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Biomedical Potential of Natural Products from Selected Tanzanian Flora: A Review

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Abstract

Natural products have been used for treatment of various diseases for thousands of years and served as sources of drug lead compounds for the improvement of livelihood. This paper presents a review on the biomedical potentials of selected natural products isolated from eight plant species indigenous to Tanzania. The review covers research work published between 2010 and 2023, and identifies 33 natural products with different pharmacological properties from Tanzanian plants. These bioactive natural products are discussed with other similar compounds isolated elsewhere from the same or different plant species to get further insights on the potential application in modern medicine based on information obtained from online search from different databases including Chemical Abstract, Google Scholar, MEDLINE, PubMed and Science Direct using different key words or phrases. The review includes antitubercular, anticancer and neuroprotective flavonoids from *Erythrina schliebenii* (Fabaceae), antitubercular and antioxidant metabolites from three mangrove species *Heritiera littoralis* (Sterculiaceae), *Xylocarpus granatum* (Meliaceae) and *Sonneratia alba* (Lythraceae). The review also covers antiplasmodial secoiridoids and iridoids from *Morinda asteroscepa* (Rubiaceae), antibacterial biflavonoids from two *Ochna* species (Ochnaceae), antiviral and antiplasmodial diterpenoids from *Croton kilwae* (Euphorbiaceae), and other constituents from these plant species. Most of these plants are rare, endemic or near endemic in Tanzania. Of these natural products, the catechinoid **13** (IC_{50} 4.5 µg/mL) was four times more active than the positive control towards radical scavenging, the biflavonoid **31** (MIC 2.2 µM) was more potent in antibacterial assay than the standard drug, whereas diterpenoids **34-36** demonstrated strong anti-proliferative effect against the malaria parasite *Plasmodium falciparum* (80-100%, at 50 µM), making them promising candidates for drug development. The review argues about challenges associated with the realization of the full potential of biomedical agents such as scalability, toxicity, solubility, and bioavailability thereby calling for concerted research endeavors to address them to exploit effusively the potential that resides in the natural products towards drug development. The mode of actions of the lead compounds must be elucidated and clinical studies conducted for targeted disease treatments.

Keywords: Tanzanian flora; antiplasmodial; anticancer; antioxidant; antiviral; antibacterial; neuroprotective; anti-inflammatory

Introduction

Natural products have been in use to treat diseases for thousands of years, formerly as components of traditional medicine and later as sources of drug lead compounds (Adamsonet al. 2021, Chuma et al. 2006). Currently, approximately 76.7% of drugs either are of natural products origin or contain natural product-inspired pharmacophores (Newman and Cragg 2020,

Seidel et al. 2020). Over a thousand plants remain in use in indigenous health systems as a means of treating various diseases in developing countries (Willcox 2004).

Tanzania is one of the top five African countries highly rich in biodiversity, with approximately 11,000 species of vascular plants accounting for more than one-third of the total plant species of tropical Africa (Nyandoro 2014, https://tz.chm-cbd.net/en/biodiversity-tanzania). The country ranked 15th globally with regard to the number of threatened species, including plant species such as *Pterocarpus angolensis* (Mninga), *Dalbergia melanoxylon* (Mpingo), *Uvariodendron gorgonis*, *Erythrina schliebenii* and *Karomia gigas*. (https://tz.chm-cbd.net/en/biodiversity-tanzania). This biodiversity has a high socio-economic value that could be tapped positively to impact human livelihood in the country, region, and globe. Despite the rich biodiversity of Tanzania, a comprehensive review of its flora's medicinal potential remains underexplored, limiting the understanding and application of these natural resources in modern medicine. Natural products derived therefrom can be utilised for various purposes, including developing new therapeutic agents for the treatment of various ailments. Although, numerous plant species are traditionally used in Tanzania for health care, so far only a limited number of them have been systematically studied for their biomedical potential and toxicological aspects (Nkunya 2005, Innocent et al. 2022). Meanwhile, this plant diversity is under threat of continued existence from human economic activities including expansion of agricultural land and exploitation for timber and wood products. Thus, implies that there is an urgent need to establish and document their biomedical potential before their disappearance. With current advances in science and technology for the elucidation of structures of compounds from such bio-resources, the establishment of their biological and physiological properties are indispensable foundations for the development of new therapeutic agents (Khan 2018).

Our group has for the past four decades (1984 - 2024) investigated Tanzania plants with focus on those either used in traditional medicine, particularly targeting those with uncommon occurrences or are endemic to Tanzania. Three mini-reviews on the chemistry of such plants have been presented (Nkunya 2005, Nyandoro 2014, Maroyi 2020). Therefore, the current review aimed to assess the biomedical potential of selected Tanzanian flora by identifying their bioactive principles to determine promising groups of compounds, which could contribute to the discovery of plant-derived drugs. In this context, the bioactive agents from selected Tanzanian flora that were recently included in our on-going phytochemical investigations are hereby reviewed. Their sources include *Erythrina schliebenii* (Fabaceae), *Morinda asteroscepa* (Rubiaceae), *Ochna holstii* and *O. kirkii* (Ochnaceae), *Croton kilwae* (Euphorbiaceae) as well as mangrove species *Heritiera littoralis* (Sterculiaceae), *Xylocarpus granatum* (Meliaceae) and *Sonneratia alba* (Lythraceae). The therapeutic potential of the reviewed natural products includes their applicability as antimalarial, anticancer, antioxidant, antiviral, antibacterial and neuroprotective agents. Insights on their potential mode of action is revealed in this review through comparative analysis with similar compounds. The review also points out the challenges for realization of the full potentials of such bioactive agents. This review will serve as important reference for researchers in the biomedical field. It is also expected to ignite more interest in unravelling the body of scientific knowledge that largely remains unexplored with respect to Tanzanian flora.

Methodology

This narrative literature review includes selected bioactive natural products from selected plants growing in Tanzania, some of which are used in ethnomedicine. The gathered information from these plant-derived products are discussed in relation to other similar compounds isolated elsewhere with emphasis on their biomedical potentials.

In this review, authors included information extracted from original articles, books, dissertations and theses from their research group published between 2010 and 2023 and carried out online search from several databases including Chemical Abstract, Google Scholar, MEDLINE, PubMed and Science Direct to compare bioactivity with similar compounds reported elsewhere in terms of potency and potential mode of action. Authors excluded their work that have been part of the similar reviews. Key search words or phrases used included name of the compound alone, name of the compound plus bioactivity reported, e.g. 3′-(3-methylbut-2-enyl)biochanin A, 3′-(3-methylbut-2-enyl)biochanin A + antibacterial activity; tribuloside, tribuloside + antioxidant; mechanism of action vs corresponding bioactivity, mode of action vs type of compound. Other broader search perspectives relating the pharmacological activity compounds with other compounds in the same category complemented these. The genera names and major class of compounds known therefrom were also searched to extend the discussion. For example, croton, croton + diterpenoids; morinda, morinda + antimalarial. The compounds' source plants selected for review are mainly those with rare occurrence, endemic or near endemic to Tanzania and have no prior review work. The findings are presented in the subsequent sections in this review.

Results and Discussion

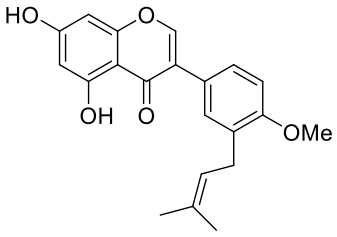
Flavonoids of *Erythrina schliebenii*

The genus *Erythrina* (family Fabaceae) comprises about 130 species, mainly distributed in tropical and subtropical areas (Zhang et al. 2016). Many of these species are used in traditional medicines to treat a variety of diseases including bronchitis, tuberculosis, cough, malaria and inflammation (Gebreheiwot et al. 2015). The genus major phytochemical categories include alkaloids, flavonoids and triterpenoids (Son and Elshamy 2020), hence they are considered responsible for *Erythrina*'s pharmacological activities (Fahmy et al. 2018, Susilawati et al. 2023).

Erythrina schliebenii Harms is an extremely endangered plant species endemic to Tanzania. The plant was twice declared extinct, then re-discovered in restricted locations with a population of less than 50 mature individuals observed within Kilwa district, Lindi region in South-eastern Tanzania (Clarke et al. 2011, IUCN SSC East African Plants Red List Authority 2012, Burgess et al. 2012). The community based conservation efforts and strategies by World Wildlife Fund (WWF)-Tanzania have led to the restoration of over 30,000 trees of this plant species (Kilimba 2021). Infusions from this plant are used in traditional medicine for the treatment of stomachache, fever, diarrhoea, prevention of jaundice of newborn babies and as an abortive agent (Nyandoro et al. 2017). As part of ongoing investigations of Tanzanian medicinal plants in search for bioactive agents, a number of flavonoids were identified from this plant species. The compounds exhibited antitubercular activity against *Mycobacterium tuberculosis* (H37Rv strain) with minimum inhibitory concentration (MIC) ranging from 36.9 - 101.8 μM, and cytotoxicity against the aggressive human breast cancer cells (MDA-MB-231) with 50% effective concentration (EC_{50}) ranging from 13.0 - 290.6 μM. Of the twenty three (23) identified flavonoids, prenylated isoflavones 3′-(3-methylbut-2-enyl) biochanin A (**1**) was the most active against *M. tuberculosis* (36.9 μM), whereas schliebenone B (**2**) was the most potent against the tested cancer cell (13.0 μM) (Nyandoro et al. 2017). Although there were no standard anticancer agents used for potency comparison, the compounds were less active compared to standard positive anti-tubercular controls used, isonicotinylhydrazine (0.3 μM) and rifampicin (0.09 μM). This was the first report of isolation of compound **2** along with other three compounds from *E. schliebenii* (Nyandoro et al. 2017). Compound **1** is also reported from *E sacleuxii*, which is only found in Kenya and Tanzania (Yenesew et al. 1998).

While there are no anti-tubercular and anticancer previously reported for

compounds **1** and **2**, a closely related compound, biochanin A (**3**), which is a phytoestrogen is acknowledged to have benefits in diet as cancer chemo-preventive agent against different cancer types. The compound is also reported to possess other pharmacological properties including anti-inflammatory, neuroprotective, anti-oxidant, anti-microbial, and hepatoprotective properties (Sarfraz et al 2020). Its main source includes soy, peanuts and red clover (Sarfraz et al 2020). Whereas mode of action **1** and **2** have not been established, anti-tumorigenic effects of **3** is ascertained to involve prohibiting cellular growth by activating cancer cell apoptosis (Sarfraz et al 2020).



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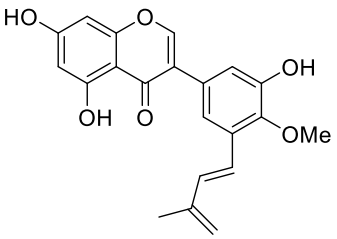

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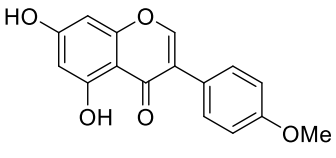


3

The triple negative aggressive human breast cancer cell line (MDA-MB-231) is one of the most commonly used cancer cell lines in biomedical research. Cancer remains one of the most devastating non-communicable diseases in the world. In Tanzania, like other developing countries cancer incidence and mortality is on increase (Lyimo et al. 2020, Makene et al. 2022), of which those associated with breast are the second leading cause of death after cervical (WHO 2020, Makene et al. 2022). Breast cancer incidence is projected to reach 82% of all cancer incidences in Tanzania by 2030 (Chao et al. 2020). Therefore, search for and discovery of such bioactive agents that can be deployed in lead compounds investigations from Tanzanian flora is of vital importance.

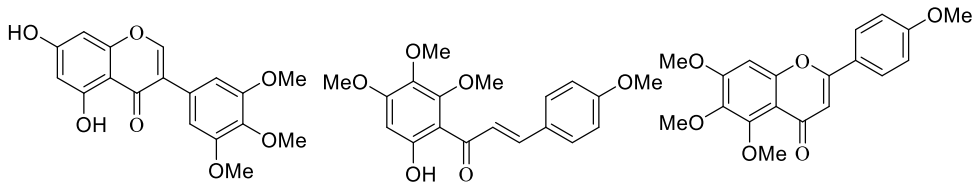
Parallel, antimicrobial agents play a big role in treatment of various microbial infections. However, pathogenic microbes including those causing tuberculosis (TB) continues to develop resistance to most drugs, resulting into serious world health problems (WHO: Global tuberculosis report 2022, Chitale et al. 2022). *Mycobacterium tuberculosis* is estimated to infect roughly a quarter of the world's population and was the second leading cause of death from infectious diseases after SARS-CoV-2 in 2020 (WHO 2020: Global tuberculosis report, Chitale et al. 2022), indicating a continued severity of microbial infection that calls for unlimited arsenal of compounds active against such disease causative agents.

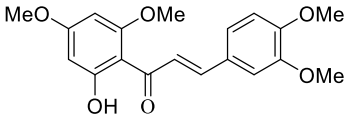
Conversely, reported antimicrobial activities of the flavonoids from *E. Schliebenii* were lower than standard drugs used as positive controls (Nyandoro et al. 2017). Some of the inherent properties that limit the full utilization of potentially active natural products and their synthetic analogues in biomedical applications are poor water solubility and low bioavailability (Prajapati et al. 2009, Shadrack et al. 2015). These phenomena can be corrected by the drug-nanocomposite complexation among other approaches (Rwegasila et al. 2016, Patel and Patel 2013). Such techniques also improve drug delivery to the targeted molecular sites. In this respect, panchovillin (**4**), one of the bioactive natural products isolated from *E. Schliebenii* that displayed moderate antimycobacterial (MIC, 93 μM) and cytotoxicity (EC_{50}, 29 μM) (Nyandoro et al. 2017), was encapsulated on a chitosan-tripolyphosphate (CS/TPP) nanocomposite and evaluated for its *in vivo* antimycobacterial activities against *Mycobacterium indicus pranii* (*MIP*) using *Galleria mellonella* larvae as an *in vivo* infection model (Rwegasila et al. 2016).

Whereas H37Rv remains the most widely used *M. tuberculosis* strain for laboratory experimentation (Chitale et al. 2022), non-pathogenic species such as *MIP* are usually deployed as proxy for the anti-TB investigations. Thus, in the modelled experiment, the efficacy of compound **4** against *MIP* was tremendously enhanced at a remarkably low concentration (0.289 nM/mg bw) when encapsulated in the CS nanomaterials compared to non-encapsulated **4** (80 nM/mg bw) providing an avenue for its improved biomedical applications (Rwegasila et al. 2016). This flavonoid has also been isolated from *Desmodium styracifolium* growing in Vietnam, but without any activity reported (Phan et al, 2010).

Efficacy of most natural products tends to diminish when subjected to *in vivo* models (Abourashed, 2013). However, the findings indicated that panchovillin (**4**), retained its antimycobacterial efficacy, even when applied to an *in vivo* system. Moreover, although a toxicological assessment was not carried out, survival of the larvae by 71 and 40%, after 48 hrs of the assay when treated with both free and encapsulated panchovillin (**4**), respectively compared to 100% death in positive control (*MIP* only), impliedly indicates the safety of compound **4**. Thus, the findings should be taken as a yardstick for similar studies aiming at improving the efficacy of bioactive natural products towards drug discovery endeavours (Rwegasila et al. 2016). Nonetheless, the mechanism of action of this compound towards antitubercular activity remains a subject of the future.

Similarly, neurodegenerative disorders are among non-communicable diseases with increasing challenges accounting for substantial increase in the proportions of the disease burden worldwide. Parkinson's disease (PD) is one of such neurodegenerative disease manifested by the constant loss in dopaminergic neurons in the *substantia nigra pars compacta* of the midbrain. Currently PD has no cure, but its treatment and management is based on the use of L-dopa and other dopamine receptor agonists, most of which exert some adverse side effects. The use of natural products and their herbal medicine sources in treatment and management of the disease is currently becoming the auspicious ventures in biomedical research due to their anticipated low side effects (Lynch and Berry 2007). Flavonoids such as those from *E. Schliebenii* have attracted the devotion in biomedical research and the pharmaceutical industries due to their diverse biological activities including anti-oxidant, anti-inflammatory, anti-depressant and anti-ageing properties. Indisputably, some flavonoids have shown promising activities in managing neurodegenerative diseases such as Alzhermer's and PD (de Andrade Teles et al. 2018). Thus, of the investigated flavonoids from *E. schliebenii* (Nyandoro et al. 2017), 6-hydroxy-2,3,4,4′-tetramethoxychalcone (**5**) and 6-methoxyhamiltone A (**6**) were revealed to be prominent neuroprotective potential when studied for behavioural and biochemical indicators of PD using *Drosophila melanogaster* model (Siima et al. 2020). The compounds offset the rotenone-induced neurotoxicity, climbing disability and levels of malondialdehyde (MDA) in *D. melanogaster* at the final lowest non-toxic concentrations of 11.0 μM. MDA is used to estimate the damage of tissues by reactive oxygen species (ROS). The findings also substantiated the role of these compounds as antioxidants as they down regulated the mRNA expressions of superoxide dismutase (SOD) and catalase (CAT) genes that were raised via rotenone in the brain tissues of *D. melanogaster*. Generally, for all measured parameters, there was a statistically significant difference between either PD flies and PD flies that were co-treated with the test compounds or between either PD flies and those treated with L-DOPA (standard drug used), ($p < 0.05$). However, there was no significant difference between PD flies co-treated with L-DOPA and compounds treated groups. Therefore, these compounds have a great potential for discovery of neuroprotective therapeutic agents.





The chalconoid **5** and flavonoid **6** are also known from *Chromoleana odorata*, a medicinal plant growing in Vietnam and many other tropical countries (Wafo et al. 2011, Dat et al. 2009). The two compounds have not been assessed for their mode of action towards neuroprotective properties. However, a compound analogous to **5**, tetramethoxychalcone (2′-hydroxy-4,3′,4′,6′-tetramethoxychalcone, **7**) from *Chloranthus henryi* is reported to suppress lipopolysaccharide-induced inflammatory responses in BV2 microglia by targeting different mechanistic pathways including inflammatory enzymes and inflammatory mediators such as cytokines (TNF-α, IL-1, IL-6), hence considered a promising therapeutic agent for neurodegenerative and related aging-associated diseases (Luo et al. 2016). Therefore, besides indication of compounds **5** and **6** to act as neuroprotective agents through suppression of oxidative stress in rotenone-induced PD in *Drosophila* model, their explicit mode of action needs to be established prior to clinical validation in the course of developing them as neuroprotective drugs.

Flavonoids and ellagic acid derivatives of the Tanzania mangrove species

Mangroves comprise trees, shrubs, palms, epiphytes, ground ferns and grasses. About 70 mangrove species in 27 genera and 20 families are recognized worldwide (Yessoufou and Stoffberg 2016). They grow in saline coastal sediment habitats, stabilizing the coastline, reducing erosion from storm surges, currents, waves, and tides. Phytochemical studies of the various mangrove species documented them to be rich sources of metabolites with a wide range of biological and physiological properties that can be tapped for medicinal, agrochemical uses and other applications (Bandaranayake 1999). Tanzania is among the countries that covers the largest area of mangroves in Africa with 10 different mangrove species, three of them namely *Heritiera littoralis* Dryand (Sterculiaceae) *Xylocarpus granatum* J. König (Meliaceae) and *Sonneratia alba* Smith (Lythraceae) have been investigated for their bioactive constituents (Chacha 2010, Christopher et al. 2014, Begum 2018).

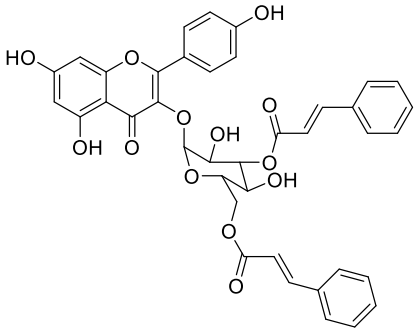
Heritiera littoralis is an endangered species of mangrove species with economic and medical importance. Its decoction of seeds and stem is traditionally used for the treatment of diarrhoea, dysentery, stomachache as well as the control of mosquitoes. The edible seeds of *H. littoralis* are also used as teeth cleaners (Christopher et al. 2014). Phytochemical investigations of *H. littoralis* growing in Tanzania afforded cinnamolyglycoflavonoid, 3''-cinnamoyltribuloside (**8**), its precursor tribuloside (**9**), two flavonoid glycosides afzelin (kaempferol-3-*O*-rhamnoside, **10**), astilbin (**11**), among other constituents. Compounds **8-11** exhibited antimycobacterial activity against the non-pathogenic *Mycobacterium* species *M. madagascariense* (MM) and *M. indicus pranii* (MIP) with MICs in the range of 0.8 - 1.6 mg/mL, with compound **6** being the most potent for both strains (0.8 mg/mL). However, the compounds were less active than the standard drug ciprofloxacin (MIC value of 0.01

mg/mL). Moreover, compounds **8**, **9** and **11** exhibited DPPH radical scavenging capacity of 74.7, 63.7, 83.7%, respectively at 0.05 mg/mL, each. Compound **9** had comparable radical scavenging capacity as gallic acid, a positive standard used (85.8% at 0.05 mg/mL) (Christopher et al. 2014). These findings demonstrated the compounds to be potential anti-tubercular and antioxidant agents necessitating further investigations.

After its first isolation from *H. littoralis* growing in Tanzania, compound **8** has so far been obtained from two Chinese medicinal plant species, *Camellia nitidissima* (Wang et al, 2020) and *Sterculia lychnophora* (Oppong eta al. 2020). The compound is reported to inhibit the NO production and mRNA expression of iNOS involved in lipopolysaccharide (LPS)-activated RAW 264.7 cells and the expression of a series of inflammatory cytokines, both at the mRNA level and protein level (Wang et al, 2020) indicating its mechanisms towards anti-inflammatory and antioxidant properties. Its precursor tribuloside (**9**) is reported from among other sources, *H. littoralis* found in Japan (Yoshio et al. 2000) and Chinese medicine plant *Tribulus terrestris* widely distributed in other tropical regions (Bhutani et al 1969, Cao et al. 2024).

Apart from its antioxidant and antimicrobial (Christopher et al. 2014) and anti-inflammatory properties, compound **9** is reported to enhance melanogenesis through activating the phosphodiesterases (PDEs)/cyclic adenosine monophosphate (cAMP)/ protein kinase A (PKA) (PDE/cAMP/PKA) pathways without any toxic effects on cells. This complements its biomedical potential in clinical prescriptions to promote pigmentation (Cao et al. 2024). Recently, this compound has also been proven efficacious in treatments of acute lung injury by targeting different molecular pathways and targets (Yang et al. 2024).

Compounds **10** and **11** are also known from other sources including grapes (Trousdale and Singleton 1983). Compound **10** has been reported to inhibit neuroinflammation by preventing the phosphorylation of mitogen-activated protein kinases (MAPKs) (Lim et al. 2023, Kciuk et al. 2024). It is also known to boost antioxidant defences by increasing the activity of the NRF2/heme oxygenase-1 (HO-1) signalling pathway possibly through glycogen synthase kinase-3β (GSK-3β) inhibition (Jung et al.2017, Kciuk et al. 2024). Similarly, compound **11** is reported to exert its anti-inflammation, anti-oxidation, and immune-suppression activities by activating the ROSs/PPARγ pathway to suppress effector CD4+ T Cell activities through direct binding with Cytochrome P450 1B1 (Ding et al. 2022). Therefore, flavonoids **8-11** are antioxidants with potential development of neuroprotective and anticancer agents in addition to other pharmacological actions (Rabaan et al. 2022).



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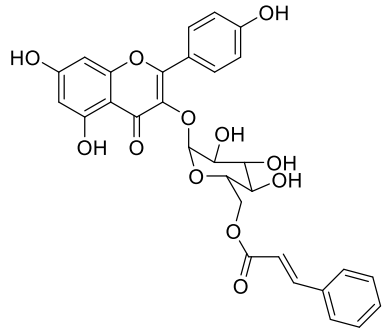

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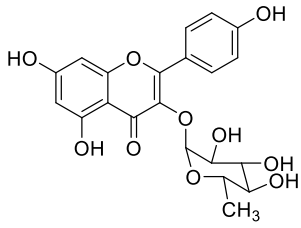

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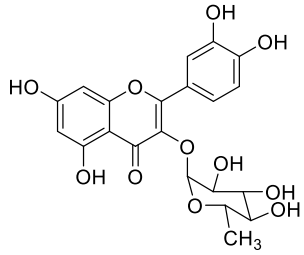
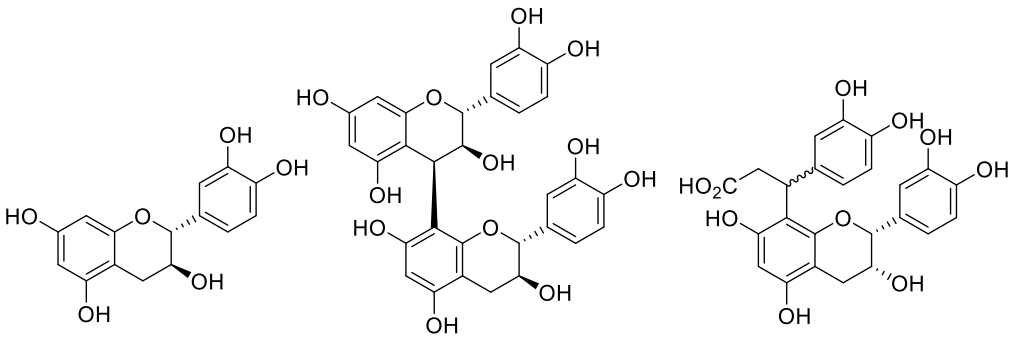


11

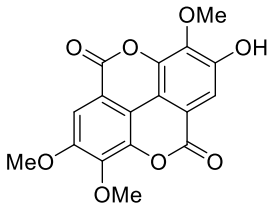
Another group of flavonoids has also been obtained from *Xylocarpus granatum* growing in Tanzania. *X. granatum* is among the three species of the genus *Xylocarpus* distributed along the seacoasts of Africa, South Asia, and South Pacific islands (Tomlinson 1986). This mangrove species is used in traditional medicine for the treatment of swelling of breast, elephantiasis, dysentery, diarrhoea and other abdominal ailments (Rouf et al. 2007). Chemical analysis of the stem bark extract from *X. Granatum* collected from Kisakasaka Mangrove Reserve, Zanzibar, Tanzania yielded three flavonoids namely, catechin (**12**), catechin-(4β→8)-catechin (**13**) and a new flavonoid derivative dihydrocaffeic acid-(3→8)-epicatechin (**14**). All compounds exhibited higher DPPH radical scavenging capacity compared to butylated hydroxytoluene (BHT), a commercially available antioxidant. Compound **13** displayed an outstanding activity with 50% inhibitory concentration (IC_{50}) value of 4.5 µg/mL, which was almost four times more active than BHT (IC_{50} 18.2 µg/mL) (Chacha 2010). The DPPH radical scavenging capacities correlated to the number of hydroxyl groups corroborating previously reported structure-activity relationships (SARs) for flavonoids (Chacha et al. 2005).



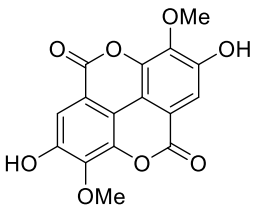
12 **13** **14**

While *X. granatum* growing in Tanzania has so far remained the only source of dihydrocaffeic acid-(3→8)-epicatechin (**14**), compounds **12** and **13** have been reported elsewhere. Catechin (**12**) is ubiquitous within the plant kingdom (Nile and Park, 2014) whereas catechin-(4β→8)-catechin (**13**) is of rare occurrence having been reported from only one additional plant species, *Potentilla erecta* (Schleep et al. 1986). Catechin (**12**) is a nontoxic dietary flavonoid with multiple well-established pharmacological and nutraceutical benefits including antioxidant, anticancer, anti-mutagenic, antimicrobial, anti-inflammatory and anti-neurodegenerative properties, both *in vitro* and *in vivo* (Nile and Park, 2014). It acts as an antioxidant either directly by scavenging ROS and metal ion chelation or indirectly as antioxidant enzymes (e.g., SOD, CAT, and GSH) inducers and stress-related signal pathway (TNF and NF-κB) suppressors (Nile and Park, 2014). Indeed, these are in agreement with the observed remarkable DPPH radical scavenging capacity of the rare compounds **13** and **14** obtained from Tanzanian *X. granatum* meriting their further exploration for their potential biomedical applications.

Sonneratia alba is the most widespread species of the genus *Sonneratia*, and the only species of the genus *Sonneratia* found in Tanzania. In traditional medicine, different concoctions of *S. alba* are used to treat asthma, ulcer, diarrhea, wounds, fever, hemorrhages, intestinal parasites, coughs as well as in febrifuge medication (Bandaranayake1998). Its sepals are reported to have antioxidant and anti-lipid peroxidation properties (Nuntavan et al. 2003). Chemical analysis of constituent of *S. alba* growing in Tanzania afforded 3,3′,4-tri-*O*-methylellagic acid (**15**) and other metabolites, which were found to be inactive against *E. coli*, *B. subtilis* and *S. epidermis* at 30 µg/mL screening concentration (Begum 2018). Moreover, compound **15** is known for its stimulatory effects on cellular proliferation, megakaryocyte differentiation (Xiaoping et al. 2014), and antioxidant properties (Herawati and Firdaus 2013). It is worth noting that the bark extract of *S. alba* is used as a preservative in the production of alcoholic traditional beverages from palm trees by playing an important role in preventing the formation of acetic acid, which is generated from the oxidation of ethanol (Firdaus and Sinda 2000). The preservative property of this plant is thought to be attributed to the presence of antioxidant compound 3,3′-di-*O*-methylellagic acid (**16**) which has been reported from *S. alba* and *S. caseolaries* (Herawati and Firdaus 2013). The compound is reported to exhibit potent antioxidant activity (IC_{50} 11.35 µg/mL) than ascorbic acid (IC_{50} 17.64 µg/mL), one of the well-known antioxidant (Herawati and Firdaus 2013). Hence, *S. alba* which is widely spread across the shores of Indian Ocean and considered least concerned according to the International Union of Conservation of Nature (IUCN) Red List can be of interesting commercial source of these essential bioactive compounds.



15



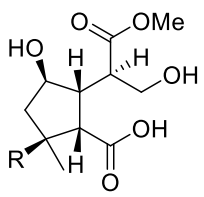
16

Free radicals play a significant role in the pathogenesis of some non-communicable and old age-related diseases, including neurodegenerative disorders, cancer, cardiovascular diseases, diabetes, and inflammation and their associated conditions or complications. Compounds that can scavenge free radicals as reviewed in a preceding section have great potential in ameliorating these diseases.

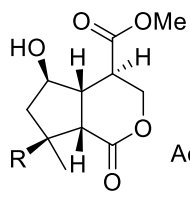
Seco*-iridoids and iridoids of *Morinda asteroscepa

Morinda asteroscepa K. Schum (Rubiaceae) is a small tree endemic to Tanzania and Malawi. It is classified as a vulnerable species in the IUCN Red List of Threatened Plant Species (Hamilton and Bensted-Smith 1989, Lovettand Clarke 2019). This plant species is used in folk medicine as a remedy for malaria and convulsing, especially for children in Tanzania (Hamilton and Bensted-Smith 1989). Members of the genus *Morinda* are known to accumulate diverse natural products including iridoids, glycosides, flavonoids, and anthraquinones with different bioactivities including antimalarial (Oladeji et al 2022, Singh and Sharma 2020).

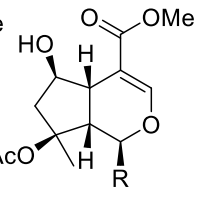
Despite being preventable and curable, malaria continues to be a major concern in countries with low and lower middle income, particularly in Africa that account for 94% of malaria cases and 95% deaths as per WHO world malaria report of 2022. Tanzania is among ten countries with the highest cases and deaths, accounting for 3% of the global cases and 4.1% of global deaths in 2020 (Monroe et al. 2022). WHO 2022 report has also indicated a concern on partial artemisinin resistance in Africa, with the most recent records in Tanzania. Emergence and spread of antimalarial drug resistance, especially in the malaria endemic areas of Sub-Saharan Africa challenges malaria control efforts, necessitating a constant search for therapeutic alternatives for this old menace. Thus, as part of investigations of bioactive natural products from Tanzanian medicinal plants, constituents of *M. asteroscepa* were explored for antiplasmodial activities against 3D7 strain of *P. falciparum* (Zandi et al. 2020). Seven antimalarial compounds including two secoiridoids **17** and **18**, and five iridoids **19-23** were discovered from the leaf and stem bark methanol extracts. The crude leaf extract (IC_{50} 10 μg/mL) and compounds **17-19** and **21** (IC_{50} 10 μM) exhibited mild antiplasmodial activities against the tested parasite as compared to the standard drug (Artenusate, IC_{50} = 0.00048 μM) (Zandi et al. 2020). The reported antiplasmodial activities of the extracts and the isolated compounds support the indigenous use of this plant in Tanzania for the treatment of malaria. Toxicological evaluation of the crude extract used in traditional medicine and the active ingredients along with elucidation of their probable mechanisms of action remains the subject of future studies.



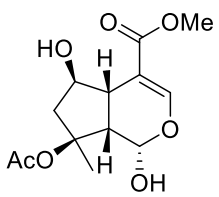
17: R = OH
18: R = OAc



19: R = OAc
20: R = OH

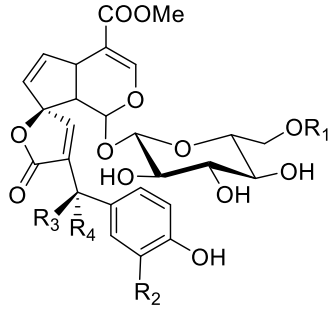


21: R = Glucose
23: R = OH



22

Iridoids belong to a family of monoterpenoids comprising the cyclopentan[*c*]-pyran system. This class of compounds offers a wide range of biological properties such as antileishmanial, anticancer, antiplasmodial, neuroprotective and anti-inflammatory potency, some of which have been patented (Hussain et al. 2019, Ndongwe et al. 2023). Apart from Rubiaceae, a number of bioactive iridoid derivatives have also been reported from several other plant families (Hussain et al. 2019). Antimalarial iridoids have also been isolated from other species within the genus *Morinda* including *M. morindoides*, a plant species used in traditional medicine for the treatment of malaria in some African countries (Tamura et al. 2010, Hashim et al. 2021). Thus, phenylpropanoid conjugated iridoids (**24-28**) were isolated from the leaves of *M. morindoides* as potent anti-malarial principles against *P. falciparum* (IC_{50} 0.04 – 21.9 μM). Interestingly, all the compounds exhibited little cytotoxicity against the mammalian host KB 3-1 cells at 150 μM. Compound **28** displayed the most potent anti-proliferative effect against the malaria parasite (IC_{50} = 0.04 μM) with negligible cytotoxicity (6% at 150 μM) (Tamura et al. 2010). These phenylpropanoid conjugated iridoids are among the most active anti-malarial ingredients so far obtained from members of the genus *Morinda* (Tran et al. 2022), justifying their further studies including exploring their mode of action and laboratory synthesis.



	R_1	R_2	R_3	R_4
24	Ac	OMe	H	OH
25	Ac	H	H	OH
26	H	OMe	H	OH
27	H	H	H	OH
28	H	OMe	=O	=O

Although compounds **17-23** from *M. asteroscepa* were not assessed for toxicity, some similar antimalarial compounds are known to exert cytotoxicity against adult mouse brain cells (Hashim et al. 2021) while others are non-cytotoxic (Tamura et al. 2010). These reviewed findings further indicate that iridoids and their derivatives are promising lead compounds for anti-malarial and other drugs agents, however further studies to validate and improve their safety and efficacy are vital.

Biflavonoids of *Ochna* species

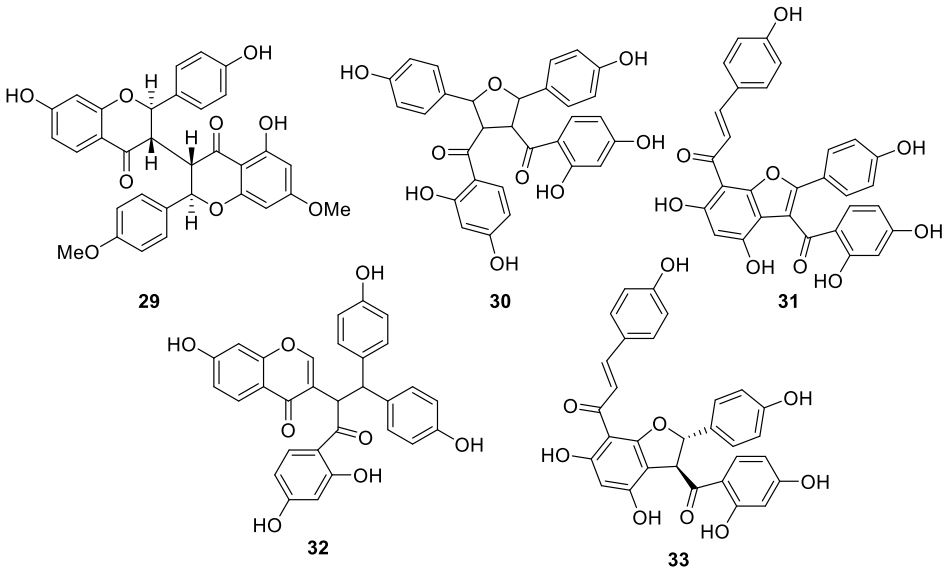
The genus *Ochna* (Ochnaceae) comprises about 86 species occurring in Madagascar and in tropical Africa, Asia and the America (Bandi et al. 2012). Members of this genus are used in traditional medicine to treat various disease conditions including bacterial infections and are known to metabolize

biflavanones, chalcones, and related compounds with various biological activities (Bandi et al. 2012, Awadh et al. 2014). There are about 47 species of *Ochna* growing in Tanzania, of which two namely *Ochna holstii* Engl. and *Ochna kirkii* Oliv. were included in the ongoing phytochemical ventures to search for bioactive natural products from Tanzanian medicinal flora.

Ochna holstii is widely distributed ranging from South Sudan to South Africa as far as Eastern Cape. It is claimed to relinquish evil spirits from children in some parts of Tanzania (Kalenga et al. 2021a). It is also used by the Maasai tribe in Tanzania for milk preservation in lieu of some apparent health benefits and by Venda tribe in South Africa for the treatment of HIV (Parker et al. 2007, Sigidi et al. 2017). Its crude extract is reported to exhibit activity against measles virus and HIV (Parker et al. 2007, Sigidi et al. 2017). On the other hand, *O. kirkii*, is native Tanzania and Mozambique, where it is mainly used as an ornamental plant (Teo et al. 2011, Kalenga et al. 2021b). The constituents of the two *Ochna* species were evaluated for their antibacterial effect alongside cytotoxicity to assess their therapeutic applicability. Of all isolated constituents of *O. holstii*, the biflavanoid holstiinone A (**29**) exhibited significant and selective antibacterial activity against *B. subtilis* with MIC values of 14 μM, while bichalconoid lophirone F (**30**) showed moderate cytotoxicity with EC_{50} 24 μM against MCF-7 human breast cancer cell line (Kalenga et al 2021a). Calodenin B (**31**) and lophirone A (**32**) from *O. Kirkii* were the two most active antibacterial constituents against *B. subtilis* with MIC values of 2.2 and 28.0 μM, respectively, the former being potent than the positive control ampicillin (EC_{50} = 11.5 μM). Equally and interestingly, compound **31** had low cytotoxicity against the MCF-7 (EC_{50} 219.3 μM), with approximate SI of 99.5, while **32** had strong cytotoxic effect with EC_{50} 19.2 μM (SI = 1.5) (Kalenga et al. 2021b). Thus, whereas compound **31** is a promising antibacterial agent against Gram-positive strains, compound **32** is a potential anticancer agent.

Antibacterial selectivity index (SI), which is also known as therapeutic index (TI) is the ratio between the concentrations leading to 50% lysis of human cells and the minimum concentration inhibiting bacterial growth ($SI = HC_{50} / MIC$) (Ilić et al. 2013). This parameter is used to quantify the selectivity of potential antimicrobial agents against is potential cytotoxicity. The larger the SI values, the greater the cell selectivity. For the case study above, cancer cell lines were simultaneously used to predict both the potential toxicity of the assayed compounds against malignant cells and as the indicative SI. The latter can further be substantiated by the use of normal cells. Generally, $SI \geq 10$ is considered as a desirable therapeutic quality of a bioactive compound (Awouafack et al. 2013, de Souza 2019).

Biflavonoids are of common occurrence within the genus *Ochna*. Thus, for instance, six biflavonoid and related compounds have been reported from *O. macrocalyx*, a species native to Kenya, Malawi, Mozambique, Tanzania, Zambia, and Zimbabwe. Of its metabolites, compound **31** showed a significant cytotoxicity (IC_{50} 7±0.5 μM) whereas **33** showed moderate cytotoxicity (IC_{50}, 35±7 μM) against MCF-7 breast cancer cells. In antibacterial assays performed using three different strains of multi-drug resistant *Staphylococcus aureus* (RN4220, XU212 and SA-1199-B) compounds **31** and specifically **33** showed remarkable antibacterial activity (MICs **31**: 64, 8, 16 μg/mL; **33**: 8, 8, 8 μg/mL, respectively (Tang et al. 2003). These earlier findings are comparable to those from Kalenga et al., (2021a, 2021b).



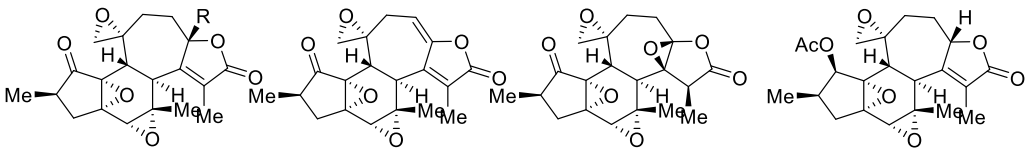
Although the mode of action of these compounds toward antibacterial and cytotoxic activities has not been elucidated, flavonoids have been established to exert antibacterial activities via various mechanisms of action including suppressing nucleic acid synthesis, cytoplasmic membrane function, and energy metabolism (Xie et al. 2014). They have also been found to reduce adhesion and biofilm formation as well as membrane permeability, all of which are important for bacterial growth (Xie et al, 2014). On the other hand, the cytotoxicity effect of flavonoids on anticancer cells has been established to take place through different modes, including modulating ROS scavenging enzyme activities, arresting the cell cycle, and inducing apoptosis (Kopustinskiene et al. 2020). The elaborated compounds **29 - 33** could be hypothesized to exert their antibacterial and cytotoxicity via any of these mechanisms, hence requiring specific studies to confirm. Moreover, different pharmacological studies have revealed biflavanones and chalconoids similar to those pointed above to possess not only antimicrobial and cytotoxic activities, but also antimalarial, anti-inflammatory, anti-proliferative and anti-HIV activities with different levels of efficacy (Bandi et al. 2012), to mention a few, indicating their broad spectrum of biomedical potential, warranting further explorations towards drug discovery.

Diterpenoids and other metabolites of *Croton kilwae*

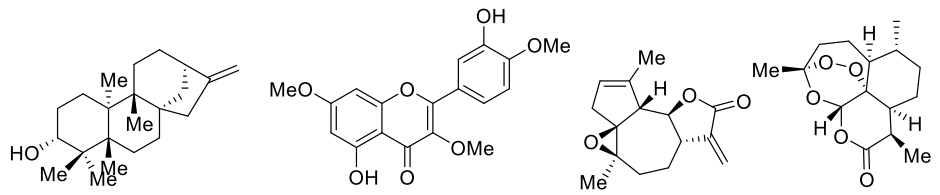
Besides antimalarial and other plant-derived pharmacological principles, anti-viral agents constitute another important class of therapeutics. Viral infections affecting mankind include HIV, hepatitis B, herpes, severe acute respiratory syndrome (SARS), influenza, Ebola, Zika, respiratory syncytial and human rhinoviruses, just to list a few. All these, other constantly emerging and re-emerging viral infections require prompt interventions. Respiratory syncytial virus (RSV) is one of the major cause of pneumonia and bronchiolitis in infants and has been reported to be a global cause of morbidity and mortality to infants in the first six months of life (Piedimonte and Perez 2014). Similarly, human rhinoviruses (HRVs) are associated with upper respiratory infection and play important role in lower respiratory tract infection (Jacobs et al. 2013). HRVs are also associated with asthma pathogenesis (Song 2016). Thus, through a continued search for bioactive agents from Tanzanian flora, the constituents of plant species of the genus *Croton* were screened against RSV and HRVs.

The genus *Croton* (Euphorbiaceae) comprises nearly 1300 species occurring in the tropical and subtropical regions of both hemispheres (Salatino et al. 2007) of which 17 species are represented in Tanzania (Mahambo et al. 2023). *Croton* species are used widely in folk medicine in Tanzania and beyond to treat various ailments (Munissi et al. 2020), demonstrating biomedical potential as revealed by their chemistry that is largely dominated by bioactive diterpenoids (Xu et al, 2018). Thus, phytochemical investigations on *Croton kilwae* Radcl.-Sm., a plant species endemic to southeastern Tanzania and northern Mozambique (Radcliffe-Smith 1982), yielded bioactive compounds including six novel crotofolane diterpenoids (**34**-**39**) and other metabolites that were evaluated for their antiviral activities against RSV and HRV type-2 (HRV-2) in HEp-2 and HeLa cells, respectively. Of the compounds obtained from *C. kilwae*, a kaurane diterpenoid *ent*-3β,19-dihydroxykaur-16-ene (**40**) and a flavonoid ayanin (**41**) displayed a remarkable antiviral activity against RSV, while exhibiting significant to marginal cytotoxic effects on HEp-2 cells that resulted in selectivity indices of 4.9 and 16.4 (Mahambo et al. 2023). Besides its anti-RSV, compound **41** also strongly exhibited anti-HRV-2 (IC_{50} value of 1.8 μM) without substantial toxicity in HeLa cells (SI > 55.6) (Mahambo et al. 2023), suggesting its therapeutic quality against the viruses.

Compounds **35** and **38** exhibited modest HRV-2 at relatively high concentrations (IC_{50} of 44.6 μM for both, with SI > 2.2) in HeLa cells. Moreover, compounds **34**-**39** showed lack of both anti-RSV activity and cytotoxicity for HEp-2 cells at concentrations up to 100 μM. Contrary, their structural analogues isolated from *C. megalocarpus*, growing in Kenya have been revealed to inhibit HIV-1 replication (Terefe et al. 2022a, 2022b), further indicating the biomedical potential that resides in this type of natural products, which thus far have been reported from few *Croton* species (Mahambo et al. 2023). On the other hand, a sesquiterpenoid traded as Arglabin (**42**), with partial structural scaffold similar to **34**-**39**, is an approved drug in cancer chemotherapy that acts by inhibiting farnesyl transferase (Atanasov et al 2015), indicating such structural moiety to be important anticancer pharmacophore. Compound **42** is obtainable from *Artemisia glabella* Kar. & Kir., a plant species growing exclusively on the region of the Central Kazakhstan (Adekenov et al. 1982, Adekenov 2016).



34: R = H; **35:** R = OH; **36:** R = OMe **37** **38** **39**



40 **41** **42** **43**

Enthused by their multi-epoxidised structures and polyoxygenation, the latter being reminiscent of artemisinin (**43**) from the Chinese antimalarial herb *Artemisia annua*, compounds **34**-**39** were also assayed for antimalarial activity against chloroquine-resistant *P. falciparum* Dd2 strain of malaria parasite. Of these compounds, **34**-**36** were the most potent, inhibiting parasite growth at 80-100% (at 50 μM, that is, ten-fold lower than

standard drug Artesunate), yet with low (<10%) or no hemolysis indicating them to possess a promising scaffold in antimalarial lead compounds development (Mahambo et al. 2023). Development of synthetic analogues of these compounds along with SARs studies can be undertaken to optimise their pharmacological activities.

Challenges for realization of the full potentials of natural products as lead compounds for drug development

Natural products (NPs), despite providing valuable resources for the development of drugs, face challenges in a variety of aspects, a few of which are hereby pointed. These include the scantiness of the natural product obtained, seasonal variability, rarity of the source plant, source plant habitat loss, and structural complexity of some natural products for cost effective synthesis thereby limiting their scalability. Toxicity levels of natural products, replication in natural products isolation and characterization as well as solubility and bioavailability are additional challenges encountered in the development of NPs-derived drugs.

In most cases, the bioactive compounds are present in too low concentrations to be efficiently and sufficiently isolated. Thus, paucity of the pure compounds obtained from biological sources including plants limits their evaluations for bioactivities towards drug development. Seasonal and geographical-dependent chemical composition leading to variability of the plant constituents also limits re-collection source and re-isolating the target bioactive compounds (Amirkia and Heinrich 2014, Simoben et al. 2023). Moreover, if a compound is derived from a rare and endangered plant species, supply of such compounds often becomes a major setback. A compounding problem is a constant threat of losing potentially valuable plant resources with pharmacologically active principles due to the threat of extinction by deforestation owing to clearance of land accompanied by the increased human population and other economic activities as for the case example of *Erythrina schliebenii* (IUCN SSC East African Plants Red List Authority 2012). Gratitude to WWF-Tanzania strategies and other efforts that has led to restoration of this plant species to the forest (Kilimba 2021). These commendable strategies can be applied to conserve other plant resources within their wild niche. Such approach also serves to reduce the impending variability in the active ingredient content in medicinal plants while ensuring their sustainable utilization. Moreover, guidelines on good agricultural and collection practices (GACP) for medicinal plants in order to promote sustainable plant collection techniques and to reduce the ecological problems associated with wild-crafting of medicinal plants developed by WHO (WHO 2003) and European Medicines Agency (EMA) (EMA, 2006) need to be observed.

In some cases, supply issues of natural products can be solved by semi-synthesis or total synthesis of the biomedical agent in demand, or by the development of synthetic analogues with more desirable pharmacophore traits. Nonetheless, synthetic approaches also in some instances face the challenge to obtain significant quantities of potential new drug candidates, due to often-high structural complexity of some NPs including possession of numerous oxygen-containing substituents and chiral centres. Thus, long synthetic routes associated with additional production costs hamper drug development of lead compounds from nature (Atanasov et al. 2021). For instance, the recently discovered bioactive heptenolide, namely cleistenolide from Tanzanian and Mozambican medicinal plant (Samwel et al. 2011, Pereira et al. 2016), has attracted interests of a number of synthetic chemists' research groups some trying to optimize its yield for biomedical applications (Benedeković et al. 2020). However, all synthetic strategies reported thus far have produced insufficient quantities compared to its natural source. Besides counter-challenges associated with synthesis, this approach remains as one of the strategies to solve the problem that might arise due to an increased interest in extracting and purifying large quantities of NPs from source plant collections, which usually brings the risks of

over-exploitation and habitat destruction due to extensive wild-crafting and unsustainable harvesting techniques. Moreover, synthesis provides structural analogues for SAR studies and possible strategies to identify the modes of action of active compounds.

Apart from the challenges related to supply of natural products, the toxicity of promising drug lead compounds jeopardizes their therapeutic applications in terms of their safety and efficacy. Toxicity in cell or whole animal models, both intrinsic and extrinsic toxic effects from herbal-derived medicine needs to be evaluated. The myth that natural products are inherently safe is a misleading belief. In fact, some natural products on the market have been found to be toxic or contain toxic compounds (Pauzi et al 2022). This is the essence of determining selectivity index (SI), which is the ratio of the toxic concentration of a sample against its effective bioactive concentration (Indrayanto et al. 2021). The ideal drug whether naturally or synthetically derived should only be toxic at relatively high concentrations, but with desirable therapeutic effects at very low concentrations. Therefore, quality control and assurance through evaluation of SI value for any research on herbal sample and/or isolated compounds is very crucial for determining biosafety and a need for further research and development. Thus, in evaluating any anti-cancer activity of a natural product for drug candidacy, its cytotoxicity against non-malignant cell lines must be determined in order to compute the SI value (Indrayanto et al. 2021). Similarly, SI is used for determining the desirability of anti-viral, anti-microbial and antiplasmodial active compounds, some examples of which are presented in the previous sections of this review. SI $\geq$ 10 is generally recommended as an acceptable criterion of a selective bioactive compound (Awouafack et al. 2013, de Souza 2019). Thus, not all bioactive natural products pass the SI criterion.

Another challenge associated with natural products research fallouts from the redundancy of activities involved in the isolation, structural determination and bioassay systems. With over a hundred thousand known natural products, there is a tendency for re-isolation of known metabolites even if the work is conducted through the bioassay-guided fractionation approach. Although this is generally acceptable if the targeted assay is new, it is annoying to waste resources on the isolation and structure elucidation of known metabolites. Hence, there have been some efforts in the development of dereplication strategies in natural product isolation and characterization (Beutler 2019). Such approaches include applications of analytical techniques coupled to a variety of NPs databases such as the Dictionary of Natural Products and METLIN platform. The latter method includes a high-resolution MS/MS database with fragment similarity searches. Metabolomics techniques coupled with computational approaches can also be applied to generate plausible NP analogue structures and their respective simulated spectra. These tactics provide accurate information on the metabolite composition in NP extract, thus helping to prioritize NPs for isolation and identification, to accelerate dereplication, thus helping to annotated unknown analogues and new NP scaffolds (Atanasov et al. 2021, Conrado et al. 2024). However, in drug repurposing, old drugs or drug leads of both natural and synthetic origin may be useful in treating previously unleashed diseases or newly emerging infections. This is exemplified by aspirin, a synthetic derivative of salicylic acid initially popularly used as a painkiller and antipyretic, was later established as an anti-clotting agent, paving its way to the current widespread use as a preventive treatment for cardiovascular and cerebrovascular diseases (Montinari et al. 2019). Therefore, however important the dereplication is in the process of screening natural product mixtures to facilitate the discovery of new potentially pharmacologically active substances, the known molecules should not completely be ignored.

Solubility and bioavailability are key features in ensuring the efficacy of bioactive compounds. As pointed out earlier in this review, the solubility and bioavailability of

some natural products hamper their development as drug molecules. Solubility and bioavailability may be enhanced by different techniques such as structural modifications, particle size reduction, solid dispersion, complex formation, nanotechnology approaches, micellar solubilisation and prodrugs formation (Alshamrani et al. 2022). Despite some registered success of these approaches, they are still challenged by varied mechanisms of absorption of hydrophilic and lipophilic bioactive natural products, and the associated costs (Gao and Hu 2010). However, it should be noted that the challenges associated with solubility and bioavailability in the development of pharmaceutical formulations are not limited to natural products alone, but rather extended to all to other chemical entities intended as a drug agent or lead.

Besides the noted challenges, NPs remain a prominent source of structural diversity than standard synthetic approaches and thus offer significant opportunities for finding novel lead compounds. To realise the full potential that resides in NPs, the encountered challenges should continue to be addressed by different strategies, few of which are pointed above in addition to other scientific and technological advances including genetic engineering and biosynthetic studies to develop systems for obtaining valuable natural products on a large scale.

Conclusion

Historically, NPs have been the most prolific sources of active compounds some of which have saved as drug leads. Equally, the presented review identifies plant metabolites that can be considered potential compounds for antiplasmodial, anticancer, antioxidant, antiviral, antibacterial and neuroprotective lead compounds for drug development. These include a catechinoid **13** that was four times more active than the positive control towards radical scavenging promising the development of a neuroprotective, anti-inflammatory, or anticancer agent, the nontoxic antibacterial candidate biflavonoid calodenin B (**31**) with potency than the positive control (ampicillin), and nontoxic diterpenoids **34 - 36** that demonstrated auspicious antimalarial potency. The latter category of compounds could be advanced through synthetic chemistry to obtain structural analogues for SARs studies. Despite the pointed challenges in the discovery and development of drugs from phytochemical sources and possible scientific and technological advances to overcome them, this review provides a comparative analysis of selected bioactive metabolites thus unraveling the body of scientific knowledge that largely remains unexplored including the mechanism of action of the identified NPs with respect to metabolites from Tanzanian flora and beyond. In addition, the review calls for the necessity of the quality assurance of the plant extracts used in folk medicine and their isolated constituents based on evaluation of their toxicities and safety. This should go along with sustainable medicinal plant harvesting for sustainable utilization as informed by relevant policies and conventions. Finally, for the development of alternative therapeutic agents from some of the identified potential lead compounds, more studies are needed to elucidate their mechanism of action in a wide variety of experimental models as well as in clinical trials pertaining to their targeted disease treatments.

Conflicts of Interests

The authors declare no conflicts of interests.

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