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A Review of Ethnomedicinal Uses, Phytochemistry and Pharmacology of Nigerian *Crotons*

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Authors' contributions

This work was carried out in collaboration between all authors. Author AHA managed literature search of the manuscript. Author AMA managed production of manuscript under supervision of author SMI. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Approximately 80% of the world's population relies on traditional plants to produce and synthesize contemporary medications. In the past, the production of plants as sources of pharmaceuticals or medicines for wound healing and treatment was based on superstition and experience that was passed down from one generation to the next. The majority of these plants belong to the families Euphorbiaceae, Leguminoceae, Rutaceae, and Piperaceae. The Euphorbiaceae family includes *Croton* plants. They are found in tropical and sub-tropical areas of both hemispheres and comprise of 1,300 species of trees, shrubs, and herbs. This work is a critical review of chemical constituents,

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ethnomedicinal, phytochemistry and pharmacology of various Nigerian *Croton* species. The term "ethnomedicinal potentials" refers to the therapeutic applications of plants that have positive pharmacological effects on both human and animal bodies. Prior to the development of modern medicine, certain *Croton* species were used to cure rheumatism, diabetes, diarrhea, cancer, and other illnesses. Active alkaloids are abundant in the *Croton* genus. In addition to triterpenoids, flavonoids, sesquiterpenoids, phytosterols, N-containing chemicals, cyclohexane derivatives, aliphatic molecules, ferulic acid ester derivatives and diterpenoids are said to be widely distributed throughout the African *Crotons*.

Keywords: Croton; Nigeria; phytochemistry; euphorbiaceae; African; traditional.

1. INTRODUCTION

Approximately around 80% of the world's population used medicinal plants to produce and synthesize contemporary medications. In the past, production of plants as sources of medications for wound healing and treatment was based on superstition and experience that were passed from generation to generation, essentially through word of mouth (Folkloric) (Sofowora, 1993). The majority of these plants belong to the families *Euphorbiaceae, Leguminoceae, Rutaceae*, and *Piperaceae*. The *Euphorbiaceae* family comprises of *Croton* plants. They are found in tropical and sub-tropical environments of both hemispheres and comprise of about 1,300 species of trees, shrubs, and herbs (Salatino et al. 2007). There are approximately 292 species of *Croton* in Africa, and eleven (11) of them are found in Nigeria. *Croton hirtus* was recently discovered in Nigeria, Sierra Leone, Cote d'Ivoire, Republic of Congo and Gabon. Around the world, C*roton* species are applicable to treat a variety of conditions including cancer, diarrhea, intestinal worms, discomfort, ulcers, and weight loss (Salatino et al. 2007; Koutchiko et al. 2022; Isyaka, 2020). The term "ethnomedicinal potentials" refers to the therapeutic applications of plants that possess positive pharmacological effects on both human and animals. Prior to the development of modern medicine, certain *croton* species were used to treats rheumatism, diabetes, cancer, and other illnesses (Amaral and Barnes, 1998). Antihypertensive, antimalarial, antimicrobial, and myo-relaxant are some other actions of *Croton* isolates that have been determined (Salatino et al. 2007). Active alkaloids are abundant in the *Croton* genus (Amaral and Barnes, 1998; Birhanu, 2021). In addition to triterpenoids, flavonoids, sesquiterpenoids, phytosterols, N-containing chemicals, cyclohexane derivatives, aliphatic molecules, and ferulic acid ester derivatives, diterpenoids are said to be widely distributed throughout the African *Croton* (Isyaka, 2020).

2. ETHNOMEDICINAL PROPERTIES AND GEOGRAPHICAL REPRESENTATION OF *CROTONS* GENUS IN NIGERIA

African traditional healers have traditionally used medicinal plants as permanent supply to cure a number of severe diseases (Segla et al. 2022). In Africa, South Asia, and Latin America, *Croton* species have long been used to cure a variety of infections and digestive issues (Wu and Zhao, 2004; Xu et al. 2018; Mahmoud et al. 2020). The detailed discussion of the various *Croton* species are as follows;

2.1 *Croton gratissimus* Burch

This plant is indigenous to central and tropical West Africa. Senegal, Sudan, Botswana, and South Africa are among its locations (Njoya et al. 2018; The Ferns, 2014). Freestyle and sub-freestyle are its two divisions (Isyaka, 2020). Sub *gratissimus* differs from *gratissimus* in that it has stellate hairs on the upper leaf surface, whereas *gratissimus* does not. They can be found in South Africa's far north, Zimbabwe, and Botswana (Isyaka, 2020). It is used by the indigenous community as essential oil, food flavoring, and medicine (The Ferns, 2014). Malaria is treated with an infusion made from bark slashes. Bleeding gums are treated with the burned and powdered bark (The Ferns, 2014). Soup created from a leaf decoction is used as a wash to cure headaches, fever, and diarrhea (Burkil, 2004). The shoots are used as a febrifuge, tonic, and to ease menstruation pain. Additionally, the root is employed as an aperient (Burkil, 2004). Its bark extract has long been used as a styptic, cathartic, and treatment for a variety of ailments, pleurisy, uterine disorders, and intercostal neuralgia (Palgrave, 2002). Because of their fantastic aroma, its young

branches are dried and ground into powder for use in perfume industries (Palgrave, 2002).

2.2 *Croton* gratissimus VAR. Gratissimus

The Republic of Congo and South Africa are home to this species of *Croton* (Burkil, 2004). The plant material was gathered from Nigeria, which is said to be the primary location for *Croton zambesicusis,* its used in treatment of conditions such as malaria, hypertension, diabetes, arthritis and urinary tract infection (Ndhlala et al. 2013).

2.3 *Croton hirtus* L'Her., Stirp

The annual herb *Croton hirtus* L'Her., Stirp. reaches a height of approximately 60 cm (Burkil, 2004). It is famous across the West Indies and tropical America, has recently been documented in Nigeria, Sierra Leone, Cote d'voire, and Benin, and is now naturalized throughout the tropics, its used in treatment of various conditions such as diabetes, inflammatory conditions, cancers and pyreticosis (Koutchiko et al. 2022; Isyaka, 2020; Ezeabara and Okonkwo, 2016).

2.4 *Croton lobatus* (L.)

The base of this annual herbaceous plant turns woody. Senegal, Gambia, Guinea Bissau, and Nigeria are among their environments (Burkil, 2004). It is referred to as "gaasayaa" in Hausa, "ajekofole" in Yoruba, and "Okwe-one" in Igbo. Traditionally, the boiled leaves are injected as a therapy for gynecological infections. When combined with palm oil, the leaves are applied topically to rheumatism and coastal discomfort. As a purgative, the leaf and bark infusion is administered orally or by injection (Burkil, 2004). In Nigeria, it is used to lessen scorpion sting agony. They are used to treat headaches, skin conditions, and ulcers. In Togo (Prota), the leaf sap is applied as an eye drop. In the event of an abortion or hiccup, the flower and root decoction is given as an antispasmodic (Prota). A leaf infusion is used to alleviate fever, and when combined with honey and palm oil, it can be applied topically on stiff limbs (Prota) (Burkil, 2004).

2.5 *Croton macrostachyus* (Hoscht.)

Locally it is named as ‘Bisana’, in Amharic; ‘Bakkaniisa’, in Afan Oromo and popularly referred to as ‘Rush slide’ in English (Abdisa, 2019). In the tropics, it is the most dominant plant (Käppeli et al. 2011). It is a medium-sized deciduous tree that is indigenous to Ethiopia, Eretria, Kenya and Nigeria (Karmali et al. 2010). In addition, it is found in Liberia, Malawi, Zambia, and Zimbabwe. Moreover, Congo (DR) and Angola are home to it infrequently (Isyaka, 2020; JSTOR, 2019). The bark, fruits, leaves, roots, and seeds of *Croton macrostachyus* are said to have a variety of medicinal qualities and are used as herbal remedies for at least 61 illnesses and ailments (Abdisa, 2019). Blood clots, cancer, constipation, diarrhea, epilepsy, malaria, stomach discomfort, typhoid and wounds are among the conditions for which it has a long medicinal application (Abdisa, 2019; Khameneh et al. 2016). Crushed leaves of *Croton macrostachyus* are used to treat hemorrhoids, and the shoots are used to treat fever and edema. Its stem bark is macerated and used as a uterotonic to discharge retained placenta and as an abortifacient (LeJeune et al. 2001). A decoction, infusion, or maceration of its leaves, root bark, and stem bark is used as a vermifuge and purgative throughout Madagascar and tropical Africa (Isyaka, 2020; Mazzanti, 1987). To prevent bloating, its powdered roots are consumed with milk (Isyaka, 2020). Ethiopian indigenous people compress the roots and fruits to make a water infusion that is used to treat venereal infections (Isyaka, 2020; Tefera et al. 2012). The Nandi and Kikuyu community of Kenya utilized the leaf juice to heal wounds and the root and leaf decoctions to treat malaria (Isyaka, 2020; Jeruto et al. 2011). The plant's decoction, which is made from several parts, is used to cure female infertility, constipation, and stomachaches. An infusion of the bark is used to cure rheumatism and chest issues in East Africa (Isyaka, 2020; Tane et al. 2004).

2.6 *Croton membranaceus* Müll. Arg

West tropical African countries including Ghana, Cote d'Ivoire, and Nigeria are home to this perennial plant (Isyaka, 2020; The Ferns, 2014). Urinary retention brought on by measles and an enlarged prostate can be cured with its root bark (The Ferns, 2014). The herb is used as a treatment for a number of gastrointestinal issues by the Yoruba people of Nigeria (Isyaka, 2020; Adesogan, 1981).

2.7 *Croton* nigritanus

The shrub *Croton nigritanus* can reach a height of three meters (Burkil, 2004). Senegal, Benin, Guinea, Nigeria, and west tropical Africa are among its locations (The Ferns, 2014). In the past, the plant was reportedly collected from the wild and used to make regional medicines. In

Sierra Leone's Scarcies River region, the herb is applied as a compress to wounds (Burkil, 2004).

2.8 *Croton* Penduliflorus Hutch

It resembles a spreading-crowned tree. West tropical Africa, including Gabon, Nigeria, Sierra Leone, and the Central African Republic, are homes to it (The Ferns, 2014). In Ghana, the leaf infusion is used to treat fever, while in Cote d'Ivoire, it is used to treat menstruation abnormalities (The Ferns, 2014). Its seeds contain oil that is used as a purgative (Prota). The seed extract is used to treat gastrointestinal issues and uterine cancers in Nigeria (Isyaka, 2020; Adesogan, 1981).

2.9 *Croton* Pseudopulchellus Pax

East Kenya, Cote d'Ivoire, Burkina Fasso, Nigeria, and Ethiopia are the primary locations for this *Croton* genus in tropical Africa (Isyaka, 2020; The Ferns, 2014). The leaves are traditionally applied to the chest as a medicine for chest ailments and used as a treatment for ulcers (Burkil, 2004). The decoction of the roots is used to treat asthma. To treat a head cold, the powdered root is consumed as snuff (Burkil, 2004). Burning *Croton pseudopulchellusis* and using the smoke to flavor fresh milk is a common condiment in Kenya's coastal regions (Pakia et al. 2003). Additionally, it is utilized to treat tussive and viral infections (Isyaka, 2020; Prozescy et al. 2001). In South Africa's central and southern regions, this *Croton* species is used to treat TB symptoms like fever, coughing, and blood in sputum (Njoya et al. 2018; Lall and Meyer, 1991).

2.10 *Croton* Sylvaticus (Hochst.)

Tropical regions of Africa, including, Tanzania, and Kenya, are home to this ornamental tree, which grows quickly (The Ferns, 2014). Guinea and southern Nigeria are usual places to find it (Isyaka, 2020). Traditional remedies for TB, fever, digestive issues, and stomach pain in Tanzania and Kenya include decoctions of leaves and root bark (Njoya et al. 2018). Additionally, it is used as a purgative to reduce inflammation and as a malaria wash (Kapingu et al. 2012). Elephantiasis is treated with *Croton sylvaticus* wood shavings (Burkil, 2004). Ear infections are treated with the juice of young leaves (The Ferns, 2014). Rheumatism, gastrointestinal disorders, dropsy, and uterine issues are all treated with the bark decoction (The Ferns, 2014). On swellings, the ground roots are applied as a poultice (Kapingu et al. 2012). To relieve excruciating stomachaches, the ground bark is soaked in milk (Isyaka, 2020). In Gazaland (present-day Zimbabwe and Mozambique), the bark powder is also used as a fish poison and applied topically on scarifications to alleviate rheumatism, chest pains, and inflammation (Isyaka, 2020). Additionally, cattle gall-sickness is treated with the powdered bark (Watt and Breyer-Brandwijk, 1962). The root is used to cure pleurisy and as a therapy for indigestion. Malaria is also treated with several plant parts (Isyaka, 2020; Beentje, 1994).

2.11 *Croton zambesicus* Mull. Arg

Sierra Leone, Mali, Dahomey, Niger, Gambia, and Nigeria are home to these shrubs or tiny trees (Burkil, 2004). In Sierra Leone and Nigeria, *Croton zambesicus* is used as a traditional medicine for a variety of purposes. The roots are used as an aperient, and the leaf decoction is used as a fever wash. Convulsions and dysentery are treated internally with it (Isyaka, 2020). In Benin, the leaf decoction is also used to treat urinary tract infections and lower blood pressure (Okokon et al. 2005). The Ibibios of Nigeria utilize the root as an antidiabetic and antimalarial, while the Sudanese use it to relieve menstrual pain (Isyaka, 2020; Okokon et al. 2005; El-hamidi, 1970).

2.12 Phytochemistry and Pharmacology of Nigerian *Crotons*

Many research work has been carried out on various species of *Croton* plants which yields the isolation of terpenoid, diterpenoids, triterpenoids, non-terpenoid such as alkaloids, flavonoids, lignans (Rosandy et al. 2018). Isolation of megastigmane glycosides (Kawakami et al. 2011). Phytochemical analysis of the leaves and stems of *C. gratissimus* revealed the presence of alkaloids, amino acids, phenolic compounds, flavonoids, carbohydrates, terpenoids, saponins and fixed oils and fats (Naidoo, 2018). *Croton gratissimus burch* was reported to predominantly yielded cembrane diterpenoids including a new cyclo-cembranoid skeleton (1) (Langat et al. 2011). α-Glutinol(2), lupeol (3), eudesm-4(15)-ene-1β,6α-diol (4) and 24-ethylcholesta-4,22-dien-3-one (5) have also been reported from *C. gratissimus* (Mahmoud et al. 2020; Langat et al. 2011). Isolated flavonoids (6–11), 3-methoxy-4-hydroxybenzoic acid (12), and benzyltetrahydroisoquinoline alkaloids laudanine (13) and laudanosine (14) from C. *gratissimus* (Canelo et al. 2017). Isolated fourteen compounds such as caryophyllene oxide (15),

1β-methoxycaryolan-9β-ol (16), kaur-16-en-19-oic acid (17), *cis*-ozic acid (18), spathulenol (19), lupeol (3), 7δ-methoxyopposit-4(15)- en-1β-ol (20), germacra-4(15),5,10(14)-trien-1β-ol (21), β-sitosterol (22), *ent*-kaur-16-en-18-ol (23), 15-methoxy-*neo*-clerodan-3,13-dien-16,15-olide-18-oic acid (24), 6α-methoxyeudesm-4(15)-en-1β-ol (25), sucrose (26) and N-methyl-*trans*-4-hydroxy-L-proline (27) from *Croton gratissimus* (Canelo et al. 2017; Langat et al. 2008). Also reported the presence of (−)-(1*R**,4*R**,10*R**)-4-methoxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide(28), (−)-(1*S**,4*R**,10*R**)-1-hydroxy-4-methoxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide(29), (−)-(1*S**,4*S**,10*R**)-1,4-dihydroxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide(30), (−)-(1*S**,4*S**,10*R**)-1,4-dihydroxycembra-2*E*,7*E*,11*Z*-trien-20,10-olide(31), (+)-(10*R**)-cembra-1*E*,3*E*,7*E*,11*Z*,16-pentaen-20,10-olide(32), (+)-(10*R**)-cembra-1*Z*,3*Z*,7*E*,11*Z*,15-pentaen-20,10-olide(33), (+)-(5*R**,10*R**)-5-methoxycembra-1*E*,3*E*,7*E*,11*Z*,15-pentaen-20,10-olide(34), (+)-(1*S**,4*S**,7R*,10*R**)-1,4,7-trihydroxycembra-2*E*,8(19),11*Z*-trien-20,10-olide (35), (−)-(1*S**,4*S**,7*S**,10*R**)-1,4,7-trihydroxycembra-2*E*,8(19),11*Z*-trien-20,10-olide (36) and (+)-(1*S**,4*R**,8*S**,10*R**)-1,4,8-trihydroxycembra-2*E*,6*E*,11*Z*-trien-20,10-olide (37) in the leaves of C. *gratissimus*. Four flavonoids, kaempferol (38), isovitexin (39), helichryroside-3-methyl ether (40) and tiliroside (41) was found in the leaf extract of *C. gratissimus* var. *gratissimus* (Ashwell et al. 2013). *Croton gratissimus var. sub gratissimus* was reported to contain α-phellandrene (42), germacrene D (43), and 1,8-cineole (44) and contains antimicrobial property (VanVuuren, 2007; Lawal et al. 2017). In *Croton gratissimus var. gratissimus*, the hexane, ethyl acetate, butanol and 20% aqueous methanol extracts showed weak antioxidant capacity and acetyl cholinesterase (AChE) inhibitory effects (Isyaka, 2020; Ndhlala et al. 2013).

Croton hirtus L. found in Costa Rica are reported to have bisnor-[15-16]-13α- hydroxy-2-oxodolabra-1(10)-3-diene (45), 15,16-dihydroxy-2-oxodolabradan-3-ene (46), 16- hydroxy-2,15-dioxodolabradan-3-ene (47), twelve kaurane diterpenoids;16α,17-dihydroxy-7- oxokaurane (48), 6β,16α,17-trihydroxy-7-oxokaurane (49), 3α,16α,17-trihydroxy-7- oxokaurane (50), 3α,6β,16α,17-tetrahydroxy-7-oxokaurane (51), including two cyclopropakauranes, 7β,11β,16α,17-tetrahydroxycyclo-[3,18]-kaurane (52), 16α,17- dihydroxy-7-oxocyclo-[3,18]-kaurane (53), the hirtusanes, 16α,17-dihydroxy-7-oxohirtusan- 3-ene (54), 16α,17-dihydroxy-7-oxohirtusan-3,5-diene (55), 3β,4β-epoxy-16α,17-dihydroxy-7-oxohirtusan-5-ene (56), 3α,4α-epoxy-16α,17-dihydroxy-7-oxohirtusan-5-ene (57), 3β-H-16α,17-dihydroxy-7-oxohirtusan-4(19)-ene (58), 3β,16α,17-trihydroxy-7-oxohirtusan-4(19)- ene (59), five germacradiene esters, 6β,8α-dihydroxy-8-*O*-benzoylgermacra-1(10)-*Z*,4*E*-dien-14-oic acid (60), 6β,8α-dihydroxy-6-*O*-acetyl-8-*O*-benzoylgermacra-1(10)-*Z*,4*E*-dien-14-oic acid (61), 6β,8α-dihydroxy-8-*O*-benzoylgermacra-1(10)*E*,4*E*-diene (62), 6β,8α-dihydroxy-6- *O*-acetyl-8-*O*-benzoyleleman-1(2),3(4)-dien-14-oic acid (63), 6β,8α-dihydroxy-8-*O*-benzoyleleman-1(2),3(4)-dien-14-carboxyl-γ-lactone (64) (Rosandy et al. 2018). Isolated (-)-5,8-dihydroxyjatrophan-3-one (65) and (+)-14,16,17- trihydoxykauran-1-one (66) from the root of *Croton hirtus* occurring in Malaysia. The main compounds found in the oil of the leaves from Croton *hirtus* collected at Simões were spathulenol (19), E-caryophyllene (67), bicyclogermacrene (68), α-cadinol (69) and cubenol (70) (De Lima et al., 2012). Dihydro-β-ionol-*O*-[arabinosil (1-6) glucoside](71), dihydro-β-ionol-*O*-[arabinosel(1→6) glucoside] (72), β-sitosterol (22) and isorhamnetin-3-*O*-rutinoside (73) was recently isolated (Dall'Acqua et al. 2021). The essential oil of *Croton hirtus* of Ivory Coast shows the presence of terpene derivatives, monoterpenes and sesquiterpenes (Daouda et al. 2014). The toxicity of the essential oils found in *Croton hirtus*, showed 50% lethal concentration. *C*. *hirtus* extract prevents NO-mediated inflammation by suppressingNF-κB and inflammatory cytokines. The methanolic extracts presented the highest 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,20-azino-bis(3-ethylbenzothiazoline)-6-sulfonic acid (ABTS), and ferric reducing antioxidant power (FRAP) values (De Lima et al., 2012; Dall'Acqua et al. 2021; Kim et al. 2020). Its water, methanol and ethyl acetate extracts exhibited inhibitory effects on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), with a higher activity observed for dichloromethane, while the methanol extract showed the highest impact against *tyrosinase* (Dall'Acqua et al. 2021).

Brazilian sample of *Croton lobatus* was reported to contain tertiary and quaternary alkaloids and hemolytic saponins (Farnsworth et al. 1969; Willaman and Li 1970). Compounds such as diterpenes; geranylgeraniol (74), triglyceride lobaricide (75) and triterpenes; betulinic acid (76) have been isolated from the stems and leaves of *Croton lobatus* (Prota). In *Croton lobatus*, betulinic acid (76) is said to be a potent HIV-1

antiviral compound and research have showed that *Croton lobatus* inhibits the growth of plasmodium falciparum and geranylgeraniol (74) induces opoptosis in leukemia cell lines activity against strains that are sensitive to chloroquine as well as resistant ones (Prota), it is said to contain higher amount of anti-oxidant phytochemicals (Fasola et al. 2016). Its methanol leaf extracts retards arteriogenic risk factors therefore it can be used as herbal therapy for the treatment of diabetes mellitus and associated cardiovascular complication (Fasola et al. 2016). The ethanol leaf extracts of *Croton lobatus* shows the gastro-protective potential in albino rats (Ezugwu et al. 2018). Aqueous leaf extract of *C. lobatus*aids in the prevention of threatened abortion, management of pregnancyand infertility (Enohor and Oshomoh, 2020). Tannins, triterpenoids, and saponin are reported to be responsible for its antimicrobial activity (Kilani et al. 2019). *Croton lobatus* leaf extracts could be used in diabetes and gout treatments, based on the antioxidant results of a-amylase inhibition and xanthine oxidase (Chodaton-Zinsou et al. 2020). Methanol leaf extract of *Croton lobatus* possesses significant analgesic and anti-inflammatory activities (Anafi et al. 2017).

Croton macrostachyus is rich in terpenoids (diterpenoids and triterpenoids) and essential oils that contain monoterpenoids, sesquiterpenoids, and some shikimate-derived compounds. Previous studies showed the existence of crotin (a chalcone) (77), lupeol (3) (a triterpene), crotepoxide (78) (a cyclohexanediepoxide), proteins, fatty acids, saponins, resins and alkaloids (Carlet et al. 2012). Some of the compounds isolated from *C. macrostachyus* include crotomacrine (79), halim-5,10-en-19,6β;20,12-diolide (80), floridolide (81), a labdane; crotomachlin (82) and four trachylobane diterpenoids; trachyloban-19-oic acid (83), trachyloban-18-oic acid (84), 3α,18,19-trihydroxytrachylobane (85), 3α,19-dihydroxytrachylobane (86) as well as four triterpenoids; betulin (87), a derivative of betulinic acid (76), acetyl aleuritolic acid (88), and sitosterol palmitate (89). *Cis*-clerodane (90) and 3β-Acetoxy tetraxer-14-en-28-oic acid (91) (Abdisa, 2019; Meresa, 2019). The essential oil extracted from the leaves confirm the presence of 69.16% terpenoids; Germacrene D (43), caryophyllene (67), 1-methyl-4-(6-methyhept-5-en-2-yl) cyclohexa-1, 3-diene (92), β – Capaene (93), β – Pinene (94), linalool (95) and α – Copaene (96) along with ester benzyl benzoate (97), hydrocarbons; Naphthalene (98) and Cyclododecane (99), heterocyclic compounds; Indole (100) and Piperidine (101),fatty acid; Hexadecanoic acid (102), and amine; Phenylephrine (103) (Block et al. 2002).

Pharmacological studies shows that *Croton macrostachyus* has a wide range of pharmacological effects such as anti-diarrhea, and sedative, antidiabetic, anti-inflammatory, antileishmanic and larvicidal effects. *Croton macrostachyus* stem bark extract is active compared to studies in which anti-plasmodial activity has been implicated in a number of classes of secondary plant metabolites, including alkaloids and sesquiterpenes, inonoids, and quassinoids (Abdisa, 2019; Kiranmayi et al. 2010). *Croton Macrostachyus* is effective against diarrhea (Burt, 2004). The chemical constituent in *Croton macrostachyus*; terpenoids such as abietic acid (104) and steroids such as phytosterols (105) have been shown to inhibit the production of prostaglandin E2, which plays a crucial role in stimulating intestinal secretion and hence it has antidiarrheal activities (Abdisa, 2019; Linscott, 2011; Liu et al. 2004). The anthelmintic activity, the analgesic and anti-inflammatory effects of the aqueous and methylene chloride/methanol stem bark extracts, the antimicrobial and antifungal activities of the methanol and dichloromethane extracts of the leaves and stem, and the antibacterial and antileishmanial activities of the plant's essential oils were all confirmed by numerous pharmacological studies of *C. macrostachyus*, according to the report (Meresa, 2019). With minimum inhibitory concentration values of 3.75 mg/ml and 7.5 mg/ml, respectively, the methanol extract of *C. macrostachyus* demonstrated a strong effect in inhibiting the growth of tested isolates in both in vitro and in vivo settings. It also demonstrated stronger antibacterial activity against *S. aureus than E. coli* (Aylate et al. 2017).

The root bark of *Croton membranaceus* contains scopoletin (106) and julocrotine (107) (glutamiride Alkaloid). Traces of calcium oxalate crystals were also reported in its root bark (The Ferns, 2014). Furano-clerodane diterpenoid; crotomembranafuran (108), labdane diterpenoid; gomojoside H (109), sitosterol; sitosterol 3-*O*-β-*D*-glucoside (110) and DL-threitol (111) are reported to have been isolated from its root extract (Isyaka, 2020; Bayor et al. 2009). According to reports, *Croton membranaceus* exhibits antibacterial activity. Certain phase I metabolizing enzymes are induced and inhibited

by *Croton membranaceus*, whereas phase II metabolizing enzymes are modestly induced (Asare et al. 2020). According to in vitro studies, *C. membranaceus's* aqueous and organic stem extracts both exhibit some antioxidant properties (Afriyie et al. 2022).

The seed extract of *Croton penduliflorus* shows the presence of fatty acid. Isolated from the root bark of West African *Croton penduliflorus* is a halimane diterpenoid; Penduliflaworonsin (112) (Isyaka, 2020). In addition, julocrotine (107) and lupeol (3) was also reported from the West African *C. penduliflorus* (Block et al. 2006). Although essential oils derived from *C. penduliflorus* seeds have been shown to be hypocholesterolemic, they may also increase the risk of anemia. Investigation of the gastrointestinal effects and acute toxicity of the essential oils extracted from *C. penduliforus* seeds, revealed that the oil caused inflammatory reactions in the colon, ileum, and jejunum, as well as hypersecretions in every section of the gastrointestinal tract. Of the visceral organs, the liver, lung, and myocardium were the most affected (Ojokuku et al. 2011; Asuzu and Chineme, 1988). It has been shown that the methanolic extract of *C. penduliforus* seeds increases the concentrations of albumin, total protein, sucrose, and maltase in pregnant rats (Sarwar, 2011). The chicks' foot pad oedema was considerably reduced by the hydro-ethanolic extract of *C. penduliflorus* stem bark (Baah et al. 2017). In the agar-well diffusion method, the stem bark extract of *C. penduliflorus* shown activity against the Gram-negative bacterium P. aeruginosa but not E. coli, and against the Gram-positive bacteria *S. aureus, K. pneumoniae, E. faecalis, and B. subtilis* (Baah et al. 2017).

The leaves of *Croton pseudopulchellus* are found to contain taxalbumincrotin (113) (Burkil, 2004). Langat, (2009), isolated seven kaurane diterpenoids, a labdane (114-120), three sesquiterpenoids (36, 121-122), triterpenoids (88,123) and stigmasterol (124) (Isyaka, 2020). Langat (2009) revealed that Phytochemical investigation of the root bark extract of *Croton pseudopulchellus* led to the isolation of five secondary metabolites namely, 18-methoxycarbonyl-18-methoxycarbonyl-15,16-epoxy-*ent*-cleroda-3,13(16),14-triene-,20,19-olide (megalocarpoidolide B) (125), 7,8-dehydrocrotocorylifuran (126), vitexin (127), lupeol (3) and acetyl aleuritolic acid (128) (Tatsimo et al. 2020). The acetone extract of C. pseudopulchellus' aerial parts had a minimal inhibitory concentration (IC50) of 0.1 mg/mL against Mycobacterium tuberculosis, and a chloroform extract of the stem bark of the plant exhibited 82% minimum inhibitory activity at 50 mg/mL against PfUP1, a strain of Plasmodium falciparum that is resistant to chloroquine, and a minimum inhibitory concentration (IC50) of 3.45 mg/mL against the kidney cells of vervet monkeys (Isyaka, 2020; Prozescy et al. 2001; Langat, 2009). Vitexin (127) showed antimicrobial activities with minimum inhibitory concentration and minimum microbicidal concentration values ranged between 16 and 32 µg/mL and interesting antioxidant properties very close to those of vitamin C and butyl hydroxyl toluene (BHT) (Tatsimo et al. 2020).

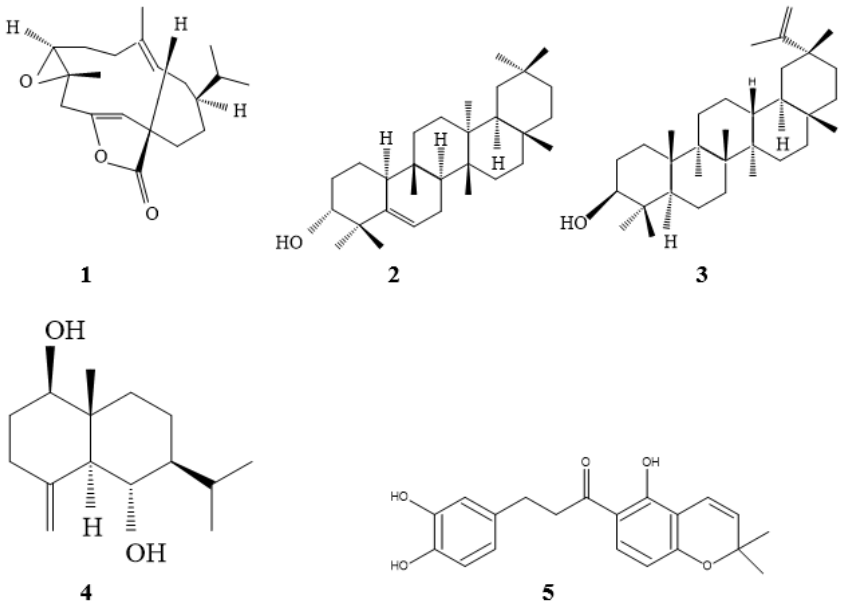
The seed of *Croton sylvaticus* is said to contain an oil composed of palmitic acid, stearic acid, linoleic acid and tiglic acid. Other research shows the presence of glutarimide alkaloid; julocrotine (107), lupeol (3) and penduliflaworonsin (112) in the stem bark and tannins in its bark (The Ferns, 2014). The roots are reported to contain the toxalbumin crotin; a glycoprotein molecule that is attached to crotin, a dihydrochalcone (130) and glycosylated protein (Watt and Breyer-Brandwijk, 1962). Hydrodistillation of the leaves is reported to have shown the presence of over fifty-two components including caryophyllene oxide (15) and α-humulen-1,2-epoxide (131) (Mwangi et al. 1998). β-sitosterol (22), stigmasterol (125) and a clerodane diterpenoid, hardwickiic acid (132) was been reported from the leaves of East African *C. sylvaticus* (Isyaka, 2020; Mwangi et al. 1998). Three labdane diterpenoids namely; 18-*nor*-labd-13(*E*)-ene-8α, 15-diol (133), labd-13(*E*)-ene-8α, 15-diol (134) and austroinulin (135) were isolated from the stem bark of *Croton sylvaticus* (Okerio et al. 2019). Hydrodistillation from *C. sylvaticus* leaves shows the presence of β-caryophyllene oxide (15) and α-humulene-1,2-epoxide (131) as the major constituents (Kapingu et al. 2012; Kapingu et al. 200). Three compounds, namely 2-[N- (2-methylbutanoyl)]-N- phenyl-ethylglutarimide (107), lup-20(29)-en-3b-ol (3) and ent-(12R)- methyl-15.16-epoxy-9.10-friedolabda-5(1O),13(16),14-trien-19-oate20,12 lactone (112) were isolated from the leaves of *C. sylvaticus* (Abdisa, 2019; Meresa, 2019). The phytochemical investigation of the leaf extracts of C. *sylvaticus* yielded a clerodane diterpenoids namely sylvaticinol (136) and 3-hydroxy-3-((Z)-4-hydroxy-but-1-enyl)- 2,2,4- trimethyl-cyclohexanone (137) (Langat et al. 2008). Further phytochemicals analysis of the stembark and leaves of C. *sylvaticus* yielded trans-phytol

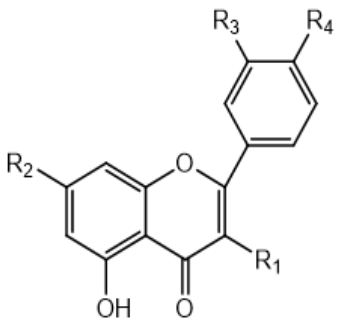
(138), lupenone (139), 3β-acetoxylup-20(29)-ene (140), β-amyrin (141), lignoceryl trans-ferulate (142) and (+)-syringaresino (143) (Langat, 2009; Aderogba et al. 2013). Isolation of 3,3,4,5,7-pentahydroxyflavone (144) and 3,4,5,7-tetrahydroxyflavone (145) from methanol leaf extracts of *C*. *sylvaticus* was carried out (Langat et al. 2008).

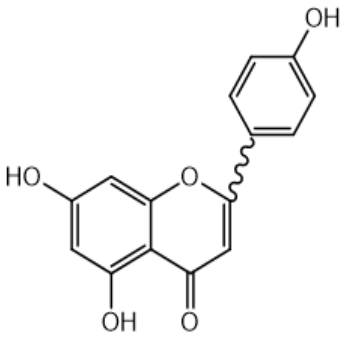
Previous research on *Croton sylvaticus* shows the presence of antiplasmodial activity, low to high toxicity and the inhibitory of acetyl cholinesterase (Njoya et al. 2018). The aqueous methanol extracts showed anti-inflammatory and anti-oxidants activities. Both the water and methanol extracts of *C*. *sylvaticus* exhibited very promising 5-lipoxygenase inhibitory activity (The Ferns, 2014; Frum and Viljoen, 2005). Hardwickiic acid (132) showed a significant antileishmanial activity on L. donovani promastigotes (Crentsil et al. 2020). The crude extract (1:1MeOH in CH_2Cl_2) was found to be active at the tested concentration of 10 µg/ml exhibiting cell inhibition of 86 % against drug sensitive leukemia cell (Okerio et al. 2019).

In *Croton zambesiscus*, five flavone-C-glycosides, vitexin (128), orientin (146), vicenin-1 (147), saponaretin (148) and iso-orientin (149) (Wagner et al. 1970). The leaves and bark of Benin and Cameroon *Croton zambesicus* was reported to contain diterpenoids belonging to clerodane (150-151) labdane (152), kaurane (153) (Block et al. 2006; Block et al. 2005). Trachylobane (154-159) (Ngadjui et al., 1999). Pimarane (160-161) (Block et al. 2005). Phytol (162) classes (Isyaka, 2020). Other compounds reported from *C*. *zambesicus* include lupeol (3), betulinic acid (76), betulin (87) and sitosterol glycoside (110). Monoterpenes, sesquiterpenes, and aliphatic chemicals are present in the essential oils extracted from *Croton Zambesicus* leaves (Isyaka, 2020). The antibacterial properties of *C. zambesicusha* stem bark have been investigated. Rats subjected to pyrethroid-based insecticides showed improved testicular health after consuming *Croton zambesicus* leaf extracts (Crentsil et al. 2020). Rats' fecal production increased significantly and dose-dependently when they were given *Croton zambesicus* root extract (Ezeabara and Okonkwo, 2016). Benin uses *Croton gratissimus* burch. as an anti-malarial, anti-hypertensive, and antimicrobial to treat urinary tract infections (Block et al. 2002). *Croton gratissimus* leaf extract has positive effects on the immune system, liver, and kidney, making it a potential treatment for hypertension. *Croton gratissimusis* extracts have been shown to have potent antibacterial property (Isyaka, 2020; Segla et al. 2022; Morobe et al. 2018). *Croton gratissimus* showed strong antioxidant properties without any toxicity (Ahamed et al. 2021). The methanolic leaf and stem extracts showed significant activity against a variety of bacterial isolates (Naidoo, 2018).

STRUCTURES

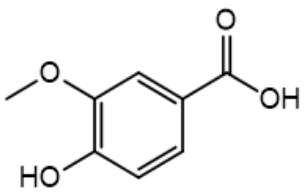






6 R_1 = OMe, R_2 = OH, R_3 = OMe, R_4 = OMe
7 R_1 = OMe, R_2 = OMe, R_3 = OH, R_4 = OMe
8 R_1 = OMe, R_2 = OMe, R_3 = OMe, R_4 = OMe
9 R_1 = OMe, R_2 = OH, R_3 = OH, R_4 = OMe
10 R_1 = OMe, R_2 = OMe, R_3 = OH, R_4 = OH

11



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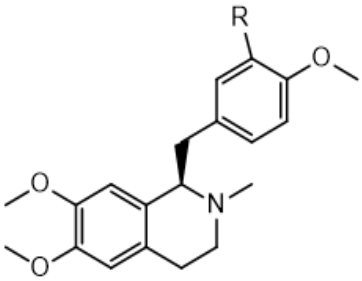
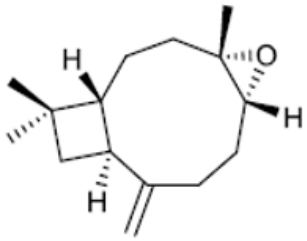


13 OH
14 OMe



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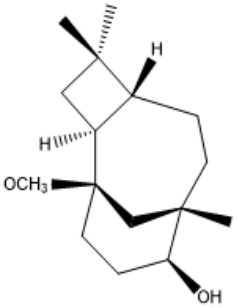

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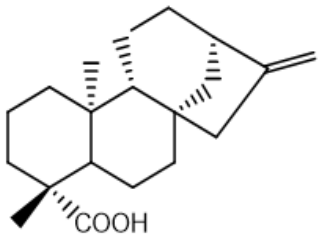

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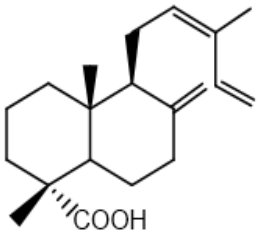

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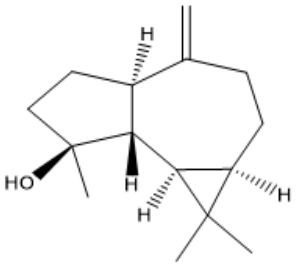

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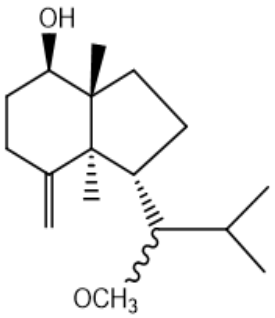

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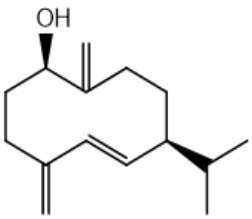

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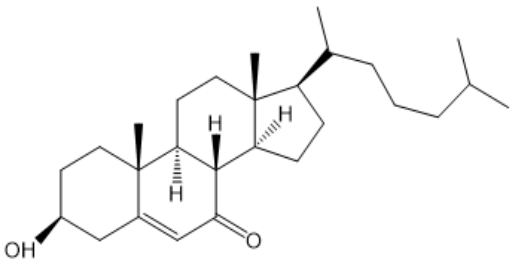

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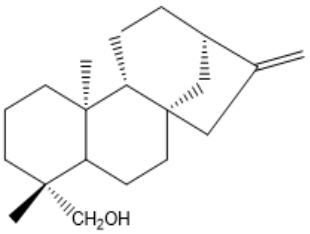

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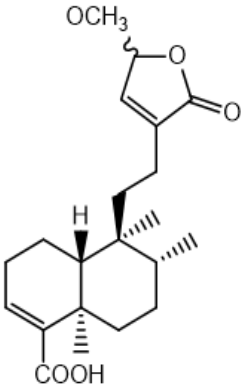

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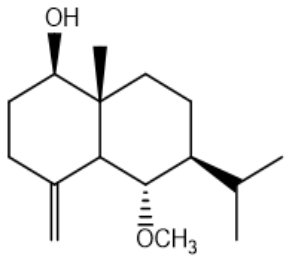

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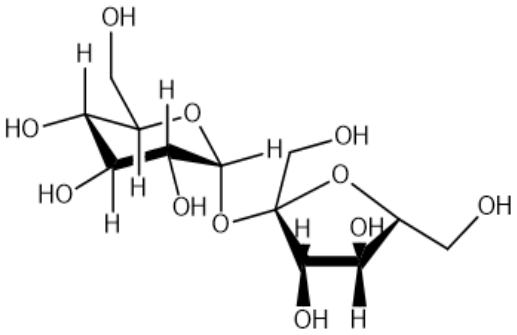

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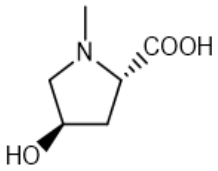

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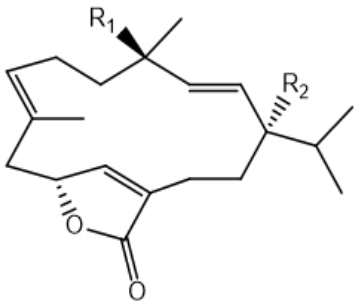
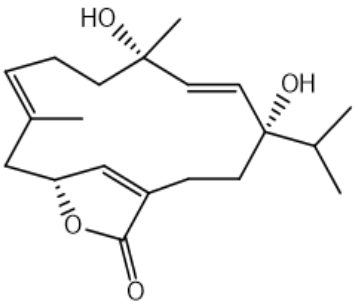


28 $R_1 = OCH_3$, $R_2 = H$
29 $R_1 = OCH_3$, $R_2 = OH$
30 $R_1 = OH$, $R_2 = OH$



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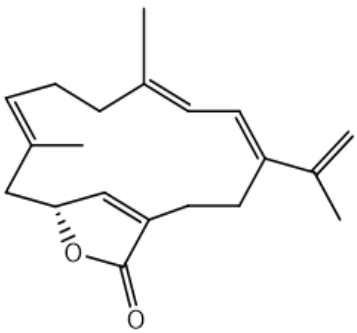

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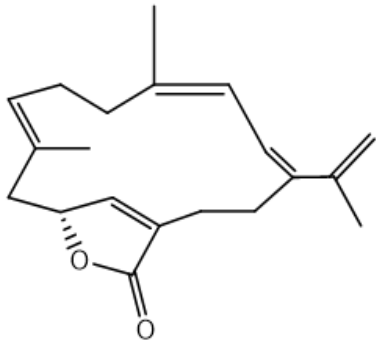

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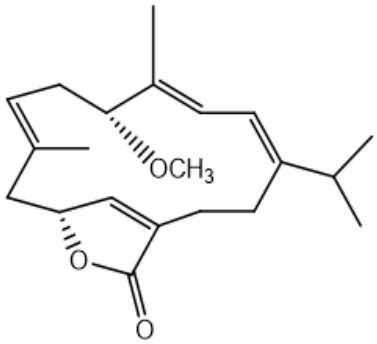

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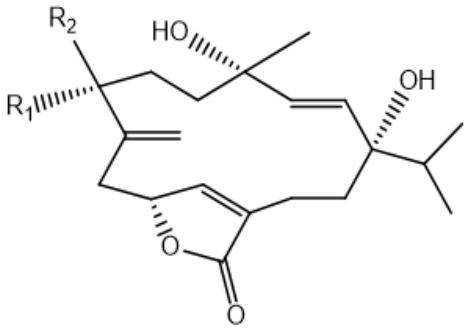
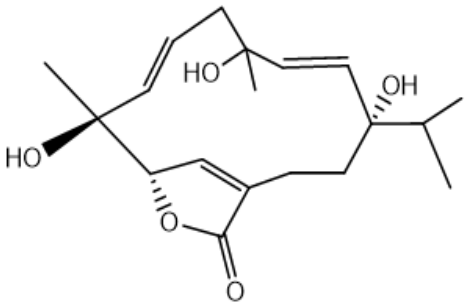


35 R_1 = OH, R_2 = H
36R_1 = H, R_2 = OH



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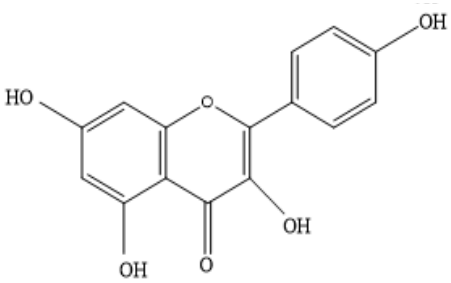

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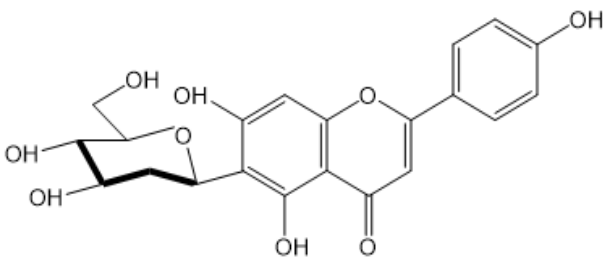

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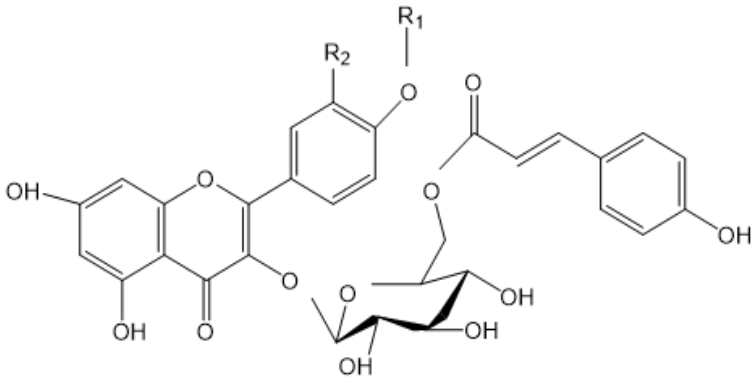

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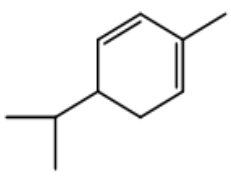
41R_1 = R_2 = H



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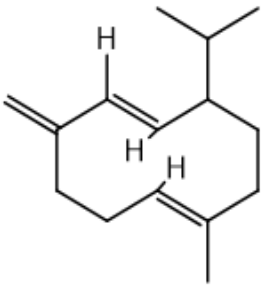

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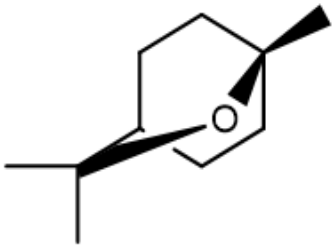

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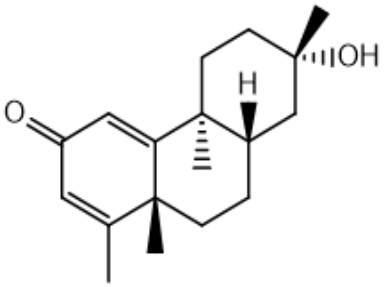

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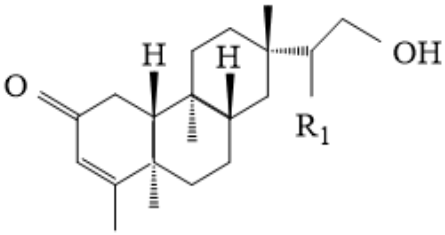
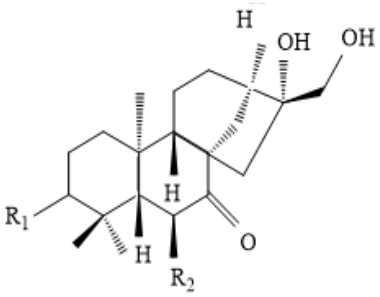
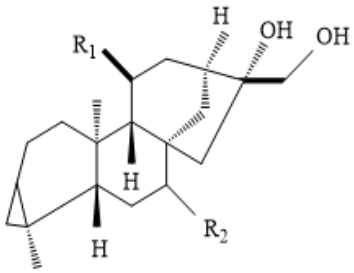
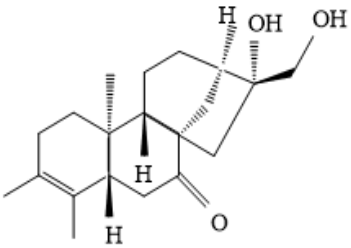


46 R_1 = OH
47 R_1 = O



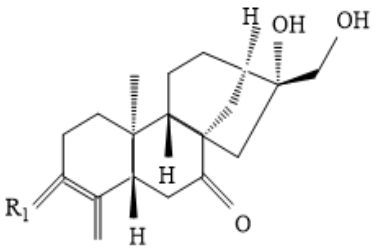




48 $R_1 = R_2 = H$
49 R_1 = H, R_2 = OH
50 R_1 = OH, R_2 = H
51 $R_1 = R_2$ = OH

52 R_1 = OH, R_2 = β-OH
53 R_1 = H, R_2 = O

54
55(5, 6)
56 (5,6) 3,4-epoxide
57 (5,6) 3,4-epoxide



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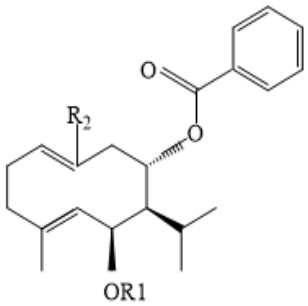
59 R_1 = OH, CH_3



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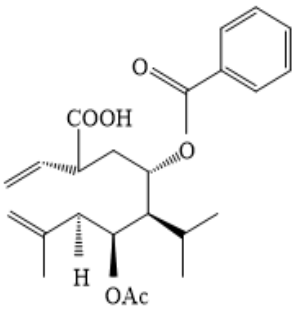
61 R_1 = Ac, R_2 = CO_2H
62 R_1 = H, R_2 = CH_3



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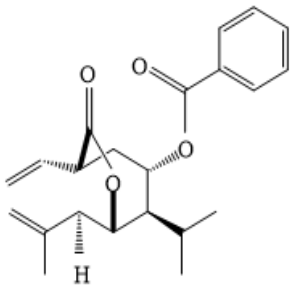

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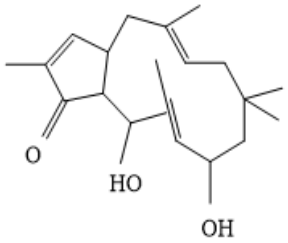

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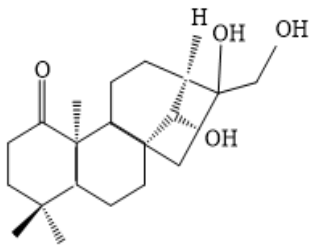

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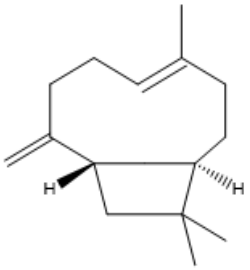

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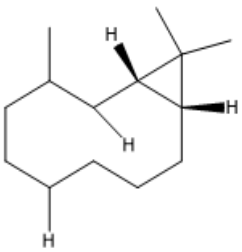

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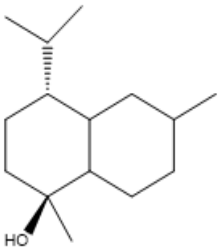

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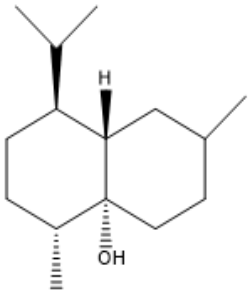

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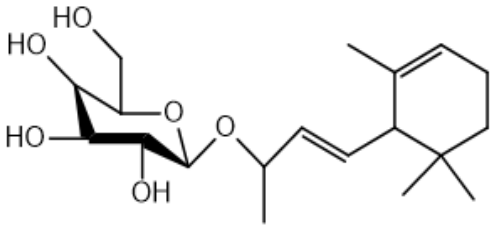

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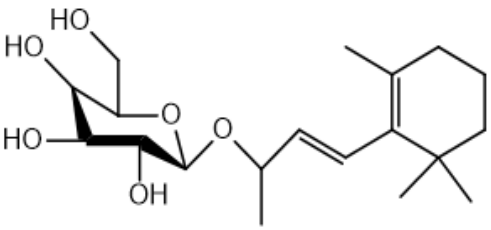

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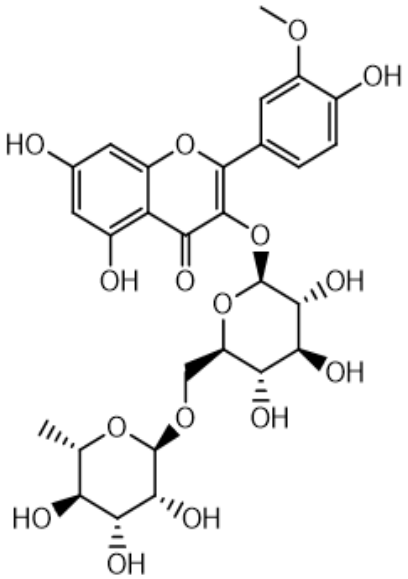

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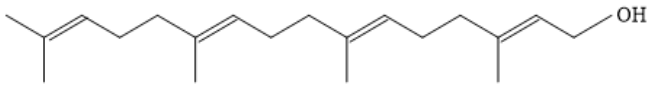

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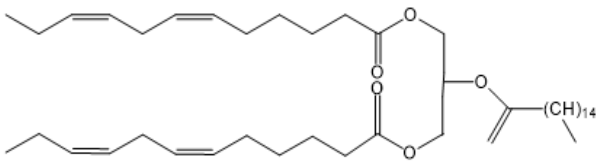

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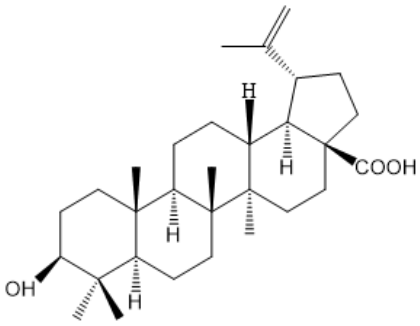

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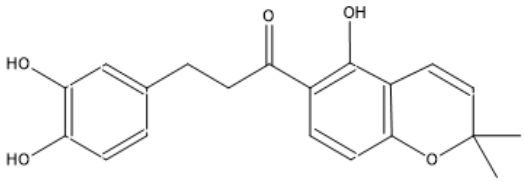

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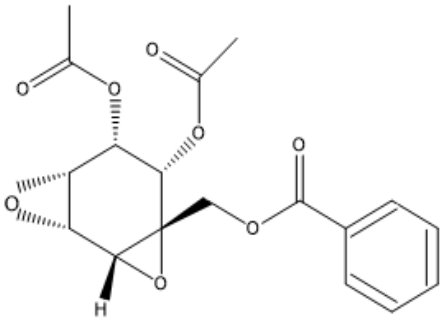

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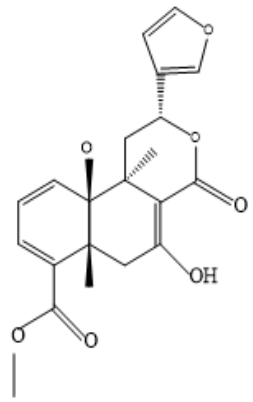

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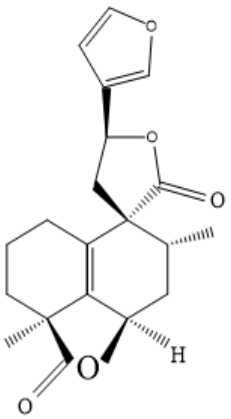

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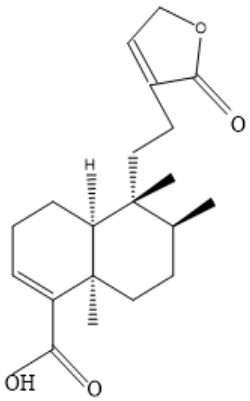

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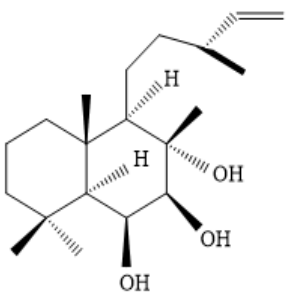

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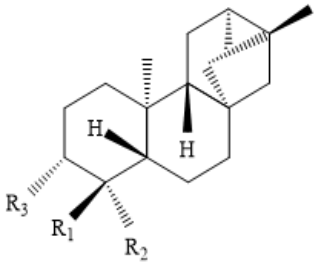
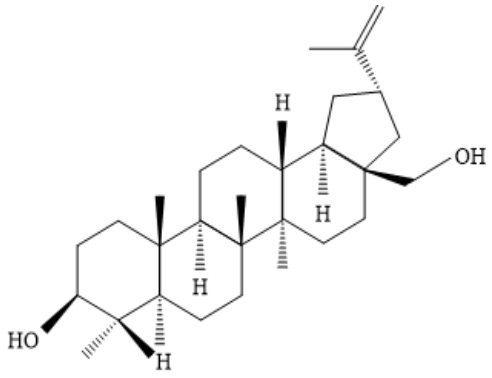


83 $R_1 = CH_3$, $R_2 = CO_2H$, $R_3 = H$
84 $R_1 = CO_2H$, $R_2 = CH_3$, $R_3 = H$
85 $R_1 = CH_2OH$, $R_2 = CH_2OH$, $R_3 = OH$
86 $R_1 = CH_3$, $R_2 = CH_2OH$, $R_3 = OH$



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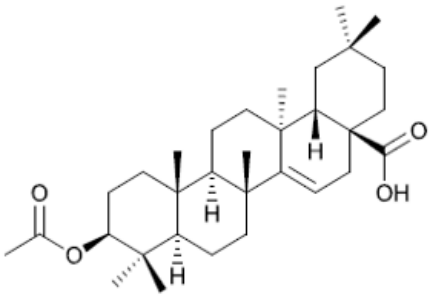

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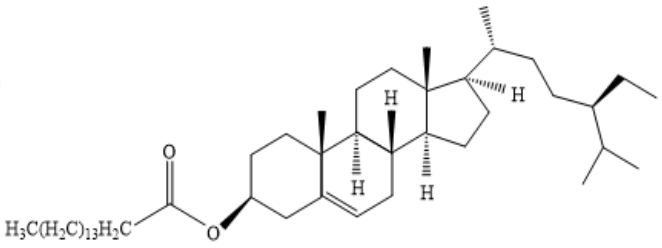

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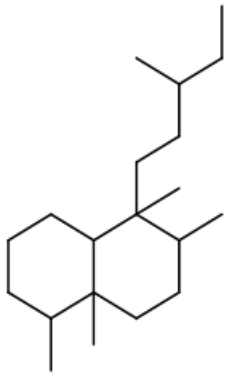

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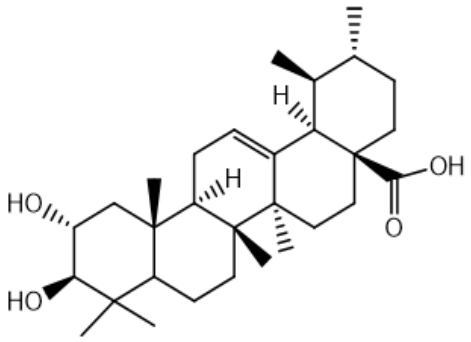

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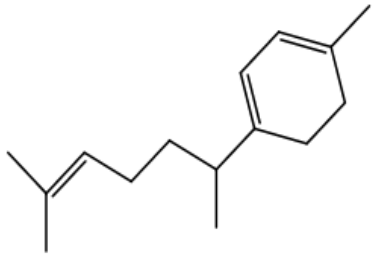

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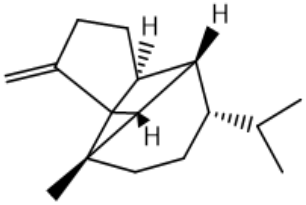

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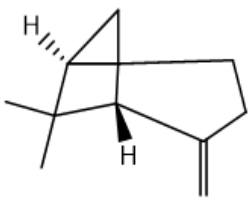

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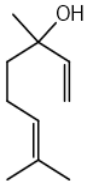

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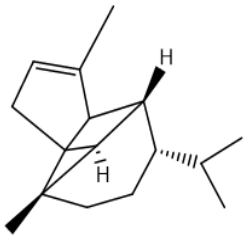

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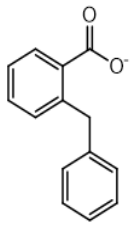

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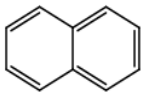

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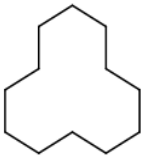

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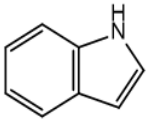

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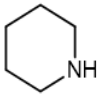

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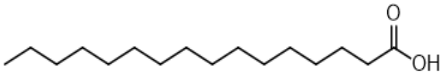

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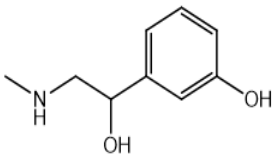

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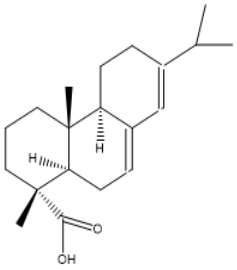

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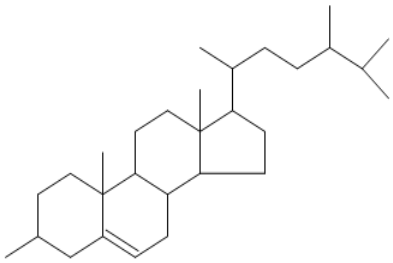

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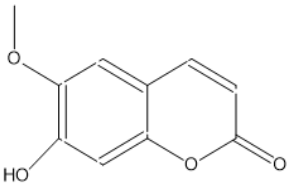

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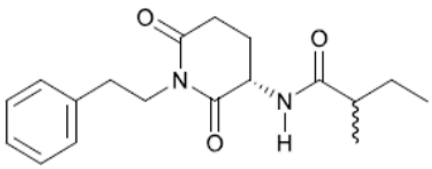

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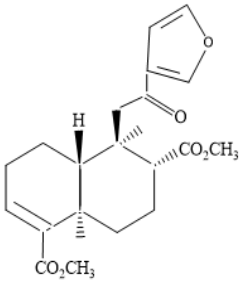

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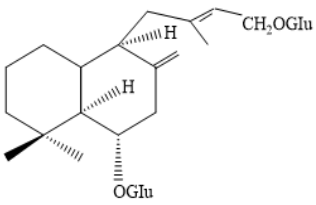

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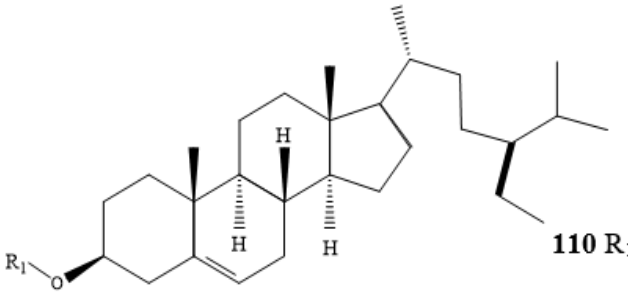
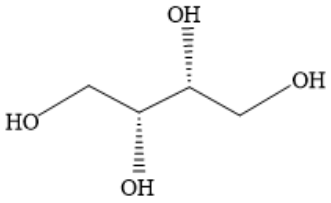


110 R_1 = Glu



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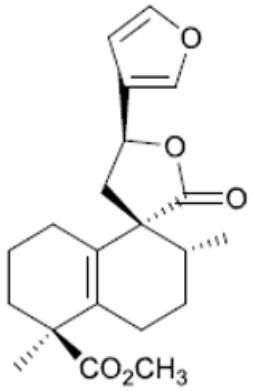

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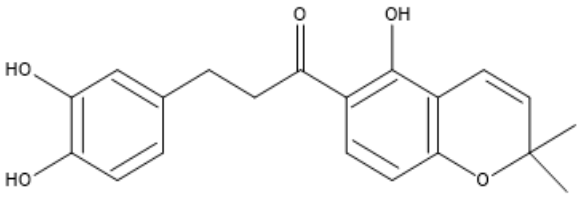

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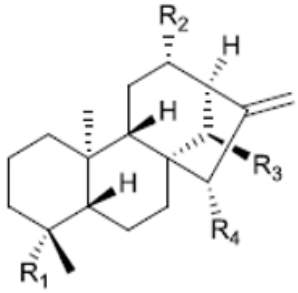
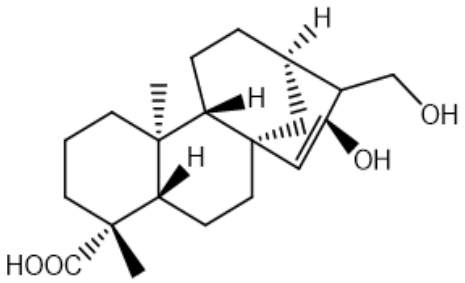
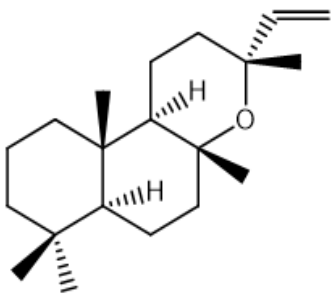




120

114 $R_1 = CO_2H$, $R_2 = R_3 = R_4 = H$
115 $R_1 = CHO$, $R_2 = R_3 = R_4 = H$
116 $R_1 = CO_2H$, $R_2 = OH$, $R_3 = R_4 = H$
117 $R_1 = CO_2H$, $R_2 = OCOCH_3$, $R_3 = R_4 = H$
118 $R_1 = CO_2H$, $R_2 = H$, $R_3 = H$, $R_4 = OH$
119 $R_1 = CO_2H$, $R_2 = H$, $R_3 = OH$, $R_4 = H$



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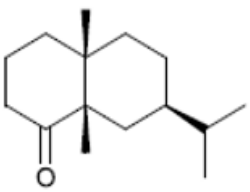

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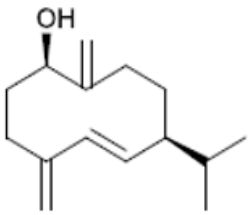

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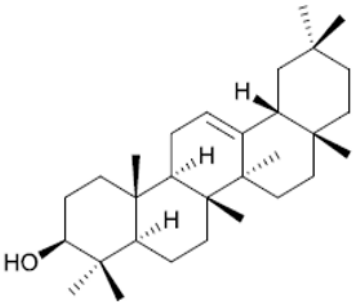

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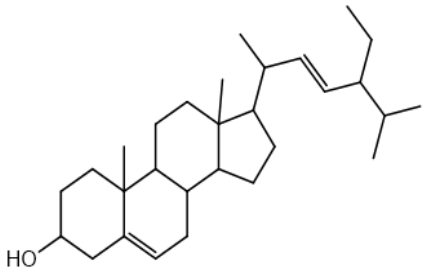

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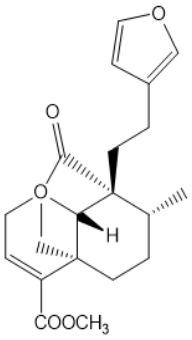

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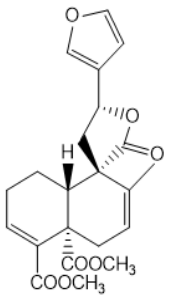

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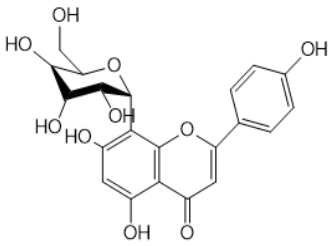

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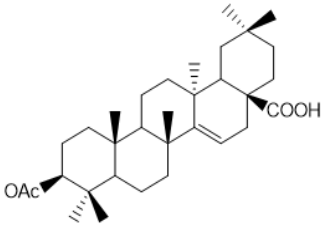

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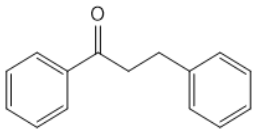

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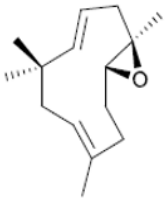

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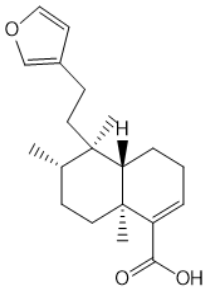

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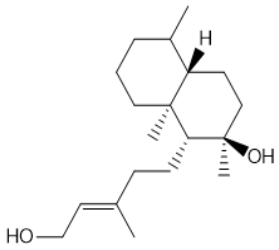

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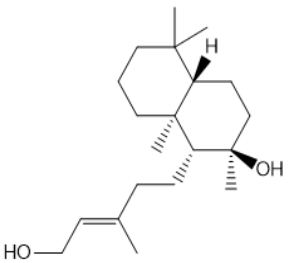

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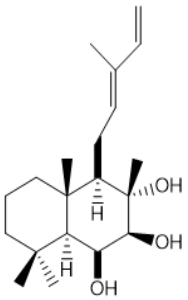

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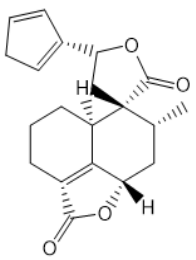

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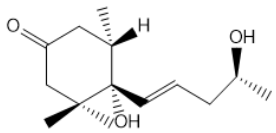

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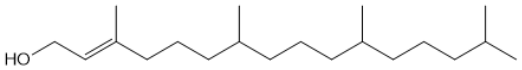

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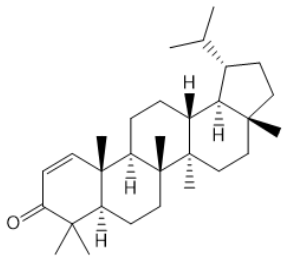

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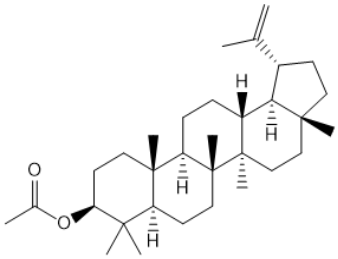

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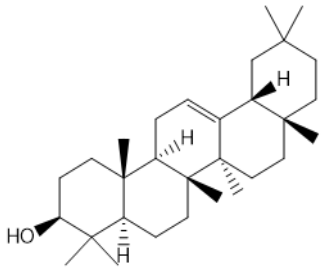

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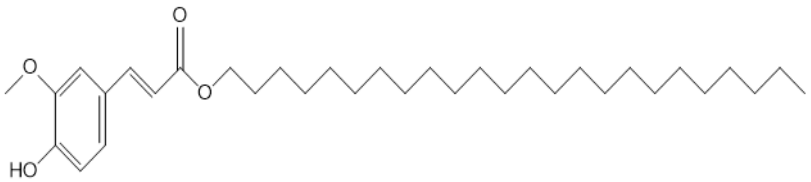

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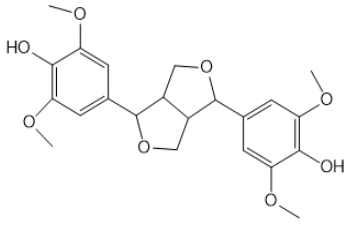

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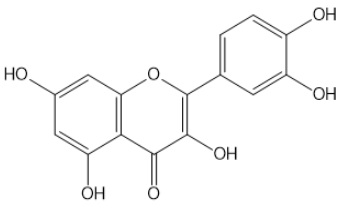

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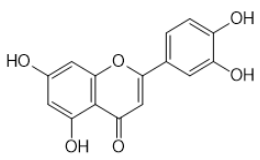

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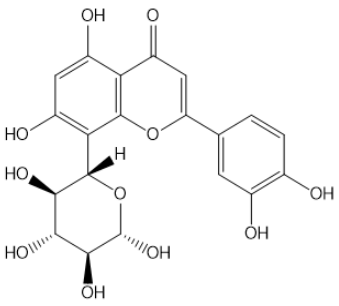

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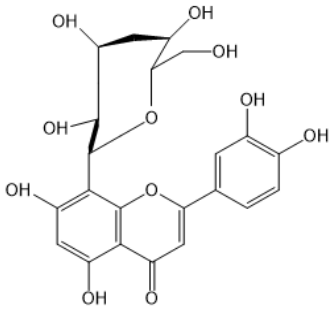

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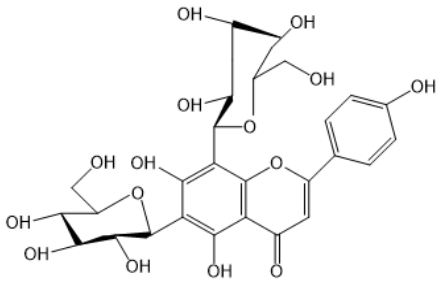

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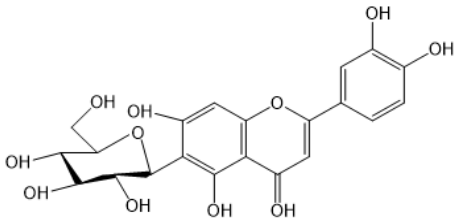

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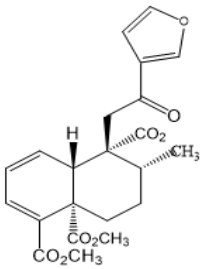

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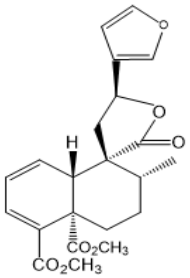

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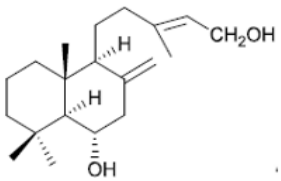

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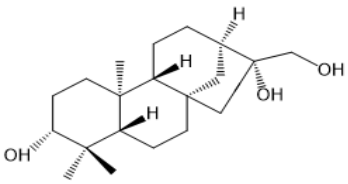

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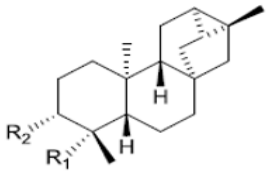
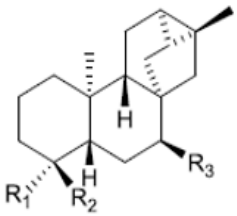
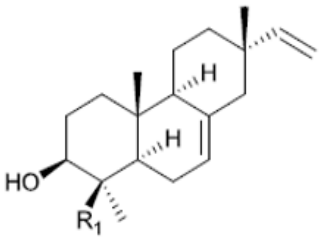


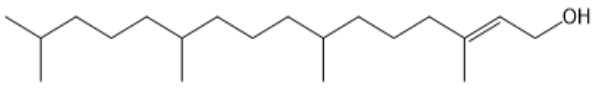
154 $R_1 = CH_2OH$, $R_2 = OH$
155 $R_1 = CH_3$, $R_2 = O$
156 $R_1 = CH_2OH$, $R_2 = O$
157 $R_1 = CH_3$, $R_2 = OH$



158 $R_1 = CH_2OH$, $R_2 = CH_3$, $R_3 = OAc$
159 $R_1 = CH_2OH$, $R_2 = CH_3$, $R_3 = OH$



160 $R_1 = CH_2OH$
161 $R_1 = H$



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3. CONCLUSION

The genus *Croton* is a member of the *Euphorbiaceae*. They are found in tropical and sub-tropical areas of both hemispheres and comprise 1,300 species of trees, shrubs, and plants. More than 292 species of the genus *Croton* are known to exist in Africa, whereas 11 species of the genus including *Croton gratissimus, Croton gratissimus* var. *gratissimus, Lobatus,hirtus, membranaceus, macrostachyus, penduliflorus, pseudopulchellus, sylvaticus*, and *zambesicus* are found in Nigeria. Found all throughout the world, *Croton* species are most commonly used in traditional medicine to cure conditions like cancer, constipation, diabetes, dysentery, external wounds, intestinal worms, discomfort, ulcers, and weight loss. Nigerian *Croton* species have many ethnomedical applications and contain a variety of bioactive chemicals, such as terpenes, alkaloids, and flavonoids, which give them pharmacological properties like antibacterial, antileishmanial, antiplasmodial, antioxidant, and anticancer properties.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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