Heliyon 10 (2024) e23640

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Trema orientale (L.) Blume: A review of its taxonomy, traditional uses, phytochemistry, pharmacological activities and domestication potential

Yaw Appau [a,*], Paa Kwesi Gordon [b], Seyiram Kumordzie [a], Michael Odoi Kyene [c], Peter Atta-Adjei Jnr [a]

[a] Department of Plant Development, Centre for Plant Medicine Research, P.O. Box 73, Akuapem-Mampong, Ghana
[b] Department of Microbiology, Centre for Plant Medicine Research, P.O. Box 73, Akuapem-Mampong, Ghana
[c] Department of Pharmaceutics, Centre for Plant Medicine Research, P.O. Box 73, Akuapem-Mampong, Ghana

ARTICLE INFO

Keywords:
Trema orientale
Domestication potential
Taxonomy
Phytochemistry
Medicinal plant

ABSTRACT

Trema orientale (L.) Blume is an important medicinal plant with multiple applications for treating several disease conditions. This study compiled published data on botanical, traditional uses, phytochemistry, pharmacology, and antimicrobials, coupled with discussing the conservation and domestication potential of *T. orientale*. Data were sourced from databases such as Google Scholar, PubMed, Scopus, Elsevier Plants of the World Online (Kew Science), Global Biodiversity Information Facility (GBIF), and World Flora Online (WFO), using key search terms: *Trema orientale* or *orientalis*, phytochemistry pharmacology, taxonomy, and domestication with Boolean operators to include and exclude articles for the review. The review indicated that molecular studies have shown that *T. orientale* is closely related to a sister group of Cannabis through plastome phylogenetic evidence which accounts for its transfer from Ulmaceae to the Cannabaceae family. *T. orientale* is distributed across several African countries and has recently been assessed as the Least Concern by the IUCN Red List of Threatened Species. Nevertheless, deforestation continues to pose an extinction risk to their population. Currently, 31 compounds have been isolated from different parts of *T. orientale* justifying many traditional uses accredited to it. *T. orientale* is considered a dose-dependent safe remedy for the treatment of infectious diseases, cancer, cardiovascular diseases and other disease conditions ascribed to it except for its continuous application. This review underscores the domestication potential of *T. orientale* including evidence of molecular markers, soil seed banks, and promising outcomes of germination experimentations. This, therefore, presents significant gains toward sustainable utilization of *Trema orientale*.

1. Introduction

The use of plants as medicine has been the backbone of mankind's existence on Earth. This is particularly important in most tropical countries where their rich plant biodiversity affords them the luxury to select from the plethora of plant resources with therapeutic potential. In developing countries, the use of plant medicine is the primary medical remedy for many people especially, among the

* Corresponding author.
E-mail address: yawappau84@gmail.com (Y. Appau).

https://doi.org/10.1016/j.heliyon.2023.e23640
Received 12 May 2023; Received in revised form 23 November 2023; Accepted 8 December 2023
Available online 13 December 2023

rural population for treating and managing various disease conditions [1]. About 80 % of the world's population depends on herbal medicine because it is less costly, readily and easily accessible to consumers [2].

The application of plant medicine as primary healthcare has been heightened in the 21st century [3]. It is now more popular among the elite who hitherto doubted the efficacy and safety of plant medicine. This could be attributed to the integration of orthodox synthesis of drugs into the plant medicine production system [4]. As a result, many chemical constituents with multiple medicinal potentials have been isolated from plants, confirming the medicinal potency of most plants [5–7]. In addition, the availability of *in-vitro, ex-vivo* [8–11], and clinical trials of some plants to ascertain their efficacies have been studied [12,13]. The recognition by the World Health Organization (WHO) of the effectiveness of herbal remedies and the subsequent support to countries to develop and improve herbal medicine has also assuaged fears and myths associated with the use of plant medicine [14]. Literature has reported on the medicinal potency of several plants for treating common ailments like cancer, malaria, fever, asthma, and diarrhoea [15–19].

Trema orientale (L.) Blume. is an evergreen tree in the family Cannabaceae. Some of its common names include charcoal tree, gunpowder tree, pigeon wood, hop out, Indian charcoal tree, and Indian nettle tree. It has a widespread distribution across several zones, particularly in the tropics, and some temperate zones. It is indicated that almost all parts of the plants have some medicinal application [20]; stem bark for the treatment of malaria [21], leaves are used as dewormers for hookworms and roundworms [22], inflammatory and respiratory diseases [23]. It thrives well in the humid tropics and it is mostly sourced from the wild.

Forest biodiversity is an important source of plant resources [24]. However, land use changes particularly the conversion of rich biodiversity areas for farming, physical developments, and mining with its attendant problem of climate change pose a serious extinction risk to the sustainable utilization of plants in general particularly *T. orientale*. For instance, Uganda reported that rapid habitat loss has exacerbated the already dwindling population sizes of *T. orientale* [25], although previous authors have widely reviewed the importance of *T. orientale* in terms of phytoconstituents [26–28], and mechanical and wood properties [29–31]. Yet, there is a dearth of review data on the botany/diversity and domestication potential of *T. orientale* demonstrated by literature. Thus, this review sought to highlight the botany, availability, medicinal importance, and domestication potential, in addition to the pharmacological and phytoconstituents of *Trema orientale*. This review exemplifies a comprehensive documentation of available literature on *T. orientale* in contemporary times.

2. Methodology

Information for this review was gleaned from Google Scholar, Research Gate, PubMed, Science Direct, Elsevier, Taylor and Francis and other online resources such as the POWO and WFO. The keywords used in the search engines are Trema, taxonomy, phytochemistry, biological activity, traditional uses and domestication of *Trema orientalis*. These keywords were used together with other terms relating to the subject of the review and were used interchangeably during the search process. For Google Scholar, Google, Research Gate, Scopus, Elsevier, Taylor and Francis and PubMed we only searched for peer-reviewed articles published between 2000 and 2022 with the keyword "*Trema*. From our analysis of the search results, it was realized that most of the articles reported on the wood/mechanical properties of *T. orientale*. The next action was to search with Boolean operators (AND, OR or AND NOT, +) to combine or exclude the key terms that directly relate to the purpose of this review in all the databases searched. Thus, we used the terms 'taxonomy', 'phytochemistry', 'biological activity, 'traditional uses', and 'domestication potential' of the Genus Trema in the searches (Table 1). This excluded some of the documents resulting in articles mainly reporting on the phytochemistry, and biological/ pharmacological activities of the Genus Trema with little information on the botanical and conservation aspects. Further screening with specific emphasis on *Trema orientale* using the same keywords excluded some of the articles. We analyzed each of the remaining articles and key points relating to phytochemistry, and biological activity summarized. We, therefore, resorted to the POWO, WFO Plant List, and GBIF databases to analyze the taxonomic data using these keywords 'botanical description'; 'traditional uses'; and 'domestication of *T. orientale*' together with the Boolean operators (Table 1). All documents directly relating to the inclusion criteria were analyzed and included in the review.

3. Taxonomy of *Trema orientale*

Trema orientale, formerly *Trema orientalis* in the Kingdom Plantae falls under the taxonomic rank of vascular plants Phylum Tracheophyta and a subdivision Spermatophytina (spermatophytes, seed plants, or phanérogames). It is also categorized under the class Magnoliopsida and associated with the order Rosales. Nested within the Rosales are four families, which in the past have been variously delimited in an order of Urticales. The Urticales informally referred to as Urticalean Rosids, comprise Ulmaceae, Moraceae,

Table 1
Key search criteria.

Trema OR Trema orientalis OR Trema orientale
AND
Phytochemical OR Phytoconstituents + Pharmacology OR Biological activity
AND
Taxonomy OR Botany OR Botanical description
AND/OR
Domestication OR Cultivation
Economic importance OR Traditional uses

Urticaceae and Cannabaceae. These families are grouped based on their shared characteristics and they include taxa with small, unisexual and wind-pollinated flowers [32,33]. It is worth noting that, the distinctive characteristics of these plant families have led to their worldwide classification as culturally and economically important plants. *T. orientale* previously belonged to Ulmaceae but is currently an accepted species in Cannabaceae. Molecular studies have shown that *T. orientale* is closely related to a sister group of Cannabis through plastome phylogenetic evidence [34]. Further knowledge on the uses of some species, particularly, in the genera Cannabis L., Celtis L., Trema Lour. and Humulus L. has been reported in previous studies [35,36]. They contribute immensely to addressing critical challenges facing humanity such as healthcare, poverty and food security. For instance, *Cannabis sativa* is used as a bast fiber plant; hemp, and the euphoric medicinal plant; marijuana [33,37].

The family Cannabaceae consists of 9 genera and 109 accepted species (https://powo.science.kew.org/; accessed on January 25, 2023). The family is predominantly of trees and shrubs but is also represented by herbs and vines. They are dioecious or sometimes monoecious, leaves are alternate, opposite, compound or sometimes simple. Other studies reported that Cannabaceae is currently recognized as a distinct family consisting of Cannabis L. and Humulus L. which was initially separated from the family Moraceae by Rendle [34,37,38]. Molecular studies on Cannabaceae remain unresolved because of limited taxon and character sampling, however, some morphological characters can be used for their identification [39].

3.1. Distribution, habitat and description Trema orientale (L.) Blume

T. orientale, is a large shrub or medium-sized tree found in the tropical and sub-tropical wet regions. It has an extensive root system that enables it to survive long periods of drought [40]. The height varies depending on the location and climatic conditions. In general, it prefers sites that experience high rainfall and the form it takes is dependent on the individuals' access to water, thus, it can grow from 8 ft to 20 ft in height [41,42]. It has a short basally swollen bole, heavy branching rounded to spreading crown and slender branchlets covered with white velvety hairs (Fig. 1c). The stem bark is grey or dark brown, smooth, and marked with parallel longitudinal lines and corky spots (Fig. 1d). It produces a creamy-white to light yellow, fibrous, bright green latex immediately beneath the bark when slashed [23,43]. The leaves are long, simple, alternate, stipulate along drooping branches about 14 cm long, and the stipules are three-nerved at the base, with unequal size (Fig. 1b). The leaf surface is papery, glabrous, rough to the touch and dull at the adaxial surface with short grey hairs below. The edges are finely toothed all around with an unequal-sided blade [43]. Leaf margins are closely serrated from near the base, whereas the juvenile leaves are rough and hairy, up to (15 × 9 cm) but become smooth when they mature. The plant is pollinated by bees and flowers from December to February, producing cymes about 5–10 mm long [44]. Flowers are mostly

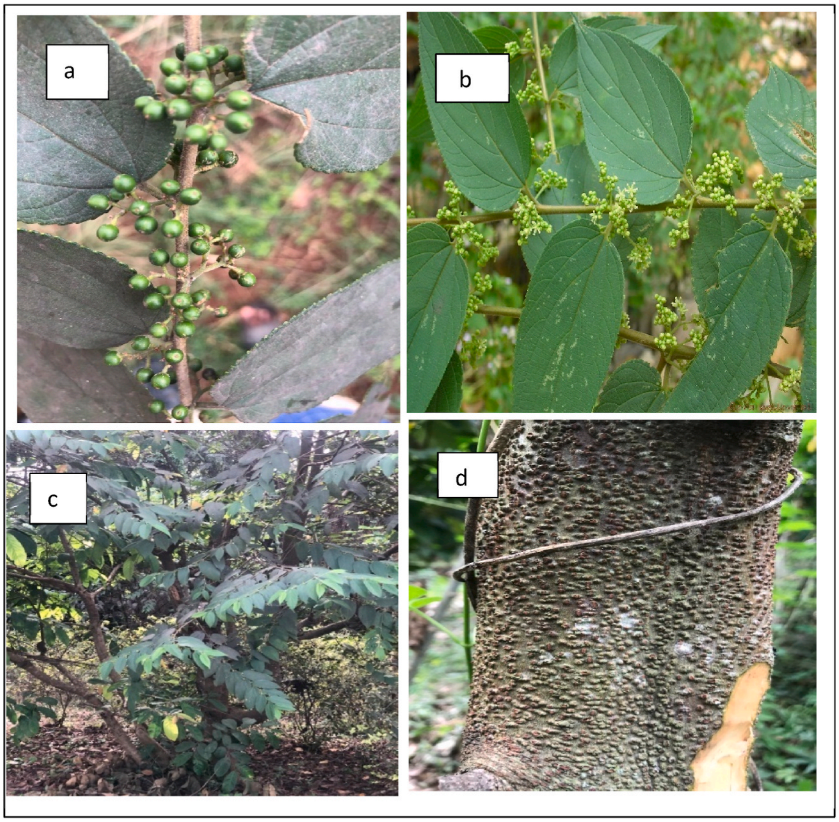


Fig. 1. Pictures of different parts of *Trema orientale.* a: Fruits; b: Leaves; c: Whole tree; d: Stembark

male with a few female (bisexual) flowers at the top; small, inconspicuous and greenish-cream. Bracts are 1 mm. long, triangular; pedicels short or absent. The fruits are small and round drupes and can either be green or dark purple but turn black when ripe [44] (Fig. 1a).

T. orientale is a widely distributed tree species that remains abundant despite deforestation in some parts of its habitat. The native habitat of this species is tropical and subtropical regions. It covers three continents and encompasses 65 countries; particularly Africa and continental Asia [23] (Fig. 2). It has been introduced to Hawaii, Mauritius and Reunion. The species is not common across its whole range but it has a large population. It is also common in secondary forests and grows well in both heavy and light soils, it can also be established on flood-damaged river banks [40,46]. This species has most recently been assessed for the IUCN Red List of Threatened Species in 2017 and is listed as Least Concern. The estimated Area of Occupancy (AOO) is 1560.000 km^2 and the Estimated Extent of Occurrence (EOO) is 26,493,751.440 km^2 [45,46]. *T. orientale* has been referred to differently in different locations (Table 2).

3.2. Traditional medicinal uses

Almost all the parts of *T. orientale* have traditionally been used for the treatment of several diseases all over the world, especially in Africa. The leaves have reportedly been used for the treatment of coughs and sore throats while the bark is used to make cough syrup. Other reported uses include remedies for asthma, bronchitis, gonorrhoea, malaria, yellow fever, toothaches, and intestinal worms [47]. Sometimes, the leaves and fruits are processed into infusions and taken for conditions such as bronchitis, pneumonia, and pleurisy [48]. In Ghana, the leaves only or with fruit, enrich the recipe by crushing the leaves in lemon juice for cough treatment [49]. The stems and twigs have been useful in the management and treatment of respiratory disorders, fevers, toothache, and venereal diseases in West Africa [50]. The Ghana Herbal Pharmacopeia reported on its use as a dewormer for hookworm and roundworm treatment [22]. In Nigeria, *T. orientale* has also been used for restoring tired muscles and aching bones [50].

4. Phytoconstituents of *T. orientale*

The major groups of phytochemicals present in *Trema orientale* are tannins, flavonoids, saponins, cardiac glycoside, phytosterols, fatty acids, carbohydrates, iridoids, xanthones and phenolic compounds [33,52,53]. Some isolated compounds from various parts of the plant and their structures are listed in Table 3 below.

5. Pharmacological activities/studies

There have been several studies over the years on *Trema orientale* including *in-vitro* and *in-vivo* studies using different extraction methods and/or part of the plant to establish its pharmacological effects. These reports include anti-inflammatory, antimicrobial, antidiabetic, antioxidant, and antidepressant activities among others. The main pharmacological studies on *T. orientale* are abridged and highlighted under this topic [23,33].

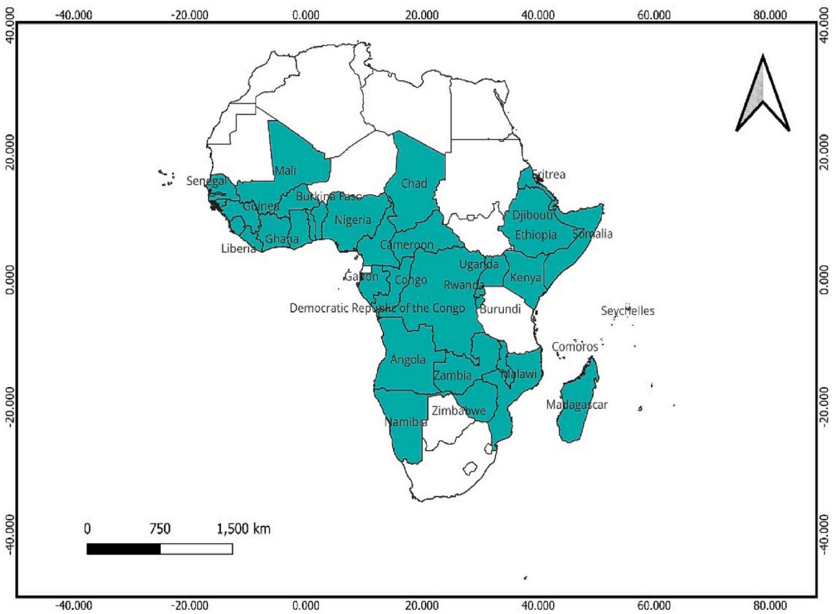


Fig. 2. Map of Africa showing the distribution of *Trema orientale* (Source: author's construct).

Table 2
Common/vernacular names for *Trema orientale* (L.) Blume.

Location/Country	Common/Vernacular names
Ghana	Osesea (Twi); Wadzawadza (Ewe)
Nigeria	Afere, Afefe, Anyinyin (Yoruba); Telemukwu (Igbo), Ehun-ogo (Bini)
Angola	Kipesi (Umbundu); Mugudisisola (Kimbundu); Nsengue-nsengue (Kikongo); tjimonomono (Cokwe)
Kenya	Mzunguzungu (Taita)

5.1. Anthelmintic activity

The antiparasitic effects of crude extract of *Trema. orientale* bark and wood with hexane, ethanol and water against *Caenorhabditis elegans* have been reported. The research confirmed that a concentration higher than 1 mg/ml of the extracts has inhibitory activity against *C. elegans* within the first 2 h of exposure and lethal activity after 7 days of exposure [32]. Similarly, an *in-vitro* anthelmintic evaluation of 70 % ethanolic leaf extract of *T. orientalis* on nematode larvae of sheep and goats was studied. To achieve the nematode larval mortality, larvae were isolated and counted from the faeces of the ruminants using the Baermann set-up/technique and exposed to different concentrations of the extracts. The results showed that the concentrations had anthelmintic activity against nematode larvae [68].

5.2. Cardioprotective activity

An *in-vivo* antihypertensive effect of ethanol extracts of *Trema orientale* was conducted on male Wistar albino rats. Crude ethanolic extract of the plant was obtained using its leafy stem. N(G)-Nitro-L-Arginine-Methyl Ester (L-NAME) was administered to the rats two weeks before the commencement of the treatment, to induce hypertension. The animals were monitored for four weeks during the treatment period and the blood pressure (BP) of the experimental animals was recorded by the use of a non-invasive BP system. At 500 mg/kg body weight (bw), *T. orientale* reduced mean arterial pressure from 154.8 ± 7.84 to 103 ± 5.6 mmHg [69]. Likewise, it is indicated that *T. orientale* is a potential antihyperlipidemic agent, reducing the risks of cardiovascular diseases. This study was carried out in Wistar albino rats by inducing the rat models with 25 % fructose for 15 days and Triton, treating them with ethanolic leaf extract of the plant. Blood samples were then collected from the animals to conduct biochemical analysis including but not limited to Total Cholesterol, High-Density Lipoprotein Cholesterol and Low-Density Lipoprotein Cholesterol. The biochemical tests and histopathology studies revealed that the plant has hypolipidemic activity [70].

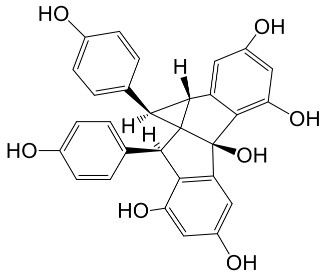
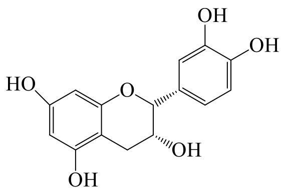
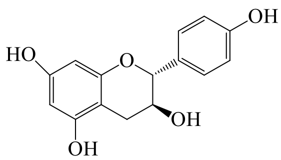
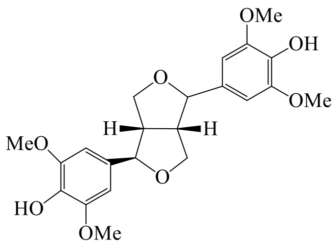
5.3. Anticancer activity

A recent study has been conducted to assess the anticancer effect of *T. orientale* aerial parts using methanol for the extraction process. *In-vitro* cytotoxicity assay was carried out in eight human cell lines and normal fibroblast cells, thus HCT116 (colorectal carcinoma cell line), A2780 (ovary adenocarcinoma), MRC5 (normal fetal lung fibroblast), MCF7 (breast adenocarcinoma), HT29 (colon adenocarcinoma), HepG22 (liver cancer cell line), TK10 (kidney renal cell adenocarcinoma), MDA231 (breast cancer cell line), and PC3 (prostate cancer cell line). It is indicated that the leaf extract was highly toxic to HCT116 cell lines at 2.256 ± 0.85 μg/mL, as compared to the other parts and therefore, a clonogenicity assay was conducted to determine the growth inhibitory effects of the plant. The results showed that HCT116 cells significantly declined, about 98 % at 7.5 μg/mL after fourteen days of incubation and exhibited the strongest clonogenic activity [71]. Similarly, Kabir et al. [72] studied the anticancer potential of *T. orientale* methanolic leaf extracts in Swiss albino mice against Ehrlich ascites carcinoma (EAC). The animals were transplanted with EAC and treated for six days with the crude extract, intraperitoneal EAC cells were then collected, harvested and counted by hemocytometer. The LD_{50} of the extract was 3120.650 mg/kg bw, proving its safety at a dosage of as high as 800 mg/kg bw. The *in-vivo* evaluation at 400 mg/kg bw showed that the extract inhibited nearly 59 % growth of tumour cells in comparison with the control group, with considerable apoptotic characteristics. To validate this outcome, an *in-vitro* test using 3- [4, 5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay was also conducted. The MTT assay of the plant extract was cytotoxic with an IC_{50} value of 29.952 ± 1.816 μg/mL, demonstrating that the plant has an anti-cancer effect.

5.4. Antioxidant activity

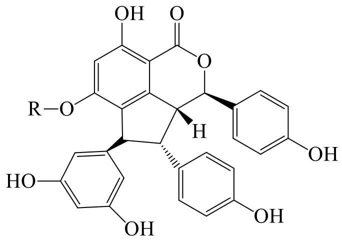
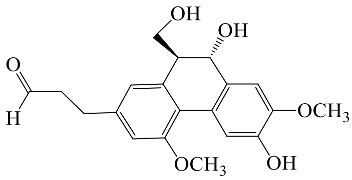
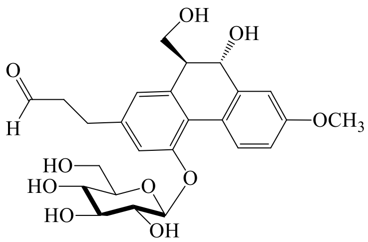
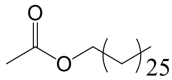
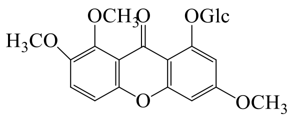
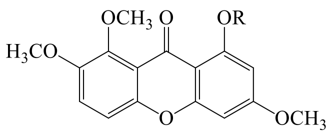
The antioxidant activity of the leafy stem of *T. orientale* with its ethanolic crude extract using 2, 2-diphenyl-1-picryl-hydrazyl (DPPH), Ferric reducing capacity (FRC), superoxide anion and hydrogen peroxide (H_2O_2) assays was studied by Madjid et al. [73]. The FRC assay was established to have the best activity with 6007.8 ± 175.57 μmol AAE g-1. The scavenging activities of H_2O_2 and superoxide anion resulted in between 88.52 ± 0.68 % to 91.33 ± 4.01 % while DPPH also showed promising inhibitory activity of 83.86 ± 1.88 and 99.46 ± 0.38 when compared to ascorbic acid. Likewise, methanolic extracts of *T. orientale* leaf, root, stem and aerial parts were evaluated for their antioxidant activity using a DPPH assay [74]. However, no scavenging activity was noted for the aerial parts while the IC_{50} value of the leaf, root, stem extracts and ascorbic acid were 13.1 ± 0.2, 7.4 ± 0.2, 6.4 ± 0.2 and 1.01 ± 0.4 μg/mL, respectively. Following the same approach using DPPH assay, Saleh et al. [75] determined the antioxidant activity of *T. orientale* ethanolic extract of the leaves. The IC_{50} of the free radical scavenging activity was 9.27 μg/mL, which proves the antioxidant potential

Table 3
Structures of compounds isolated from the various parts of *T. orientalis*.

Sr. No.	Compound Name	Structure	Plant Part	Reference
1.	(−) -ampelopsin F		Stem	[26]
2.	(−)-Epicatechin		Stem	[26,51]
3.	(+) -Catechin		Stem	[26]
4.	(+) -Syringaresinol		Stem	[26]

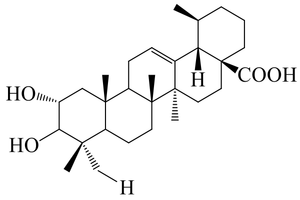
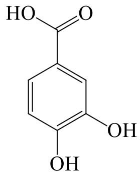
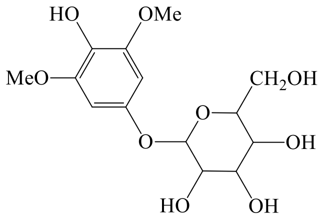
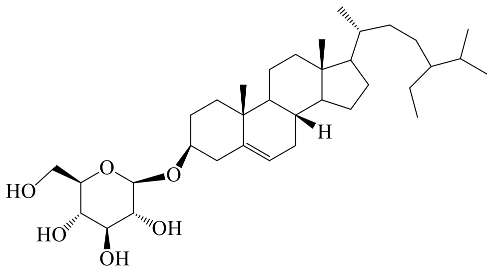
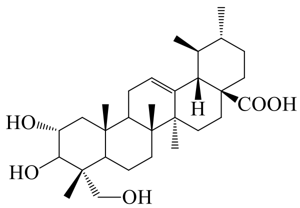
(*continued on next page*)

Table 3 (*continued*)

Sr. No.	Compound Name	Structure	Plant Part	Reference
5.	(3R*,3aR*,4R*,5S*)-6-OR-arabinopyranosyl-8-hydroxy-3-(4-hydroxyphenyl)-4-(4-hydroxyphenyl)-5-(3,5-dihydroxyphenyl)-3,3adihydrocyclopenta [1,2,3-de] isobenzopyran-1-one	 R= α–arabinopyranosyl	Root Bark	[52]
6.	(9S*,10S*)-3-[7-(3,10-dihydroxy-9-hydroxymethyl-2,5-dimethoxy)-9,10 -dihydrophenanthrenyl] propenal		Stem Bark	[52]
7.	(9S*,10S*)-3- [7-(5-*O*- ß -glucopyranosyl-10-hydroxy-9-hydroxymethyl-2,6-dimethoxy)-9,10-dihydrophenanthrenyl] propenal		Stem Bark	[52]
8.	1-octacosanyl acetate		Stem	[53]
9.	1-*O*-glucosyldecussatin		Stem Bark	[54]
10.	1-*O*-primeverosyl-decussatine	 R= primeverosyl	Stem Bark	[55]

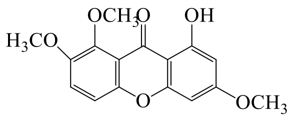
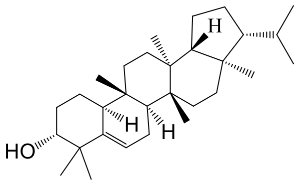
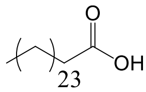
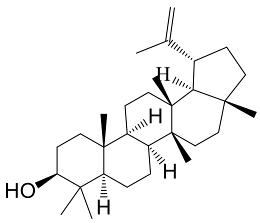
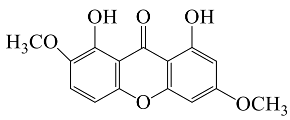
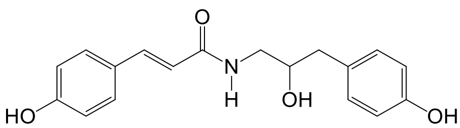
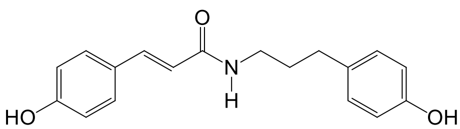
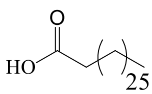
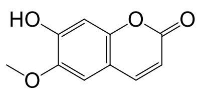
(*continued on next page*)

Table 3 (*continued*)

Sr. No.	Compound Name	Structure	Plant Part	Reference
11.	2a, 3a, 23-trihydroxyurs-12-en-28-oic acid		Root Bark	[56,57]
12.	3,4-dihydroxybenzoic acid		Root Bark	[58]
13.	3,5-dimethoxy-4-hydroxyphenyl -1-*O*-*β*-D-glucoside		Stem	[26]
14.	3-*O*-ß-glucopyranosyl-ß-sitosterol		Root Bark	[59]
15.	3ß-dihydroxyurs-12-en-28-oic acid		Root Bark	[56]

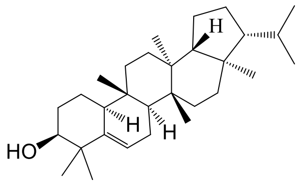
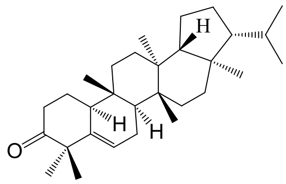
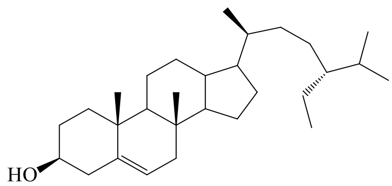
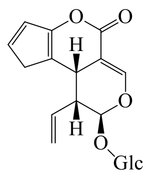
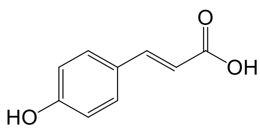
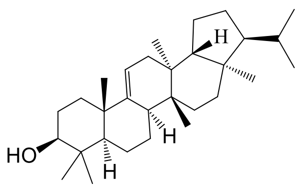
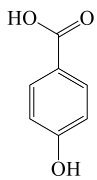
(*continued on next page*)

Table 3 (*continued*)

Sr. No.	Compound Name	Structure	Plant Part	Reference
16.	Decussatin		Stem Bark	[60]
17.	Episimiarenol		Stem	[61]
18.	Hexacosanoic acid		Root Bark	[62]
19.	Lupeol		Stem Bark	[63]
20.	Methylswertianin		Stem Bark	[64]
21.	*N-(trans-ρ*-coumaroyl) octopamin		Stem	[26]
22.	*N-(trans-ρ*-coumaroyl*)* tyramine		Stem	[26]
23.	Tetracosanoic acid		Stem	[53]
24.	Scopoletin		Stem Bark	[65]

(*continued on next page*)

Table 3 (*continued*)

Sr. No.	Compound Name	Structure	Plant Part	Reference
25.	Simiarenol		Stem	[61]
26.	Simiarenone		Root Bark	[58]
27.	β-sitosterol		Root Bark	[59]
28.	Sweroside		Stem Bark	[66,67]
29.	*Trans*-4-hydroxy-cinnamic acid		Stem	[26]
30.	Trematol		Stem	[53]
31.	*ρ*-hydroxybenzoic acid		Stem Bark	[63]

of the plant. The same analysis was conducted for its aqueous extract but did not show antioxidant activity. Recently, Al-Robai et al. [71] used DPPH and 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays to establish the antioxidant activities of methanolic extract of *T. orientale* aerial parts using ascorbic acid, propyl gallate, and Trolox as positive controls. All the extracts exhibited free radical scavenging activities in both methods. The DPPH method recorded a scavenging activity of 79.6 % while ABTS recorded 84.43 % for the leaf extract; ascorbic acid, propyl gallate, and Trolox as 92.86 %, 82.30 and 78.72 %, respectively in the ABTS method. This shows that the plant extract was more effective than propyl gallate, and Trolox. Although there was a significant difference between the DPPH and ABTS assay results, the values indicated that the leaves had the strongest activity, followed by bark, twigs and fruits in that order.

5.5. Antimicrobial activity

A study in India using 15 isolates of *Staphylococcus aureus* indicated that acetone extract of *T. orientalis* inhibits the growth of the organism with a MIC value of 3.7 mg/ml and biofilm inhibitory concentration value of 2.7 mg/mL [76]. It is also indicated that methanolic extract from *T. orientale* leaves has an antibacterial effect against some Gram-positive and Gram-negative bacteria. The mean zones of inhibition for *Bacillus subtilis, Micrococcus luteus, Escherichia coli, Salmonella enterica* serotype Typhi, *Shigella dysenteriae, Klebsiella pneumoniae* and *Pseudomonas vulgaris* were 11.20 ± 0.81 mm, with *S.* Typhi and *S. dysenteriae* being more susceptible. However, this study showed that *Xanthomonas campestris* and *Pseudomonas denitrificans* were resistant to the extract [77].

A study was conducted to understand the inhibitory activity of granules against *Salmonella* spp. using wet granulated granules formulated from methanolic leaf extract of *T. orientalis* as the active ingredient. Excipients used in the formulation included sucrose, polyvinylpyrrolidone, sorbitol, lactose and water and with the concentrations of 0.25 mg/200g, 12.5 mg/200g and 6.5 mg/200g of the granules, to which the organism was susceptible to all three concentrations [78]. This finding is consistent with a study by Rahman et al. [77] which was conducted on *S. Typhi.* Similarly, Napiroon et al. [37] sampled *T. orientalis* from various regions of Thailand to make lipophilic extracts and fractions to evaluate the presence of cannabinoids and their antimicrobial activities. The extracts inhibited *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* with minimum inhibitory concentrations (MICs) ranging between 31.25 and 125 μg/mL. Likewise, the antimicrobial efficacy of *T. orientalis* aerial parts was assessed using methanolic crude extracts of the leaves, fruits, bark and twigs against two Gram-positive, and two Gram-negative bacteria and opportunistic yeast. Using *E. coli, K. pneumoniae, S. aureus, Enterococcus faecalis* and *Candida albicans* as the test organisms, the results indicated inhibitory activity of the leaves against only *C. albicans* while the bacteria were resistant to other parts of the plant [71]. This finding is however contradicting other studies which reported that *S. aureus* was susceptible to the plant. This could however be attributed to the different extraction methods used [37,77].

The susceptibility patterns of *S. aureus, P. aeruginosa, E. coli, S.* Typhi*, S. dysenteriae, Streptococcus faecalis, Proteus mirabilis,* Haemolytic *Streptococcus viridian, Aspergillus niger, C. albicans* and *Aspergillus flavus* to methanol and petroleum ether extracts of *T. orientale* leaves were also investigated [79]. *Salmonella Typhi* was the most susceptible organism against both extracts, confirming other studies [77,78]. Nevertheless, *S. aureus* and *S. dysenteriae* exhibited resistance to the extracts which are different from other reports [37,76,77] but confirmed Al-Robai et al. [71] findings. These inconsistencies could be attributed to differences in the inoculum size, extract concentrations, methods used and the geographical area of the plant as described by Eloff [80].

6. Safety and toxicity studies

It is indicated that the methanolic leaf extract of *T. orientalis* is less toxic to cells with LC_{50} of 170.2 μg/mL when compared to vincristine sulphate standard which has LC_{50} of 2.5 μg/mL using the brine shrimp lethality bioassay [77].

In-vivo research was undertaken to explore how methanolic leaf extract of *T. orientale* affects the liver of Wistar rats. Cadmium chloride was administered to the animals, followed by *T. orientale* extract of dosages 100 and 200 mg/kg bw and observed for 21 days. Blood and tissue samples were collected from the rats for biochemical tests and histopathology studies. The total protein and alanine aminotransferase (ALT) in rats treated with cadmium chloride plus the extract was not significantly different from the control group. Histology studies revealed mild toxicity in the liver tissues when the extract was continuously administered raising important concerns about dosage [81].

Acute and sub-acute toxicity studies in Wistar albino rats were conducted using methanolic extract of *T. orientale* aerial part. Doses of 1, 2, 3, and 4 g/kg were used for the acute toxicology as animals were observed for 14 days. The animals were administered with 0.25, 0.5 and 1 g/kg bw of the extract, observed for 28 days and sacrificed for blood and tissue examinations during the sub-acute toxicity study. No death or changes in behaviour or toxicity were observed during the acute toxicity, proven the lethal dose (LD_{50}) being greater than 2 g/kg. Alkaline phosphatase, total protein and albumin increased significantly in groups administered as with higher doses [82]. They concluded that the plant is safe at a lower concentration, and this agrees with the study [81].

In a similar study, it was established that *T. orientale* methanolic leaf extract doses of 100 and 200 mg/kg were toxic after continuous administration to Wistar rats. They reported an increase in haematology test parameters in rats treated with only the extract and animals that were administered with both the extract and Cadmium. The study also proved that the leaves of *T. orientalis* have both hematoprotective and hematopoietic properties which could support patients with anaemia [83].

7. Domestication potential

Domestication is the introduction of an organism into a new environment other than its natural habitat with conducive conditions for its survival [84]. The domestication process to a large extent focuses on the morphological and genetic assessment between a species and its existing wild relatives [85], and basically to improve its suitability and perpetual outcome of its benefits for human consumption, especially in yield, taste, cultivation practices, and storage [86]. Among all considerations, it is noted that the identification of individual species with desirable traits is the foremost in selecting species for domestication [87,88]. In addition, targeting species with improved palatability, increased productivity of harvested parts, ease of growth, and harvest on farmlands [89]. Consequently, an important task is to focus on the qualitative traits of species such as tree form, fruit shape, and sweeter pulp [90], which could result in 60 % of the progeny resembling the mother tree, especially in terms of productivity and ease of cultivation [91]. An equally important factor for improved domestication is the environment and condition of the seeds.

Studies have indicated a significant presence of *T. orientale* in soil seed banks in different forest ecosystems [92]. Likewise, studies by Hall & Swaine [93], also reported on the abundance of *T. orientale* in Ghanaian forests. In Thailand, viable seeds of *T. orientale* were found in soil seed banks 175 m from the mother tree [94]. Yet only a small fraction may germinate under favourable conditions due to the dormant nature of the seeds [95,96]. Though several species of birds aid in the seed dispersal of *T. orientale*, fleshly ripe fruits rarely germinate and mostly decay especially in storage [97–99]. Hence, requiring intervention to preserve and accelerate its germination process. A recent study by Nugraheni and Yuniarti [100], recommended that the optimum condition to maintain seed viability for at least one month and speed germination of *T. orientale* is to dry it for 24 hr, and put it in an air-tight aluminium foil container in an air condition room. Similarly, the highest growth uniformity of 74.75 % and 72 % before storage and after storage respectively was obtained by subjecting *T. orientale* seeds to a hydrated-dehydrated procedure [99]. Studies by Rodrigues and Rodrigues [101], indicated the potential of enhancing the seeds of *T. orientale* through different pre-treatment options. Among other pre-sowing treatments, the authors indicated that soaking and depulping the seeds in concentrated H_2SO_2 for 2 hr and 15 min respectively yielded the highest germination and healthy plantlet. The prospect of vegetative propagation of *T. orientale* has also been indicated in the literature. It is reported that rooted cuttings treated with 300 ppm of naphthalene acetic acid exhibited the highest percentage of germination when planted in sandy soil [102]. These outcomes significantly contribute to the sustainable propagation and utilization of *T. orientale*.

8. Conclusions

This review documents the traditional uses, taxonomy, domestication potential, pharmacological activities and phytoconstituents of *T. orientale* in a bid to highlight its medicinal importance. *T. orientale* forms an important component of the herbal remedy of many people in Africa due to its multiple applications. This has been attributed to its rapid decline coupled with its germination difficulties. Nonetheless, it is established that there is enormous potential to improve seed quality through molecular markers and germination trials (pre-sowing treatments). This review demonstrates the phytochemical and medical properties of *T. orientale* and establishes that, at safe dosages, it may be used as a potent herbal remedy for a wide range of health conditions like infectious diseases, cancer and cardiovascular diseases. Phytochemical studies show the presence of phytosterols, flavonoids, tannins, saponins, cardiac glycosides, fatty acids, and phenolic compounds as secondary metabolites. Some compounds have however been isolated from the plant and there is a need for further studies to specify the compounds accounting for these activities, with their pharmacodynamics and pharmacokinetics.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Yaw Appau: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Paa Kwesi Gordon:** Methodology, Validation, Writing - original draft, Writing - review & editing. **Seyiram Kumordzie:** Methodology, Writing - original draft, Writing - review & editing. **Michael Odoi Kyene:** Methodology, Writing - original draft, Writing - review & editing. **Peter Atta-Adjei Jnr:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] G. Marisco, T.S.S. Silva, R. Assunção, M. Brendel, C. Pungartnik, The use of herbal medicine in a rural community in vitória da conquista, bahia, Brazil: an indication for pharmacological studies, Int J Complement Alt Med 7 (1) (2017), 00214, https://doi.org/10.15406/ijcam.2017.07.00214.
[2] World Health Organization, WHO global report on traditional and complementary medicine, Available online at: https://www.who.int/traditional-complementary-integrativemedicine/WhoGlobalReportOnTraditionalAndComplementaryMedicine2019.pdf, 2019. Accessed on 9th March, 2023.
[3] J. Ozioma, E. O, C.O.A. Nwamaka, Herbal medicines in african traditional medicine, Herbal Medicine (2019), https://doi.org/10.5772/intechopen.80348.
[4] A.N. Welz, A. Emberger-Klein, K. Menrad, Why people use herbal medicine: insights from a focus-group study in Germany, BMC Compl. Alternative Med. 18 (2018) 92, https://doi.org/10.1186/s12906-018-2160-6, 2018.
[5] C.J. Dawurung, M.T.H. Nguyen, J. Pengon, et al., Isolation of bioactive compounds from medicinal plants used in traditional medicine: rautandiol B, a potential lead compound against Plasmodium falciparum, BMC Complement Med Ther 21 (2021) 231, https://doi.org/10.1186/s12906-021-03406-y.
[6] A. Altemimi, N. Lakhssassi, A. Baharlouei, D.G. Watson, D.A. Lightfoot, Phytochemicals: extraction, isolation, and identification of bioactive compounds from plant extracts, Plants 6 (4) (2017) 42, https://doi.org/10.3390/plants6040042.
[7] I.B. Suffredini, H.S. Sader, A.G. Gonçalves, A.O. Reis, A.C. Gales, A.D. Varella, R.N. Younes, Screening of antibacterial extracts from plants native to the Brazilian amazon rain forest and atlantic forest, Braz. J. Med. Biol. Res. 37 (3) (2004) 379–384, https://doi.org/10.1590/s0100-879x2004000300015.
[8] V. Soni, K. Keswani, U. Bhatt, D. Kumar, H. Singh, In vitro propagation and analysis of mixotrophic potential to improve the survival rate of Dolichandra unguis-cati under ex vitro conditions, Heliyon 7 (2) (2021), e06101.
[9] B.B. Yikna, A.S. Yehualashet, Medicinal plant extracts evaluated in vitro and in vivo for antidiabetic activities in Ethiopia: bases for future clinical trials and related investigations, Evid. base Compl. Alternative Med.: eCAM 2021 (2021), 9108499, https://doi.org/10.1155/2021/9108499.
[10] P.A. Kweyamba, D. Zofou, N. Efange, J.-C.N. Assob, J. Kitau, M. Nyindo, In vitro and in vivo studies on anti-malarial activity of Commiphora africana and Dichrostachys cinerea used by the Maasai in Arusha region, Tanzania, Malar. J. 18 (1) (2019), https://doi.org/10.1186/s12936-019-2752-8.
[11] R.A. El-shiekh, D.A. Al-Mahdy, M.S. Hifnawy, E.A. Abdel-Sattar, In-vitro screening of selected traditional medicinal plants for their anti-obesity and anti-oxidant activities, South Afr. J. Bot. 123 (2019) 43–50, https://doi.org/10.1016/j.sajb.2019.01.022.
[12] A. Kheiri, S. Amini, A.N. Javidan, M.M. Saghafi, G. Khorasani, The effects of Alkanna tinctoria Tausch on split-thickness skin graft donor site management: a randomized, blinded placebo-controlled trial, BMC Compl. Alternative Med. 17 (1) (2017), https://doi.org/10.1186/s12906-017-1741-0.
[13] M.H. Al Rashid, A. Kundu, V. Mandal, P. Wangchuk, S.C. Mandal, Preclinical and clinical trials of Indian medicinal plants in disease control, in: S. Sen, R. Chakraborty (Eds.), Herbal Medicine in India, Springer, Singapore, 2020, https://doi.org/10.1007/978-981-13-7248-3_09.
[14] J. Buragohain, Ethnomedicinal plants used by the ethnic communities of tinsukia district of Assam, India, Recent Res. Sci. Technol. 3 (2011) 31–42.
[15] S. Asiimwe, J. Namukobe, R. Byamukama, et al., Ethnobotanical survey of medicinal plant species used by communities around Mabira and Mpanga Central Forest Reserves, Uganda, Trop. Med. Health 49 (2021) 52, https://doi.org/10.1186/s41182-021-00341-z, 2021.
[16] T. Asafo-Agyei, H.R. Blagogee, S.O. Mintah, M. Archer, F. Ayertey, A.C. Sapaty, P. Atta-Adjei Jnr, D. Boamah, J. Asiedu-Larbi, A.A. Appiah, Ethnobotanical studies of medicinal plants used in traditional treatment of malaria by some herbalists in Ghana, J. Med. Plants Res. 13 (16) (2019) 370–383.
[17] K.S. Appiah, C.P. Oppong, H.K. Mardani, R.A. Omari, S. Kpabitey, C.A. Amoatey, S. Onwona-Agyeman, Y. Oikawa, K. Katsura, Y. Fujii, Medicinal plants used in the Ejisu-Juaben municipality, southern Ghana: an ethnobotanical study, Medicines (Basel, Switzerland) 6 (1) (2018) 1, https://doi.org/10.3390/medicines6010001.
[18] A. Adeniyi, A. Asase, P.K. Ekpe, B.K. Asitoakor, A. Adu-Gyamfi, P.Y. Avekor, Ethnobotanical study of medicinal plants from Ghana; confirmation of ethnobotanical uses, and review of biological and toxicological studies on medicinal plants used in Apra Hills Sacred Grove, Journal of herbal medicine 14 (2018) 76–87. https://doi:10.1016/j.hermed.2018.02.001.
[19] P. Tugume, E.K. Kakudidi, M. Buyinza, et al., Ethnobotanical survey of medicinal plant species used by communities around Mabira Central Forest Reserve, Uganda, J Ethnobiology Ethnomedicine 12 (2016) 5, https://doi.org/10.1186/s13002-015-0077-4, 2016.
[20] C.V. Yanes, Germination of a pioneer tree from equatorial Africa, Turrialba 27 (2007) 301–302.
[21] J.O. Olanlokun, O.M. David, A.J. Afolayan, In vitro antiplasmodial activity and prophylactic potentials of extract and fractions of *Trema orientalis* (Linn.) stem bark, BMC Compl. Alternative Med. 17 (1) (2017), https://doi.org/10.1186/s12906-017-1914-x.
[22] B. Akendengue, Medicinal plants used by the Fang traditional healers in Equatorial Guinea, J. Ethnopharmacol. 37 (2) (1992) 165–173.
[23] M.B. Adinortey, I.K. Galyuon, N.O. Asamoah, *Trema orientalis* Linn. Blume: a potential for prospecting for drugs for various uses, Phcog. Rev. 7 (13) (2013) 67–72. https://doi:10.4103/0973-7847.112852.
[24] FAO, Global Forest Resources Assessment 2020. Main Report. Rome, 2020, https://doi.org/10.4060/ca9825en. https://www.fao.org/documents/card/en/c/ca8753en. Accessed on 11th May 2023.
[25] A.C. Otieno, M. Buyinza, R.A. Kapiyo, B.O. Oindo, Local communities and collaborative forest management in West bugwe forest reserve, eastern Uganda, Environ. Res. J. 7 (2013) 69–78.
[26] W.L. Kuo, Y.L. Huang, S.T. Wang, C.L. Ni, B.J. Shien, C.C. Chen, Chemical constituents of *Trema orientalis*, J. Chin. Med. 18 (1) (2007) 2.
[27] S.A. Aboaba, I.M. Choudhary, Chemical composition and biological activities of the volatile oils of *Palisota hirsuta* (Thunb) K. Schum and *Trema orientalis* (L) Blume, Int. J. Chem. 7 (2) (2015) 21.
[28] P.T. Mpiana, K.N. Ngbolua, V. Mudogo, D.S.T. Tshibangu, E.K. Atibu, D.D. Tshilanda, N.M. Misengabu, Antisickle erythrocytes haemolysis properties and inhibitory effect of anthocyanins extracts of *Trema orientalis* (Ulmaceae) on the aggregation of human deoxyhemoglobin S in vitro, J. Med. Sci. 11 (3) (2011) 129–137.
[29] Y. Kono, A. Ishida, S.T. Saiki, K. Yoshimura, M. Dannoura, K. Yazaki, S.I. Aikawa, Initial hydraulic failure followed by late-stage carbon starvation leads to drought-induced death in the tree *Trema orientalis*, Commun. Biol. 2 (1) (2019) 8.
[30] M.S. Jahan, N. Chowdhury, Y. Ni, Effect of different locations on the morphological, chemical, pulping and papermaking properties of *Trema orientalis* (Nalita), Bioresour. Technol. 101 (6) (2010) 1892–1898.
[31] M.S. Jahan, S.P. Mun, Effect of tree age on the cellulose structure of Nalita wood (*Trema orientalis*), Wood Sci. Technol. 39 (2005) 367–373.
[32] L.J. Mcgaw, A.K. Jäger, J. Van Staden, Antibacterial, anthelmintic and anti-amoebic activity in South African medicinal plants, J. Ethnopharmacol. 72 (2000). www.elsevier.com/locate/jethpharm.
[33] A. Parvez, M.A.K. Azad, M.Z. Islam, M.M.R. Munna, S.M. Shaheen, M.M. Rahman, A.K. Azad, A phytochemical and pharmacological review on *Trema orientalis*: a potential medicinal plant, Pharmacologyonline 3 (2019) 103–119.
[34] M.Q. Yang, V.R. Velzen, T.F. Bakker, A. Sattarian, Z.D. Li, T.S. Yi, Molecular phylogenetics and character evolution of Cannabaceae, Taxon 62 (3) (2013) 473–485.
[35] C. Orwa, A. Mutua, R. Kindt, R. Jamnadass, A. Simmons, Agroforest Tree Database: A Tree Reference and Selection Guide Version 4.0 2009, 2009. Available from: http://www.worldagroforestry.org/af/treedb. (Accessed 10 January 2023).
[36] L. St-Laurent, B.R. Baum, K. Akpagana, J.T. Arnason, Leaf trichome morphology and density in West African Trema spp. (Ulmaceae: Celtidoideae). Canadian Journal of Botany 78 (1) (2000) 34–39, https://doi.org/10.1139/b99-157.
[37] T. Napiroon, K. Tanruean, P. Poolprasert, M. Bacher, H. Balslev, M. Poopath, W. Santimalecworagun, Cannabinoids from inflorescences fractions of *Trema orientalis* (L.) Blume (Cannabaceae) against human pathogenic bacteria, PeerJ 9 (2021), e11446, https://doi.org/10.7717/peerj.11446.
[38] S. Jugl, A. Okpeku, B. Costales, E.J. Morris, G. Alipour-Haris, J.M. Hincapie-Castillo, N.E. Stetten, R. Sajdeya, S. Keshwani, V. Joseph, Y. Zhang, Y. Shen, L. Adkins, A.G. Winterstein, A. Goodin, A mapping literature review of medical Cannabis clinical outcomes and quality of evidence in approved conditions in the USA from 2016 to 2019, Med. Cannabis Cannabinoids 4 (1) (2021) 21–42, https://doi.org/10.1159/000515069.
[39] H.L. Zhang, J.J. Jin, M.J. Moore, T.S. Yi, D.Z. Li, Plastome characteristics of Cannabaceae, Plant Diversity 40 (2018) 127–137.
[40] J. Mark, A.C. Newton, S. Oldfield, M. Rivers, The International Timber Trade: a Working List of Commercial Timber Tree Species, Botanic Gardens Conservation, International, Richmond, 2014.

[41] D. Jin, K. Dai, Z. Xie, J. Chen, Secondary metabolites profiled in Cannabis inflorescences, leaves, stem barks, and roots for medicinal purposes, Sci. Rep. 10 (3309) (2020) 1–14, https://doi.org/10.1038/s41598-020-60172-6.
[42] GBIF, Global biodiversity information facility (GBIF), Published on the internet at: https://www.gbif.org, 2023. retrieved 30th January 2023.
[43] C. Orwa, A. Mutua, R. Kindt, R. Jamnadass, S. Anthony, Agroforestree Database: a Tree Reference and Selection Guide Version 4, 2009, 0. http://www.worldagroforestry.org/sites/treedbs/treedatabases.asp.
[44] M.A. Hyde, B.T. Wursten, P. Ballings, P. Coates, Flora of Zimbabwe, Available at: http://www.zimbabweflora.co.zw, 2017.
[45] IUCN, The IUCN red list of threatened species. Version 2022-2. https://www.iucnredlist.org;, 2023 retrieved 30th January 2023.
[46] GeoCAT, Geospatial Conservation Assessment Tool, 2023. Facilitated by the Royal Botanic Gardens, Kew. Published on the internet at, http://www.geocat.org. Retrieved on 27th January 2023.
[47] Z.K. Rulangaranga, Some important indigenous medicinal and aromatic plants in the wild flora of Tanzania mainland, Tropical Forestry Action Plan, Working Paper 24 (1989) 398–405.
[48] J.M. Watt, M.G. Breyer-Brandwijk, The Medicinal and Poisonous Plants of Southern and Eastern Africa Being an Account of Their Medicinal and Other Uses, Chemical Composition, Pharmacological Effects and Toxicology in Man and Animal. (Edn 2), 1962.
[49] Ghana Herbal Pharmacopoeia, 1992. vols. 141–143, The Advent Press: Accra, Ghana.
[50] E.S. Ayensu, Medicinal Plants of West Africa, Reference Publications, Inc., USA, 1978, p. 218. St. Clair River Drive, Algonac, Michigan 48001.
[51] G. Comte, Structure of Original Glycosides Isolated from *Juniperus phoenicea* L. (Cupressaceae): Norterpenes, Furanones and Phenylpropanes, 1996, p. 286.
[52] Dijoux-Franca, M-Geneviève, Diderot Noungoué Tchamo, Cherel Bruno, Max Cussac, Etienne Tsamo, Anne-M Mariotte, New dihydrophenanthrene and phenyldihydroisocoumarin constituents of *Trema orientalis*, J. Nat. Prod. 64 (6) (2001). ACS Publications: 832–835.
[53] C.A. Obafemi, L. Ogunkoya, J.A.K. Quartey, E.S. Waight, Structure of the triterpenoid alcohol trematol, Phytochemistry 18 (3) (1979) 496–497, https://doi.org/10.1016/S0031-9422(00)81901-9.
[54] K. Ishimaru, H. Sudo, M. Satake, Y. Matsunaga, et al., Amarogentin, amaroswerin and four xanthones from hairy root cultures of Swertia japonica, Phytochemistry 29 (1990) 1563–1565.
[55] I. Miura, K. Hostettmann, K. Nakanishi, 13C NMR of naturally occurring xanthone aglycones and glycosides, Nouv. J. Chim. 2 (1978) 653–657.
[56] H. Kojima, H. Ogura, Configurational studies on hydroxy groups at C-2, 3 and 23 or 24 of oleanene and ursene-type triterpenes by NMR spectroscopy, Phytochemistry 28 (1989) 1703–1710.
[57] S.B. Mahato, A.P. Kundu, 13C NMR spectra of pentacyclic triterpenoid-A compilation and some salient features, Phytochemistry 37 (1994) 1517–1575.
[58] H.R. Arthur, W.H. Hui, The Structure of simiarenol from the Hong Kong species of Rhododendron simiarum, Tetrahedron Lett. 14 (1965) 937–943.
[59] O. Espejo, J.C. Llavot, H. Jung, F. Giral, Spirostanic diosgenin precursors from Dioscorea composita tubers, Phytochemistry 21 (1982) 413–416.
[60] R.K. Chaudhuri, F. Zymalkowski, A.W. Frahm, 13C NMRspectroscopy of polymethoxyxanthones, Tetrahedron 34 (1978) 1837–1840.
[61] R.P. Rastogi, B.N. Mehrotra, Compendium of Indian Medicinal Plants, Central Drug Research Institute, 1990.
[62] D.N. Tchamo, G. Cartier, M.-G. Dijoux-Franca, A.-M. Tsamo Mariotte, "Xanthones and other constituents of *Trema orientalis*", Pharmaceut. Biol. 39 (3) (2001) 202–205.
[63] L. Ogunkoya, O.O. Olubajo, D.S. Sondha, Simiarenone from *Trema orientalis*, Phytochemistry 12 (1973) 732–733.
[64] D. Barraclough, H.D. Locksley, F. Scheinmann, M.T. Magalhaes, O.R. Gottlieb, Applications of proton magnetic resonance spectroscopy in structural investigation of xanthones, J Chem Soc (B) (1970) 603. –612.
[65] S.S. Sankar, R.D. Gilbert, R.E. Fornes, 13C NMR studies of some hydroxycoumarins and related compounds, Org. Magn. Reson. 19 (1982) 222–224.
[66] P. Junior, Recent developments in the isolation and structure elucidation of naturally occurring iridoid compounds, Planta Med. 56 (1990) 1–13.
[67] K. Machida, J. Asano, M. Kikuchi, Caeruleosides A and B, bis-iridoid glucosides from Lonicera caerulea, Phytochemistry 39 (1995) 111–114.
[68] S.W. Fomum, I.V. Nsahlai, In vitro control of parasitic nematodes of small ruminants using some plant species containing flavonoids, Trop. Anim. Health Prod. 49 (2) (2017) 375–382, https://doi.org/10.1007/s11250-016-1203-6.
[69] A.A.R. Adjileye, A.M.O. Amoussa, R. Adamou, B. Awede, A. Sanni, A. Laleye, L. Lagnika, Antihypertensive effect of Dialium guineense Wild. and *Trema orientalis* L. in L-NAME-induced hypertensive rats, The Journal of Phytopharmacology 9 (1) (2020) 5–11, https://doi.org/10.31254/phyto.2020.9102.
[70] S. Jose, C. Pramod, S.P. Jose, Evaluation of hypolipidemic activity of ethanolic extract of *Trema orientalis* L. Blume leaves, J. Pharmacogn. Phytochem. 9 (4) (2020).
[71] S.A. Al-Robai, S.A. Zabin, A.A. Ahmed, H.A. Mohamed, A.A.A. Alghamdi, A.A.E. Ahmed, Phenolic contents, anticancer, antioxidant, and antimicrobial capacities of MeOH extract from the aerial parts of *Trema orientalis* plant, Open Chem. 20 (1) (2022) 666–678, https://doi.org/10.1515/chem-2022-0183.
[72] M. Kabir, A.-N. Abdullah, B.K. Dash, M. Hasan, S. Akhter, M. Rahman, *Trema orientalis* (Linn.) leaves promotes anticancer activity in Ehrlich ascites carcinoma (EAC) in Swiss albino mice, J. Basic Clin. Physiol. Pharmacol. 31 (2) (2020).
[73] A. Madjid, O. Amoussa, L. Lagnika, R.A. Adjileye, *Trema orientalis* L. and Dialium guineense Wild. used to manage hypertension in Benin: phytochemical study and antioxidant activity, Journal of Medicinal Plants Studies 7 (3) (2019) 43–48.
[74] V.B. Chiribagula, A.S. Bakari, P.O. Ndjolo, B.J. Kahumba, J.-B.L. Simbi, Phytochemical screening and antioxidant activity of methanolic extracts of 53 antimalarial plants from Bagira in Eastern DR Congo, GSC Biological and Pharmaceutical Sciences 12 (2) (2020) 99–118.
[75] A. Saleh, S.M. Zainal-Ariffin, S.F. Yahaya, A.G. Khaleel, Antioxidant activities and estimation of phenol and flavonoid contents in the extracts of *Trema orientalis* L. Blume, Niger. Vet. J. 41 (2) (2021) 73–84, https://doi.org/10.4314/nvj.v41i2.1.
[76] S.K. Panda, R. Das, R. Lavigne, W. Luyten, Indian medicinal plant extracts to control multidrug-resistant S. aureus, including in biofilms, South Afr. J. Bot. 128 (2020) 283–291, https://doi.org/10.1016/j.sajb.2019.11.019.
[77] M.M. Rahman, N. Bairagi, M.M. Kabir, M.J. Uddin, Antibacterial potentiality and brine shrimp lethality bioassay of the methanol extract of *Trema orientalis* leaves, South Asian Research Journal of Natural Products 1 (2) (2018) 1–9, https://doi.org/10.9734/SARJNP/2018/41394.
[78] E.B. Wijaya, Antibacterial activity test of *Trema orientalis* L. Blum. (Anggrung) granule extract against bacteria Salmonella spp. with the wet granulation method, Indonesia Natural Research Pharmaceutical Journal 5 (1) (2020) 45–53.
[79] P.O. Fabowale, A.O. Ogundare, P. Awoyinka, O. Agunloye, *Trema orientalis* linn. Blume: susceptibility patterns of selected multiple antibiotic resistant bacteria and fungi to the leaf extracts, South Asian Journal of Research in Microbiology (2020) 25–32, https://doi.org/10.9734/sajrm/2020/v8i230190.
[80] J.N. Eloff, Avoiding pitfalls in determining antimicrobial activity of plant extracts and publishing the results, BMC Compl. Alternative Med. 19 (Issue 1) (2019), https://doi.org/10.1186/s12906-019-2519-3.
[81] J.E. Olajide, S. Momoh, O.J. Achimugu, E.R. Jegede, Effects of *Trema orientalis* leaves extract on hematological parameters of cadmium induced toxicity in wistar rats, IOSR Journal of Biotechnology and Biochemistry (IOSR-JBB) 6 (1) (2020) 1–7.
[82] T. Hemalatha, M. Ahino, G.A.D. Saravana, Acute and sub-acute toxicity study of *Trema orientalis* (L.) Bl. methanol extract in rats, J. Drug Deliv. Therapeut. 9 (1-s) (2019) 307–311, https://doi.org/10.22270/jddt.v9i1-s.2353.
[83] J.E. Olajide, M. Sanni, O.J. Achimugu, M.S. Suleiman, E.R. Jegede, V.D. Sheneni, Effect of methanol extract of *Trema orientalis* leaf on some biochemical and histopathological indices of wistar albino rats with cadmium-induced - hepatotoxicity, Scientific African 10 (2020), e00568, https://doi.org/10.1016/j.sciaf.2020.e00568.
[84] H.G. Lund, Sow's ears and silk pursesnon-timber forest product identification, assessment and monitoring, in: R.R.B. Leakey, A.B. Temu, M. Melnyk, P. Vantomme (Eds.), Domestication and Commercialization of Non-timber Forest Product in Agroforestry Systems, 1996.
[85] F. Leal, M.J. Cohn, Loss and re-emergence of legs in snakes by modular evolution of Sonic hedgehog and Hoxd enhancers, Curr. Biol. 26 (2016) 2966–2973.
[86] Y.H. Chen, R. Gols, B. Benrey, Crop domestication and its impact on naturally selected trophic interactions, Annu. Rev. Entomol. 60 (1) (2015) 35–58, https://doi.org/10.1146/annurev-ento-010814-020601.
[87] I.G. Carrillo-Angeles, M.E. Queijeiro-Bolaños, G.X. Malda-Barrera, H. Suzán-Azpiri, Aesthetic growth of a native tree species with desirable characteristics for urban green areas in arid and semiarid environments, Urban For. Urban Green. 33 (2018) 12–15. http://doi:10.1016/j.ufug.2018.05.001.

[88] Z. Tchoundjeu, E.K. Asaah, P. Anegbeh, A. Degrande, P. Mbile, C. Facheux, A.J. Simons, Participatory domestication into practice in West and central Africa, For. Trees Livelihoods 16 (1) (2006) 53–69, https://doi.org/10.1080/14728028.2006.9752545.
[89] R.S. Meyer, M.D. Purugganan, Evolution of crop species: genetics of domestication and diversification, Nat. Rev. Genet. 14 (2013) 840–852.
[90] R.R.B. Leakey, E.K. Asaah, Underutilized species as the backbone of multifunctional agriculture - the next wave of crop domestication, Acta Hortic. (979) (2013) 293–310, https://doi.org/10.17660/actahortic.2013.979.
[91] A.I. Sirnons, ICRAF's strategy for domestication of non-wood tree products, in: R.R.B. Leakey, A.B. Temu, M. Melnyk, P. Vantomme (Eds.), Domestication and Commercialization of Non-timber Forest Product in Agroforestry Systems, 1996.
[92] R.F. Quintana-Ascencio, M. Gonzalez-Espinosa, N. Rimirez-Marcial, G. Dominguez Vazuez, M. Martinez-Ico, Soil seed banks and regeneration of tropical rain forest from Milpa fields at the Sewa Lacandina, Chiapas, Mexico, Biotropica 28 (1996) 192–209.
[93] J.B. Hall, M.D. Swaine, Seed stocks in Ghanaian forest soils, Biotropica 12 (4) (1980) 256, https://doi.org/10.2307/2387695.
[94] A.S. Cheke, W. Nanakorn, C. Yankoses, Dormancy and dispersal of seeds of secondary forest species under the canopy of a primary tropical rain forest in Northern Thailand, Biotropica 11 (2) (1979) 88–95.
[95] Y. Shimizu, A vegetation change during a 20-year period following two continuous disturbances (mass-dieback of pine trees and typhoon damage) in the Pinus-Schima secondary forest on Chichijima in the Ogasawara (Bonin) Islands: which won, advanced saplings or new seedlings? Ecol. Res. 20 (2005) 708–725.
[96] H.D.R. Muhanguzi, J. Obua, H. Oreym-Origa, O.R. Vetaas, Forest site disturbances and seedling emergence in Kalinzu Forest, Uganda, Trop. Ecol. 46 (1) (2005) 91–98.
[97] M.D. Swaine, J.B. Hall, Early succession on cleared forest land in Ghana, J. Ecol. 71 (2) (1983) 601–627.
[98] Z. Wang, M. Cao, G. Li, L. Men, G. Duo, T. Zha, W. Zong, *Trema orientalis* seeds dispersed by birds and its ecological role, Zool. Res. 23 (2002) 214–219.
[99] N. Yuniarti, R. Kurniaty, D. Syamsuwida, Study on priming methods to enhance the viability and vigor of Trema (*Trema orientalis* Linn. BLUME) seeds, Indonesian Journal of Forestry Research 6 (2019) 69–83, https://doi.org/10.20886/ijfr.2019.6.1.69-83.
[100] Y.M.M.A. Nugraheni, N. Yuniarti, The impact of drying time and storage room on the viability of Trema (*Trema orientalis* Linn. Blume) seed, in: IOP Conference Series: Earth and Environmental Science, vol. 1109, IOP Publishing, 2022, 012097. No. 1.
[101] C.R. Rodrigues, B.F. Rodrigues, Enhancement of seed germination in *Trema orientalis* (L.) blume—potential plant species in revegetation of mine wastelands, J. Sustain. For. 33 (1) (2013) 46–58, https://doi.org/10.1080/10549811.2013.807745.
[102] D. Danu, A.A. Pramono, N. Siregar, The effect of rooting media and growth regulator concentrations on *Trema orientalis* rooting cuttings, Prosiding Seminar Nasional Masyarakat Biodiversitas Indonesia 5 (No. 2) (2019) 299–302.