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Review Article

Croton gratissimus Burch. (Lavender croton): A Review of the Traditional Uses, Phytochemistry, Nutritional Constituents and Pharmacological Activities.

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ABSTRACT

Croton gratissimus Burch. is a deciduous shrub used in traditional medicines and a local traditional herbal tea in South Africa. *C. gratissimus* is used in treating several disease conditions, including cough, influenza, colds, malaria, fever, bleeding gums, chest complaints, indigestion, skin inflammation, earache, respiratory disorders, diabetes, and oedema.This review focuses on the botanical attributes, distribution, traditional uses, phytochemistry, nutritional constituents and pharmacological properties of *C. gratissimus*. A wide-range search of previous literature on various scientific databases, including Google, Google Scholar, Science Direct, PubMed, Scopus, theses, dissertations, and ethnobotanical textbooks, was conducted. The search showed that *C. gratissimus* has several reported traditional uses, with over 55 compounds identified and isolated from it. Some of the compounds include cembrane-, trachylobane- and pimarane- type diterpenes, triterpenes, sesquiterpenes, sterols, flavonoids and flavonoids glycosides. The bioactive compounds had biological activities such as antioxidant, antiplasmodial, anticancer, antibacterial, vasorelaxant, and cholinesterase inhibitory action. *C. gratissimus* is reported to have antimicrobial, antidiabetic, antiparasitic, antiviral, antioxidant, haemostatic, anticancer, anti-inflammatory, toxicity, and immune-boosting properties. Other pharmacological activities of *C. gratissimus* include analgesic, anticonvulsant, antipyretic, nephroprotective, and ulcerogenic properties. *C. gratissimus*' nutritional constituents include total sugar, protein, amino acids, fat, dietary fibre, carbohydrate, energy, ash, moisture, dry matter, and calcium. It is hoped that the present review will add further value to the scientific research on *C. gratissimus* and boost the increased interest in the study, development, and sustainable commercial exploitation of *C. gratissimus* as a medicine and as a health herbal tea.

Keywords: *Croton gratissimus*, Traditional uses, Phytochemistry, Indigenous herbal tea, Pharmacological activities, Nutritional constituent.

Introduction

Croton gratissimus Burch. is a multi-stemmed deciduous shrub or small tree. It is a slender tree with a characteristic 'V-shaped crown.[1,2] The drooping leaves are fine and spread upwards, with terminal branches bending downwards. *C. gratissimus* is an attractive and versatile plant with the ability to grow into a huge tree in certain environmental circumstances.[1] *C. gratissimus* has been a delightful aesthetic tree capable of attracting insects like butterflies.[3]
C. gratissimus belongs to the spurge family (Euphorbiaceae). *Croton gratissimus* is one of several species in the Croton's genus. Croton is a widespread genus taxonomically established by Carolus Linnaeus in 1737. The genus - *Croton* is commonly called rushfoil. The name Croton was derived from the Greek word- *Kroton*, which implies ticks because of the close semblance of the seeds to ticks.

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The specific name *gratissimus* retained its original Latin form meaning 'most pleasing' (*gratus* - pleasing; *issimus* -most).[1]
Several common and local names had been used to describe *Croton gratissimus*. In Zulu, *C. gratissimus* is commonly called umahlabekufeni, while in Afrikaans, it is often referred to as bergboegoe or laventelkoorsbessie. The San people cut across Angola, South Africa, Botswana, Namibia, and Zimbabwe called *C. gratissimus*, macquassie.[4] The Venda tribe commonly call it mufhorola, while the Tswana people call it moologa.[5] The Basotho people call it Mooloha (Personal communication). Van Vuuren and Viljoen[6] also reported another Afrikaans name koorsbessie" ("koors" = fever), implying the plant can be used as a pyrogenic. The English names of *C. gratissimus* include lavender croton and lavender fever berry.[1,4] A replete of literature had reported the extensive traditional uses of *C. gratissimus*.[4,7-11] Lavender croton has been used traditionally to treat cough, fever, bleeding gums, chest complaints, indigestion, skin inflammation, earache, respiratory disorders and oedema.[7-9,12] Other local uses include its application in treating uterine disorders, stomach disorders, pleurisy or pleurodynia, influenza, colds, diabetes and malaria.[6,10,11,13,14] Interestingly, following the vast ethnopharmacological uses of Lavender croton, a good number of pharmacological studies supporting the uses have been done, with many studies yet to be explored. The pharmacological activities of the extracts and bioactive compounds done on *C. gratissimus* include antimicrobial, antipyretic, antidiabetic, antiviral, antioxidant, haemostatic, anticancer, anti-inflammatory, toxicity, antiulcer, anticonvulsant, and antiparasitic activities. Others include nephroprotective, analgesic, testicular, gastric emptying and immune-

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boosting properties. The phytochemical constituents of *C. gratissimus* revealed that the plant has many isolated compounds with biological activities. Following the oral tradition of using the plant as an herbal tea amongst the Tswana people of South Africa, the plant is currently being developed for commercialization as an herbal tea at the department of Pharmacology, University of the Free State, South Africa. The herbal tea is called Moologa tea (Figure 1), whose name was adopted from the local name (Personal Communication). In this review, we focused on the traditional uses, botany, chemical constituents, nutritional constituents and pharmacological activities of *C. gratissimus*. It is envisioned that it will spur further research that will support the sustainable commercialization of *C. gratissimus*.

Figure 1: Moologa tea: *Croton gratissimus* var. *gratissimus.* A formulation of the IKS Research Unit, Department of Pharmacology, University of Free State, South Africa

Materials and Methods

Data and Information acquisition

This paper comprehensively explored *C. gratissimus* with its corresponding botanical synonyms from published pieces of literature. Our search with no time frame indicated was focused on the botany, toxicity, traditional and medicinal uses, phytochemistry, nutritional qualities and pharmacological activities of *C. gratissimus*. The search terms used in obtaining the relevant data included ("*Croton gratissimus*" "*Croton gratissimus*" AND "Botanical description" OR "Traditional uses" OR "Medicinal uses" OR "Toxicity" OR "Pharmacological activities" OR "Biological activities" OR "Phytochemicals") OR ("Phytochemicals in *Croton gratissimus*" AND "Medicinal uses" OR "Toxicity" OR "pharmacological activities" OR "biological activities"). Databases such as Science Direct, Google Scholar, Scopus, PubMed, thesis, dissertations, botanical websites and ethnobotanical manuals/textbooks were exhaustively explored. The information obtained was restricted to only that published in the English language.

Results and Discussion

Botanical attributes and distribution of C. gratissimus

Croton gratissimus Burch belongs to the Euphorbiaceae family. *C. gratissimus* can be described as a small tree or shrub (Figure 2) with a height disparity depending on its geographical location. In South Africa, it may grow up to a height of 10 m and further north of Africa to a height of 20 m.[1] The aromatic foliage (Figure 2d) is lance-shaped to elliptical, simple, alternate and beautiful with silvery undersides and a distinct dark green adaxial surface. Dotted on the leaves are cinnamon coloured glandular scales. The monoecious plant bears spikes (10 cm long) of small, creamy to golden yellow coloured inconspicuous flowers (Figure 2b). The little yellow matured fruit of *C. gratissimus* has a three-lobed capsule formed within the last triannual of the year. The capsule dries out in late autumn and dispersed it seed by an explosion, a distance away from the mother plant. The scattered seeds have a caruncle and may be noxious. The plant has a rough grey aromatic bark (Figure 2c).[1,3,4,15] *Croton gratissimus* has been separated into two varieties, viz.; *C. gratissimus* var. *gratissimus* and *C. gratissimus* var. *subgratissimus*. The *gratissimus* variety lacks hairs on the upper surface, while the *subgratissimus* variety has stellate hairs on the upper surface. In this review, we focused on the *gratissimus* variety.

C. gratissimus is common in the northern parts of South Africa.[1] Lavender croton can be found over a wide range of altitudes, in a variety of woodland vegetation types but majorly associated with stony soils and rocky outcrops (Figure 2a).[4, 16] Lavender croton is naturally well distributed in Senegal, Sudan, Ethiopia, Namibia and Botswana. It is common along the fringing forest and savannah.[2] According to CJBG (Conservatoire et Jardin botaniques) and SANBI (South African National Biodiversity Institute)[17], and GBIF (Global Biodiversity Information Facility)[18], *Croton gratissimus* is mainly distributed across West Africa and Southern Africa and sparsely found in Central and East Africa (Figure 3). A sift of the synonyms of the names in Latin of *Croton gratissimus* on The Plant list database (http://www.theplantlist.org/) showed it had ten synonyms (Table 1).[19] *C. gratissimus* is a watery latex plant assessed in 2005 by R.H. Archer and J.E. Victor for its conservation status and was listed amongst the least concerned (L C.) species in the Red List of South African plants.[15,20]

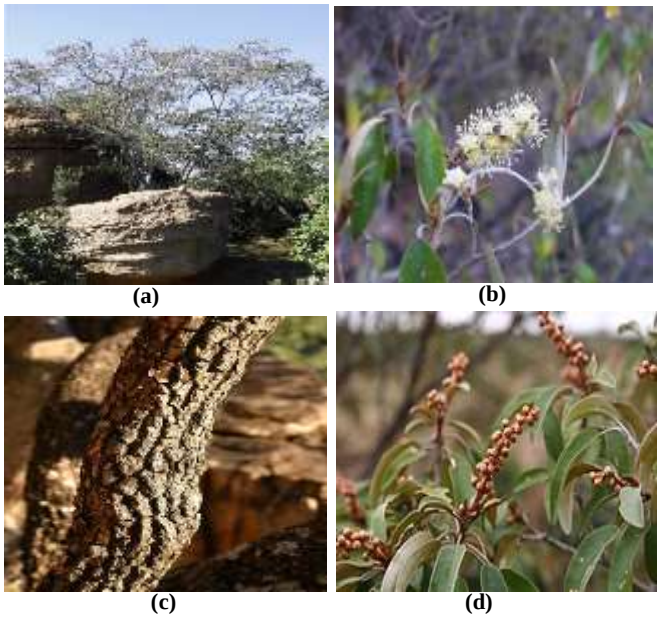

Figure 2: *Croton gratissimus* Burch. (a) whole plant (b) flower (c) bark (d) dormant flower buds with leaves (Photograph credit:[21], distributed under a CC-BY-SA 3.0 license)

Table 1: Botanical synonyms of *Croton gratissimus* Burch

Accepted name of origin plant	No	Synonyms
Croton gratissimus Burch.	1	*Croton amabilis* Müll.Arg.
	2	*Croton antunesii* Pax
	3	*Croton gratissimus* var. *gratissimus*
	4	*Croton microbotryus* Pax
	5	*Croton welwitschianus* Müll.Arg.
	6	*Croton zambesicus* Müll.Arg.
	7	*Oxydectes amabilis* (Müll.Arg.) Kuntze
	8	*Oxydectes gratissima* (Burch.) Kuntze
	9	*Oxydectes welwitschiana* (Müll.Arg.) Kuntze
	10	*Oxydectes zambesica* (Müll.Arg.) Kuntze

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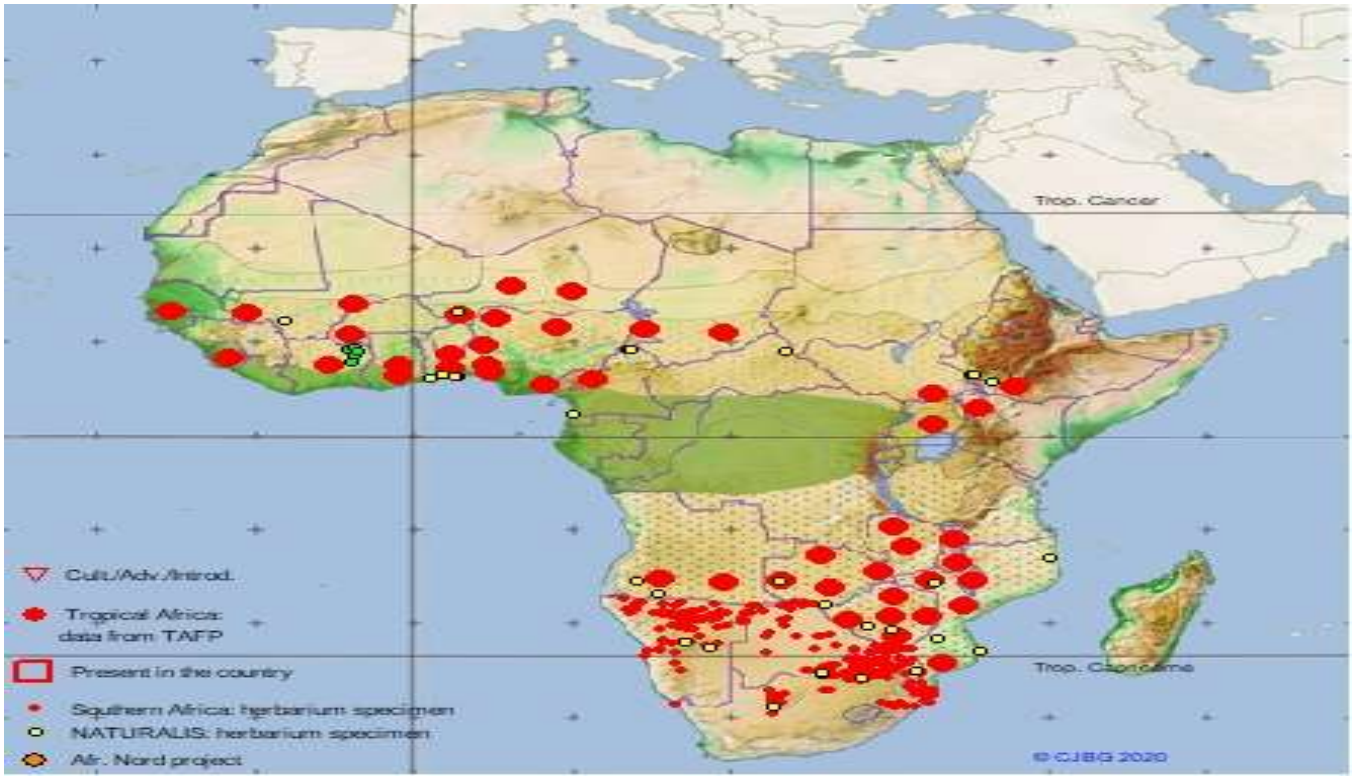

Figure 3: Distribution of *Croton gratissimus* Burch. in Africa[17]

Traditional uses of C. gratissimus

In our literature search, *Croton gratissimus* was found to have a wide range of ethnopharmacological and traditional uses (Table 2). The Zulus in South Africa, use the bark to treat fever[7] while the Basotho used the powdered bark against bleeding gums. The bark is also used to treat chest complaints, skin inflammation, indigestion, earache, and oedema.[7-9,12] Von Koenen[9] reported the combination of the bark and root to treat respiratory disorders. The dried powdered bark of *C. gratissimus* combined with the bark of *Ocotea bullata* is used to manage uterine conditions.[6] Also, the Zulus used the milk infusions of the bark as a laxative to manage gastrointestinal disorders and use the powdered bark to treat uterine conditions and pleurisy or pleurodynia.[13] Another ethnic group, the Venda people of South Africa, uses the dried leaf's smoke to treat influenza, colds, and fevers.[14] The Bapedi Traditional Healers in the Limpopo province of South Africa use the dried, pounded root with warm water or decoction or steam to treat wheezing, asthma and nasal congestion.[22] The infusions of leaves are used to treat cough while the dried powdered leaves are used as perfume and as an ingredient for smoking in managing rheumatic patients. The hot water extracts of *C. gratissimus* leaves have served as an alternative to lavender water.[4,7,12] In a striking oral tradition of *C. gratissimus*, the plant was used as an herbal tea amongst the Tswana people in South Africa. The Tswana people locally called it moologa (Personal communication).

The Bakgatla tribe (a clan of the Batswana people) who live predominantly in South Africa and Botswana, uses a cold infusion of the leaf to make eye lotion for animals and the root charm medicine. In the first fruit harvest ceremony, the Ngwaketsi women of the Tswana chiefdom an ethnic group majorly from Botswana, carry wands of *C. gratissimus*. Though this plant's toxicity is in doubt, Namibia's people use it as livestock feed[1,7] and for treating tetanus.[23] An aromatic calamus-like oil had been produced from the leaf, stem and fruit locally with some commercial potential.[4,7] The fruit generally can be explored as a spice to flavour food and the seed to flavour tea. *C. gratissimus* is also a good source of wood.[2] In Nigeria, a soup made from the leaf is used to treat and manage dysentery, while the root is used as an aperient.[24] Similarly, Ajibesin *et al.* [25] reported that Nigeria's people used the leaf to treat diarrhoea, dysentery, and malaria. They also traditionally apply the root against diabetes and malaria.[10,11] In South West Nigeria, Traditional healers use the leaf and stem bark to treat fungal and bacterial infections.[26] Like the bark, the crushed fruits are aromatic, giving a pleasant-smelling powder useful in cosmetic products.[24,27] The stem had been used as wood in hut-posts and beams as an alternative to timbers.[24] The Sudanese used the root to treat menstrual pains and constipation[28] and the seed against microbial infectious, cough, malaria and HIV-1.[29]

In the Benin Republic, a decoction of the leaf is used to treat hypertension, urinary tract infections and malaria with fever as a major symptom.[30,31] According to Ngadjui et al. [28], in central and tropical West Africa, *C. gratissimus* is used against fever, dysentery and convulsions. In Botswana, a decoction of the leaf is used to treat cough.[32] The Zimbabweans treat the same ailment with inhaled smoke from the leaves[33] and use the infusions of the root to treat stomach pains and sexual disorders.[34] Traditional healers in Botswana use the plant to treat and manage HIV/AIDS.[33] In Cameroon, the stem bark is used to treat malaria and fever.[35] Of the different parts of the plant utilized for medicinal purposes, the leaves and roots were the most applied plant parts. The shoot, root, stem, fruits and oil are sparingly used in traditional medicine.

Chemical properties

The genus *Croton* is commonly known for its rich diterpenoid content. To date, cembrane diterpenoids (cembranolides) and trachylobane-type diterpenoids have also been predominantly identified in *Croton gratissinum*, while some flavonoids and flavonoids glycosides have been reported as well. Although the chemical constituent of different species of the genus *Croton* has recently been reviewed[39], an update of the chemical constituents identified specifically in *Croton gratissinum* to date is presented in Table 3. The corresponding chemical structures of some of these compounds are shown in Figure 4. Diterpenoids and flavonoids exhibit a series of biological activities. The biological activities of *Croton gratissinum* extracts such as anti-oxidative, antiplasmodial, anticancer, and cholinesterase inhibitory effect and vasorelaxant activity have been related to the existence of some of these bioactive compounds (Table 3).

Table 2: Traditional uses of *Croton gratissimus*

S/NO	Preparations	Plant parts	Local traditional uses	References
1.	Decoction, infusion, oil	Bark, Leaves, stem, fruits, oil	Fever, bleeding gums, coughs, rheumatism, cathartic, eruptive irritant, intercostal neuralgia, gastrointestinal and uteri disorders	4, 7, 12
2.	Decoction	Leaf	Vermifuge, convulsion and headache	2
3	Tonic	Shoot and root	To tone the body and as febrifuge and treatment of menstrual pains	2,24
4	Decoction	Leaf	Antihypertension, antimicrobial (urinary infections) and malaria-linked fever	30, 31
5	Fumes (Heated pastes)	Leaf with goat fat and two Croton species	Insomnia, restlessness	36
6	Infusions, decoctions	Root	Abdominal pains and aphrodisiac. chest complaints, coughs, fever and sexually transmitted diseases such as syphilis	9, 34
7	Smoke	Leaf	Influenza, colds and fevers	14
8	Steam bath	Leaf	Sore linked with sexually transmitted infections	8, 37
9	Incisions	Bark with the root of Amaryllidaceae species	Swellings	8
10	Infusion or decoction of crushed bark	Fresh bark	Candidal infections	38
11	Decoction/steam inhalation	Dried root	Nasal congestion	22

Nutritional constituents of C. gratissimus

The leaf of *C. gartissimus* was assessed for its nutritional content. The infusion of the leaf using standard methods, as reported in Matsabisa et al. [65], was utilized in determining the nutritional constituents of *C. gratissimus*. The infused leaf prepared and formulated as a tea had a relatively low total sugar (14.3 %) and a 0.00 g/100g of glucose, fructose, sucrose, maltose and lactose. The calculated carbohydrate of 71.32 % and a total non-structural carbohydrate of 14.3 % was observed. A 0.05 % water-soluble carbohydrate was recorded with no starch content. The energy content of the leaf of *C. gratissimus* was 583 KJ/100g and had a total dietary fibre of 55.0 g with a calcium level of 0.89%. The tea had a total fat value of 3.43 % with a moisture content of 7.32 %, ash (5.13 %), protein (12.8 %) and dry matter (92.68 %). The tea had all essential amino acids with contents ranging from 0.05 to 1.20 g/100g. The indigenous *C. gratissimus* tea was compared with four commercially available teas (Green- *Camellia sinensis* (L.) Kuntze, Joko- *Camellia sinensis* (L.) Kuntze, Honey bush- *Cyclopia* sp, Rooibos- *Aspalathus linearis*, and Five roses- *Camellia sinensis* (L.) Kuntze) in South Africa. The study revealed that *C. gratissimus* tea was not substantially different from the commercial teas in sugar, fibre and amino acid content. The leaf of *C gratissimus* had no detectable caffeine content compared to the Joko (5,806 mg/g or 14,515 mg/2.5g teabags) and Green tea (6,527 mg/g or 16, 3175 mg/2.5g teabag).

Pharmacological properties

Antimicrobial activity

In a 2010 research steered by van Vuuren and Naidoo[66], the extracts and essential oils from *C. gratissimus* were assessed for antimicrobial potential against organisms linked with urogenital and sexually transmitted infections. In the study, using the micro-well minimum inhibitory concentration (MIC) assay, the extracts (dichloromethane: methanol (1:1) and aqueous) and the essential oil had a MIC range between 1- > 16 mg/mL against the six tested organisms (*Candida albicans* ATCC 10231, *Trichomonas vaginalis* clinical strain, *Ureaplasma urealyticum* clinical strain, *Oligella ureolytica* ATCC 43534, , *Neisseria gonorrhoeae* ATCC 19424 and *Gardnerella vaginalis* ATCC 14018). The dichloromethane methanol extract showed note-worthy antimicrobial activity (MIC= 1 mg/mL) against *Gardnerella vaginalis.* At the same time, the essential oil displayed fascinating and note-worthy susceptibility (1 mg/mL) against *Oligella ureolytica* and *Neisseria gonorrhoeae*. Moderate antimicrobial activity (4 mg/mL) of the essential oils of *C. gratissimus* was observed against *Ureaplasma urealyticum*. In an earlier study, Van Vuuren and Viljoen[6] carried out an independent and combinatorial *in vitro* antimicrobial study of the various parts of *C. gratissimus*. They observed that the minimum inhibitory concentration (MIC) and fractional inhibitory concentration (FIC) results showed incongruent efficacies for the various plant part combinations, the highest was against *Cryptococcus neoformans* when the root and leaf were combined (MIC 0.4 mg/ml and FIC 0.4). The isobolograms results showed the most potent interaction against *B. cereus* and *C. albicans*. Furthermore, in the study, the hydro-distilled essential oil had reasonable activity (4-11 mg/mL) against six tested organisms (*Enterococcus faecalis* (ATCC 29212), *Bacillus cereus* (ATCC 11778), *Klebsiella pneumoniae* (ATCC 13883), *Pseudomonas aeruginosa* (ATCC 9027), *Candida albicans* (ATCC 10231), *Cryptococcus neoformans* (ATCC 90112)) and poor susceptibility (13- 32 mg/mL) against three pathogens (*Staphylococcus aureus* (ATCC 12600), *Staphylococcus epidermidis* (ATCC 2223), *Escherichia coli* (ATCC 11775)). Interestingly, the isolates (*P. aeruginosa*, *E. coli*, and *K. pneumoniae*) were most susceptible to the leaf extracts, while the root and bark had the same susceptibility activity. The combinatorial studies of the different parts (leaf, root and bark) of *C. gratissimus* showed increased antimicrobial efficacy (lower MIC values) or equivalent (same MIC value) for the tested organisms apart from *S. epidermidis*, where the combined MIC was lower than the MIC of the root and leaf when autonomously studied but greater than the MIC attained for the extracts from the bark of *C. gratissimus*. The leaf and root combination displayed the most potent efficacy (of the 1:1 combination) with five additive profiles and a singular synergistic profile for the tested organisms. It should be noted that the combination of the leaf and root had been utilized for treating infections of the lungs.

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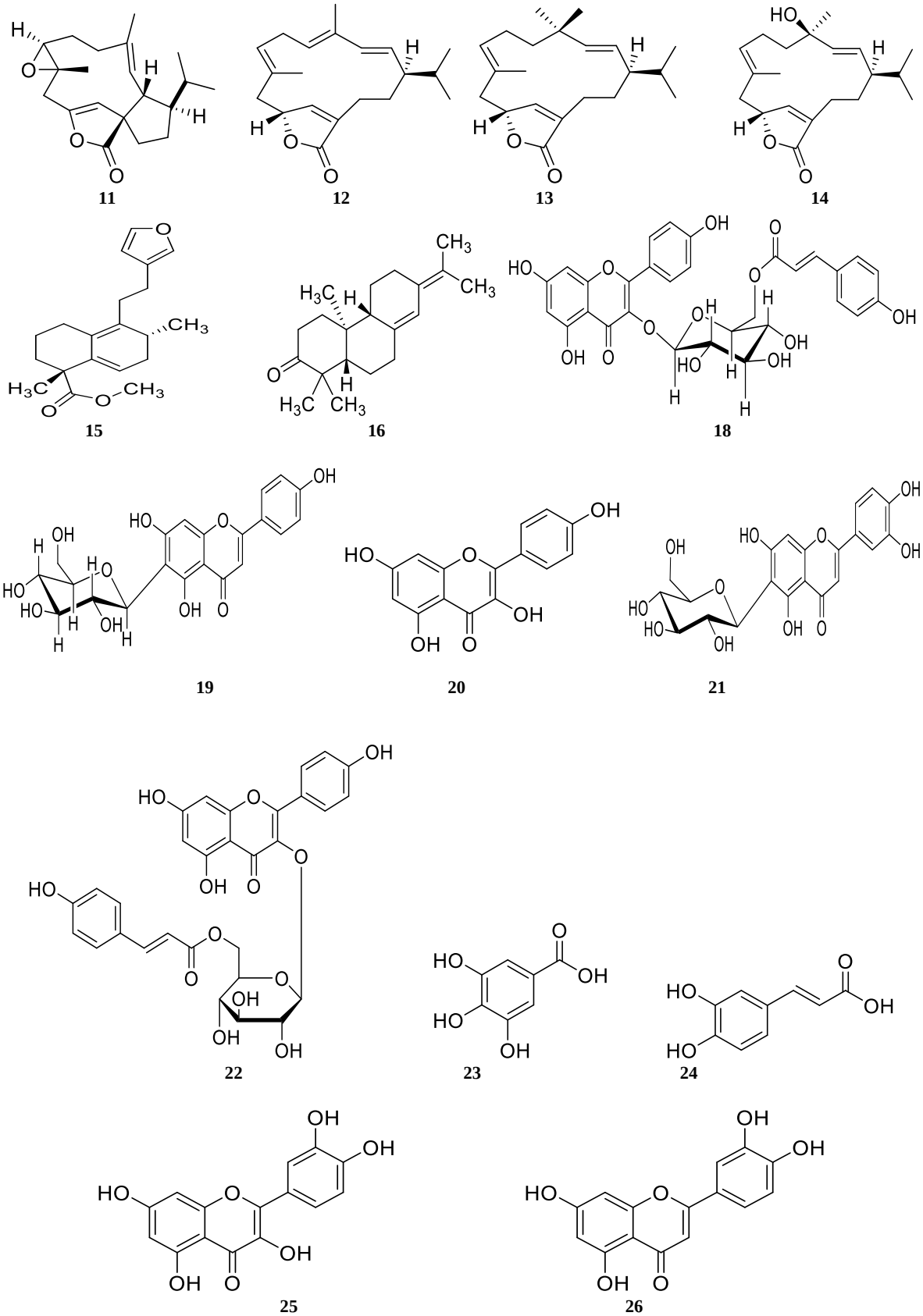

Figure 4: Structures of selected compounds isolated from *Croton gratissimus*

This study further established the plant's folk use to treat respiratory infections. Abo and co-workers, in their study, observed that the aqueous methanol extracts of *C. zambesicus* had significant antimicrobial activity against *Proteus mirabills, Staphylococcus aureus* (NCTC 6571), *Bacillus megaterium* and *Bacillus subtilis.* The results were akin to the antimicrobial activity of ampicillin at 10 µg/mL. Abo and co-workers, in their study, observed that significant antifungal activity relative to tioconazole (0.5 mg/mL) was recorded for the petroleum ether and chloroform fractions at 25 and 50 mg/mL of *Croton zambesicus* (*C. gratissimus*) stem bark with zones of inhibition ranging between 12 – 22 mm against *Aspergillus niger, Microsporum* spp., *Penicillium* spp. and *Candida albicans*. The antimicrobial activity of the methanol extracts (25, 50 and 100 mg/mL) of the leaf and stem bark against similar fungal isolates had a zone of inhibition of 8 – 20 mm. *Candida albicans* was resistant to the methanol extract of *C. zambesicus* leaf at 25 and 50 mg/mL. The study affirms the plant's traditional use to manage dysentery, diarrhoea, and other intestinal ailments.[26] In establishing scientific evidence for the ethnomedical use of *C. gratissimus* for skin and respiratory infections in the Eastern Cape, South Africa, Mthethwa and colleagues evaluated the plant for its antibacterial activities to inhibit *Staphylococcus aureus* and *Staphylococcus epidermidis*.[33] The antibacterial methods explored were Kirby-Bauer disk diffusion and micro-dilution technique. The extract displayed good to moderate anti-staphylococcal bioactivity in the different assays. The extract at 0.1 g/mL had antibacterial activity (average zones of inhibition= 22 – 27 mm and MIC=0.2 µg/mL) against multi-drug resistant *S. aureus* and *S. epidermidis* isolated from humans.

Antidiabetic

The leaf decoction of *C. gratissimus* has been reported in ethnomedical practice to manage diabetes. Nevertheless, only a few systematic studies have reported on the antidiabetic effect of *Croton gratissimus.* Administration of ethanolic leaf and root extracts of *Croton zambesicus* lowered blood glucose in alloxan-induced diabetic rats. These effects were comparable to the reference drugs, chlorpropamide and glibenclamide.[11,67] Still, the process via which these extracts lower blood glucose has not been investigated.

Anticancer

A few research have highlighted the antiproliferative properties of *Croton gratissimus*. The cytotoxicity of acetone and ethanol extracts of *Croton gratissimus* has been demonstrated on A549 (human lung cancer), MCF-7 (breast cancer) cells, Caco-2 (colon cancer), HeLa (cervical cancer), and on non-cancerous (Vero) cell lines. Compared to other Croton species (*C. pseudopulchellus* and *C. sylvaticus*), *Croton gratissimus* demonstrated a higher selectivity index (SI) on the cancer cell lines except MCF-7 indicating selective toxicity to cancer cells.[68] Activation of caspase-dependent apoptosis was suggested as a possible mechanism of cytotoxicity. Also, cembranolides isolated from *Croton gratissimus* stem bark have shown reasonable activity against ovarian cancer cell line- PE01 and paclitaxel-resistant cell line- PEO1TaxR.[41] Also, the antiproliferative effect of *Croton gratissimus* on wil-2 human leukemia cells was comparable to the effect exhibited by the anticancer drug- doxorubicin.[69] Block and colleagues demonstrated the cytotoxicity of some trachylobane and isopimarane-type diterpenoids isolated from purified HSCCC(High-Speed Counter-Current Chromatography) fractions of *Croton zambesicus* leaf extract. Ent-trachyloban-3b-ol- one of the isolated compounds, showed cytotoxicity (IC_{50} =7.3 mg/ml) against Hela cells.[30] Other trachylobane diterpenoids (ent-18-hydroxy-trachyloban-3-one and ent-trachyloban-3-one) and an isopimarane-type diterpenoid (isopimara-7,15-dien-3b-ol) exhibited non-selective cytotoxicity against both cancers (HeLa, HL-60) and non-cancer (WI-38) cell lines.[31] The cytotoxicity of the genus *Croton* has been partly attributed to the presence of diverse diterpenoids. Diterpenoids exert their cytotoxic effects *via* mechanisms such as cell cycle progression inhibition and apoptosis induction.[70]

Antioxidant activities

C. gratissimus has been reported to inhibit free radicals and decrease ferric oxidation *in vitro*. Abdalaziz et al.[71] demonstrated the capacity of the chemical fractions of the fruits to scavenge free radicals, with concomitant reducing power *in vitro*. Ahamed et al.[72] further asserted the capability of the ethanol extract of *C. gratissimus* to hunt free radicals *in vitro*. The effect of *C. gratissimus* on the antioxidant defence system was demonstrated by the ability of the ethanol extracts of its leaves to improve catalase activity and arrest lipid peroxidation in testes of normal albino rats.[73] The antioxidant protective effect of the water extract and fraction (n-butanol) of the leaf was demonstrated by their ability to attenuate oxidative stress in carbon tetrachloride-induced oxidative kidney injury. This is depicted by the exacerbated glutathione, SOD and catalase activities while arresting lipid peroxidation.[74] Ofusori et al.[75] also reported similar observations for the ethanolic leaf extract in diabetic rats' serums. The ethanol root extract as well as the methanol, ethyl acetate and chloroform fractions showed various oxidant generation degrees by producing reduced glutathione and methaemoglobin as a possible mechanism for its antiplasmodial activity.[76]

Anti-inflammatory properties

C. gratissimus has been reported for its anti-inflammatory activities. This is evidenced by reports on the anti-inflammatory activities of *Croton gratissimus* roots ethanolic extract, which was studied via Xylene–induced ear oedema, carragenin-induced oedema, and Egg-albumin- induced inflammation in mice.[77] The water, acetone and ethanol extracts of *C. gratissimus* leaves displayed potent repressive effects on stimulated RAW 264.7 macrophages with LPS. The acetone and ethanol extract also displayed a potent inhibitory effect on 15-lipoxygenase activity.[68] The root extracts have also been reported for their suppressive effect against respiratory oxidative burst in neutrophils and macrophages.[78]

Table 3: Phytochemical compounds from *Croton gratissimus*

Compound class/Plant part	Compound names	Chemical Formula	Biological activities	References
Cembrane Diterpenes/ Leaf	(-)-(1R*,4R*,10R*)-4-Methoxycembra-2E,7E,11Z-trien-20,10-olide **(1)**	$C_{21}H_{32}O_3$	The acetyl derivatives of Compounds 8 and compound 12 demonstrated antiplasmodial activity against a chloroquine-sensitive strain of *Plasmodium falciparum* with IC_{50} values of 13.5 µg/ml and 20.8 µg/ml respectively compared to chloroquine with IC_{50} 27.0 ng/ml	40
	(-)-(1S*,4R*,10R*)-1-Hydroxy-4-methoxycembra-2E,7E,11Ztrien-20,10-olide **(2)**	$C_{21}H_{32}O_4$		
	(-)-(1S*,4S*,10R*)-1,4-Dihydroxycembra-2E,7E,11Z-trien-20,10-olide **(3)**	$C_{20}H_{30}O_4$		

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	(-)-(1S*,4S*,10R*)-1,4-Dihydroxycembra-2E,7E,11Z-trien-20,10-olide **(4)**	$C_{20}H_{30}O_4$	-	
	(+)-(10R*)-Cembra-1E,3E,7E,11Z,16-pentaen-20,10-olide **(5)**	$C_{20}H_{26}O$	-	
	(+)-(10R*)-Cembra-1Z,3Z,7E,11Z,15-pentaen-20,10-olide **(6)**	$C_{20}H_{26}O$		
	(+)-(5R*,10R*)-5-Methoxycembra-1E,3E,7E,11Z,15-pentaen-20,10-olide **(7)**	$C_{21}H_{30}O_3$	-	
	(+)-(1S*,4S*,7R*,10R*)-1,4,7-Trihydroxycembra-2E,8(19),11Z-trien-20,10-olide **(8)**	$C_{20}H_{30}O_5$	-	
	(-)-(1S*,4S*,7S*,10R*)-1,4,7-Trihydroxycembra-2E,8(19),11Z-trien-20,10-olide **(9)**	$C_{20}H_{30}O_3$	-	
	(+)-(1S*,4R*,8S*,10R*)-1,4,8-Trihydroxycembra-2E,6E,11Z-trien-20,10-olide **(10)**	$C_{20}H_{30}O_5$	-	
	(+)-(1R*,10R*)-cembra-2E,4E,7E,11Ztetraen- 20,10-olide **(11)**	$C_{20}H_{28}O_2$	-	
	(+)-(1R*,4S*,10R*)-4-hydroxycembra-2E,7E,11Z-trien-20,10-olide **(12)**	$C_{20}H_{30}O_3$	-	
Cembrane Diterpenes/Stem bark	(+)-[1R*,2S*,7S*,8S*,12R*]-7,8-Epoxy-2,12-cyclocembra-3E,10Zdien-20,10-olide **(13)**	$C_{20}H_{28}O_3$	Compounds 13 and 15 were moderately cytotoxic against the taxane sensitive (PEO1) and resistant (PEO1TaxR) human ovarian cancer cells	41
	(+)-[1R*,10R*]-Cembra-2E,4E,7E,11Z-tetraen-20,10-olide (**11)**	$C_{20}H_{28}O_2$	-	
	(+)-[1R*,4S*,10R*]-4-Hydroxycembra-2E,7E,11Z-trien-20,10-olide **(12)**	$C_{20}H_{30}O_3$	-	
	(-)-[1R*,4R*,10R*]-4-Hydroxycembra-2E,7E,11Z-trien-20,10-olide **(14)**	$C_{20}H_{30}O_3$	-	

Diterpenes/Leaf	12-β-furanyl-halima-5,9-dien-4-methylcarboxylate (gratissihalimanoic ester) **(15)**	$C_{20}H_{26}O_3$	Both gratissimone and gratissihalimanoic ester showed no antimicrobial activity at 1 mg/ml against Gram-negative bacteria strains (*Pseudomonas aeruginosa* and *Escherichia coli*) and Gram-positive bacteria strains (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus cereus*)	42
	(5S,9R,10S)-ent-abiet-8(14),13(15)-dien-3-one (gratissimone) **(16)**	$C_{20}H_{30}O$		
	Ent-18-hydroxy-trachyloban-3-one **(17)**	$C_{20}H_{30}O_2$	Inhibited KCl and noradrenaline-induced rat aorta contraction	43, 44
	Ent-trachyloban-3 β -ol **(18)**		Demonstrated cytotoxicity on HeLa cells (IC_{50} = 7.3 µg/ml) with greater potency than the crude dichloromethane leaf extract (IC_{50} = 36.2 µg/ml) but lower potency than standard anticancer drug, camptotecin (IC_{50} = 0.01 µg/ml)	30
			Inhibited the growth of HL-60 cancer cell line and induced a caspase-dependent apoptosis	45
	Ent-18-hydroxy-trachyloban-3-one **(17)**	$C_{20}H_{30}O_2$	Demonstrated varying cytotoxic effects on cancer cell lines (HeLa, HL-60) and non-cancer cell lines (WI-38).	31
	Isopimara-7,15-dien-3β-ol **(19)**	$C_{20}H_{32}O$	**HeLa**: Enttrachyloban-3-one > Ent-18-hydroxy-trachyloban-3-one > Trans-phytol> Isopimara-7,15-dien-3β-ol **HL-60**: Enttrachyloban-3-one > Ent-18-hydroxy-trachyloban-3-one> Trans-phytol> Isopimara-7,15-dien-3β-ol **WI-38**: Trans-phytol> Ent-18-hydroxy-trachyloban-3-one> Enttrachyloban-3-one > Isopimara-7,15-dien-3β-ol	
	Enttrachyloban-3-one (**20**)	$C_{20}H_{30}O$		
	Trans-phytol **(21)**	$C_{20}H_{40}O$		
	Ent-18-hydroxytrachyloban-3β-ol **(22)**	$C_{20}H_{32}O_2$	Compounds-**22** and **23** demonstrated vasorelaxant activity by inhibiting KCl -induced rat aorta contraction, although a higher vasorelaxant activity was noted for the mixture of both trachylobane and pimarane-type diterpenes Non-cytotoxic on HeLa cells	46
	Ent-18-hydroxyisopimara-7,15-diene-3β-ol **(23)**	$C_{20}H_{32}O_2$		
Diterpenes/Stembark	7b-acetoxytrachyloban-18- oic acid **(24)**		-	47
	Trachyloban-7b, 18-diol **(25)**		-	
	Crotonadiol **(26)**	$C_{19}H_{23}O_1$	-	
	Crotocorylifuran **(27)**	$C_{22}H_{26}0_7$	-	
	crotozambefurans A **(28)**	$C_{22}H_{24}O_7$	-	28
	crotozambefurans B **(29)**	$C_{23}H_{28}O_7$	-	

	crotozambefurans C **(30)**	$C_{21}H_{22}O_7$	-	
Triterpene/ Leaf	α-amyrin **(31)**	$C_{30}H_{50}O$	Non-cytotoxic on HeLa, HL-60 and WI-38 cell line (IC_{50} >30 mg/mL). Antihyperglycemic effect; Anti-inflammatory activity; Antioxidant action; Antifungal effect	31,48
	Lupeol **(32)**	$C_{30}H_{50}O$	Antiprotozoal; Anti-inflammatory; Anticancer activity	40
	α-glutinol **(33)**	$C_{30}H_{50}O$	Antiinflammatory effect	49, 50
Sesquiterpenes	4(15)-eudesmene-1β,6α-diol **(34)**	$C_{15}H_{26}O_2$	-	40
Sterols/ Leaf	β-sitosterol **(35)**	$C_{29}H_{50}O$	Non-cytotoxic effect on HeLa, HL-60, and WI-38 cell lines. Inhibits the growth of KKU-M213 human cholangiocarcinoma cell line.	31, 51
	Stigmasterol **(36)**	$C_{29}H_{48}O$		
Flavonoid and Flavonoid glycoside/ Leaf	quercetin-3-O-β-6$^{//}$-- (p-coumaroyl) glucopyranoside-3$^{/}$-methyl ether (helichrysoside-3$^{/}$ -methyl ether) **(37)**	$C_{31}H_{28}O_{14}$	*In vitro* antioxidant activity Isovitexin was not cytotoxic to the Vero cell line, while Tiliroside and helichrysoside-3$^{/}$-methyl ether showed slight cytopathic effect only at the highest concentration (200 µg/ml)	52
	kaempferol-3-O- β -6$^{//}$ (p-coumaroyl) glucopyranoside (tiliroside) **(38)**	$C_{30}H_{26}O_{13}$		
	apigenin-6-C-glucoside (isovitexin) **(39)**	$C_{26}H_{28}O_{14}$		
	Kaempferol-3-O-β-6$^{//}$ (p-coumaroyl) glucopyranoside (tiliroside) **(38)**	$C_{30}H_{26}O_{13}$	Compounds-**38, 39** and **40** demonstrated *in-vitro* antioxidant activity radical scavenging, inhibition of lipid peroxidation and $Fe3^{+}$ reducing ability) and acetylcholinesterase inhibitory effect.	53
	Apigenin-6-C-glucoside (isovitexin) **(39)**	$C_{26}H_{28}O_{14}$		
	Kaempferol **(40)**	$C_{15}H_{10}O_6$		
	Isoorientin **(41)**	$C_{21}H_{20}O_{11}$	Exhibits Anti-inflammatory effects via electively cyclooxygenase-2 (COX-2) inhibition, reduce expression of inflammatory proteins: TNF-α; IL-6, IL-1-β, 5-LOX.	52, 54
	kaempferol-3-β-D-(6″-O-trans-p-coumaroyl) glucopyranoside **(38)**	$C_{30}H_{26}O_{13}$	Increased phase II detoxifying enzyme activities and antioxidant effects; Cytopathic action; Acetylcholinesterase inhibitory effect.	55, 56
	Gallic acid **(42)**	$C_7H_6O_5$	Antidiabetic action insulin sensitivity through activation of PPAR-γ and Akt signaling; Cardioprotective effects; Antimicrobial action.	57, 58
	Caffeic acid **(43)**	$C_9H_8O_4$	Antioxidant activity; Anticancer effect.	
	Quercetin **(44)**	$C_{15}H_{10}O_7$	Anti-inflammatory; Antioxidant action; Immunomodulating effects; Antimicrobial action.	
	Luteolin **(45)**	$C_{15}H_{10}O_6$	Anticancer effects.	59

	Apigenin **(46)**	$C_{15}H_{10}O_5$	Antidepressant, anticancer, antioxidant, antidiabetes, anti-inflammatory.	60
				61, 62, 63
Flavonoid/Fruit	Quercetin-3,3′,4′-trimethylether **(47)**	$C_{18}H_{16}O_7$	Flavonoids demonstrated varying	64
	Ayanin **(48)**	$C_{18}H_{16}O_7$	antileishmanial antiplasmodial and	
	Retusin **(49)**	$C_{19}H_{18}O_7$	antitrypanosomal activities.	
	Naringenin **(50)**	$C_{15}H_{12}O_5$	Quercetin-3,7′-dimethylether demonstrated the	
	Quercetin-3,4′-dimethylether **(51)**	$C_{17}H_{14}O_7$	highest antileishmanial (IC_{50} = 4.5 ± 0.3 μM)	
	Quercetin-3,7′-dimethylether **(52)**	$C_{17}H_{14}O_7$	and antitrypanosomal activity (IC_{50} 2.4 ± 0.5 μM) among all 5-flavonoid tested.	
Alkaloid/Fruit	Laudanine **(53)**	$C_{20}H_{25}NO_4$	The alkaloids laudanine and laudanosine, showed only marginal antileishmanial activity	
	Laudanosine **(54)**	$C_{21}H_{27}NO_4$	against L. donovani axenic amastigotes (IC50 > 150 μM).	
Benzoic acid/Fruit	Methoxy-4-hydroxybenzoic acid **(55)**	$C_8H_8O_4$	Demonstrated a low antiprotozoan activity	

-=No reported biological activity yet; COX-2=Cycloxygenase-2, TNF-α=tumor necrosis factor-α; IL-6=interleukin-6; 5-LOX=5-lipoxygenase; IL-1-β= interleukin 1-β; PPAR= Peroxisome proliferator-activated receptor gamma; Akt/PKB = Protein kinase B.

Haemostatic studies

The dichloromethane and aqueous extracts and fractions of *C. zambesicus* (syn. *C. gratissimus*) leaf were reported on hemostasis[79] Robert and colleagues observed that the tested extracts and fractions at 1 mg/mL had no hemolytic and antiplatelet (at 200 µg/mL) activity. In contrast, the extracts and fractions showed reasonable but noteworthy inhibitory coagulant potential, probably mediated via the direct inhibition of, factor Xa (Fxa), thrombin and tissue factor/factor VIIa complex (T.F./FVIIa). The water extract, precisely the aqueous fraction, displayed the most significant anticoagulant activity. The extracts and fractions (100 µg/mL) repressed the thrombin's amidolytic activity, FXa and marginally T.F./FVIIa compared to the positive control -Argatroban at 0.05 µg /mL that only pointedly repressed thrombin. This report confirms the traditional use of *C. gratissimus* in managing cardiovascular diseases.

Nephroprotective activity

Okokon and colleagues, in 2011, investigated the ethanolic extract of *C. zambesicus* root for its kidney-protective potential against a gentamicin-induced kidney injury.[80] In the research, *C. zambesicus* root extract at 24 and 54 mg/kg had better nephroprotective activity than the highest dose of 81 mg/kg against the assessed biochemical parameters (urea, uric acid, and creatinine) and ions (chloride, sodium, potassium, and bicarbonate). Similarly, the results corroborated an earlier study on the nephroprotective activity of *C. zambesicus* root extract in diabetic rats.[81] Additionally, Okokon et al. [80] observed remarkable adverse changes in the rats' kidney histology treated with gentamicin and paracalcitriol (reference drug). The histological injuries include oedematous glomerular associated with oedematous interstitium, periarteriolar haemorhage, thyroidization(colloidal casts), atrophic and degenerated glomerular, inflammatory cells infiltrate, congested and dilated capillaries as well as ruptured and degenerated glomerular. However, the simultaneous administration of the ethanolic extract of *C. zambesicus* root between 24 and 54 mg/kg showed a decrease in histological injuries.

Analgesic effect

Formalin-induced paw licking, acetic acid-induced writhing, and thermal-induced pain in mice were utilized to determine the analgesic potential of the ethanol extract of *C. zambesicus* root.[77] In the experiment, the extract (27-81 mg/kg) greatly reduced (P<0.05- 0.001) the acetic acid-induced abdominal constrictions and stretching of hind limbs in correspondence with the dose. The results of the investigation were comparable to the negative control and the standard drug (ASA, 100 mg/kg). In the formalin-induced paw licking method, the extract displayed a noteworthy (P < 0.05- 0.001) reduction in hind paw licking in a dose-related manner compared to the conventional drug (ASA, 100 mg/kg). The extract's administration exhibited a substantial (P < 0.05- 0.001) dose-dependent increase in the latency response to the hot plate-induced pain in the mice.

Anti-ulcerogenic effect

Okokon and Nwafor[82] evaluated the antiulcer effect *C. zambesicus* ethanol extract using three ulcer models (ethanol, indomethacin, and reserpine-induced models). In the indomethacin-induced ulcer model, a significant (P<0.05-0.001) dose-dependent (27 – 81 mg/kg) progressive decline in the ulcer index (10.41- 4.50) compared to the control (indomethacin) was noticed in the rat pre-treated with *C. zambesicus* ethanol root extract. The extract also displayed a preventive ratio ranging between 30.18 – 69.82. The extract's effect demonstrated a significant (P<0.001) decrease in mucosal damage, indicating a possible participation of prostaglandin in the anti-ulcerogenic activity of the extract. Similarly, in the ethanol-induced ulcer model, the extract exerted a significant (P<0.001) dose-dependent (27 – 82 mg/kg) reduction in the ulcer index (4 – 1.83). The extract's effect in the reserpine-induced ulcer model showed a progressive increase in the preventive ratio (20-63.4). The extract exhibited a significant (P<0.001) decrease in the ulcer index (11 – 5.16) in a correspondingly increase in the dose (27 – 81 mg/kg). In a different study, the ethanol extract of *C. zambesicus* leaf was evaluated via the indomethacin, ethanol, and histamine-induced ulcer models in rats. In each model, the ethanol extract of the leaf showed a significant (P<0.001) reduction in the ulcer index with a corresponding increase in the preventive ratio compared to the ulcerogens (indomethacin, ethanol and histamine). The extract's gastroprotective effect increased correspondingly to the increase in the dose (200 – 600 mg/kg). [83]

Antiparasitic studies

The antiplasmodial prospect of *C. zambesicus* was determined via the drug sensitivity test against the multi-drug resistant (K1) and the chloroquine-sensitive (NF54) *Plasmodium falciparum* strain in a microtiter plate.[29] The methanol extract of *C. zambesicus* seed had considerable inhibitory activity against the K1 and NF54 strains with the corresponding IC_{50} of 7.81 and 3.79 µg/mL. Similarly, in a parasite lactate dehydrogenase (pLDH) assay to measure the viability of the parasite against the chloroquine-sensitive *P. falciparum* strain (D10), the dichloromethane extract of *C. zambesicus* leaf was found to

be highly active against the plasmodium (IC_{50} = 3.5 µg/mL).[84] In an animal model, chloroquine-sensitive *P. berghei berghei* infected mice (25-32 g) were treated with *C. zambesicus* leaf ethanol extract (50 - 200 mg/kg) to assess the blood schizontocidal effect.[10] The extract displayed a dose-dependent schizontocidal activity in the initial and confirmed infections and in the repository activity. The antiplasmodial effect was lower than the positive control drugs (chloroquine 5 mg/kg, pyrimethamine 1.2 mg/kg/day) [10]. Okokon and Nwafor[76], in their antiplasmodial research, explored the ethanol extract (27- 81 mg/kg) and fractions (54 mg/kg) of *C. zambesicus* root in a mice-infested chloroquine-sensitive *P. berghei berghei*. The extract had a dose-dependent significant (P < 0.01–0.001) decrease in parasitaemia (Schizonticidal activity) compared to the controls (distilled water 0.2mL, chloroquine 5 mg/kg, pyrimethamine 1.2 mg/kg/day) during the initial and established infections period. Again, the extract at all doses had a significant (P < 0.01) mean survival time (MST) much extended than the control (distilled water). The fractions (ethyl acetate, chloroform, and methanol) had a relative chemosuppressive activity of 75.39, 76.89 and 77.27%, correspondingly. In Boyom et al.[35], the methanol extract of *C. zambesicus* stem bark displayed antiplasmodial effect against chloroquine-resistant *P. falciparum* W2 strain (IC_{50} = 5.69 ug/mL). The extract was not active against the *Trypanosoma* spp (*T. cruzi* strain and *T. brucei rhodesiense* strain in the prolonged incubation low inoculation (LILIT) test for the antitrypanosomal study.[29]

In the antileishmanial activity, the multipoint test was explored to assess the susceptibility of *L. donovani* against the methanol extract of the seed. The extract had an IC_{50} more significant than 30 µg/mL.[29] In a different study, the 70% ethanol extract and fractions of *C. zambesicus* root were assessed against promastigotes of *Leishmania major* (DESTO) in a 96 – well microplate.[78] The study revealed that the fractions (n-hexane, butanol, dichloromethane, ethyl acetate, and water), and the crude extract expressed significant antileishmanial activity against *Leishmania major* promastigotes. The ethyl acetate fraction had the greatest antileishmanial activity at an ED_{50} of 51.10 µg/mL. These studies strengthen the folk use of the plant as an antimalarial agent.

Anticonvulsant activity

The anticonvulsant prospect of *C. zambesicus* root was assessed using the picrotoxin and pentylenetetrazol (PTZ)- induced convulsion model in mice.[82] In the anticonvulsant study, the ethanol extract within the administered dose (27 – 81 mg/kg) had no protective effect against clonic and tonic convulsion in the pentylenetetrazol and picrotoxin-induced convulsion in mice. However, the extract could significantly (P<0.01-0,001) delay the commencement and latency of convulsion induced by pentylenetetrazol and picrotoxin in the mice .[82]

Immunomodulatory effect

The immunomodulatory capacity of the ethanol root extract of *C. zambesicus* via antioxidant cellular activity in neutrophils, whole blood, and macrophages in a chemiluminescence study was done. The extract at the least doses induced oxidative stress and, in contrast, had an antioxidant activity at the higher doses, particularly in full blood. The extract had an inhibitory oxidative activity of -27.90-66.90% in whole blood, 16.50 - 87% in intracellular neutrophils, 39.30 -71.70% in extracellular neutrophils and 4.31- 98.50% in macrophages.[78]

Neuropharmacological activity

The neuropharmacological effect of *C. zambesicus* aqueous extract at 1000 and 1500 mg/kg in mice extended the thiopental sodium-induced sleeping time, while at 20 and40 mg/kg, the extract in a dose-dependent manner had a significant (P<0.05) decline in gross locomotor activity in chicks of 2-day old. The extract administered at 40-60 mg/kg (i.p) caused sedation and sleep with a significant (P<0.05) decline at the beginning and an upsurge in the period of sleep. The subcutaneous administration of the extract had no significant (P > 0.05) effect on stereotyped behaviour in chicks induced with apomorphine. The neuropharmacological study revealed that the aqueous extract of *C. zambesicus* leaf had central nervous system (CNS) depressant, sedative, and hypnotic properties.[85]

Antipyretic activities

The antipyretic effect of *C. zambesicus* was evaluated using the 2, 4 – Dinitrophenol (DNP)- induced pyrexia, D-amphetamine-induced pyrexia and yeast-induced pyrexia.[77] In the DNP-induced pyrexia, the ethanol extract of the root at 27, 54 and 81 mg/kg significantly (P<0.05-0.001) reduced hyperthermia in the rats compared to acetic, salicylic acid-ASA (standaed drug) at 100 mg/kg. The antipyretic activity was dose-independent. At 81 mg/kg, the extract exerted the best antipyretic effect by significantly reducing the rat's temperature from 36.68 to 34.38 oC in the D-amphetamine-induced pyrexia rats. The dose-dependent antipyretic effect was significant (P < 0.05-0.001) compared to the control (distilled water, 10 mL/kg). An increasing dose-dependent reduction in temperature was expressed in the yeast-induced pyrexia rats. The extract had an antipyretic effect more significant than the ASA at 100 mg/kg. The antipyretic effect was significant (P < 0.05-0.001) compared to the control (distilled water, 10 ml/kg).

Toxicity studies

Claims on the general safety of medicinal plants emanate from their prolonged anecdotal use in treating diseases. However, not all these claims have been scientifically validated, hence caution in using the medicinal plant. Therefore, medicinal plants' safety assessment allays concerns relating to their potential toxicological impact and adverse reactions, especially on chronic consumption. In a study, the potential toxicity of *C. gratissimus* revealed the necrosis of liver and kidney in rats when treated daily with methanol and aqueous seed extracts at 75 and 300 mg/kg, correspondingly, for fourteen days.[86] The tissue damage was observed despite an improvement in haematological indices.

Furthermore, treatments resulted in intestinal lymphocyte infiltration, demonstrating the plant's potential to cause intestinal injury. The ethanolic leaf extract administered at 100 - 400 mg/kg for twenty-one days also suppressed haemopoiesis and caused anaemia in rats.[87] However, data from previous studies suggest that either at lower doses or shorter exposure to *Croton zambesicus*, there are beneficial effects against toxicant-induced organ injury.[80, 88] More studies evaluating the dose and duration-related potential toxicity of *C. gratissimus* are warranted. Furthermore, elucidation of specific plant components that may be responsible for the observed toxic or tissue-protective effects is required.

Other Biological activities

The bark extract of *C. gratissimus* had no inhibitory HIV activity over the 5 - 150 µg/mL concentration range.[89] In a different study, the leaf extract of *C. gratissimus* was described to prevent HIV-IIb replication via MT-4cells.[33] In a different research, Ofusori and colleagues evaluated the activity of *C. zambesicus* ethanol extract against specific testicular parameters (sperm progressivity, sperm concentration, sperm motility, , malondialdehyde and catalase activities) in mice. The study showed that the extract administration to the mice resulted in a substantial increase in sperm production, sperm motility and sperm progressivity and a decrease in malondialdehyde and catalase activity in all the groups.[73] Additionally, the ethanol extract of the leaf of *C. zambesicus* was assessed for gastric emptying ability and gastric mucosa integrity in rats with diabetes. The activity of *C. zambesicus* leaf ethanol extract on nitric oxide (NO), histomorphometry, and prostaglandin E2 (PGE_2) levels in streptozotocin (STZ) -induced diabetic Wistar rats was also evaluated.[90] The results revealed a substantial increase (P<0.05) in gastric emptying capacity in the pre-treated group of rats (78.40 ± 2.99%) while the four weeks treated group recorded 72.80 ± 5.82% compared to the untreated STZ-induced diabetic group (39.20 ± 6.15%). In the NO and PGE_2 experiments, the extract decreased significantly (p<0.05) NO and PGE_2 in the rat serum in the untreated diabetic rats compared to the extract group. The histomorphometry of the stomach tissues was significantly (p<0.05) improved in the group administered the extract likened to the STZ-induced diabetic rats.

Conclusion

The current review summarizes the traditional uses, botanical features, nutritional constituents, chemical components, and C. gratissimus extracts and bioactive compounds' pharmacological activities. The study indicated the plant's effectiveness in treating and managing infectious and non-infectious diseases. It is appropriate to note that the present review may add scientific value and boost the sustainable commercialization of *C. gratissimus* herbal tea (Moologa tea). It is expected that the commercialization of *C. gratissimus* herbal tea will significantly boost the bioeconomy of the communities involved in the cultivation/growing of the plant with the potential of the product becoming a local and an international pharmaceutical /herbal product. It is important that more pragmatic research outlining the *in vivo* models, molecular expression, and mechanistic studies of *C. gratissimus* be focussed on and addressed considering the myriad of previous pharmacological reports. Clinical studies may be required to validate these claims' benefits in humans, particularly under disease conditions.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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