

Sustainable Uses and Prospects of Medicinal Plants

Sustainable Uses and Prospects of Medicinal Plants presents information on less known and underexplored medicinal plant species in various regions of the world. The book investigates current advances in medicinal plant science and includes detailed information on the use of green nanotechnology, characterization of plants, conservation, revitalization, propagation, and pharmacological activities of selected plants. A volume in the *Exploring Medicinal Plants* series, it collects information on less-known medicinal plant species in various regions of the world for documentation profiling their ethnobotany, developments in their phytochemistry, and pharmacological activities and provides an in-depth look at some specific herbal medicines of importance, threatened and less known species, and addresses sustainable utilization and conservation of medicinal plants to ensure existence and use.

Appropriate for plant and biodiversity conservation organisations, community leaders, academicians, researchers, and pharmaceutical industry personnel, the book comprises innovative works with information of what is expected to address sustainability in the future.

Exploring Medicinal Plants

Series Editor

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Wolaita Sodo University Ethiopia

Medicinal plants render a rich source of bioactive compounds used in drug formulation and development; they play a key role in traditional or indigenous health systems. As the demand for herbal medicines increases worldwide, supply is declining, as most of the harvest is derived from naturally growing vegetation. Considering global interests and covering several important aspects associated with medicinal plants, the *Exploring Medicinal Plants* series comprises volumes valuable to academia, practitioners, and researchers interested in medicinal plants. Topics provide information on a range of subjects, including diversity, conservation, propagation, cultivation, physiology, molecular biology, growth response under extreme environment, handling, storage, bioactive compounds, secondary metabolites, extraction, therapeutics, mode of action, and healthcare practices.

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Sustainable Uses and Prospects of Medicinal Plants

Learnmore Kambizi and Callistus Bvenura

Sustainable Uses and Prospects of Medicinal Plants

Edited by
Learnmore Kambizi and Callistus Bvenura



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2 Protecting the Endemism of Threatened Cyclotide- Rich Medicinal Plants *The Tropical African Experience*

Alfred Francis Attah and Adeola Tawakalitu Kola-Mustapha

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2.1 INTRODUCTION

An estimated 430,000 plant species have been reported to grow on planet earth as human co-tenants (Lughadha et al., 2016; Kougioumoutzis et al., 2021), as sustainable sources of food, and as nature-derived medicines (Butt et al., 2021). The occurrence and spread of these plants appear to be different across continents of the planet (Kougioumoutzis et al., 2021), most probably resulting from the corresponding interactions between ecological and evolutionary processes (Eco-evolutionary processes) that have helped plants to integrate properly to their adaptable habitats (Burak et al., 2018). Eco-evolutionary processes have, therefore, triggered an uneven distribution of plants across the continents, leading to continental geographies with megadiverse plant species and countries within these continents sharing differing levels of overall richness of plant species (Linder and Evolution, 2014).

The most recent report by the World Health Organization (WHO) recognized the increasing role played by the mainly plant-based traditional and complementary medicine achieving the Sustainable Development Goal 3—ensuring healthy lives and promoting well-being for all at all ages—to achieve targeted Universal Health Coverage (UHC) (World Health Organization, 2019; Ganguly and Bakhshi, 2020). A conservative estimation suggests that about 1.2 billion population in Africa depends on plants, especially the therapeutic potentials of plant biodiversity for their primary healthcare needs (World Health Organization, 2019). (The population estimate is based on data from the United Nations, Department of Economic and Social Affairs, Population Division; www.Worldometers.info.) This updated figure, representing about 90% of African population seems to

have been encouraged by the devastating COVID-19 pandemic (Attah et al., 2021); The unavailability of a globally accepted Western medicine has put a greater pressure on plant biodiversity in a continent, whose majority of member states have weak regulations on plant conservation and sustainable utilization. At least 10% of the known global plant species are found growing unevenly across Africa (Senkoro et al., 2020), and about 70% of African plant species are limited to the tropical African region (Sosef et al., 2017), where plant endemism, according to RAINBIO and a recent report, has been estimated to be 50% (Raven et al., 2020). Endemism of plants represents the nativity of plant species to a geographical location, region, country, or continent (Linder and Evolution, 2014). Several of these endemic plant species have found useful applications as food and local medicines to the human populations living around their geographical distribution (Attah et al., 2016b; Burlando et al., 2019; Senkoro et al., 2020; Attah et al., 2021). Scientific investigations of less than 1% of African plants have revealed the presence of several pharmaceutically useful metabolites—alkaloids, glycosides, tannins, terpenes, essential oils, polysaccharides, peptides, and therapeutic proteins (van Wyk and Prinsloo, 2020). Among the therapeutic biopolymers of pharmaceutical interest is the fortuitous discovery of a class of mini protein molecules called cyclotides from African ethnomedicine (Craik et al., 1999) (Figure 2.1). Cyclotides represent a unique class of 2–4 kDa knottin peptides having a circular knot backbone and intercysteine loops defining the peptide structural architecture (Craik et al., 1999). As members of the gene-encoded peptides, cyclotides are ribosomally synthesized and post-translationally modified peptides (RiPPs)



FIGURE 2.1 Map of Africa showing countries where cyclotides have been identified in plants collected; regions of highest endemism of cyclotide-rich flora are in Nigeria, Gabon, Cameroon, Congo, Central African Republic, Democratic Republic of the Congo, Ethiopia, Uganda, Kenya, Rwanda, Burundi, Tanzania, and Madagascar. (Adapted from <https://www.freeworldmaps.net/africa>).

whose mature peptides are mostly generated by proteolysis following removal of the leader as well as recognition sequences (Luo and Dong, 2019). Their sequence variability outside the conserved region has encouraged a wide range of bioactivities that extends beyond their suitability for drug development (Camarero and Campbell, 2019). Additionally, cyclotides possess intrinsic phytochemical capability for an ecologically compatible plant protection (Oguis et al., 2019). Meanwhile, host defense-related function has been associated with cyclotide expression in plants (de Veer et al., 2019; Slazak et al., 2021). This means cyclotide expression appears to be common with plants endemic to regions that are more prone to pests, diseases, and climatically extreme environments as found in tropical Africa (Yeshak et al., 2011; Oguis et al., 2019; Gattringer et al., 2021; Slazak et al., 2021). The notable wide variations in conditions associated with rainy and dry seasons common to tropical climates, tropical Africa, in particular, has been proposed to have encouraged more pathogen distribution within the region, as these pathogen carriers (pests) and the disease-causing organisms require water and humid conditions for spread or reproduction (Guernier et al., 2004). Thus, the hypothesis regarding the association between the cyclotide-producing plants and their higher distribution in plants growing around the humid tropics, wetlands, and other extreme habitats remains to be elaborately investigated. For instance, the distribution of a host of plants expressing cyclotides (including *Oldenlandia affinis*, *Rinorea denata*, *Rinorea oblongifolia*, *Rinorea subintegriifolia*, *Clitoria ternatea*, *Viola abyssinica*, *Viola odorata*) are often limited to these extreme conditions that encourage pest/pathogen attack, such as moist and swampy environment (Yeshak et al., 2011; Attah et al., 2016a; Slazak et al., 2021; Gattringer et al., 2021). Plants growing within this region will tend to require additional arsenal of defense molecules to adapt to unstable extreme environments where they grow (Figure 2.1).

Abundant expression of knottin peptides, including cyclotides, within the plant organs in response to the increased level of threat in their immediate environment may provide some explanation to the uneven distribution of cyclotides in plant species and families across Africa—a factor that may closely be associated with their resilience and sustained endemism. For instance, *Oldenlandia affinis* (Roem. & Schult.) DC. Rubiaceae, an endemic herb common to the tropics, especially tropical Africa where it has been linked to the discovery of cyclotides (Figure 2.2), is commonly found growing in proximity to a body of water or during the rainy season in Nigeria. Recently, though this plant has become scarce within this region, just as the species is no longer found growing in locations (such as Sobi Hills, Ilorin) documented by Herbarium samples deposited some decades back at the Forest Herbarium, Ibadan, Nigeria.

Importantly, *O. affinis* and other cyclotide-expressing genera such as *Rinorea* and *Allexis* (Violaceae) are used in Traditional Medicine across tropical Africa (Weidmann and Craik, 2016; Attah et al., 2016b; Nworu et al., 2017; Gattringer et al., 2021) where they are endemic; however, no attention has been accorded to their conservation despite myriads of increasing threats from divergent sources endangering

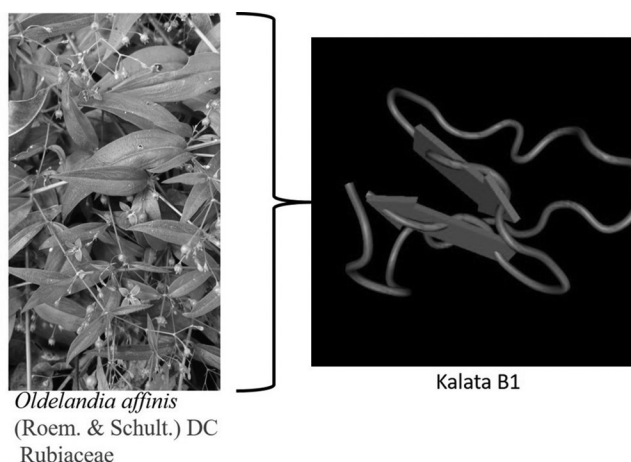


FIGURE 2.2 Cyclotide-rich African *Oldenlandia affinis* and the first cyclotide blueprint, Kalata B1 detected and isolated from the plant. PDB ID: 1JJZ

TABLE 2.1
Conservation Status and IUCN Classification of African Plants Expressing Cycloptides Based on the International Union for Conservation of Nature (IUCN) Red List of Threatened Species

S/N	African Plant	Habit	Endemism Status	Conservation Status	IUCN Classification	Authors' Comment
1	<i>Clitoria ternatea</i> L. Fabaceae	Herb	Unassessed	Unassessed	Unassessed	Plant has not received any conservation attention
2	<i>Oldelandia affinis</i> (Roem. & Schult.) DC Rubiaceae	Herb	Unassessed	Unassessed	Unassessed	Threatened; currently very scarce in the wild; no longer found growing in locations of the previous herbarium collection
3	<i>Rinorea dentata</i> (P. Beauv.) Kuntze Violaceae	Shrub	Unassessed	Unassessed	Unassessed	Threatened due to logging, habitat loss, and divergent human uses
4	<i>Rinorea oblongifolia</i> (C.H.Wright) C.Marquand ex Chipp Violaceae	Understory tree	Unassessed	Unassessed	Unassessed	Threatened due to logging, habitat loss, and divergent human uses
5	<i>Rinorea ilicifolia</i> (Welw. ex Oliv.) Kuntze Violaceae	Understory tree	Unassessed	Unassessed	Unassessed	Threatened due to logging, habitat loss, and divergent human uses
6	<i>Rinorea brachypetalata</i> (Turez.) Kuntze Violaceae	Shrub/small tree	Not threatened	Unassessed	Unassessed	Vulnerable due to logging, habitat loss, and divergent human uses
7	<i>Allexis obanensis</i> (Baker f.) Melch. Violaceae	Understory tree	Vulnerable	IUCN based—Not threatened (Cameroon)	Threatened	Threatened due to logging, habitat loss, and divergent human uses
8	<i>Allexis cauliflora</i> (Oliv.) Pierre Violaceae	Understory tree	Vulnerable	Unassessed	Threatened	Threatened due to logging, habitat loss, and divergent human uses
9	<i>Allexis batangae</i> (Engl.) Melch. Violaceae	Understory tree	Vulnerable	Unassessed	Unassessed	Threatened due to logging, habitat loss, and divergent human uses
10	<i>Allexis zygomorphia</i> Achound. & Onana Violaceae	Understory tree /Shrub	Vulnerable	IUCN based—Vulnerable (Cameroon)	Threatened	Threatened due to logging, habitat loss, and divergent human uses
11	<i>Viola abyssinica</i> Steud. ex Oliv. Violaceae	Herb	Vulnerable	Unassessed	Unassessed	Threatened due to climate change and habitat loss
12	<i>Viola odorata</i> L. Violaceae	Herb	Vulnerable	Unassessed	Least concern	May soon be threatened due gradual habitat loss

Source: <https://www.iucn.org>.

the species. The loss of important plant biodiversity endemic to tropical Africa necessitates their conservation to protect their endemism. Emerging evidence suggests that African plant biodiversity faces existential threat (extinction) until the end of the current 21st century of the Gregorian calendar (Stévant et al., 2019). The tropical African flora has been classified under the ‘high level of extinction risk’ (Stévant et al., 2019), and many cyclotide-rich medicinal plants within the genera *Rinorea* and *Allexis* have been listed under the International Union for Conservation of Nature (IUCN) Red list (Table 2.1). Many species within the cyclotide-rich plant taxons have not been assessed, making their status unknown on the IUCN Red list. A typical example of such is *Clitoria ternatea* L. (Fabaceae), native to the humid as well as subhumid tropics, including tropical Africa. *C. ternatea* is a knottin peptide-expressing plant with application in medicine and sustainable agriculture (Oguis et al., 2019). This may indicate that this plant is facing more daring threat of extinction in Africa where relevant regulations are not enforced in many member states. Another instance is the genus *Allexis* whose four known species are restricted to tropical central and Western coast of Africa, yet the three accessed species of this genus have all been categorized as vulnerable on the IUCN Red list, while many more endemic Violaceae and Rubiaceae cyclotide-rich plants have not been evaluated despite their overutilization and overexploitation. To highlight the ever-increasing threats to cyclotide-rich plants endemic to Sub-Saharan Africa, we document for the first time, these endangered and highly valued ethnomedicinal plants whose poor to non-existent conservation status deserves an urgent attention to forestall imminent extinction. In addition, we also present the compelling need to protect the endemism of these important African bioresources whose role in Traditional Medicine, nutrition, and ecological balance buttresses their classification as biofactories of lifesaving metabolites.

2.2 AFRICAN HERBAL ETHNOMEDICINE AND CYCLOTIDE DISCOVERY

The African flora provides a rich source of medicinal plant and plant parts useful in the management of some clinical conditions, and for several decades, the use of herbs, herbal concoctions, and traditional phytomedicines has proved invaluable (Mahomoodally and Medicine, 2013). Evaluating the chronology of primary care and treatment in Africa is incomplete without recognizing the role of herbal ethnomedicine. With a very high biodiversity of plants and cultures, various plant species serve as treatments in different regions and communities. One of such uses led to the early discovery of cyclotides by Lorents Gran—a Norwegian doctor who discovered that African women drank a tea derived from the plant *Oldenlandia affinis* (Rubiaceae) to accelerate the birth of their children (Gran, 1973b; Weidmann and Craik, 2016). The plant was found to contain cyclotides that have uterotonic activity, hence validating its use for such purpose. Complementary and Alternative Medicine (CAM) has been the oldest form of treatment, particularly in Africa. Despite the limited knowledge with regard to the pathophysiology of diseases and mechanism of action of plant extracts, some herbs have been found to be clinically effective in the management of some conditions. Plant biodiversity in Africa provides a rich source of numerous plant species with abundant constituents and metabolites with similar or dissimilar constituents. Some components or peptides may occur across multiple genera and species among endemic plants in the region e.g., cyclotides. Cyclotides are macrocyclic peptides discovered in plants. They are distinguished by their unique cyclic cystine knot (CCK) structural pattern. A head-to-tail cyclic backbone is cross-braced with a cystine knot generated by six conserved Cys residues in the CCK motif (Gran, 1973a; de Veer et al., 2019). Cyclotides are intriguing because of their unusual structure, which confers extraordinary stability, as well as their natural activities as plant defense peptides, and their vast variety of uses as bioactive molecules in agriculture and medicine (de Veer et al., 2019). The presence of cyclotides in some endemic African plants may account for their different uses in ethnomedicine. One example is *Rinorea dentata* (Violaceae family). *Rinorea dentata* (P. Beauv.) Kuntze is a tropical plant that grows in the rainforests of Liberia, Cameroon, Uganda, and Nigeria. Parts of its ethnomedical uses among local settlers in the J4 region of the Omo Forest Reserve in Ogun State, Nigeria, the plant’s natural habitat, chew its stem for oral hygiene as a malaria treatment and to shorten labor or make birth easier in farm animals (Attah et al., 2016b). *Allexis cauliflora*—a plant native to Cameroon, Congo, and Gabon belongs to the Violaceae family and has been found to

contain cyclotides (Gattringer et al., 2021). Cyclotide-rich extract of the plant has also been found to inhibit human prolyl oligopeptidase (POP) activity (Gattringer et al., 2021). Other members in the same genus that contain cyclotides include *Allexis anensis*, *Allexis batangae*, and *Allexis zygomorpha*. *Rinorea brachypetala* can be tropical Africa, from Guinea East to Kenya, and to Zambia and Angola in the South (Plant Use, Online). Results of Matrix-Assisted Laser Desorption Time of Flight (MALDI-TOF) Mass spectrometry show that it also contains cyclotides (Attah et al., 2016a).

2.3 ENDEMISM OF THE CYCLOTIDE-RICH *OLDENLANDIA AFFINIS*

The Rubiaceae family's genus *Oldenlandia* contains 190 species, several of which are known to be used in traditional medicine. From the Ivory Coast in the north to South Africa Transvaal, *O. affinis* is widely dispersed in Africa's tropical zone (Figure 2.2). It can also be found on Madagascar and in western Asia, with the Malay Peninsula serving as its easternmost outpost. It grows as a weed in the grass at altitudes ranging from sea level to 1,500 m above sea level. It appears to avoid arid areas (Gran et al., 2000). There have been reports and observations on the ethnomedical uses of *O. affinis* in different cultures across the region. An aqueous extract, also known as 'Kalata-Kalata', in Congo is used to facilitate labor and childbirth. It is also used for this same activity in the Central African Republic (Gran, 1973b). *O. affinis* is blended with honey and used to treat learning disabilities in Benin Republic, and the aqueous decoction is used as an anti-colic drink. The decoction of *O. affinis* is utilized as an anti-malarial and anti-febrile medicine in several rural communities in South-Eastern Nigeria (Nworu et al., 2017). These activities are based on the presence of cyclotides peptides, which when compared to other peptides of similar size are extremely resistant to chemical, thermal, and biological degradation (Gould and Camarero, 2017). Protease inhibitory, anti-microbial, insecticidal, cytotoxic, anti-HIV, and hormone-like effects are all biological features of naturally occurring cyclotides (Gould and Camarero, 2017).

As much as cyclotides are important in herbal medicine, they can also serve as useful drug molecules in the synthesis of new drugs, hence, highlighting the importance for preservation of endemic *O. affinis* plants. Since the first isolation of cyclotides from *O. affinis* (Figure 2.1) by Lorent Gran, cyclotides have now been discovered in the plant families Rubiaceae (coffee), Violaceae (violet), Solanaceae (potato), Poaceae (grass), Cucurbitaceae (cucumber), and Fabaceae (pea) (Slazak et al., 2020). The environment has an impact on cyclotide production. Depending on the region or season, different amounts of certain peptides are detected in the same species. Changes in cyclotide gene expression levels appear to be the reason, but breakdown rates may also play a role in forming the final peptide suite (Slazak et al., 2020). The protection of the endemism of threatened cyclotide-rich medicinal plants such as *O. affinis* and other plants is highly imperative. When faced with the growing use of medicinal plants, preserving tropical biodiversity should be prioritized. Most tropical plant species lack extinction risk estimates, restricting the capacity to identify conservation priorities despite their critical importance for terrestrial ecosystems (Stévant et al., 2019).

2.4 ENDEMISM OF OTHER CYCLOTIDE-RICH VIOLACEAE PLANT FAMILY IN AFRICA: EMERGING THREATS

The threat to the endemism of cyclotide-rich plants in tropical African region is not limited to *O. affinis*, the genus *Rinorea* (family Violaceae) appear to be top on the list (The IUCN Red List of Threatened Species: <https://www.iucn.org/>). *Rinorea* Aubl. is a genus made up of an approximately 250–300 species (World Flora online Consortium—www.worldfloraonline.org), with at least 150 mostly endemic species unevenly distributed across tropical African coast including Angola, Southern Nigeria, Cameroon, Gabon, and Madagascar (Wahlert et al., 2020) (Figure 2.2). This data translates to over 60% of *Rinorea* endemism in the region whose distribution peaks up in Madagascar, recording 80% known species endemism (Wahlert et al., 2020). Following well-informed prediction, it means several or all these endemic cyclotide-producing tropical medicinal plants (Table 2.2) are facing the risk of global extinction before the end of the 21st century.

TABLE 2.2

Continental Distribution of Cyclotide-Rich African Plants. Cyclotides Documented Have Been Retrieved from Cybase—a Database of Cyclic Proteins

S/N	Botanical Source	Traditional Uses	Continental Distribution	Cyclotides Documented in Cybase
1	<i>Clitoria ternatea</i> L. Fabaceae		It is used as a source of natural food colorant. It is cultivated as a forage and fodder crop, for nitrogen fixation and improvement of soil nutrient. It is used to aid childbirth	Tropical Ciotide T1, T2, T4 (Cter P), T6, T8, T9, T10 (Cter 27), T11 (Cter 21), T12, T13, T14, T15, T16, T17, T18, T19a, T19b, T20, T21, T22α, Clotiotide T23*-T32*, Cter A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, Q, R
2	<i>Oldelandia affinis</i> (Roem. & Schult.) DC Rubiaceae	Facilitation of childbirth.	DR Congo, Central African Republic, Liberia, Sudan, South Africa, Madagascar, Nigeria	Kalata B1–B19; Kalata B20-lin
3	<i>Rinorea dentata</i> (P. Beauv.) Kuntze Violaceae	Its wood is used as a chewing stick for oral hygiene. Used as veterinary remedy for aiding parturition in livestock and for treatment of neurodegenerative disorders. Its tree trunk can be used as hardwood for tools making, construction, boat building, furniture making, etc.	Tropical rainforests of Liberia, Nigeria, Cameroon and Uganda	R. dentata A (riden A)
4	<i>Rinorea oblongifolia</i> (C.H.Wright) C.Marquand ex Chipp Violaceae	In DR Congo the wood is used in construction and for household utensils. In Sierra Leone it is used to make spoons and combs. In the Central African Republic a root extract is drunk as a purgative. It is used to calm the pain in women during childbirth. It is used to treat fever.	Nigeria, Gabon, Central African Republic, Cameroon, DR Congo, Sierra Leone, Uganda.	Unavailable
5	<i>Rinorea ilicifolia</i> (Welw. ex Oliv.) Kuntze Violaceae	The hard and heavy wood is used in Uganda to make wooden hammers, tool handles, and walking sticks. In West Africa decoctions of the whole plant are drunk to cure epilepsy. In Kenya the pulped root is steeped in water and the liquid is drunk to treat cough. It is used to calm the pain in women during childbirth and for fever.	Nigeria, Guinea east, Kenya, Angola, Mozambique, KwaZulu-Natal, South Africa, Madagascar, Benin, Burundi, Cameroon, Central African Republic, Comoros, Congo, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya	Unavailable

(Continued)

TABLE 2.2 (Continued)
Continental Distribution of Cyclotide-Rich African Plants. Cyclotides Documented Have Been Retrieved from Cybase—a Database of Cyclic Proteins

S/N	Botanical Source	Traditional Uses	Continental Distribution	Cyclotides Documented in Cybase
6	<i>Rinorea brachypetala</i> (Turez.) Kuntze Violaceae	Its wood is used in Kenya and Uganda for hut construction, walking sticks, and knobkerries. In DR Congo it is used in construction and to make household utensils. Boiled leaves are eaten as a vegetable and the dried, powdered leaves are sniffed to relieve headache. It is used to calm the pain in women during childbirth and for fever. Used for the treatment of brain disorders	Nigeria, Guinea, Kenya, Zambia, Angola, Sierra Leone, Cameroon, Uganda	Unavailable
7	<i>Allexis obanensis</i> (Baker f.) Melch. Violaceae		Cameroon, Nigeria (Oban Division and National Park, Cross River)	Alca 1, Alca 2
8	<i>Allexis cauliflora</i> (Oliv.) Pierre Violaceae	Bark is used to treat fever and syphilis	Congo, Cameroon, Ghana, Nigeria	Alca 1 and Alca 2
9	<i>Allexis batangae</i> (Engl.) Melch. Violaceae	Used for the treatment of brain disorders	Congo, Cameroon	Alca 1, Alca 2, Alba 1, 2, 3, 4
10	<i>Allexis zygomorpha</i> Achound. & Onana Violaceae	Used for the treatment of brain disorders	Congo, Cameroon	Alca 1 and Alca 2
11	<i>Viola abyssinica</i> Steud. ex Oliv. Violaceae	In Ethiopia, its leaves are crushed and squeezed to get the juice, which is applied to hard leather to soften it. In Madagascar it is given as an antidote and to stimulate vomiting. Along the eastern border of Congo, it is rubbed with other herbs in butter to make a massage oil.	Fernando Poo (Bioko), South Africa (Transvaal), Madagascar.	Vaby A, B, C, D, E, Varv E (Cyclovioiacin O12)
12	<i>Viola odorata</i> L. Violaceae	It is used to treat anxiety, insomnia, skin disorders, and cough. It is used to make violet scones and marshmallows	Morocco, Tunisia and North Africa	Cyclovioiacin O1, O2, O3, O4, O5, O6, O7, O8, O9, O10, O11, O12, O13, O14, O15, O16, O17, O18, O19, O20, O21, O22, O23, O24, O25, Varv A, Kalata B1, Vodo N, Vodo M, Violacin A

Source: (<https://www.cybase.org.au>) (57).

While Africa is unarguably the richest continent in terms of *Rinorea* species diversity, it is the only continent native to the genus *Allexis* Pierre (family Violaceae; Table 2.2), distributed across Tropical West and Central Africa (Olivier et al., 2018; Gattringer et al., 2021). Despite the endemism of a majority of *Rinorea* species and restricted distribution of the four known species of the genus *Allexis* in limited tropical region of Africa, flora diversity within the continent remains the most threatened due to the increasing human populations, combined effect of logging, fuelwood collection, overcollection of wild plants for research, and deforestation for agriculture and mining (van Velzen and Wieringa, 2014). The endemism of Violaceae family to tropical Africa has been demonstrated by the three largest violaceae genera—*Viola*, *Rinorea*, and *Hybanthus*, which account for around 95% global distribution of Violaceae species (Wahlert et al., 2020; Slazak et al., 2021) and the genus *Allexis* with only four accepted species names (<http://www.theplantlist.org/>; Table 2.2). While the endemism of the genus *Viola* in Africa and neighboring oceanic island appears to be restricted to extreme geographies, particularly the temperate and mountainous regions (Linder and Evolution, 2014), a few such as *Viola palmensis*, *Viola cheiranthifolia*, *Viola anagae* have recently been reported in extreme environments (Slazak et al., 2021) located outside African mainland; however, the next two largest genera based on the recent circumscription, *Rinorea* and *Hybanthus*, are mainly pantropical, occurring more in the humid seasonal tropics found within the most endangered African flora (Wahlert et al., 2020). Exhaustive ethnomedicinal surveys in the recent past no longer document several of these important cyclotide-rich African plants—an observation that further supports the level of threat to their endemism. Deliberate efforts should therefore be made to ensure sustainable utilization of cyclotide-rich African plants that are now becoming extinct in the wild. The sustainability of these threatened plants will mainly be achieved via captivity, cultivation in/or outside native range, based on IUCN Red list description and classification of plants species.

2.5 COMPETITIVE APPROACHES TO SAFEGUARD ENDEMIC CYCLOTIDE-PRODUCING AFRICAN PLANTS

There is an urgent need for the proper documentation, conservation, and utilization of the cyclotide-rich species of African flora. The chemotaxonomic relevance of cyclotides to Violaceae plant family has been emphasized (Burman et al., 2015) as species screened produced the presence of cyclotides, making them the foremost biofactories for cyclotide diversity, abundance, and species distribution (Slazak et al., 2021). The African Violaceae appears to be the least scientifically investigated family despite its apparent endangered status. Meanwhile, African Violaceae has varied uses in the Traditional Medicine. The potentials of its abundant cyclotides in sustainable agricultural plant protection as biomaterials for drug discovery/development as well as their putative clinical application should form a strong basis for further scientific investigation of the family. Therefore, efforts are needed to implement competitive steps and strategies to sustainably safeguard the endemism of cyclotide-rich African flora. This is particularly urgent in African regions with cyclotide-rich plant diversity, including Tropical West Africa, Ethiopia, Tanzania, and the Democratic Republic of the Congo (Figure 2.1), which have been described to harbor over 40% of potentially threatened endemic plant species (Stévant et al., 2019). Among others, these strategies comprise land/water protection and management, cyclotide-producing species management, education and awareness, livelihood, economic and other incentives, as well as law and policy. The botanic garden approach to plant extinction crises remains one of the easy-to-adopt strategy (Westwood et al., 2021; van Zonneveld et al., 2021). In line with Article 14 of the United Nations Convention on Biological Diversity (www.cbd.int/), adopting environmental impact assessments (EIAs) is germane before implementation of lawful projects that may pose as threats to plant biodiversity. Hence, to minimize risks associated with the environment, the adverse impacts of these projects on plant biodiversity must be identified to circumvent, minimize, or totally prevent negative consequences (Stévant et al., 2019).

2.6 FUTURE PERSPECTIVES

2.6.1 FIGHTING PLANT BIODIVERSITY LOSS IN AFRICA

Africa's fertile ground is host to a wide array of plant species scattered around the continent. An approximate one-quarter of global biodiversity comes from Africa. From tropical regions to temperate areas, and even unto arid regions, different plant varieties are native to these zones, but sadly there is a continuous decline in the number of plant species in the continent, and some species are already going extinct. The importance of preserving this biodiversity hotspot of the world is vital. Many greater numbers of African plants have not received investigative scientific attention despite their inherent potentials for drug discovery. The role of plant biodiversity underlies the pivotal point of almost all ecosystems, and ecosystems will remain adversely affected if the continuous loss of species remains unchecked. The loss of biodiversity has an impact on livelihoods, water availability, food security, and resistance to catastrophic events, especially for the poorest people in rural regions (Bank., 2019).

Tackling plant biodiversity loss is an important issue, and causal factors need to be addressed. Causal factors include overcollection, unsustainable agriculture, and forestry methods, urbanization, pollution, land use changes, the spread of invasive alien species, climate change, a lack of information about the status of most habitats, species, and other vital data (Osawaru et al., 2013). It is evident that there is much room for improvement in biodiversity-related programs and policies in Africa. Plant conservation should be prioritized and not only considered as a subset of wildlife conservation. Governmental institutions and non-governmental agencies need to not only promulgate laws but also to enforce them as well. Land use should be closely monitored, especially in regions with biodiversity of species and endemic plants. There is also a need for the development and update of national plant databases across countries in the region. Plant, animal, forest, and aquatic genetic resources in Africa, like those in other regions, are better documented than associated biodiversity; just a few nations report having national databases or knowledge-management systems dedicated to associated biodiversity (FAO, 2019).

Climate is a strong influencer of the sustainability of plant ecosystems and biomes. Plant variety is shaped by climate on a wide scale, with relatively warm and moist (beneficial, productive) locations sustaining more species (Harrison et al., 2020). Climates are fast evolving toward warmer temperatures, which is predicted to result in less water availability throughout the growing season in approximately half of the Earth's terrestrial area (McLaughlin et al., 2017). Reduction in water availability adversely affects the sustainability and preservation of plant species in the continent. Combatting plant biodiversity loss by responding to climate change requires participation and collaboration across sectors, agencies, and governments (Fernández-González et al., 2005). Climate change is an urgent issue in the 21st century that affects almost every sphere of life, and, as detailed in this chapter, it affects cyclotide-rich African tropical plants as much. While some countries are working consciously to reduce greenhouse emissions, the same level of effort is lacking in under-developed and developing countries. African countries need to put in place structured efforts and plans to reduce carbon footprint and mitigate climate change.

2.6.2 FUTURE OF AFRICAN PLANT BIODIVERSITY

Africa continues to face a reduction in biodiversity and possible extinction of some species. The continent is home to a wide array of plants scattered across towns, villages, communities, and territorial borders. The highlight of this section is to call to mind the need for action to preserve this ecosystem in all its forms and species. The future of African plant biodiversity can be sustained if proper actions are taken. Whether plant biomes will be conserved or not is dependent on the conservation efforts implemented or introduced. It is essential to have a grasp of the full diversity of plant

species in a database, characterize the rate of decline, and highlight the indices of contributing factors. According to the mid-term review report from The United Nations Environment Programme World Conservation Monitoring Centre (UNEP-WCMC, 2016), lack of institutional, financial, and technological resources as well as the capacity to implement National Biodiversity Strategies/ Action Plans (NBSAPs) limit efforts in conserving plant biodiversity. A lack of appropriate and harmonized biodiversity indicators to assess conservation needs and NBSAP progress represent contributing factors limiting the conservation of plant biodiversity. Other limiting factors include data and information deficiencies, and national budgetary constraints. (UNEP-WCMC, 2016). On the positive side, some levels of progress have been achieved in Africa towards plant conservation. The Nagoya Protocol on Access and Benefit Sharing has been approved by 30 African nations as of December 2015 (Aichi Target 16). Several other countries in the region are planning to do the same. In addition, at least one NBSAP has been submitted by 44 African Parties (Aichi Target 17) (UNEP-WCMC, 2016).

More major conservation efforts, as well as proactive measures such as adjustments in agricultural techniques, enhanced agricultural commerce and improved land-use planning, and will be required to prevent and decrease threats to world biodiversity (Tilman et al., 2017). There are several biodiversity hotspots in Africa—home to threatened plant species. One example of such spot is the Bale Mountains of Ethiopia. It supports the continent's largest area of afroalpine and subalpine ericaceous plants. Despite it being listed by UNESCO as one of the biodiversity hotspots, it has not received the needed conservation attention. The protection of critical areas like this is essential to maintain the biodiversity of the continent and prevent the extinction of threatened species (Kidane et al., 2019).

2.6.3 PROTECTION AND SUSTAINABLE USE OF ENDEMIC CYCLOTIDE-RICH SPECIES IN AFRICA

Numerous cyclotides have been isolated from the Rubiaceae, Cucurbitaceae, Fabaceae, Solanaceae, Poaceae, and Violaceae families. Many cyclotides are found only in certain plant species, although others are found in multiple species (Slazak et al., 2020, Ravipati et al., 2017). While some families are more abundant than the others and do not face any reasonable threat, some cyclotide-containing species are very rare and may face danger of extinction. Preserving the availability and continued use of these cyclotide-rich species is thus very important. The IUCN Red list provides a comprehensive database on the status of extinction risk of plants, animal, and fungi. It ranks plants on a risk scale starting from least concerned to near threatened, vulnerable, endangered, critically endangered, extinct in the wild and extinct (last on the scale) (IUCN: <https://www.iucn.org/resources/conservation-tools/iucn-red-list-threatened-species>). According to the IUCN Red list database, *Rinorea tshingandaensis* belongs to the vulnerable group (Ntore, 2021). *Rinorea frisii* and *Rinorea bullata* belong to the endangered group (Alemu, 2018; Ravololomanana, 2020), *Rinorea abbreviate*, *Rinorea key*, and *Rinorea rauschii* belong to the near threatened group (Bidault, 2020., Faranirina, 2019, Centre., 1998.). All of these species belong to the same genus with *Rinorea dentata* under the Violaceae family, which has been validated to possess cyclotides (Attah et al., 2016b). Despite the poor status of these species, there are little to no conservation efforts put in place. Conservation efforts that can help preserve these species include *ex-situ* conservation, habitat restoration, awareness, legislation, and enforcement among others (IUCN: <https://www.iucn.org/resources/conservation-tools/iucn-red-list-threatened-species>).

2.7 CONCLUSION AND PROSPECTS

Africa must be deliberate in ensuring the proper utilization of the already endangered cyclotide-rich plants. Considering the threats to the endemism of these cyclotide-producing plants, their intentional cultivation has become necessary to prevent them from getting critically endangered

and ultimately going extinct. It is, therefore, pertinent to holistically address the main drivers of biodiversity loss of cyclotide-rich plants in Africa in a timely manner, comprising divergent over-exploitation, increasing reports of invasive species, habitat loss, crude oil pollution, and climate change. Local plant habits and habitats, particularly those persisting in restricted areas must be urgently protected. Besides *in situ* conservation measures, cyclotide-rich plants endemic only to limited and restricted environments such as the genus *Allexis* as well as some endemic *Rinorea* species require additional *ex-situ* conservative strategies such as gene collection from the wild, *in vitro* collections, storage in seed banks, and medicinal plant garden (botanical garden) solutions. In Sub-Saharan Africa, only 13 endemic *Rinorea* species have been accessed and included on the IUCN Red list, representing less than 10% of *Rinorea* species known to the region; yet, over 80% of these accessed species have been classified as critically endangered, endangered, vulnerable, and near threatened (www.iucnredlist.org). One of the main hindrances to the identification and conservation of new *Rinorea* species lies in the close morphological similarity between species of the genus. This has made the identity of over 190 species from Gabon very difficult for taxonomists (Sosef et al., 2017). However, modern methods, such as the application of molecular marker-assisted authentication, are encouraged to resolve the challenges with the classification of endemic *Rinorea* species in a bid to promote their conservation and prevent misutilization (Sonibare, 2021). More importantly, the reported expression of cyclotides in every member of Violaceae family as well as the unique pattern of species cyclotide signature is of chemotaxonomic relevance, as it has the potential to aid in proper species identification, classification, and eventual conservation when morphology alone becomes inadequate (Slazak et al., 2021, Burman et al., 2015). Lastly, cyclotide fingerprint unique to individual species could serve as chemotaxonomic markers for species identification, classification, conservation, and sustainable utilization. A combined effort of molecular marker-assisted authentication and cyclotide-based chemotaxonomic approaches are suggested as deliberate background strategies that could potentially promote the protection of endemic cyclotide-rich African flora diversity.

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