ejpmr, 2022,9(3), 64-67

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.ejpmr.com

Review Article
ISSN 2394-3211
EJPMR

A REVIEW ARTICLE OF PHYTOCHEMICALCONSTITUTIONS OF CROTON GENUS

Amina El- Shaibany[1], Ibrahim Ali Alhakami[2], Abdulrahman Humaid[3*] and Mahmoud Elasser[4]

[1,2]Pharmacognosy Department, University of Sana'a, Pharmacy College.
[3]Department of Biology, Faculty of Science, Sana`a University, Sana`a, Yemen.
[3]Department of Pharmacy, Faculty of Medical Science, Modern Science University, Sana`a Yemen.
[4]The Regional Center for Mycology and Biotechnology, Al-Azhar University, 11787, Nasr City, Cairo, Egypt.

***Corresponding Author: Abdulrahman Humaid**
Department of Biology, Faculty of Science, Sana`a University, Sana`a, Yemen.
Department of Pharmacy, Faculty of Medical Science, Modern Science University, Sana`a Yemen.

Article Received on 14/01/2022 **Article Revised on 01/02/2022** **Article Accepted on 22/02/2022**

ABSTRACT
This review focuses on the chemical constituents from *Croton* species. This genus offers a great amount and variety of constituents like phorbol esters, alkaloids, di and triterpenoids as clerodanes, euphol derivatives, and flavonoids and their glycosides with notable medicinal applications. In addition, several species of Croton have a red sap, in some species containing proanthocyanidins and/or alkaloids. Diterpenes are very common in Croton, corresponding to clerodanes, cembranoid, halimanes, kauranes, labdanes, phorbol esters, trachylobanes and sarcopetalanes. Some species are aromatic due to the possession of volatile oil. The present review provides a significant clue for further research of the chemical constituents from the *Croton* species as potential medicines. It is important to mention that the occurrences of classes of secondary metabolites in Croton are a point deserving consideration, because it may end up useful inprospects of pharmacologically active substances.

KEYWORDS: *Croton*, diterpenes, Phytosterol.

INTRODUCTION

Croton L., the second largest genus of Euphorbiaceae, is an important pantropical lineage with several species that are employed in traditional medicine practices in Africa, Asia, and South America. The common names for the genus are rusffoil and croton. The genus name Croton comes from the Greek word "Kroton", which means ticks, because of the resemblance of the seeds to ticks.[1] It consists of 1200 -1300 species of herbs, shrubs, trees, and occasionally lianas that are ecologically prominent and important elements of secondary vegetation in the tropics and subtropics worldwide. This genus is ranked as the 11th largest angiosperm genus.[2, 3]

The genus occurs mostly in tropical regions worldwide, but also has some representatives in subtropical and northern temperate areas. *Croton* plants have been used widely and variedly in folk medicine all over the world.

Common ethnomedicinal uses of *Croton* plants include treatment of cancer, constipation, diabetes, digestive problems, dysentery, external wounds, fever, hypercholesterolemia, hypertension, inflammation, intestinal worms, malaria, pain, and ulcers.[4, 5] The phytochemistry of the *Croton* genus is considerably diverse, comprising of many classes of natural products mainly, alkaloids, flavonoids, terpenoids, and essential oils containing mono and sesquiterpenes.[6,7] The genus is rich in constituents with biological activities, chiefly diterpenoids such as phorbol esters, clerodane, labdane, karate, trachylobane, pimarane, etc. Croton is also rich in active alkaloids. Several species of the genus are aromatic, indicating the presence of volatile oil constituents.[8]

Phytochemistry of *Croton* genus

The phytochemistry of the *Croton* genus is considerably diverse, comprising of many classes of natural products mainly, alkaloids, flavonoids, terpenoids, and essential oils containing mono and sesquiterpenes. The section which follows herein will capture each class of compounds reported from the *Croton* genus.

Alkaloids from Croton Genus

Alkaloids are not common in Euphorbiaceae, but some *Croton* species are notable for their alkaloids. The most frequent *Croton* alkaloids are compounds identical or similar to substances found in Ranunculales, *i.e.*, alkaloids biogenetically related to benzylisoquinolines, such as morphinandienones and tetrahydro protoberberine alkaloids. Glutarimide alkaloids and a new class of sesquiterpene guaiane-type alkaloids have recently been obtained from *Croton* species.[9, 10]

Eight new alkaloids (1–8) were reported from *Croton* species. Their structures, molecular formula, names, and corresponding sources, are listed in table 1 and figure 1.[11, 12]

Pentacyclic Triterpenoids and Sterols

A quite number of phytosterols have been reported from the Croton genus. The aerial parts of *Croton Draco* contain β-sitosterol, sitosterol -3-D-glucoside (9 &10), stigmasterol, and the new sterol ergosterol-5α-8α-endoperoxide. Also, triterpenoids of various carbon skeletons have been reported from the Croton genus **(Figure 2).** The triterpene acetyl pleuritic acid (11) has been obtained from two *Croton* species; *C. cajucara* and *C. urucurana* which are native in Brazil. From methanol extracts of *C. urucurana*, stigmasterol, β-sitosterol, campesterol, and β-sitosterol-*O*-glucoside were obtained. Shoots of *C. Hieronymus* contain a C-25 analog of *trans*phytol and triterpenes, such as α- amyrin (12), α-amyrin acetate and β-amyrin lupeol and hop-22(29)-en-3β-ol, in addition to the squalene derivatives all-trans-10-methylene-2,6,10,14,18,22- hexane-3-ol and 2,6,15,19,23-pentamethyltetracosa- 2,6,10(28),14,22,28-hexaene-11-ol, and steroids, such as cholesterol, coolest-8(14)-en-3β-old, stigmasterol, gramisterol, sitosterol, campesterol, 22-dihydrobrassicasterol, lophenol (13), isofucosterol, stigmasterol, coolest-4-en-3- one, Agosta-4-22-dien-3-one and sitostanol.[9, 13]

Fixed and Essential Oils from *Croton* Genus

The discovery of *C. megalocarpus* seeds represents a potential source of fixed oils that could be a suitable alternative bio-diesel. Linoleic acid was found to be the major fatty acid, constituting 74.3% of all the fatty acids present in the oil.[14] The seeds of *C. macrostachys* were found to contain 48% oils (linoleic acid (80%), palmitic acid (12%), stearic acid (6%), and myristic acid (2%). The purgative and inflammatory activities of these oils have been demonstrated rationalizing the ethnobotanical use of *C. macrostachys* as a purgative.[15] *Croton penduliflorus* seeds produced essential oils that were found to be hypocholesterolemic but could predispose to anemia.[16] Some examples of essential oils, sources, and corresponding references from the Croton genus are given in Table 2.

Diterpenoids from *Croton* Genus

Phytochemical investigations on Croton species revealed the predominant secondary metabolites as diterpenoids, including clerodane (14), halimane (15), labdane (16), phytane (17), pimarane(18), abietane(19), atisane(20), karate(21), tagline, crotofolane, membrane, cabane, cleistanthane, gray name, and laevinane diterpenoids.

Three hundred & thirty-nine new diterpenoids were reported from *Croton* species.**[11, 13]** Some diterpenoid skeletons are summarized in Figure.3.

Clerodanes

Clerodane diterpenes, an extremely diverse group of terpenoids with more than 800 known compounds, seem to be one of the prevalent classes of terpenoids in *Croton* .[20] Ninety-two new clerodane diterpenoids were isolated from *Croton* species, including two clerodane diterpenoids with acyclic at C-9s, eight clerodane diterpenoids with butenolide at C-9, and 82 furan-clerodane diterpenoids.**[21]**

Specific examples and their reported biological activities are given in table 3 and figure 4.[13, 22]

Halimanes

Biosynthetically, halimane diterpenoids possessing the halimane carbon skeleton (**15**) lie between the labdanes (16) and clerodanes (14) in their general structure. Six new halimane diterpenoids (34–39) were reported from *Croton* species. Their names, corresponding sources, and chemical structure are collected in table 4.[11, 23]

Labdanes

Hundreds of labdanes (16) and their pharmacological values have been reported from higher plants. Thirty-six new labdane diterpenoids were isolated from Croton species.

12 new labdanes were isolated from *C. lari*. Investigation of *C. laevigatus* led to the isolation of 16 new labdanes. Among them, crotonlaevins A–B (40&41), represents rare labdanes with a dodecahydronaphtho [1,2-c] furan moiety.

Some examples of labdanes names, corresponding sources, and chemical structure are collected in table 5.[11, 24]

Abietanes

Abietanes (19) are examples of tricyclic diterpenoids which formed due to migration of the methyl group, C-17 from C-13 to C-15 in primaries (17) resulting in the formation of abietane diterpenoids. However, in plants, they are formed by cyclization of geranylgeranyl pyrophosphate, GGPP. Fourteen new abietane diterpenoids were isolated from Croton species.

Investigation of *C. caudatus* led to the isolation of 5 new abietanes (49-53). Among them, crotontomentosin A (49)was a 9,10-seco abietane. The structures, names, and corresponding sources of some isolated abietanes from some Croton species are collected in **table 6.[11, 25]**

Kauranes

Kauranes (21) are the commonest class of the tetracyclic diterpenoids reported from the *Croton* genus. There are about forty new Kaurane diterpenoids reported present in *croton* species.[13, 26] Geayine (61) is an example of Kauranes diterpenoids from *Croton geayi* **(Figure 4).**

Other Diterpenes from Croton Genus

Three new Cleistanthane diterpenoids e.g. 3-hydroxycleistantha-13(17),15-dienefrom *C.oblongifolius*, seven new Casbane diterpenoids, a total of 28 new Cembrane diterpenoids, thirty-nine new Crotofolane diterpenoids, and, fifty-six new tagline diterpenoids were isolated from Croton species. Also, Grayananes, Atisanes, Phytanes, Laevinanes, and Merediterpenoids were reported from Croton species.**[11, 27]**

Proanthocyanidins

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. Proanthocyanidins have been reported as important active principles of many *Croton* species, *i.e.*, species containing red latex. In such species, proanthocyanidins with several degrees of polymerization and molecular size comprise almost 90% of the red latex dry weight. A specific proanthocyanidin coded SP- 303, with an average molecular weight of 2,100 daltons, was isolated from the red latex of *C. lechleri*. Tannins seem to be important active principles also of *C. zambesicus.* The nature of the detected tannins in Croton species are monomers such as (+)- catechin, (-)-epicatechin, (+)-gallocatechin, (-)-epigallocatechin, and dimeric procyanidins B-1 and B-4. Dimers and trimers were also obtained and characterized as catechin-(4-α→8)-epigallocatechin, gallocatechin-(4-α→8)-epicatechin, gallocatechin-(4- α→6)-epigallocatechin, catechin-(4-α→8)-gallocatechin (4-α→8)-gallocatechin and gallocatechin-(4-α→8)-gallocatechin-(4-α→8)-epigallocatechin.**[9]**

Flavonoids and other Phenolic Substances

Flavonols and/or flavones are ubiquitous in vascular plants, at least in green tissues. Myricitrin (myricetin-3-*O*-rhamnoside was isolated from the red latex of C.

Draco and *C. panamensis*. Leaves of *C. cajucara* yielded kaempferol-3,7-dimethyl ether and 3,4,7- trimethyl ether. From leaves of *C. Novarum* Leandro, Krebs and Ramiarantsoa isolated the flavone *C*-glycoside vitexin (62). Also, the attempting (63) has been isolated from leaves and stems of *C. brasiliensis.*[9] A new flavone glucoside helichrysoside-30-methyl ether (64) was found from the leaves of *C. zambesicus.*[11]

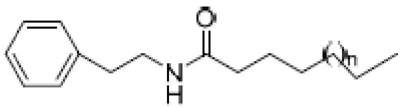
In addition, liquids are common in plant groups bearing benzylisoquinolines and related alkaloids (derived biosynthetically from tyrosine), such as Ranunculales and Magnoliales. However, only one lignoid has so far been found in *Croton*, the dihydro benzofuran lignan 3',4- *O*-dimethylcedrusin (65) which is represented in figure 2.6. It is interesting to note that this lignan co-occurs with the spine, having been found in *C. lechleri* and *C. palanostigma*, both species with red latex.**[9]**

5. Benzoate Derivatives, Pyran-2-One Derivatives, Cyclic peptides, Tropone Derivatives, and Limonoids:

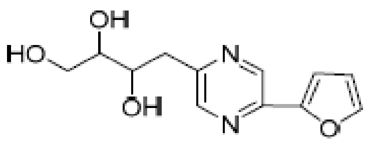
Three benzoate derivatives (66–68) were isolated from *C. sylvaticus* and *C. hutchinsonianus.*[28, 29] Also, three new pyran-2-one derivatives, crotonpyrone A (69), B (70), and C (71) isolated from *C. crassifolius*. Two cyclic peptides (72, 73) were obtained from *C. gossypifolius* and *C. urucurana*, while two tropone derivatives (74,7 5) were isolated from *C. zehntneri* and *C. argyroglossum*. From the root bark of *C. atrophies,* two new limonoids, musidunin (76) and musical (77), were found.[11, 30]

Glycosides

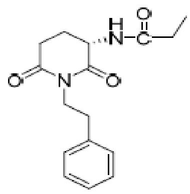
About twenty-one, new glycosides were isolated from *Croton* species. Some examples of *croton* glycosides; crotonionosides A–G (78-84) (table 7) which are obtained from the leaves of *C. cascarilloides.*[11]



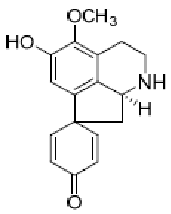
2 n=24
1 n=22



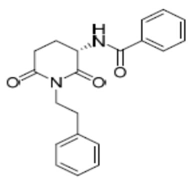
3



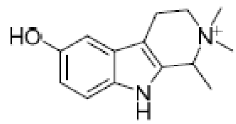
4



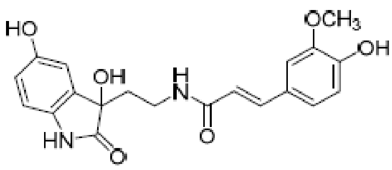
5



6

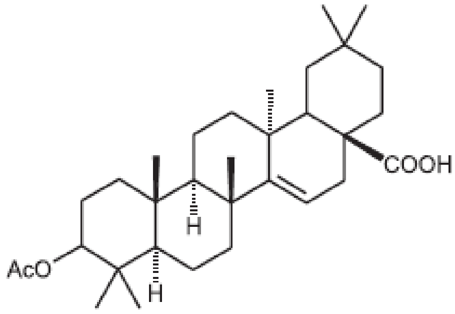


7

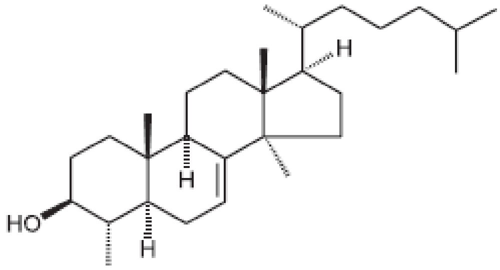


8

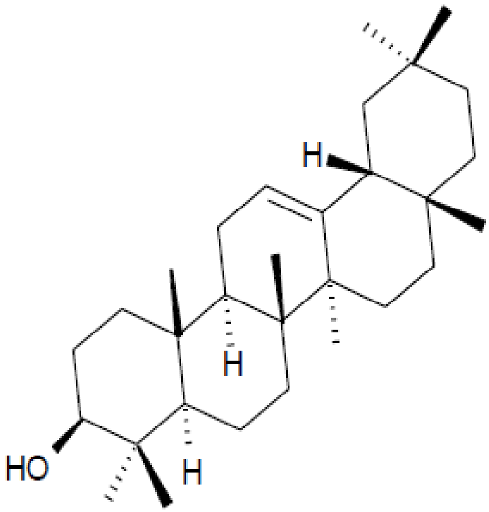
Figure 1: Chemical structure of eight alkaloids from the genus Croton.



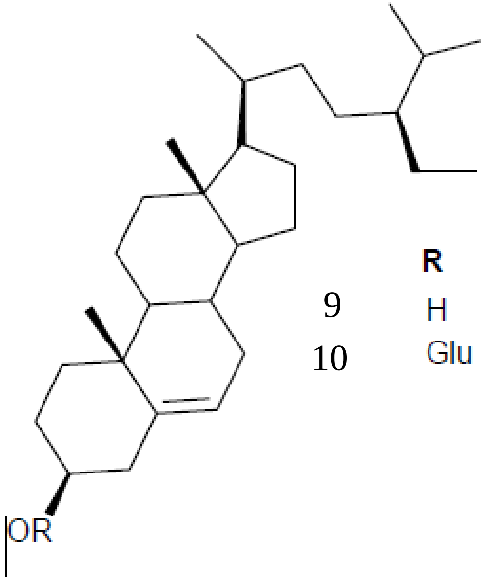
11. Acetyl aleuritolic acid



13. Lophenol



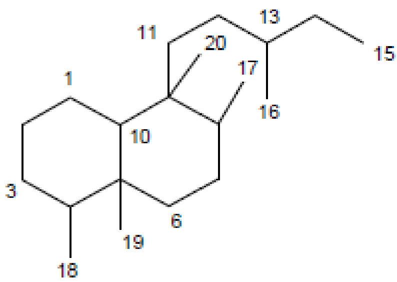
12. α- amyrin.



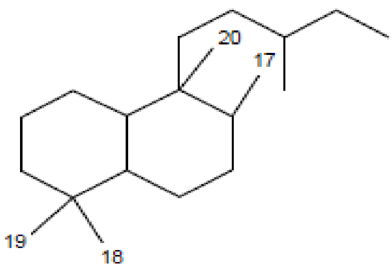
9.β-sitosterol.
10. sitosterol -3-D-glucoside

Figure 2: Triterpenoids and Phytosterols from Croton species.

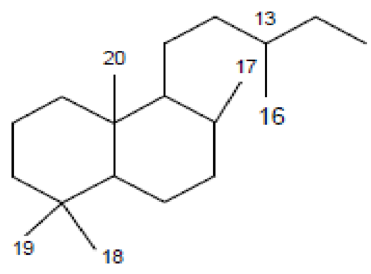
Clerodane (14)



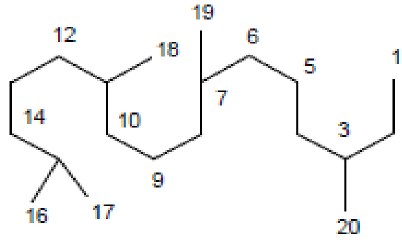
Halimane (15)



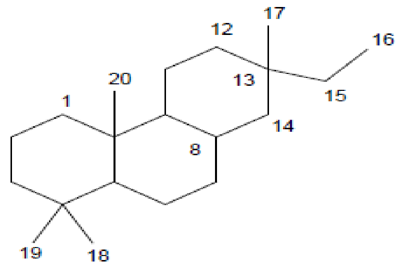
Labdane (16)



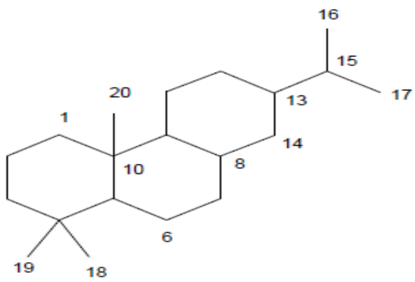
Phytane (17)



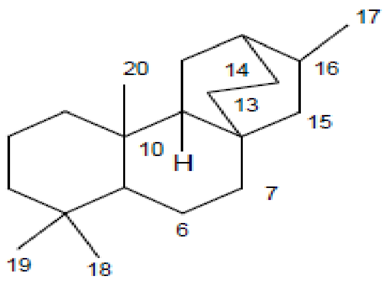
Pimarane (18)



Abiatane (19)



Atisane (20)



Kaurane (21)

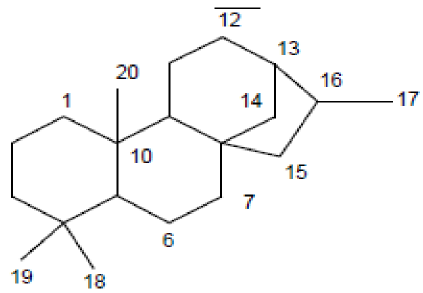


Figure 3: Carbon skeletons of diterpenoids from Croton genus.

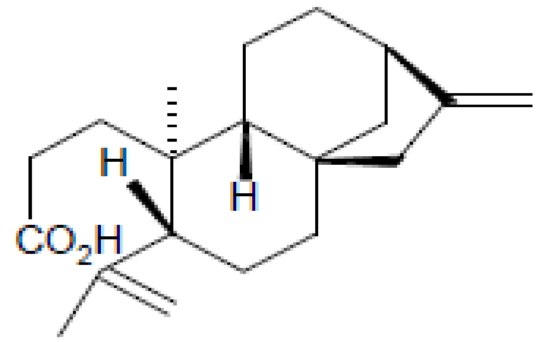
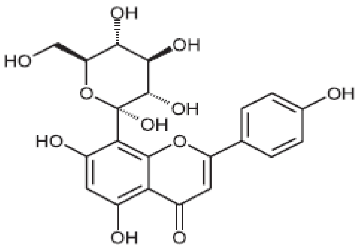
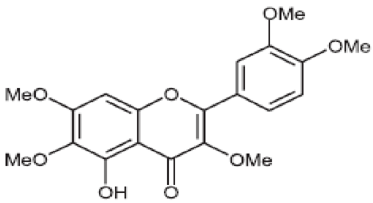


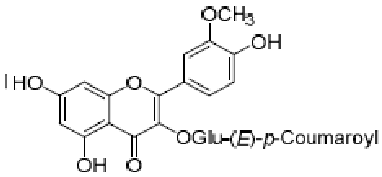
Figure 4: Geayine kaurane diterpenoid.



62. Vitexin



63. Artemetin



64.Helichrysoside-30-methylether

Figure 5: Some isolated flavonoids from Croton species.

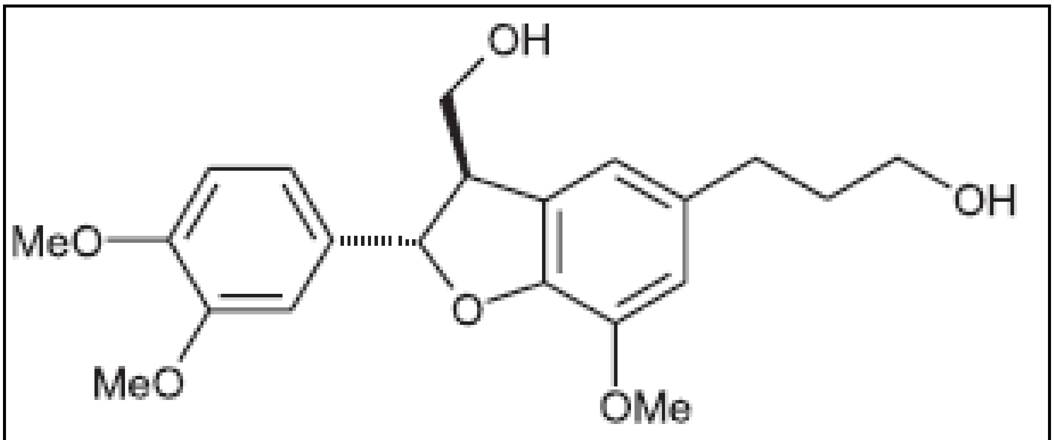
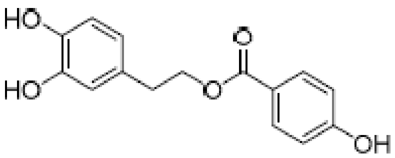
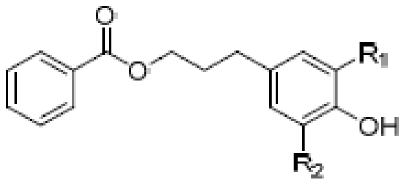


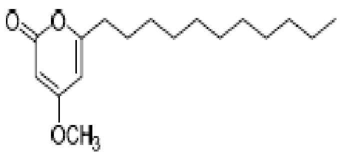
Figure 6: (65) 3,4-O-dimethylcedrusin.



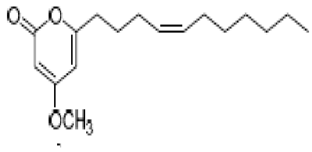
(66) 2-(3',4-dihydroxy phenyl)-ethyl-4-hydroxy benzoate



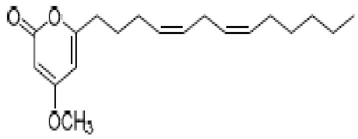
(67) 3- hydroxy-3,5-dimethoxyphenyl) propyl benzoate
(R1=R2=OCH3)
(68)3- (4-hydroxyphenyl) propylbenzoate
(R1=R2=H)



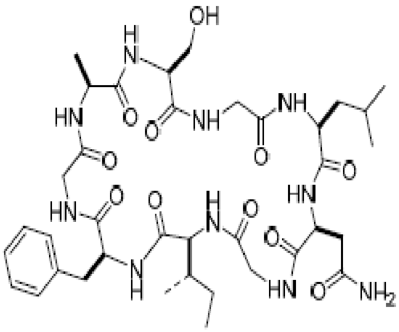
(69) Crotonpyrone A



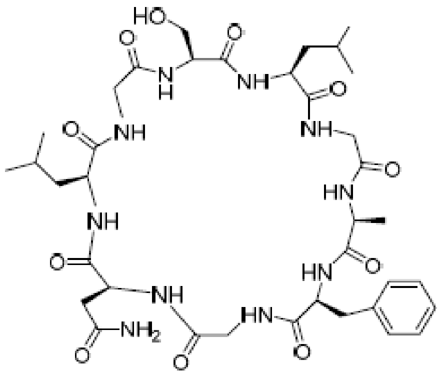
(70) Crotonpyrone B



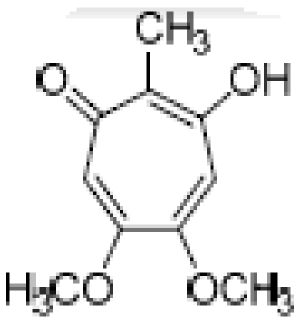
(71) Crotonpyrone C



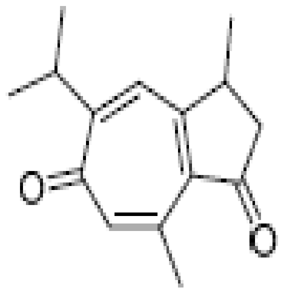
(72) Crotogossamide



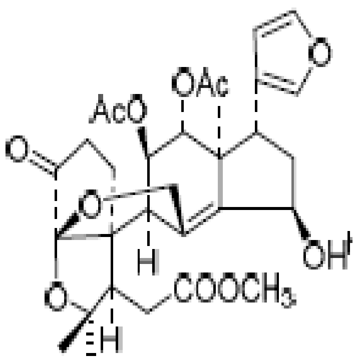
(73)[1-9-NαC]-crourorb A1



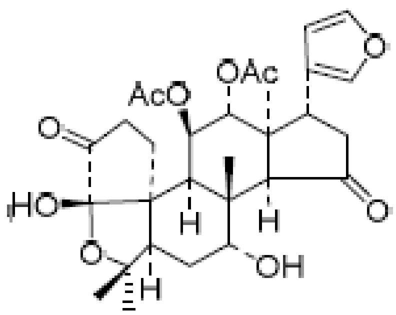
(74) Crototropone



(75) Pernambucone

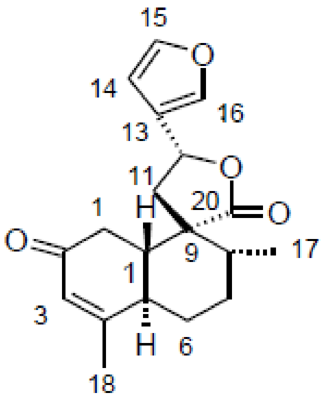


(76) Musidunin

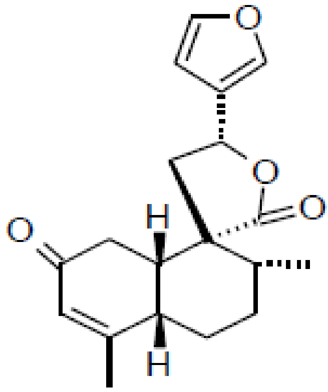


(77) Musiduol

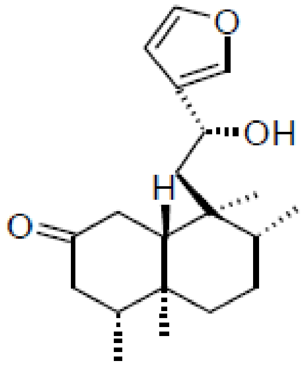
Figure 7: Benzoate derivatives, pyran-2-One derivatives, cyclic peptides, tropone derivatives, and limonoids



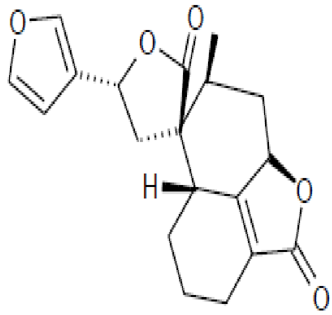
22



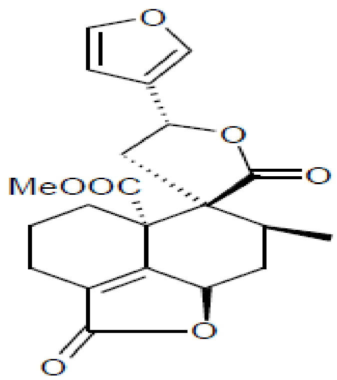
23



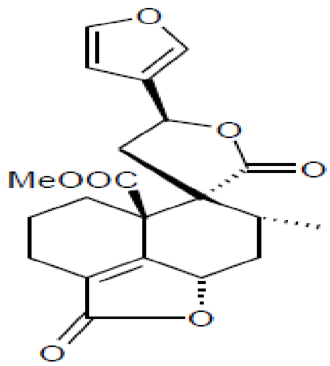
24



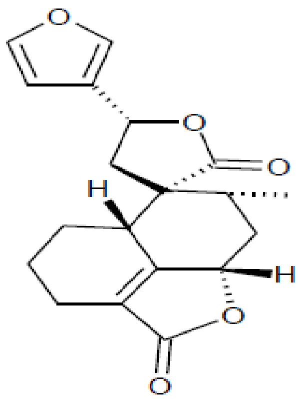
25



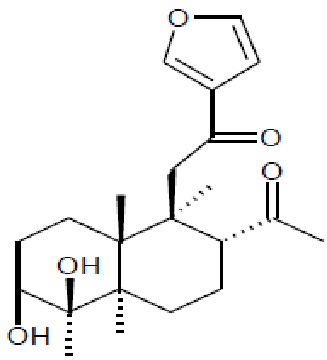
26



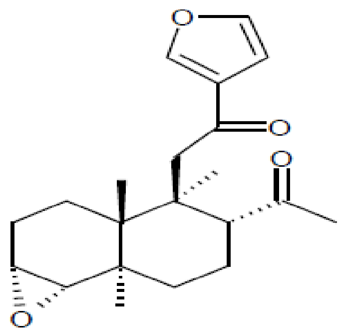
27



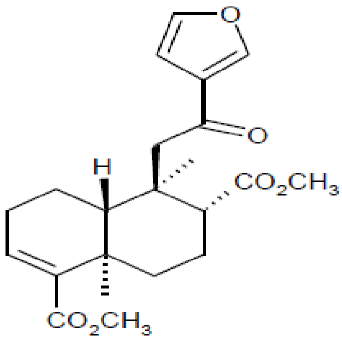
28



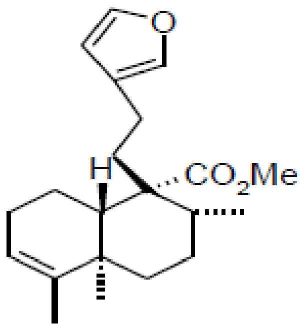
29



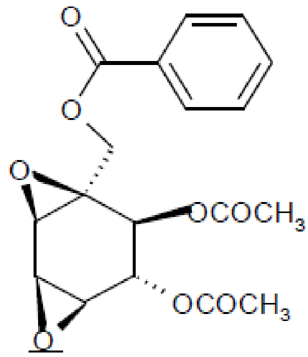
30



31



32



33

Figure 4: Clerodane diterpenoids from Croton species.

Table 1: Alkaloids from the genus Croton.

Compound Name	M. Formula	Source
Crotamide A (1)	C36H65NO	*C. sparsiflorus*
Crotamide B (2)	C38H69NO	*C. sparsiflorus*
Crotonine (3)	C12H14N2O4	*C. tiglium*
Crotonimide A (4)	C16H20N2O3	*C. pullei*
Crotsparsidine (5)	C17H17O3N	*C. sparsiflorus*
Crotonimide C. (6)	C20H20N2O3	*C. alienus*
6-Hydroxy-1-methyl-2-dimethyl-3,4-tetrahydro-b-carboline (7)	C14H19N2O	*C. heliotropiifolius*
N-trans-feruloyl-3,5-dihydroxyindolin-2-one (8)	C20H20N2O6	*C. echioides*

Table 2: Essential oils reported from some Croton species.

Source	Plant part	Essential oil	Ref.
C. aubrevillei	Dried stem bark	Monoterpenes (α-pinene, β-pinene, linalool (coriander oil and sesquiterpenes β-caryophyllene)	**[17]**
C. zambesicus	Leaves, root, and stem bark	Monoterpenes, Sesquiterpenes and Aliphatic compounds	**[6]**
C. stellulifer	Stem bark	Monoterpenes (α-phellandrene, α–pinene, ρ-cymene and linalool)	**[18]**
C. geayi	Dried aerial parts	Sesquiterpenes (caryophyllene oxide, β-caryophyllene, γ-cadinene and α-cadinene) and Monoterpenes.	**[19]**

Table 3: Clerodanes from theCroton genus and their reported biological activities.

Product	Source	Biological activity
trans-dehydrocrotonin, a nor-*ent* -clerodane diterpenoid (22) *cis*-dehydrocrotonin (23)	Amazonian *C. cajucara* (22) *C. schieddeanus* (22 and 23)	(both epimers can lower blood glucose and triglyceride in rats, Insect growth-inhibition, anti-inflammatory, anti-nociceptive (stops pain), anti-ulcerogenic (stops ulceration), anti-tumour against sarcoma 180 and Ehrlich carcinoma ascetic tumors in rats, cytotoxicity, and anti-genotoxicity
5β-hydroxy-cis-dehydrocrotonin (12R)-12-hydroxycascarillone (24)	*C. schieddeanus*	The ethanolic extract was found to decrease pressure and have avasorelaxant effect. (24) in addition to the flavonoids, 3, 7-dimethylquercetin, and again, had a synergistic role in the total vasodilator response induced by the plant
Isoteucvin (25) Jatropholdin (26) Teucvin derivative (27) Teucvin (28)	*C. jatrophoides*	Amoebicidal, have root development inhibition property and anti-feedant activity against the colorado potato beetle.
Chiromodine (29) Epoxy-chiromodine (30)	*C. metacarpus*	NA
Furano-clerodane, crotomembranafuran(31)	*C.membraneaceus*	NA
Clerodane diterpenoid (32)	*C. cajucara*	NA
Crotepoxide, Crotomacrine, Floridoline, Hardwickiic 12-Oxo-hardwickiic acid (33)	*C. macrostachys*	NA

Table 4: Some halimanes diterpenes from the genus Croton.

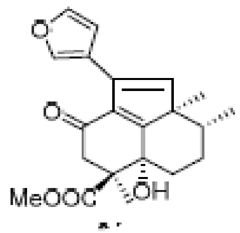
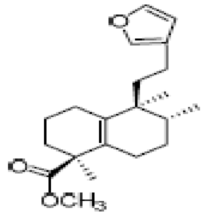
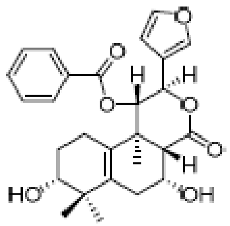
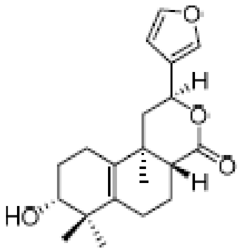
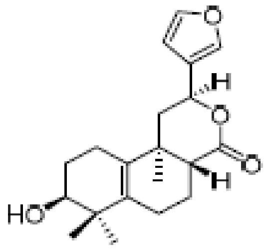
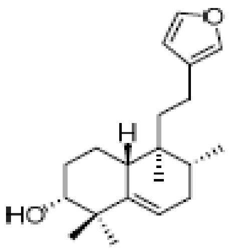
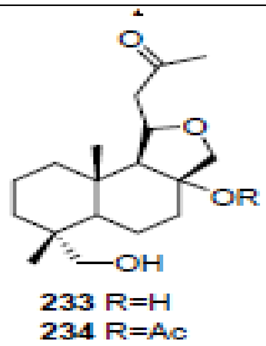
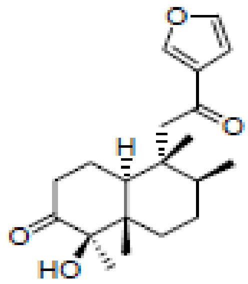
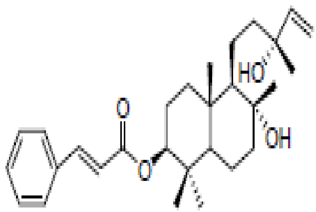
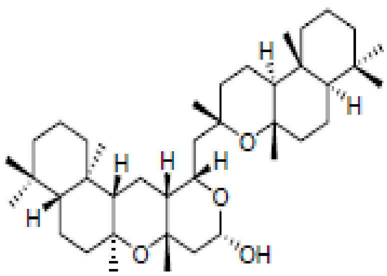
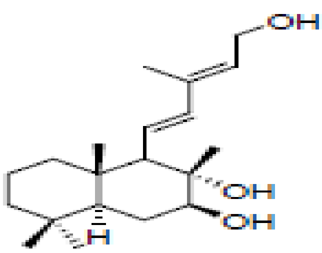
Compound Name	Source	Structure
Crassifoliusin A (34)	*C.crassifolius*	
Crotontomentosin F(35)	*C.caudatus*	
Crolaevinoid A (36)	*C.laevigatus*	
Crolaevinoid B (37)	*C. laevigatus*	
Crothalimene A (38)	*C.dichogamus*	
Crothalimene B (39)	*C.dichogamus*	

Table 5: Labdane diterpenoids from Croton species.

Name	Source	Chemical Structure
crotonlaevins A–B (40&41)	*C. laevigatus*	 **40 R=H** **41R=AC**
15,16-epoxy-4-hydroxy-labda-13(16),14-dien-3,12-dione (42)	*C. jacobinensis*	
Crotondecalvatin A (43)	*C. decalvatus*	
Bicrotonol A (44)	*C. crassifolius*	
Labdinine N (45)	*C. lari*	

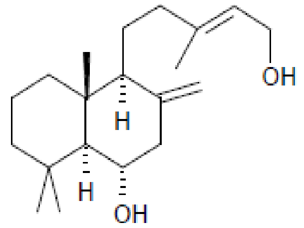
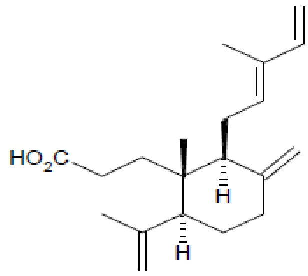
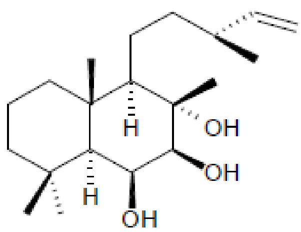
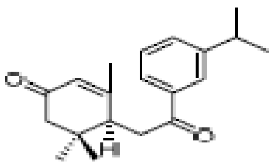
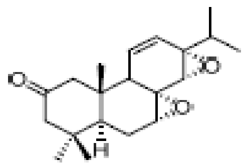
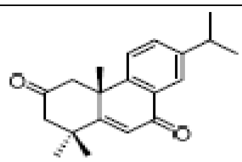
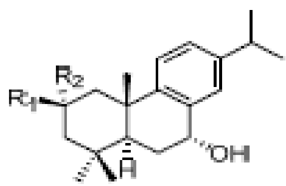
Crotonadiol(46)	*C. zambesicus*	
Maruvic acid(47)	*C. matureness*	
Crotomachlin (48)	*C. macrostachyus*	

Table 6: Abietane type diterpenoids from the genus Croton.

Product	Source	Chemical Structure
Crotontomentosin A (49)	*C. caudatus*	
Crotontomentosin B (50)		
Crotontomentosin D (51)		 296
Crotontomentosin C (52: R1=R2=O)		
Crotontomentosin E (53: R1=OAC, R2=H)		

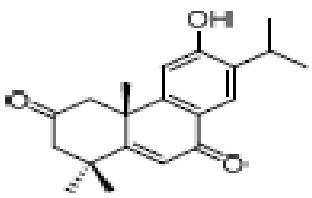
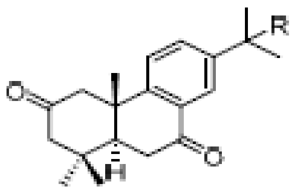
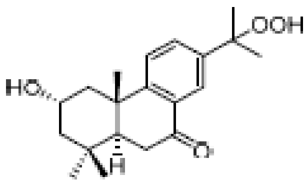
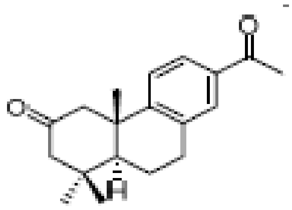
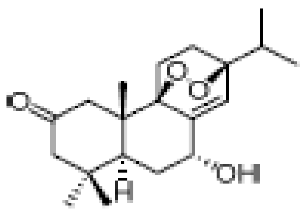
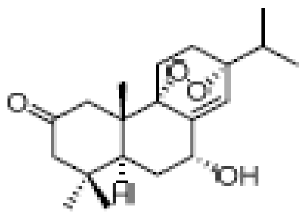
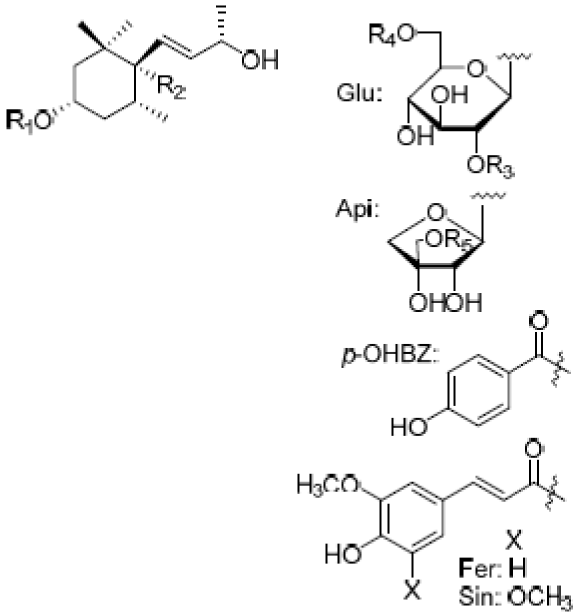
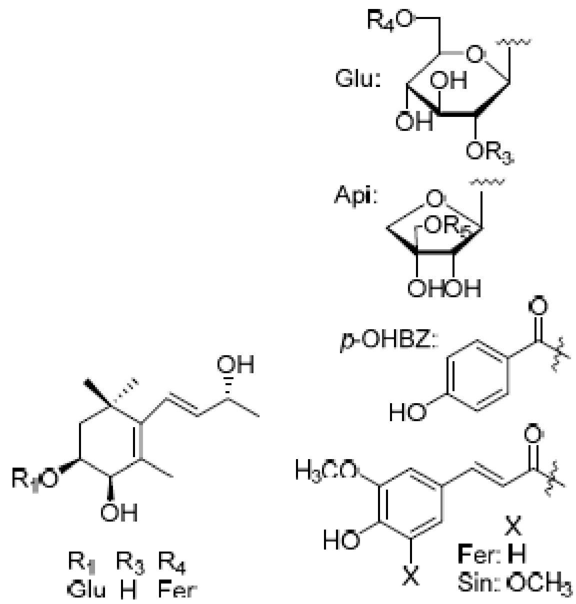
Crotolaevigatone A (54)	*C. laevigatus*	
Crotolaevigatone B (55: R= H)		
Crotolaevigatone C (56: R= OH)		
Crotolaevigatone D (57)		
Crotolaevigatone E (58)		
Crotolaevigatone F (59)		
Crotolaevigatone G (60)		

Table 7: Glycosides from the genus *Croton*.

Product	Chemical Structure
Crotonionosides A–F (78-83) R_1 R_2 R_3 R_4 R_5 Glu OH H Fer Glu OH H Sin Glu OH Api H H Glu OH Api H *p*-OHBZ Glu OH Api H Sin Glu H Api H	
Crotonionosides G (84)	

CONCLUSION

In the present review, we systematically summarized the chemical constituents of the genus *Croton*. Diterpenoids are characteristic components for *Croton* species. The diterpenoids with clerodane, tagline, karate, crotofolane, labdane, and membrane skeletons are the most studied diterpenoids isolated from *Croton* species to provide a better understanding of the chemical components from *Croton* species as future potential medicines.

REFERENCES

1. Mahbubur RA, Akter M: Taxonomy and Medicinal Use of Euphorbiaceae (Spurge) Family of Rajshahi, Bangladesh. Research in Plant Sciences, 2013; 3: 74-80. DOI: 10.12691/plant-1-3-5.
2. Caruzo A, Amp A, Cordeiro C: Taxonomic revision of Croton section Cleodora (Euphorbiaceae). Phytotaxa, 2013; 121(1): 1–2.
3. Rizk AF: The chemical constituents and economic plants of the Euphorbiaceae. Botanical Journal of the Linnean Society, 1987; 94: 293–326.
4. Ramírez G: Sangre de Drago Croton lechleri Muell. Arg. Natura Medicatrix, 2003; 21: 213-217.
5. A Review on Traditional and Pharmacological Uses of Croton bonplandianum with Special Reference to Phytochemical Aspe European Journal of Medicinal Plants, 2008; 1-10.
6. Boyom F, Keumedjio, F, Dongmo P, Ngadjui, B,

Zollo P, Block S, Baccelli C, Tinant B, Meervelt LV, RozenbergR, Jiwan JL, Llabrès G, Pauw-Gillet MC, Quentin- Leclercq J: Diterpenes from the leaves of Croton zambesicus. Phytochemistry, 2004; 65: 1165-1171.

7. Neto MA, Alencar JW, Cunha AN, Silveira, ER: Volatile Constituents of *Croton Lundianus* (F. Diedr.) MMuell. and *C. glandulosus* (L.) Muell. Journal EssentialOil Research, 1994; 6: 191–194.
8. Antonio S, Maria L. Faria S, Giuseppina N: Traditional uses, Chemistry and Pharmacology of Croton species (Euphorbiaceae). J. Braz. Chem. Soc, 2007; 18(1): 11-33.
9. Salatino A, Salatino MLF, Negri G: Traditional uses, Chemistry and Pharmacology of Croton species (Euphorbiaceae). J. Brazil. Chem. Soc, 2007; 18: 11-33.
10. Milanowski DJ, Winter RE, Elvin-Lewis MP, Lewis WH: Geographic distribution of three alkaloid chemotypes of *Croton lechleri* Journal of Natural Products 2002, 65, 814-819.
11. Xu WH, Liu WY, Liang Q: Chemical Constituents from Croton Species and Their Biological Activities. Molecules 2018, 23, 2333; doi:10.3390/molecules23092333.
12. Palmeira JS, Conserva L, Silveira E: Two clerodanes diterpenes and flavonoids from Croton brasiliensis. J Braz Chem Soc, 2005; 16: 1420-1424
13. Ndunda, B. Phytochemistry and bioactivity investigations of three Kenyan croton species. 2014. Ph.D. Thesis, University of Nairobi, Nairobi Kenya.
14. Wu JH, Leah E Cahill, Mozaffarian D. Effect of Fish Oil on Circulating Adiponectin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Endocrinol Metab, 2013; 98(6): 2451–2459. DOI: 10.1210/jc.2012-3899
15. Mazzanti, G, Bolle P, Martinoli, L, Piccinelli, D, Grgurina, I, Animati F, Mugne Y: Croton macrostachys, a Plant used in Traditional Medicine: Purgative and Inflammatory Activity, 1987; 19: 213-219.
16. Ojokuku SA, Odesanmi OS, Magbagbeola OA: The effects of Oral Administration of Croton penduliflorus Seed Oil and Medroxy Progesterone Acetate on Fasting Blood Sugar, Lipid and Haematology of Pregnant Rabbits, International Journal of Tropical Medicine, 2011; 6(2): 35-38.
17. Menut C, Lamaty G, Bessiere JM., Seuleiman AM, Fendero P, Maidou, E., Denamganii, J: Aromatic plants of tropical Central Africa. XXII. Volatile constituents of Croton aubrevillei J. Leonard and C. zambesicus Muell. Arg. Journal of Essential Oil Research. 1995, 7: 419-422.
18. Martins AP, Salgueiro LR., Goncalves MJ, Vila R, Tomii F, Adzet T, da Cunha AP, Configural S, Casanova J: Antimicrobial Activity and Chemical Composition of theBark Oil of Croton stellulifer, an Endemic Species from Sao Tome Principe., Planta Medica, 2000; 66(7): 647–650.
19. Radulovic N, Mananjarasoa E, Harinantenaina L, Yoshinori A.: Essential oil composition of four Croton species from Madagascar and their Chemotaxonomy. Biochemical Systematics and Ecology, 2006; 34: 648 –653.
20. Maciel MA., Pinto AC, Kaiser CR. Natural and semi- synthetic clerodanes of Croton cajucara and their cytotoxic effects against Ehrlich carcinoma and human K562 leukemia cells Magn. Reson.Chem, 2003; 41: 278.
21. Li R, Morris-Nitschke SL, Lee, K.H: Clerodane diterpenes: Sources, structures, and biological activities.,Nat. Prod. Rep, 2016; 33: 1166–1226.
22. Nardi GM., Felippi R, DalBó S, Siqueira-Junior JM, Arruda DC, Delle Monache F, Ribeiro-do-Valle, R.M: Anti-inflammatory and antioxidant effects of Croton celtidifolius bark. Phytomedicine, 2003; 10: 176-184.
23. Roengsumran S, Pornpakakul S, Muangsin N, Sangvanich P, Nhujak T, Singtothong P, Chaichit N, Puthong S, Petsom A: New halimane diterpenoids fromCroton oblongifolius. Planta Medica, 2004; 70: 87-89.
24. Ngadjui BT, Folefoc GG, Keumedjio F, Dongo E, Sondengam BL, Connolly JD: Crotonadiol, a labdane diterpenoid from the stem bark of Croton zambesicus.Phytochemistry, 1999; 51: 171-174.
25. Tene M, Ndontsa BL, Tane P, Tamokou JD: Antimicrobial diterpenoids and triterpenoids from the stem bark of Croton macrostachys. International Journal of Biological and Chemical Sciences, 2009; 3(3): 538–544.
26. Kuo PC, Shen, YC, Yang ML, Wang SH, Thang TD, Dung WX, Chiang PC, Lee KH, Lee, EJ, Wu TS: Crotonkinins A and B and related Diterpenoids from Croton tonkinensis as anti-inflammatory and anti-tumor agents. Journal of Natural Products, 2007; 70: 1906–1909.
27. Roengsumran, S.; Pata, P.; Ruengraweewat, N.; Tummatorn, J.; Pornpakakul, S.; Sangvanich, P.; Puthong, S Petsom, A. New cleistanthane diterpenoids and 3,4-sec-cleistanthane diterpenoids from Croton oblongifolius. Chem. Nat. Compd, 2009; 45: 641–64.
28. Kubo I, Hanke, FJ, Asaka, Y, Matsumoto T: Insect Anti-feedant from tropical plants I. Structure of domain.Tetrahedron, 1990; 46: 1515–1522.
29. Nihei K., Asaka Y, Mine Y, Ito C, Furukawa, H., Ju-Ichi, M., Kubo I: Insect Anti-feedants from Tropical Plants: Structures of domain and dumsenin. Journal of Agricultural Food Chemistry, 2004; 52: 3325–3328.
30. Nihei K, Asaka Y, Mine Y, Yamada Y, Iigo M., Yanagisawa T: Musidunin and musical, insect antifeedants from Croton jatrophoides. J. Nat. Prod, 2006; 69: 975–977.