) [82].

3.2. Antimicrobial activity of *Croton* flavonoids

Several *Croton* species have demonstrated promising antimicrobial activities. A review on *Croton heliotropiifolius*, the extract showed low cytotoxicity against fibroblast cells, highlighting its potential as an antifungal adjuvant [32]. Similarly, the crude root extract of

Croton dichogamus demonstrated notable antimicrobial potential. The extract exhibited strong antibacterial effects against gram-positive bacteria as well as activity against *Candida albicans* [96]. Phytochemical analysis of the *Croton dichogamus* root extracts confirmed the presence of flavonoids and other bioactive compounds, and the acetonic extract exhibited antimicrobial activity against *Bacillus cereus*, with a zone of inhibition of 17.33 ± 0.58 mm and a MIC of 10.42 mg/mL [21].

Multiple *Croton* species have demonstrated promising antimicrobial and antiparasitic activities, largely attributed to their diverse flavonoid profiles. In *Croton steenkampianus*, quercetin isolated from ethanol leaf extracts exhibited notable antimalarial activity against both chloroquine sensitive (D10, IC_{50} 4.5 µM) and resistant (Dd2, IC_{50} 6.2 µM) *Plasmodium falciparum* strains, with low cytotoxicity in Vero cells (IC_{50} > 30 µM) [78]. Similarly, three flavonoids from *Croton gratissimus*, including quercetin-3,7-dimethylether, ayanin, and retusin, showed strong antiprotozoal activity. Quercetin-3,7-dimethylether was especially potent against *Leishmania donovani* (IC_{50} 4.5 µM), *P. falciparum* (IC_{50} 7.3 µM), and *Trypanosoma brucei rhodesiense* (IC_{50} 2.4 µM), ayanin also showed moderate activity across all tested parasites [72]. In *Croton menyharthii*, phytochemical studies led to the isolation of three flavonoids, myricetrin-3-*O*-rhamnoside, quercetin-3-*O*-rhamnoside, and quercetin. These compounds exhibited notable antimicrobial activity: quercetin was particularly effective against *Bacillus subtilis* and *Candida albicans*, while the others were more active against *E. coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* [77].

3.3. Anti-inflammatory activity of *Croton* flavonoids

The anti-inflammatory activity of flavonoids isolated from the genus *Croton* is also remarkable through multiple mechanisms. For example, myricitrin demonstrated significant inhibition of complement protein at 83% inhibition at 0.9 mM, indicating its potential for immunomodulatory and anti-inflammatory therapeutic applications [76]. In *Croton celtidifolius*, the ethyl acetate fraction, particularly rich in catechin, was found to significantly reduce plasma extravasation and leukocyte migration in a murine pleurisy model, confirming its anti-inflammatory effect *in vivo* [92]. Similarly, *Croton urucurana* was found to contain a set of flavonoids including gallocatechin, procyanidin B3, catechin, and epicatechin, known to reduce inflammation via suppression of pro-inflammatory cytokines, COX-2 inhibition, and ROS scavenging [91]. Besides, flavonoids identified from *Croton cajucara*, including *O*-glycosides of kaempferol and quercetin as well as *C*-glycosyl flavonoids. These compounds were tested for anti-inflammatory activity using a carrageenan-injected mouse paw edema model and all showed significant anti-inflammatory properties [84]. In *Croton blanchetianus*, a flavonoid-rich leaf fraction demonstrated strong antinociceptive activity in rodent models of pain. Flavonoids such as quercetin-3-*O*-(2-rhamnosyl) rutinoside, hyperoside, quercetin rutinoside pentoside, and quercetin hexoside deoxyhexoside were identified as major constituents responsible for the effects [87].

3.4. Anticancer activity of *Croton* flavonoids

Croton species have demonstrated significant anticancer properties, primarily attributed to their flavonoid content and ability to modulate key cellular mechanisms such as apoptosis, cell cycle progression, and growth factor regulation. The acetone extract of *Croton bonplandianus* exhibited strong cytotoxic and pro-apoptotic effects in A549 lung cancer cells, inducing apoptosis through G2/M phase cell cycle arrest. The extract demonstrated high antioxidant capacity, correlating with its phenolic (43 µg/mL), flavonoid (3.5 µg/mL) content, and showed promising cytotoxic activity with an IC_{50} of 15.68 µg/mL [97].

In *Croton betulaster*, flavonoids including rutin, casticin, apigenin, penduletin, and 5-hydroxy-7,4'-dimethoxyflavone acted as proliferation inhibitors in GL-15 glioblastoma cells, notably reducing expression of angiogenic and growth factors such as VEGF and TGF-β1 at 24 hours [80]. Similarly, *Croton celtidifolius*, rich in flavonols (myricetin, quercetin) and flavan-3-ols (epicatechin, epigallocatechin), exhibited cytotoxic effects against MCF-7 breast cancer cells and Ehrlich ascites carcinoma (EAC), with IC_{50} values of 169.0 ± 1.8 and 187.0 ± 2.2 μg/mL respectively. *In vivo* studies using EAC-bearing mice showed that latex extract at 3.12 mg/kg/day reduced tumor burden by 56 %, prolonged survival time (from 13.0 to 17.5 days), and decreased body weight gain [98]. Additionally, flavonoids such as quercetin triglycoside, kaempferol triglycoside, rutin, and quercetin 3-O-methyl ether isolated from *Croton sphaerogynus*, showed strong antiproliferative effects against multiple cancer cell lines including NCI-H460, MCF-7, and U251. The methanol fraction had the most potent effect with a GI_{50} of 0.25 μg/mL, while other fractions exhibited moderate activity (GI_{50} 1.20 and 1.05 μg/mL) [85].

3.5. Enzyme-inhibitory activity of *Croton* flavonoids

Several *Croton* species have demonstrated notable enzyme-inhibitory activities. Two flavonoids, retusin and pachypodol, were isolated from *Croton ciliatoglanduliferus*. Among them, pachypodol showed the strongest activity, inhibiting ATP synthesis with an IC_{50} of 51 μM and targeting the dehydrating enzyme [89]. In addition, the chloroform fraction (ChF) of *Croton bonplandianus* leaf extract, rich in flavonoids (95.68 μg/mL quercetin equivalent) demonstrated notable *α*-amylase (IC_{50} 95.78 μg/mL) and *α*-glucosidase (IC_{50} 126.81 μg/mL). These enzymes are key therapeutic targets in the management of type 2 diabetes, and this extract may possess significant antidiabetic potential [99].

3.6. Neuroprotective activity of *Croton* flavonoids

In *Croton betulaster*, flavonoids were shown to modulate key processes in neural development and defense. These compounds promoted astrocyte and microglial activation, protected neural progenitor cells, and stimulated neuronal differentiation and axon formation (neuritogenesis). Preclinical studies further revealed their neuroprotective effects in models of glutamate-induced toxicity and neuroinflammation, supporting their relevance in diseases such as Parkinson's [100]. The neuroprotective effects of casticin, a flavonoid from *Croton betulaster*, on rat cortical neurons *in vitro*. When neural progenitor cells were cultured on astrocyte monolayers treated with casticin, it increased the number of *β*-tubulin III- and Tbr2-positive neurons by approximately 20 % and reduced neuronal death by 50 % [79]. Additionally, in *Croton sylvaticus*, the major flavonoids identified were quercetin and kaempferol. These flavonoids exhibited acetylcholinesterase inhibitory activity with IC_{50} ranging from 60.7 to 415.0 μg/mL, suggesting potential application in the treatment of degenerative neurological diseases such as Alzheimer's [82].

3.7. Other biological activities of *Croton* flavonoids

Some other uses from the *Croton* genus are known: *Croton macrostachyus* leaves exhibited *in vivo* antimalarial activity, achieving 59.3% parasitemia suppression in *Plasmodium berghei*-infected mice at 800 mg/kg [101], *Croton urucurana* extract showed hepatoprotective and lipid-lowering effects in a metabolic fatty liver disease mouse model, improving liver enzyme levels and reducing tissue damage [102]. Additionally, *Croton tiglium* seed extract exhibited antidiabetic activity by significantly enhancing glucose uptake in 3T3-L1 adipocytes [103].

In *Croton schiedeanus*, the flavonoids ayanin and quercetin 3,7-dimethyl ether have demonstrated significant cardiovascular effects. Ayanin exhibited dose-dependent anti-

adrenergic activity in rats by lowering blood pressure and heart rate via the NO/cGMP pathway, while quercetin 3,7-dimethyl ether showed potent vasorelaxant effects in isolated aortic rings [73 - 75]. The leaf extract of *Croton bonplandianus* demonstrated strong hepatoprotective activity in a murine model of CCl_4-induced liver injury, normalizing elevated liver enzyme levels and reducing histological signs of necrosis, inflammation, and fibrosis [104]. Furthermore, flavonoids isolated from *Croton ehrenbergii* include kaempferol, tiliroside, nicotiflorine, and rutin that exhibited phytotoxic effects, inhibiting the germination and growth of *Lactuca sativa* [83]. A similar effect was observed in *Croton ciliatoglanduliferus*, where the flavonoids retusin and pachypodol disrupted the photosynthetic electron transport chain. Pachypodol, in particular, showed efficacy in both pre- and post-emergence stages, suggesting potential application as natural herbicides [88].

Thus, the flavonoid compounds isolated from the genus *Croton* are mainly flavonols, flavan-3-ols, flavones, and methoxylated flavonoids and have some biological activities such as antioxidant or anti-inflammatory activity.

4. ALKALOIDS ISOLATED FROM *CROTON* SPECIES

More than 30 alkaloids have been isolated from *Croton* species, including a variety of structural types such as benzyloisoquinolines (e.g., reticuline, laudanosine), glutarimides (e.g., julocrotine, crotonimide *A–C*), and others. The chemical structures of representative alkaloids from Croton are shown in *Figure 3*. These compounds are reported in species of the genus *Croton*, notably *Croton urucurana*, *Croton bonplandianus*, and *Croton cuneatus*. Among them, taspine is a well-studied alkaloid with wound-healing, anti-inflammatory, and cytotoxic properties, while magnoflorine and julocrotine also exhibit potent pharmacological activity. A summary of alkaloid compounds, their sources, and plant parts is presented in *Table 4*.

4.1. Antimicrobial activity of *Croton* alkaloids

Alkaloid extracts from various *Croton* species have demonstrated potent biological effects against microbial and parasitic pathogens. Example extracts from *Croton urucurana* significantly inhibited adhesion and biofilm formation of two major oral pathogens, *Streptococcus mutans* and Ca*ndida albicans, in vitro* [121]. Similarly, the leaf extract of *Croton joufra* showed dose-dependent antiparasitic effects. *In vitro*, the extract caused faster parasite death than the reference drug praziquantel (1.53 ± 0.12 h vs. 3.46 ± 0.10 h). *In vivo*, treatment at 800 mg/kg/day over three days resulted in a 94.74% reduction in egg count and a 75% decrease in parasite burden [122]. The stem bark extract of *Croton zambesicus* displayed broad-spectrum antimicrobial activity, with antibacterial effects comparable to standard antibiotics such as ampicillin and gentamicin [123].

In *Croton bonplandianum*, two noraporphine alkaloids sparsiflorine and crotsparine, were isolated and tested for antibacterial activity. Among them, sparsiflorine showed moderate efficacy against *Pseudomonas aeruginosa* with a MIC of 0.141 mg/mL [110]. Taspine, an alkaloid isolated from the red resin of *Croton lechleri*, exhibits a diverse range of biological activities, including anti-inflammatory[106], wound-healing [124] and anticancer effects [107]. Taspine hydrochloride significantly reduced carrageenan-induced paw edema in rats in a dose-dependent manner and was more potent than phenylbutazone.

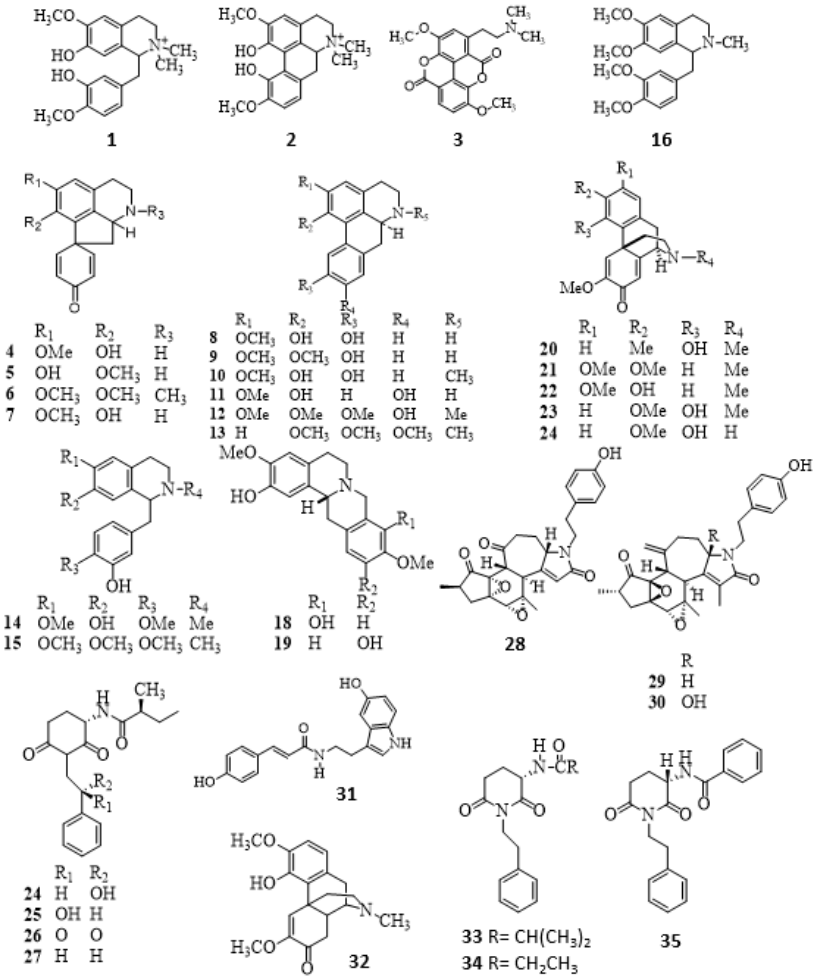


Figure 3. The structures of alkaloids from *Croton* species

Taspine also exhibited wound healing effects with an ED_{50} of 0.375 mg/kg in a rat scar model. Alongside potent cytotoxic activity against melanoma SK23 cells at concentrations as low as 0.1 µg/mL. Moreover, it demonstrated 91 % complement protein inhibition at 0.9 mM, further supporting its immunomodulatory role [76].

In *Croton pullei*, the stem methanol extract yielded several glutarimide alkaloids, including julocrotine and crotonimides A–C, which contributed to the extract's moderate antibacterial and antifungal activities especially against *Staphylococcus aureus* strains CCMB 262 and 263 [120]. Similarly, from *Croton sparsiflorus*, three noraporphine alkaloids crotsparinine, crotsparine, and sparsiflorine, were identified and found to strongly inhibit xanthine oxidase (IC_{50} 27.01 - 18.02 µM) and acetylcholinesterase (IC_{50} 48.42 - 7.42 µM) [111].

Regarding antiparasitic potential, six benzylisoquinoline alkaloids laudanidine, laudanosine, reticuline, corydine, glaucine, and cularine were isolated from *Croton linearis*. Among them, reticuline showed inhibitory effects on *Leishmania infantum* ($IC_{50} \approx 148$ µM) [115]. In the same species, reticuline, laudanidine, and 8,14-dihydrosalutaridine exhibited moderate antimalarial activity against chloroquine-resistant *Plasmodium falciparum* K_1 strain, with IC_{50} values ranging from 16.0 to 46.8 µM [119].

Table 4. Names of alkaloids from *Croton* species

No	Name of compound	Sources	Plant parts	Ref.
1	Tembetarine	*C. urucurana*	bark	[91]
2	Magnoflorine	*C. urucurana* *C. cumingii*	leaves whole plant	[86, 91, 105]
3	Taspine	*C. urucurana* *C. lechleri*	leaves latex	[91, 106-108]
4	Crotsparine	*C. sparsiflorus*	whole plant	[109-111]
5	Crotonosine	*C. sparsiflorus*	whole plant	[112]
6	Pronuciferine	*C. sparsiflorus*	whole plant	[109]
7	Crotsparinine	*C. sparsiflorus*	whole plant	[111]
8	Sparsiflorine	*C. sparsiflorus*	whole plant	[110, 113]
9	Tsuduranine	*C. sparsiflorus*	whole plant	[113]
10	Apoglaziovine	*C. sparsiflorus*	whole plant	[113]
11	Apocrotsparine	*C. sparsiflorus*	whole plant	[109]
12	Isoboldine	*C. celtidifolius*	leaves, twigs	[114]
13	Cularine	*C. linearis*	leaves	[115]
14	Reticuline	*C. linearis* *C. urucurana* *C. celtidifolius*	leaves bark leaves, twigs	[86, 114, 115]
15	Laudanidine	*C. linearis* *C. celtidifolius*	leaves leaves, twigs	[114, 115]
16	Laudanosine	*C. linearis*	leaves	[115]
17	Scoulerine	*C. flavens*	whole plant	[116]
18	Coreximine	*C. flavens*	whole plant	[116]
19	Salutaridine	*C. flavens*	whole plant	[116]
20	Sebiferine	*C. flavens*	whole plant	[116]
21	Flavinantine	*C. flavens*	whole plant	[116]
22	Sinoacutine	*C. flavens*	whole plant	[116]
23	Norsinoacutine	*C. flavens*	whole plant	[116]
24	Julocrotol	*C. cuneatus*	aerial parts	[117]
25	Isojulocrotol	*C. cuneatus*	aerial parts	[117]
26	Julocrotone	*C. cuneatus*	aerial parts	[117]
27	Julocrotonine	*C. cuneatus*	aerial parts	[117]
28	Cascarinoids A	*C. cascarilloides*	whole plant	[118]
29	Cascarinoids B	*C. cascarilloides*	whole plant	[118]
30	Cascarinoids C	*C. cascarilloides*	whole plant	[118]
31	*Trans-N*-(*p*-coumaroyl) serotonin	*C. menyharthii*	leaves	[77]
32	8,14-Dihydrosalutaridine	*C. linearis*	leaves	[119]
33	Crotonimide A	*C. pullei*	leaves, stems	[120]
34	Crotonimide B	*C. pullei*	leaves, stems	[120]
35	Crotonimide C	*C. pullei*	leaves, stems	[120]

4.2. Cytotoxic activity of *Croton* alkaloids

Taspine, an alkaloid obtained from the sap of *Croton palanostigma*, exhibited potent *in vitro* cytotoxicity, with IC_{50} values of 0.39 µg/mL against KB carcinoma cells and 0.17 µg/mL

against V-79 fibroblast cells [108]. From *Croton cuneatus*, four glutarimide alkaloids were identified: julocrotol, isojulocrotol, julocrotone, and the known julocrotonine. Among them, julocrotol showed the highest cytotoxicity, particularly against MCF-7 (breast cancer) and Hep-G2 (liver cancer) cell lines, with IC_{50} values of 21.0 µg/mL and 27.7 µg/mL, respectively. Isojulocrotol and julocrotone exhibited moderate effects, while julocrotonine was inactive [117]. In another study, julocrotine isolated from *Croton pullei* demonstrated potent antiproliferative activity against both promastigote and amastigote forms of *Leishmania amazonensis*, achieving 80% inhibition of amastigotes at an IC_{50} of 19.8 µM [125]. In *Croton sylvaticus*, the prominent alkaloid isolated was 2-[N-(2-methylbutanoyl)]-N-phenyl-ethylglutarimide. This compound was found to inhibit *Bacillus subtilis* at MIC < 12.5 mg/mL and displayed strong toxicity against *Artemia salina* larvae with an LC_{50} of 0.074 mg/mL, suggesting potent bioactivity at low concentrations [82]. Besides, from *Croton cascarilloides*, three crotofolane-type diterpenoid alkaloids, named cascarinoids A–C, were identified. In biological assays, cascarinoids B and C exhibited moderate immunosuppressive activity, especially cascarinoid C showed the ability to inhibit the proliferation of T and B lymphocyte cells with IC_{50} of 6.14 µM and 10.29 µM, respectively [114].

4.3. Neuroprotective activity of *Croton* alkaloids

Several alkaloids isolated from *Croton* species have demonstrated potential in neuropharmacology. In *Croton urucurana*, compounds such as tembetarine, magnoflorine, and taspine have been associated with immunomodulatory, wound-healing, and analgesic properties. Notably, magnoflorine is recognized for its central sedative and analgesic effects, reinforcing its potential in the management of pain and inflammation-related conditions [91]. Phytochemical investigation of *Croton flavens* has led to the isolation of the tetrahydroprotoberberine alkaloids scoulerine and coreximine. Among these, coreximine demonstrated the highest affinity to the gamma aminobutyric acid receptor (GABA) in a [^{3}H]-GABA displacement assay, suggesting potential neuropharmacological activity, possibly acting as a GABAergic modulator [116]. Additionally, the indole alkaloid, *trans*-*N*-(*p*-coumaroyl) serotonin, isolated from *Croton menyharthii* demonstrated potent acetylcholinesterase inhibition (72.6 %, IC_{50} 15.0 µg/mL), indicating possible neuroprotective effects. It also showed strong *α*-glucosidase inhibition, exceeding that of acarbose, thereby supporting traditional uses of the plant in treating neuroinflammatory and metabolic disorders [77].

4.4. Other activities of *Croton* alkaloids

In addition to their pharmacological effects above, alkaloids from *Croton* species have demonstrated other bioactivities. The chloroform latex extract rich in alkaloids from *Croton lechleri* acted as an effective green corrosion inhibitor for admiralty brass in an acidic medium, achieving 57 % inhibition at just 50 ppm [126]. In *Croton sparsiflorus*, alkaloids such as crotonosine were implicated in the plant's traditional hemostatic use, with experimental data confirming accelerated blood coagulation both *in vitro* and *in vivo* [112]. Furthermore, in *Croton urucurana*, alkaloids including magnoflorine, reticuline, and taspine contributed to cardioprotective effects in spontaneously hypertensive rats, improving cardiovascular and renal parameters after chronic administration [86].

5. TOXICOLOGICAL AND SAFETY OF *CROTON* SPECIES

While *Croton* species exhibit promising pharmacological activities, concerns regarding their safety remain. Some species, such as *Croton tiglium*, are known for their toxicity; the seeds

contain potent irritant compounds that can induce severe gastrointestinal disturbances if ingested [6]. The latex extract of *Croton urucurana* caused reproductive toxicity in rats, as demonstrated by increased liver enzymes, decreased fetal weight, and increased fetal malformations at doses of 400 - 800 mg/kg. The results suggest that the use of this plant during pregnancy poses a serious risk to maternal health and embryo-fetal development [127]. Reports on *Croton urucurana* and *Croton lechleri* suggest that their extracts are relatively well tolerated at therapeutic doses in animal models; however, high doses or prolonged exposure can result in hepatotoxicity or gastrointestinal irritation [128, 129].

To date, toxicological investigations remain largely confined to preclinical models, with comprehensive clinical toxicity evaluations still lacking. Therefore, while *Croton* species and their constituents present promising therapeutic avenues, careful evaluation of their safety, standardized dosing, and long-term toxicological effects are crucial for future development.

6. CONCLUSION

The genus *Croton* (Euphorbiaceae) is chemically rich and biologically diverse, with widespread use in traditional medicine across various regions. Among its secondary metabolites, flavonoids and alkaloids are key contributors to its biological activities. The studies highlight that *Croton*-derived flavonoids exhibit strong antioxidant properties and show promise in antimicrobial, anti-inflammatory, enzyme-inhibitory, cardioprotective, and neuroprotective applications. Meanwhile, alkaloids demonstrate a broad pharmacological spectrum, including antiparasitic, antimicrobial, cytotoxic, and neuroprotective effects. However, most research remains at the preclinical stage, with *in vitro* or animal models. Further studies are needed to clarify mechanisms of action, safety profiles, pharmacokinetics, and standardization of extracts.

In summary, *Croton* represents a valuable source of bioactive compounds. Continued investigation into its flavonoids and alkaloids may support the development of new therapeutic agents based on traditional medicinal knowledge.

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