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REVIEW

The chemistry and bioactivity of Southern African flora II: Flavonoids, quinones and minor compound classes

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Smith B. Babiaka,[a,b†] Fidele Ntie-Kang,[*a,b,c†] Bakoh Ndingkokhar,[a,b] James A. Mbah,[*b] Wolfgang Sippl,[c] and Joseph N. Yong[*b]

This review is intended to highlight the relevance of natural products in drug discovery paying particular attention on those derived from Southern African medicinal plants with diver biological activities. In this review series, a literature survey led to the collection of 864 secondary metabolites from 101 plant species from 57 plant families. A correlation between the known biological activities of isolated compounds and the ethnobotanical uses of the plants has been attempted. Part I was focused on alkaloids and terpenoids, while this part is focused on bioactivities of flavonoids, quinines and other minor, unique compound classes which correlate with their ethnobotanical uses in African traditional medicine (ATM).

1 Introduction

Natural products isolated from African medicinal plants have provided a significant contribution in the discovery and development of new drugs used in the treatment of various ailments, the country of South Africa alone having about 30,000 plant species, about 10% of the world's higher plants.[1-3] Moreover, the majority of the population living in the less developed world totally rely on natural products for their health-care needs.[4,5] Thus there is the need to revisit natural products as a starting point for drug discovery. Recently, natural products have provided new leads for compounds that have good pharmacokinetic profiles.[6] Several thousands of pure secondary metabolites have been isolated from African medicinal plants but the local populations solely depend on herbs as no approved drug has been derived from this flora.[7,8] These plant isolates have been employed in African traditional medicine (ATM), thus establishing the role of natural products in drug discovery programs. Southern Africa has a rich flora and fauna which have been recognized and exploited in the past decades given that 50 % out of the 25,000 plant species on the earth surface are endemic to the region.[8-12] Thus there is growing need to establish a report focused on biologically active secondary metabolites isolated from Southern Africa which correlates with their ethnobotanical uses in ATM from this region.

Recently, our research group has been involved in the documentation of knowledge from African flora, relevant for drug discovery programs in the continent. A number of reviews have been published in internationally recognized peer-reviewed journals on bioactive natural products and the pharmacokinetic profiles of the compounds from African medicinal plants focusing on the different countries/regions.[13-21] These have covered medicinal plants from central Africa,[13,14] West Africa,[15] and Northern Africa.[16] Other studies have been focused on developing three dimensional (3D) databases of bioactive natural product from the entire continent for virtual screening purposes[17] and assessing their drug metabolism and pharmacokintetics profiles using *in silico* model.[17b,18] Other review articles have been focused on molecules with the potential to be developed into drugs for particular diseases like malaria,[19] antimycobacterial infections like tuberculosis[20] and cancer.[21] This has received significant attention from different collaborators involved in drug discovery from medicinal plants and thus has prompted the need for the series of reviews on Southern Africa. In the first part of this review series,[22] emphasis was laid on uniq compound classes from Southern African flora having remarkable biological activities, stressing on establishing a correlation between biological activities of the derived compounds (alkaloids and terpenoids) and the uses of the plants in African traditional medicine and their chemotaxonomic classifications. The secondary metabolites from Southern Africa region includes the following countries; Angola, Botswana, Madagascar, Malawi, Mozambique Namibia, South Africa, Swaziland and Zimbabwe. In the present paper, our main focus would be on flavonoids, quinones and other minor compound classes to highlight the medicinal value and potentials of the isolated phytochemicals by discussing the bioactivity of the isolated principles versus ethnobotanical uses of the plant species.

2 Flavonoids from Southern African flora

Flavonoids continue to attract attention as potentially useful agents because they exhibit a broad spectrum of biological activities including anti-inflammatory, anti-cancercinogenic, antiviral, anti-oxidant, anti-thrombogenic and anti-therogenic properties.[23-34] In this report, summaries of the most interesting results for flavonoids which exhibit biological activities correlating with the ethnobtanical uses of the plant species of origin have been shown in Table 1, while the chemical structures of the isolated compounds are shown in Fig

1-4. In Table 2, the biological activities which correlate with the enthnobotanical uses of the plants have been highlighted in bold.

Piliostigma reticulatum (Caesalpiniaceae) is a leguminous plant that is used in ethnomedicines for the treatment of leprosy, smallpox, coughs, dysentery, fever, wounds and a variety of closely related disease conditions.[35-40] Babajide *et al*. isolated the four novel compounds; piliostigmol (**1**), 6,8-di-*C*-methylquercetin-3,3',7-trimethyl ether (**2**), 6,8-di-*C*-methylquercetin-3,3'-dimethyl ether (**3**), 3',6,8,-tri-*C*-methylquercetin-3,7-dimethyl ether (**4**) together with the known compounds; 6-*C*-methylquercetin-3-methyl ether (**5**), 6,8-di-*C*-methylkaempferol-3- methyl ether (**6**) and 6-*C*-methylquercetin-3,3',7-trimethyl ether (**7**) from the leaves of this plant.[41] Compound **1** demonstrated the highest antibacterial activity against *E. coli* (MIC = 2.57 μg/mL, 0.006 μmol), which is three times more active than amoxicillin and therefore, validates the traditional use of the plant.

Traditional healers in Eastern and Southern Africa have used *Combretum* species, for many applications including treating abdominal disorders, backache and several other diseases.[42-46] Antioxidant-directed fractionation led to the isolation of four antioxidant compounds; flavokawain (**8**), cardamomin (**9**) alpinetin (**10**) and pinocembrin (**11**) from ethyl acetate and butanol soluble fractions of the leaf extracts of *Combretum apiculatum* (Combretaceae).[47,48] Compounds **8**, **10** and **11** demonstrated antibacterial activities on *Staphyloccoccus aureus*; *Enterococcus aureus*; *Pseudomonas aeruginosa* and *Escherichia coli* as described.[47,49]

Martini *et al*. isolated 5-hydroxy-7,4'-dimethoxyflavone (**12**), quercetin-5, 3'-dimethylether (**13**), rhamnazin (**14**), rhamnocitrin (**15**), genkwanin (**16**), apigenin (**17**) and kaempferol (**18**) from *Combretum erythrophyllum* using bioassay-guided fractionation.[50] The compounds demonstrated antibacterial activities on *Staphyloccoccus aureus*; *Enterococcus aureus*; *Pseudomonas aeruginosa* and *Escherichia coli* as described.[47,49] The activities of the isolated compounds correlate with the ethnomedicinal use of the plant in traditional medicines.

Euclea divinorum (Ebenaceae) root bark is used in traditional medicine for the treatment of diarrhoea, convulsions, cancer, skin diseases and gonorrhoea.[51] Mebe *et al*. isolated the known flavonoids catechin (**19**) together with some known compounds from the chloroform extract of this plant.[52] The isolated compounds were tested for their cytotoxic activity (ED_{50} < 20 μg/mL) against a panel of cell lines using cell culture systems as described.[53] The cytotoxic activity displayed by some of the compounds confirms the ethnomecidinal use of the plant in the treatment of cancer.

Euclea undulata (Ebenaceae) is used by traditional healers in the Venda area, Limpopo Province in the treatment of diabetes. Deutschländer *et al*. isolated epicatechin (**20**) in addition to some other compounds from the crude acetone extract of the root bark of this plant.[54] The isolated compounds were evaluated for their hypoglycaemic activities by executing *in vitro* assays on myocytes, as well as their ability to inhibit the carbohydrate hydrolising enzyme *α*-glucosidase.[55] Compound **20** may have some ability to lower blood glucose levels. The hypoglycaemic activity exhibited by the compound confirms the use of the plant in traditional medicines.

Bolusanthus speciosus (Fabaceae), also known as tree wisteria, is used as an ornamental tree in gardens and parks, because of its beauty.[56] The root infusion of this plant is also used by some communities as an emetic while the dried inner bark is used to relieve abdominal pains.[57] The dried inner bark of this plant has been used to relieve abdominal pains, emitism and tuberculosis.[58] Bojase *et al*. isolated the two new isoflavonoids: 4,7,2'-trihydroxy-4'-methoxyisoflavanol (**21**), 5,7,3',4'-tetrahydroxy-5'-(2-epoxy-3-methylbutyl)isoflavanone (**22**) together with the known compounds 5,7,2',4'-tetrahydroxy-8,5'-di(γ,γ-dimethylallyl)-flavanone (**23**), 5,7,3'-trihydroxy-4'-methoxy-5'-γ,γ-dimethylallylisoflavanone (**24**), 5,7,2'-trihydroxy-4'-methoxy-6,5'-di(γ,γ-dimethylallyl)isoflavanone (**25**), 5,7,2',4'-tetrahydroxy-8,3'-di(γ,γ-dimethylallyl)isoflavanone (**26**) and derrone (**27**) from the combined ethyl acetate/methanolic extracts of the stem bark of this plant.[58] The authors further isolated the flavovoids bolusanthols A to C (**28** to **30**), along with 4 known flavonoids from the stem bark of the same plant species.[59] Compound **22** showed moderate activity against gram positive bacteria and weak activity against gram negative bacteria, while compound **21** was weakly active against both organisms in a TLC bioautography assay. The results are consistent with the traditional use of the plant in treatment of abdominal pains, associated mostly with bacterial infections.

Vangueria infausta (Rubiaceae) fruits are eaten by humans and wild animals and also used traditionally for the treatment of malaria, wounds among others.[60,61] Mbukwa *et al.* isolated the new biflavonoid 5, 7, 3', 5'', 7'', 4'''-Hexahydroxy (4'-*O*-3''')-biflavone (**31**) together with the known compounds (-)-epicatechin (**20**), epiafzelechin (**32**), dihydrokaempferol (**33**), quercetin (**34**), luteolin (**35**), dihydroquercetin-3'-*O*-glucoside (**36**), daidzein (**37**) and genistein (**38**) from aerial parts of *Vangueria infausta* (Rubiaceae).[62] Compound **31** showed higher radical scavenging activity against 2, 2-diphenyl-1-picrylhydrazyl (DPPH) reagent compared to ascorbic acid (standard) using a spectrophotometric method. But compound **31** was less sensitive to Gram-positive and Gram-negative bacterial strains and yeast (*Candida mycoderma*) compared to **34** and **35** on the Bioautographic Agar Overlay Assay. Compounds **20** and **32** were found to be active against *E. coli* at minimum loading of 50.0 and 100.0 μg, respectively. Moreover, the hypoglycaemic activity of acetone leaf exract of *Ficus lutea* (Moraceae) could be partly explained by the presence of compound **32**.[63]

Dodonaea viscosa (Sapindaceae) leaves have traditionally been administered to treat sore throat, wounds, fever, piles, boils and other diseases.[64,65] Teffo *et al.* isolated the five known flavonoids; 3, 5,7-trihydroxy-4'-methoxyflavone (**39**), 5,7,4'-trihydroxy-3,6-dimethoxyflavone (**40**), 5,7-dihydroxy-3,6,4'-trimethoxyflavone (**41**), 5-hydroxy-3,7,4'-trimethoxyflavone (**42**) and 3,4',5,7-tetrahydroxy flavone (kaempferol) (**18**) from the leaves of this plant using bioassay guided fractionation.[66] Compounds **39** and **18** demonstrated antioxidant activity (EC_{50} = 75.49 ± 1.76 μM and 35.06 ± 0.85 respectively) but lower than *L*-ascorbic acid (EC_{50} = 13.55 ± 0.28 μM) used as a standard antioxidant agent. Compound **18** was in general the most active against all the test organisms with MIC values between 16 and 63 μg/mL compared to the others.[66]

Erythrina latissima (Fabaceae-Papilionoideae) stem and roots are burnt and used for dressing open wounds.[67] Chacha *et al.* isolated the three new flavonoids 7,3'-Dihydroxy-4'-methoxy-5'-γ,γ-dimethylallylisoflavone (Erylatissin A) (**43**), 7,5'-Dihydroxy-6'',6''-dimethyl-4'',5''-dehydropyrano[2'',3'':4',5']isoflavone (erylatissin B) (**44**), (−)-7,3'-Dihydroxy-4'-methoxy-5'-γ,γ-dimethylallylflavanone (Erylatissin C) (**45**),[68] together with the ten known compounds; 7,4'-dihydroxyisoflavone (daidzein) (**37**), 7,4'-dihydroxy-3'-γ,γ-dimethylallylflavanone (abyssinone II) (**46**), 7,3'-dihydroxy-4'-methoxyisoflavone (calycosin) (**47**), 7,4'-dihydroxy-

3'-γ,γ-dimethylallyl isoflavone(neobavaisoflavone) (**48**), 3,9-dihydroxy-10-γ,γ-dimethylallylpterocarpan (phaseollidin) (**49**), 3,6a-dihydroxy-9-methoxy-10-γ,γ-dimethylallylpterocarpan (cristacarpin) (**50**), 4,2',4'-trihydroxy-3'-γ,γ-dimethylallylchalcone (**51**), 5,7,4'-trihydroxyisoflavone (genistein) (**38**), 4,2',4'-trihydroxychalcone (**52**), 3,9-dihydroxypterocarpan (demethylmedicarpin) (**53**) from the stem wood of this plant.[69-75] Compounds **45**, **50**, **51** demonstrated the highest antimicrobial activity *in vitro* against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Candida mycoderma* using the procedures described.[76-84] Compounds **37**, **49**, **51** were the most active towards radical scavenging properties using DPPH test.[91-93]

Désiré *et al*. isolated the dihydrochalcone, davidigenin (**54**) as the main active constituent using bioassay-guided fractionation from *Mascarenhasia arborescens* (Apocynaceae).[85] The antispasmodic activity demonstrated by compound **54** supports the use of the plant in traditional medicine in the treatment of intestinal spasms.

3 Quinones from Southern African flora

The summary of the most important findings on the bioactive quinones from Southern Africa flora have been given in Table 2, while the chemical structures are shown in Fig. 5. In Table 2, the biological activities which correlate with the enthnobotanical uses of the plants have been highlighted in bold.

Kigelia pinnata (Bignoniaceae) juice or water extracts of the fruits or stem bark has been used in the treatment of skin cancer. Jackson *et al.* isolated the known compounds norviburtinal and isopinnatal (**55**)[86] from the crude dichloromethane extracts using bioassay-guided fractionation.[87] The results revealed that norviburtinal showed a much greater cytotoxic effect (IC_{50} = 3.25 µg/mL), but little selectivity towards melanoma cell lines. Compound **55** (IC_{50} = 11.13 µg/mL) demonstrated slightly greater cytotoxic activity against the melanoma cell lines but its high cytotoxicity against the non-cancer fibroblasts warrants further investigation as a novel lead anticancer agent. The cytotoxic activity of the crude extracts and pure compounds of the plant corroborates its medicinal use in the treatment of skin cancer.

Bapela *et al.* isolated shinanolone (**56**), 7-methyljuglone (**57**) and diospyrin (**58**) from the shoots and roots seeds of *Euclea natalensis* (Ebenaceae).[88] The roots of this plant are used to relief toothache, headache and chest complaints amongst other uses.[89] The three naphthoquinones; shinanolone (**56**), 7-methyljuglone (**57**) and diospyrin (**58**) demonstrated significant activity against drug-sensitive and drug-resistant strains of *Mycobacterium tuberculosis* and lends credence to the ethnomedicinal use of the plant.[90]

Ultra-high performance liquid chromatography coupled to mass spectrometry (UHPLC–MS) was investigated as an ultrafast, accurate, and sensitive method in the quantification of the main compounds in 101 *Aloe ferox* exudates, harvested in South Africa.[91] The main compounds were shown to be the chromones; aloeresin A (**59**), aloesin (**60**) and the anthrones aloin A (**61**) and aloin B (**62**). Even though the identified compounds have not been tested, this plant is known to possess laxative and cathartic effects.

4 Other compound classes from Southern African flora

Table 3, is a summary of other bioactive compounds isolated from Southern African flora. The biological activities which correlate with the enthnobotanical uses of the plants have been highlighted in bold.

The coumarin scopoletin (**63**), along with betulinic acid and acacetin have been reported to three most active components of the ethanol extract of *Artemisia afra* (Asteraceae), attributable to the antimicrobial activity of the aforementioned plant extract.[92] This could partly justify the uses of this plant in traditional medicine in Southern Africa, like in the treatment of coughs, colds, diabetes, malaria, sore throat, asthma, headache, dental care, gout and intestinal worms.[93]

Mutanyatta-Comar *et al.* isolated the phloroglucinol derivatives; 2-butanoyl-4-prenyl-1-methoxy phloroglucinol (**64**), 2-(2-methylpropanoyl)-4-prenylphloroglucinol (**65**), 2-(2-methyl-butanoyl)-4-prenylphloroglucinol (**66**),[94] which are known to exhibit antibacterial, antifungal, antiviral and antioxidant activities.[95-100] The compounds were screened for antioxidant activity against Cu-induced Low Density Lipoprotein (LDP) oxidation. The results showed that compound **67** was found to be the most active inhibiting LDL oxidation at all concentrations (0.5-10 µM) while compounds **64** and **65** showed moderate activities. The activities of the isolated compounds validate the ethnomedicinal uses of *Helichrysum paronychioides* (Asteraceae).

Van Vuuren *et al*. isolated the known phloroglucinol derivative, helihumulone (**67**) from the aromatic plant *Helichrysum cymosum* (Asteraceae) used in traditional medicine to treat respiratory ailments, malaria, wound infections and other tropical diseases.[101,102] Compound **67** was active in inhibiting the growth of the malaria parasite (IC_{50} = 14.89 µg/mL) even though it was toxic. The antimicrobial and antimalarial activities demonstrated by helihumulone **(67**) confirm that of the crude extracts of the plant.

Warburgia salutaris (Canellaceae) stem and leaves have been used to treat bacterial infections and the bark of this plant is smoked for coughs and colds amongst other uses. Previous screening of this plant demonstrated promising antibacterial activity which supports its use in traditional medicine. Mohanlall *et al*., using bioassay-guided fractionation, isolated the active antimicrobial agents drimenin, 5,10-dihydro-6,7-dimethyl-4*H*-benzo[5,6]cyclohepta[1,2-*b*]-furan (**68**) from the stem bark of this plant.[103] Labuschagné *et al*. isolated 5-(hydroxy methyl) furan-2(5*H*)-one (**69**) and 5-(hydroxymethyl) dihydrofuran-2(3*H*)-one (**70**) from *Knowltonia vesicatoria* (Ranunculaceae) which demonstrated antimycobacterial activity.[104] The activity validates the traditional use of the plant in the treatment of tuberculosis. Compound **70** was active against drug-sensitive *M. tuberculosis* with an MIC of 50.0 µg/mL.

Species of the two main genera, *Combretum* and *Terminalia* from Southern Africa have been used in the treatment of syphilis, abdominal pains, conjunctivitis, diarrhoea and toothache, among other ailments.[105-107] The stilbene 2',3',4-trihydroxyl-3,5,4'-trimethoxybibenzyl (combretastatin B5, **71**) has been isolated from *Combretum woodii* (Combretaceae) leaves.[108] Compound **66** showed significant activity against *S. aureus* with an MIC of 16 µg/mL but with lower activity towards *P. aeruginosa* (125 µg/mL), *E. faecalis* (125 µg/mL) and slight activity against *E. coli*.[108]

The prenylated benzoylphloroglucinol derivatives, goudotianone 1 (**72**) and goudotianone 2 (**73**), the xanthone, 1,3,7-trihydroxy-8-isoprenylxanthone (**74**), along with other compunds have been isolated from the leaves of *Garcinia goudotiana* from Madagascar.[109] This plant is used traditionally for its antiparasitic,

antitussive and antimicrobial properties. The compounds displayed a high antimicrobial activity against some Gram-positive bacteria with a moderate cytotoxicity.[110,111] The anti-microbial properties of the isolated compounds were assessed against Gram-positive bacteria, in particular *Staphylococcus lugdunensis*, *Enterococcus faecalis* and *Mycobacterium smegmatis*. The three compounds all demonstrated moderate or high selective significant antimicrobial activities against the tested species. In particular, compound **72** was very active against *E. faecalis* C159–6 (MIC = 39 µg/mL), whereas compound 68 showed a high activity against *S. lugdunensis* T29A3 (MIC = 39 µg/mL). The compound 1,3,7-trihydroxy-2-isoprenylxanthone (**74**) was very active against the three strains with an MIC inferior to 100 µg/mL. By contrast, the three compounds showed cytotoxicity more moderate than the extracts. The prenylated xanthone (**74**) was the least cytotoxic compound.[109]

Vepris uguenensis (Rutaceae) is used traditionally in the treatment of malaria in Kenya.[110] Species of the same genus have found applications in ethnomedicines.[111-113] Cheplogoi *et al.* isolated the novel compounds, methyl uguenesonate, uguenenazole (**75**) and uguenenonamide (**76**) from the root of this plant. Methyl uguenesonate showed mild antimalarial activity against 3D7 (chloroquine susceptible, CQS) and FCM29 (chloroquine resistant, CQR) strains of Plasmodium falciparum. It was found that while compounds **75**, **76** was completely inactive against both strains of the parasite, methyl uguenesonate displayed mild activity, with IC_{50} values of 10.4 ± 4.4, 29.2 ± 3.2 against the CQS and CQR strains, respectively.[110]

Ludere *et al*. isolated the new antimalarial *α*-pyrone, lippialactone (**77**) from the aerial parts of *Lippia javanica* (Verbenaceae). This plant is used in South Africa against various chest ailments, influenza, headaches.[114] Compound **77** was active against the chloroquine sensitive D10 strain of *Plasmodium falciparum* with an IC_{50} value of 9.1 µg/mL, and is also mildly cytotoxic.

Several *Senna* species (Leguminosae - Caesalpinioideae) are used as purgatives or laxatives depending on the dose.[115] The acetone fraction of *Senna singueana* stem bark from South Africa have demonstrated anti-diabetic effects in a rat model against type 2 diabetes.[116] This plant species is also used traditionally in some parts of Ethiopia, for the treatment of a form of skin cancer.[117] Moreover, the inner bark of the plant is chewed fresh to soothe stomach spasm and smoke from the wood and bark is used as smoke baths.[117] A recent study also showed that ethanol extracts of *S. singueana* from Ethiopia have both *in vitro* and *in vivo* antimalarial properties,[118] in addition to the previously known *in vitro* radical scavenging activity.[119] Studies carried out on sister species have led to the isolation of the stilbene 3,4′,5-trihydroxystilbene (resveratrol, **78**) from *S. italica*, a plant used traditionally in the northern parts of the Limpopo province of South Africa for the treatment of STIs,[120,121] as well as *d*-pinitol (**79**) from *Senna versicolor*[122] and other compounds like alkaloids, quinines and anthraquinones.[120] A recent study by Scherzberg *et al*. has shown that structural modification of resveratrol (**78**) leads to increased anti-tumor activity, but causes profound changes in the mode of action.[120b] This is particularly the case with the analog (*Z*)-3,5,4'-trimethoxystilbene (Z-TMS). This analog has shown increased antiproliferative activity towards a number of cancer cell lines compared to resveratrol, which has been shown to inhibit tubulin polymerization *in vitro*. Cell growth inhibition was determined with IC_{50} values for Z-TMS between 0.115 µM and 0.473 µM (resveratrol: 110.7 µM to 190.2 µM). Moreover, resveratrol derivatives have demonstrated potent inhibitory properties against influenza H1N1 neuraminidase.[120c]

Erasto *et al.* isolated the two novel proanthocyanidins; cassinidin A (**80**) and cassinidin B (**81**) from the root bark of *Cassia abbreviata* (Caesalpinioideae) used in the treatment of various ailments.[123] Compounds **80** and **81** demonstrated moderate to high antimicrobial activity against both Gram-positive and Gram negative bacteria which validates the *in vitro* activity of the crude extract and the ethnomedicinal use of the plant.[124-127]

Crude extracts from *Combretum woodii* (Combretaceae) have demonstrated antibacterial activity with MIC values in the order of 0.04 mg/mL.[128] Eloff *et al*. isolated the stilbene; 2',3',4-trihydroxyl-3,5,4'-trimethoxybibenzyl (combretastatin B5) (**71**) from the leaves of this plant. Compound **81** displayed a significant activity against *S. aureus* with an MIC of 16 mg/mL which confirms the use of the species in the treatment of abdominal pains, toothache, and syphilis among other ailments.[43]

Juma *et al*. isolated the new compounds; (7*E*) (8,2')- 3,7,9,5',9'-pentahydroxy-4,4'-dimethoxyneolign-7-ene (**82**) and (9*E*,11*Z*) 14-hydroxyoctadecan-9,11-dienoic acid (**84**) from *Erythrina lysistemon* (Leguminosae).[129] Compounds **84** showed quite appreciable activity against the Gram-positive bacteria *Bacillus subtilis* which correlates with the use of the extracts from this plant in traditional medicine and the antimicrobial activities of the isolated compounds.[130,131] Mujovo *et al*. isolated the long chain alkane; 4-ethyl-nonacosane (**83**) from *Lippia javanica* (Verbenaceae).[132] Infusions of the leaves of this plant are commonly used in Africa as a tea against various ailments like malaria, cough, and headaches among other diseases.[133,134] The known triterpenoid euscaphic acid, isolated from this plant, displayed a minimum inhibitory concentration of 50 mg/mL against a drug-sensitive strain of *Mycobacterium tuberculosis* which validates the use of the plant in ethnomedicine.

5 Conclusions

In this review, we have presented an overview of the results of biological activities of selected NPs (flavonoids, quinones and minor compound classes) isolated from plants used in traditional medicine in Southern Africa (covering 10 countries). The plant sources, geographical collection sites and chemical structures of pure compounds were retrieved from literature sources comprising data collected from articles from major peer-reviewed journals, MSc and PhD theses from university libraries within the region spanning the period 1971 to 2015. We also used the author queries in major natural product and medicinal chemistry journals. The report does not claim to be exhaustive. The goal has been to document the baseline knowledge and lay the foundation for subsequent investigations.

The collected data includes plant sources, uses of plant material in traditional medicine, plant families, region of collection of plant material, isolated metabolites and type (e.g. flavonoid, terpenoid etc.), measured biological activities of isolated compounds (as commented in the literature). The study has provided a survey of the biological activities of compounds derived from Southern African flora versus the ethnobotanical uses of the plant species from which the compounds have been isolated. This series of reviews dedicated to Southern African flora is also intended to give an in depth coverage of the chemotaxonomy of the flora of Southern African and a cheminformatics analysis of the derived natural products. In this study, 864 secondary metabolites have been identified from 101 plant species from 57 plant families. Only the most interesting compounds have been discussed in this review series. The rest of the compounds have been included in the database of NPs from Southern Africa, which is under development.

From the data presented in Tables 1 to 3, the biological activities of 62 out of the 117 plant metabolites indicated in the text could be used to validate the ethnobotanical uses of the plant species. The chemical structures of the secondary metabolites could be further modified to ameliorate biological activity and virtual screening methods could be used to enhance drug discovery by docking some of the compounds towards specific drug target sites. This first part focuses on alkaloids and terpenoids[22] and the second part on flavonoids, quinines and other minor compound classes. The part III of this series of review would be focus on the cheminformatics analysis of the derived natural products.

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7 Notes and references

[a] Department of Chemistry, Chemical and Bioactivity Information Centre, Faculty of Science, University of Buea, P.O. Box 63, Buea, Cameroon; Tel.: +237 677915473; E-mail: ntiekfidele@gmail.com or fidele.ntie-kang@ubuea.cm.

[b] Department of Chemistry, Faculty of Science, University of Buea, P.O. Box 63, Buea, Cameroon; Phone: +237 677 30 67 42; E-mail: ajeck.james@ubuea.cm (JAM) or Phone: +237 677 53 73 80; E-mail: joseph.yong@ubuea.cm (JNY).

[c] Department of Pharmaceutical Chemistry, Martin-Luther University of Halle-Wittenberg, Wolfgang-Langenbeck Str. 4, 06120, Halle (Saale), Germany.

† These authors contributed equally.

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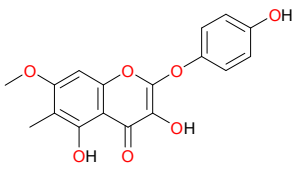
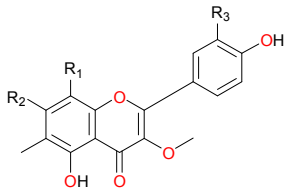
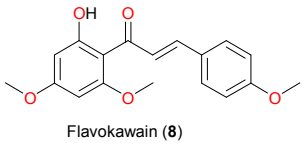
Figures and captions



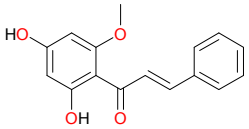
6-*C*-Methyl-2-*p*-hydroxyphenyloxychromonol or Piliostigmol (**1**)



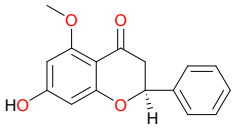
	R_1	R_2	R_3
6,8-Di-*C*-methylquercetin-3,3',7-trimethyl ether (**2**)	CH_3	OCH_3	OCH_3
6,8-Di-*C*-methylquercetin-3,3'-dimethyl ether (**3**)	CH_3	OH	OCH_3
3',6,8,-Tri-*C*-methylquercetin-3,7-dimethyl ether (**4**)	CH_3	OCH_3	CH_3
6-C-Methylquercetin-3-methyl ether (**5**)	H	OH	OH
6,8-Di-*C*-methylkaempferol-3- methyl ether (**6**)	CH_3	OH	OH
6-*C*-Methylquercetin-3,3',7-trimethyl ether (**7**)	H	OCH_3	OCH_3



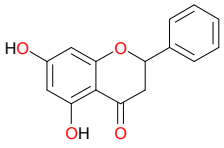
Flavokawain (**8**)



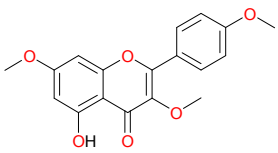
Cardamomin (**9**)



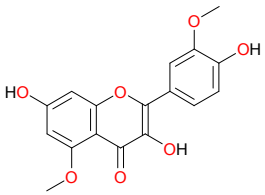
Alpinetin (**10**)



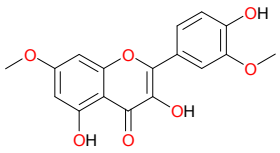
5,7-Dihydroxyflavanone or Pinocembrin (**11**)



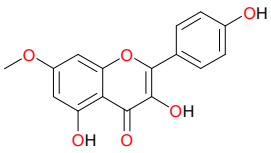
5-Hydroxy-7,4'-dimethoxyflavone (**12**)



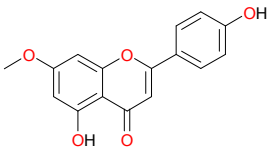
Quercetin-5,3'-dimethylether (**13**)



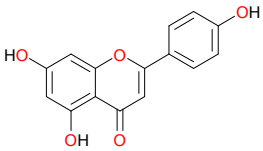
Rhamnazin (**14**)



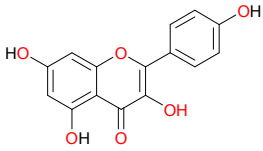
Rhamnocitrin (**15**)



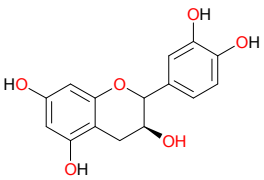
Genkwanin (**16**)



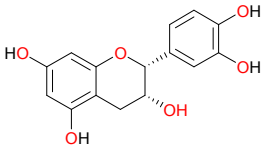
Apigenin (**17**)



Kaempferol (**18**)

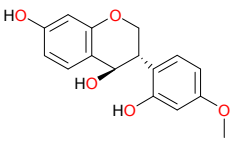


Catechin (**19**)

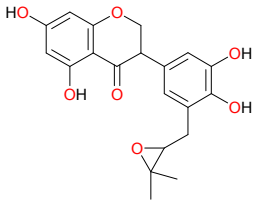


Epicatechin (**20**)

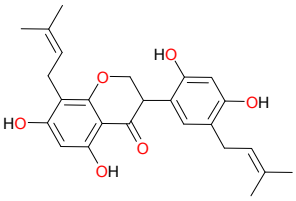
Fig. 1: Chemical structures **1** to **20**.



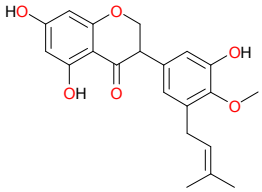
4,7,2'-Trihydroxy-4'-methoxyisoflavanol (**21**)



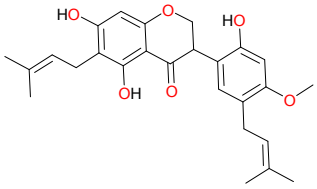
5,7,3',4'-Tetrahydroxy-5'-(2-epoxy-3-methylbutyl)isoflavanone (**22**)



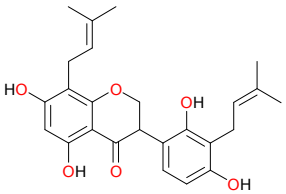
5,7,2',4'-Tetrahydroxy-8,5'-di(γ,γ-dimethylallyl)-flavanone (**23**)



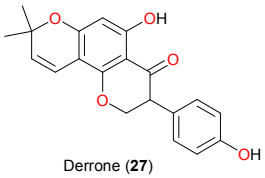
5,7,3'-Trihydroxy-4'-methoxy-5' γ,γ-dimethylallylisoflavanone (**24**)



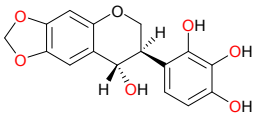
5,7,2'-Trihydroxy-4'-methoxy-6,5'-di(γ,γ -dimethylallyl)-isoflavanone (**25**)



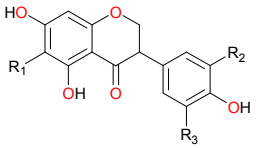
5,7,2',4'-Tetrahydroxy-8,3'-di(γ,γ -dimethylallyl)-isoflavanone (**26**)



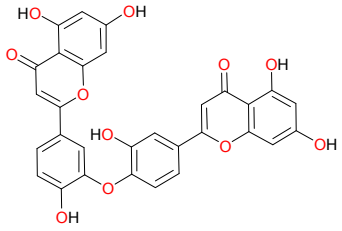
Derrone (**27**)



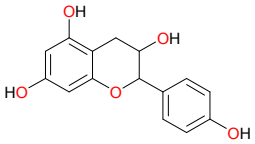
Bolusanthol A (**28**)



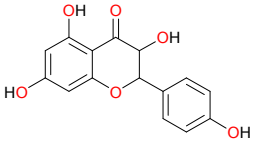
Bolusanthol B (**29**): R_1 = H, R_2 = OH, R_3 = Prenyl
Bolusanthol C (**30**): R_1 = Prenyl, R_2 = Prenyl, R_3 = H



5,7,3',5",7",4"'-Hexahydroxy (4'-O-3"')-biflavone (**31**)



Epiafzelechin (**32**)



Dihydrokaempferol (**33**)

Fig. 2: Chemical structures **21** to **33**.

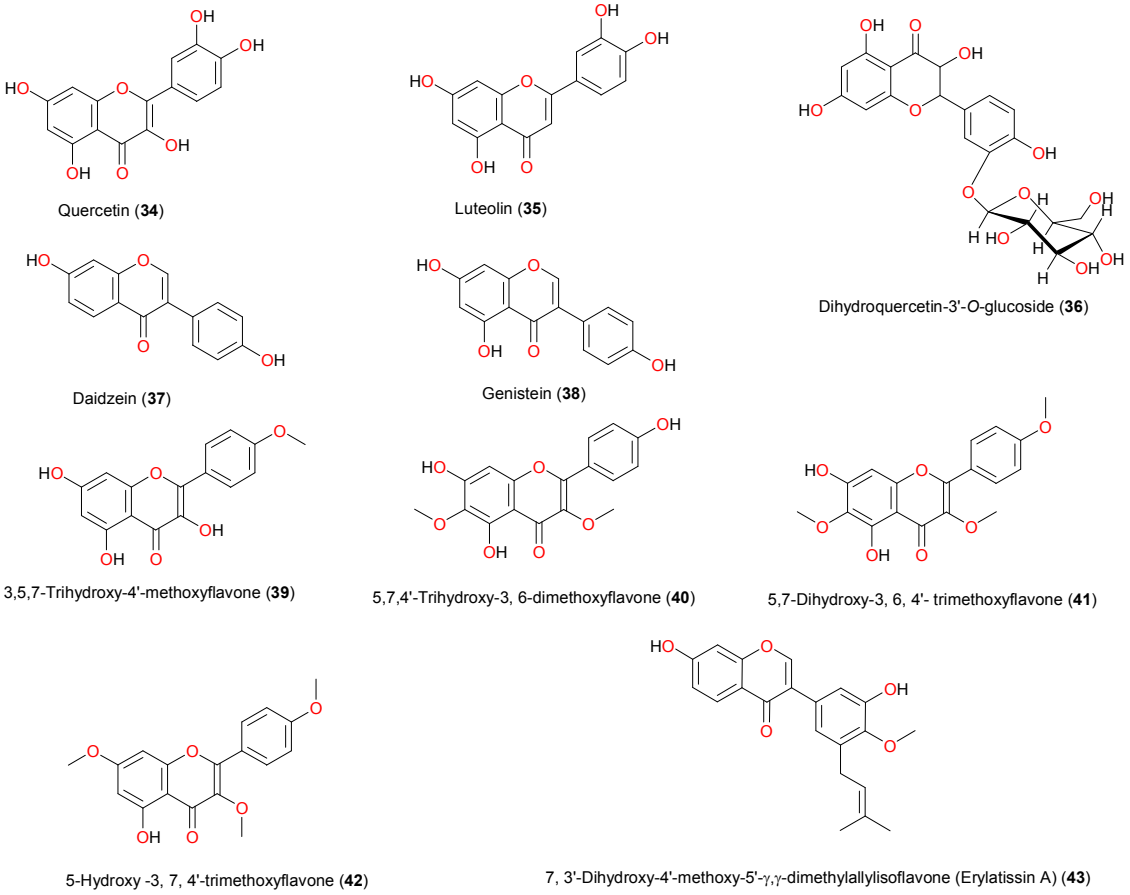


Fig. 3: Chemical structures **34** to **43**.

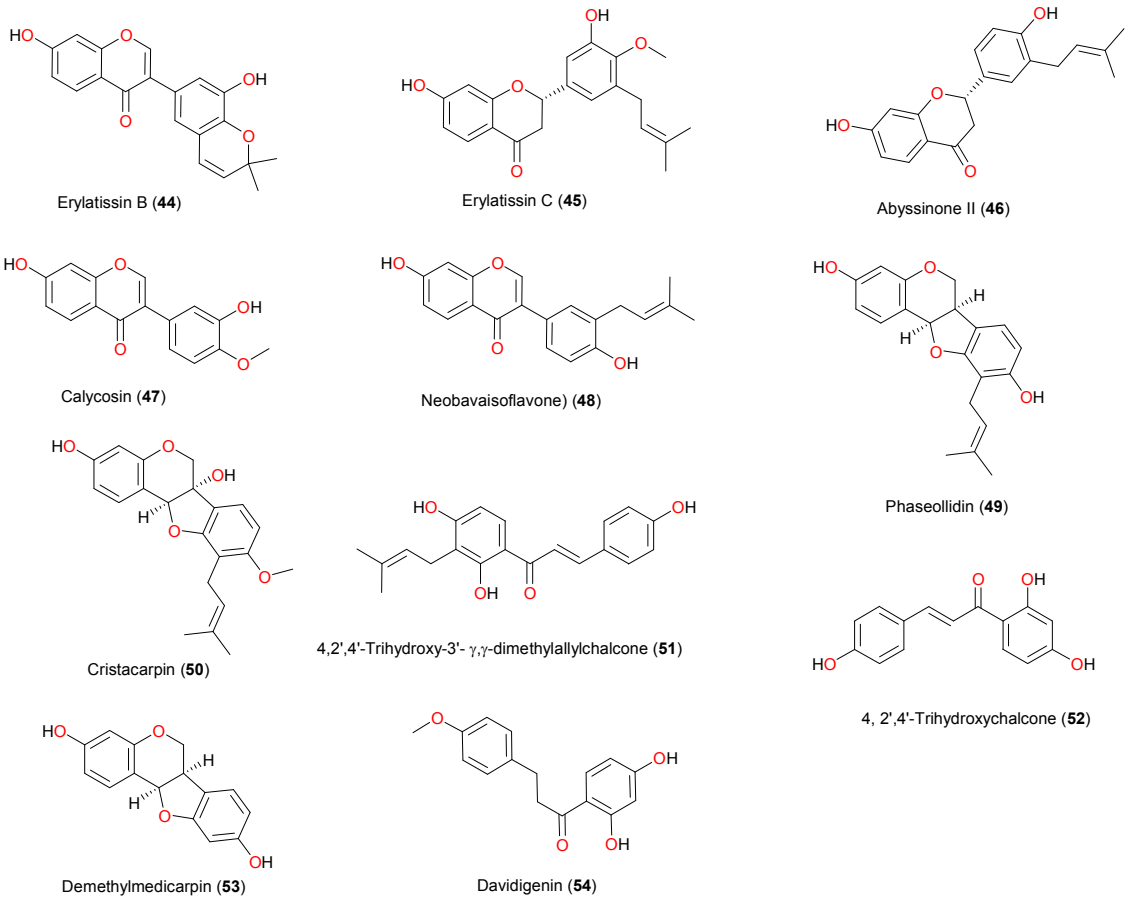


Fig. 4: Chemical structures **44** to **54**.

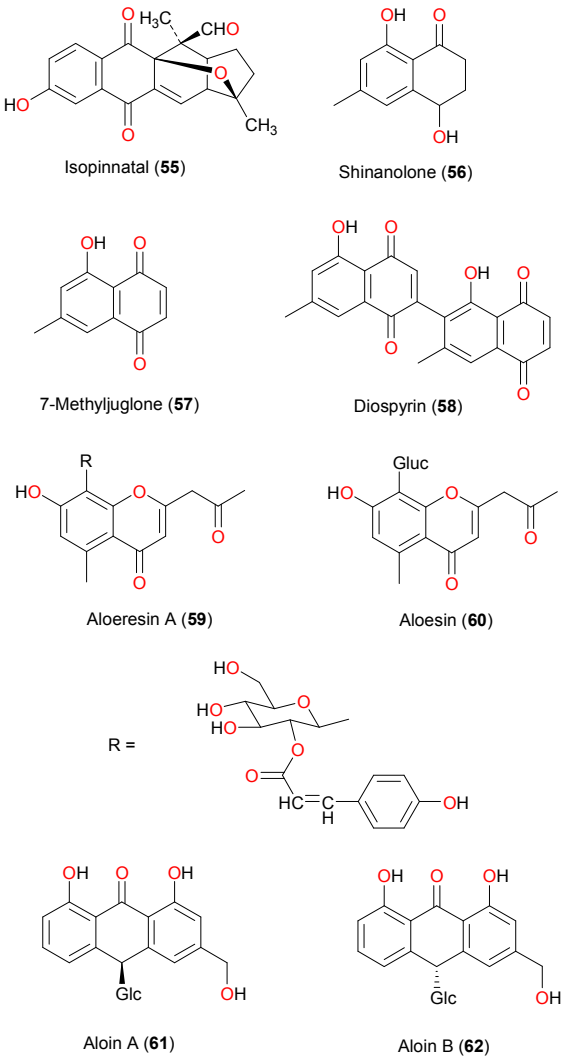
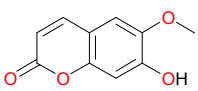
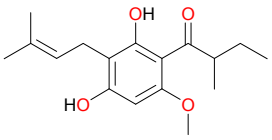


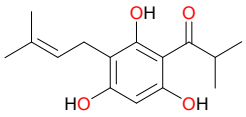
Fig. 5: Chemical structures **55** to **62**.



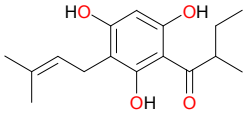
Scopoletin (**63**)



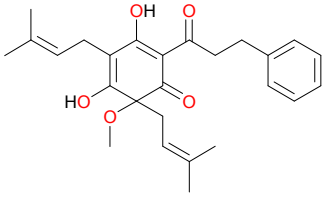
2-Butanoyl-4-prenyl-1-methoxy phloroglucinol (**64**)



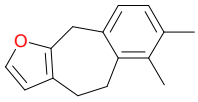
2-(2-Methylpropanoyl)-4-prenylphloroglucinol (**65**)



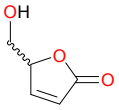
2-(2-Methyl-butanoyl)-4-prenylphloroglucinol (**66**)



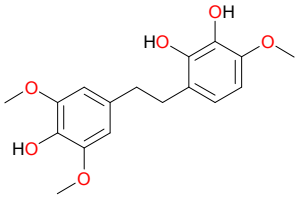
Helihumulone (**67**)



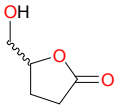
5,10-Dihydro-6,7-dimethyl-4H-benzo
[5,6] cyclohepta [1,2-b]-furan (**68**)



5-(Hydroxy methyl)furan-2(5*H*)-one (**69**)



Combretastatin B5 (**71**)



5-(Hydroxymethyl)dihydrofuran-2(3*H*)-one (**70**)

Fig. 6: Chemical structures **63** to **71**.

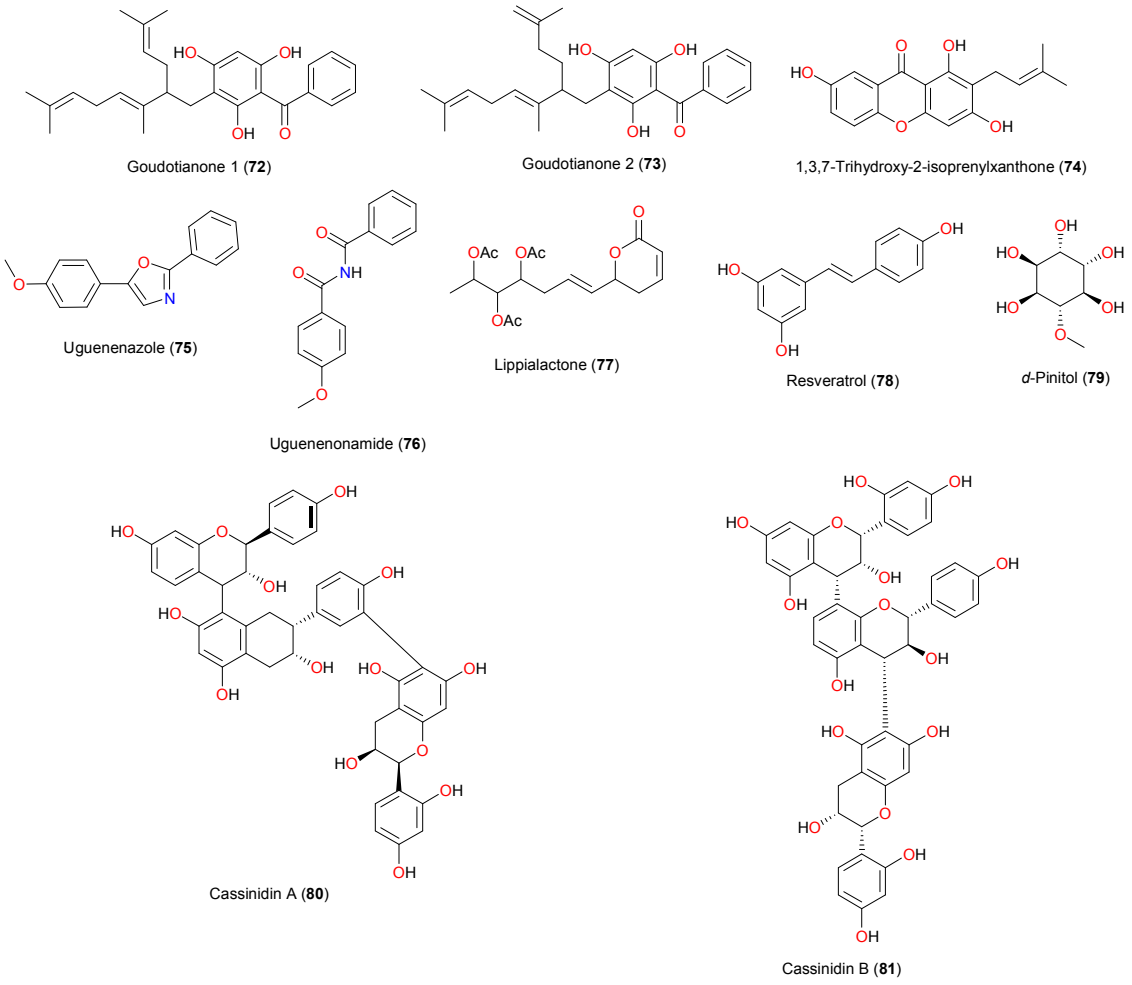


Fig. 7: Chemical structures **72** to **81**.

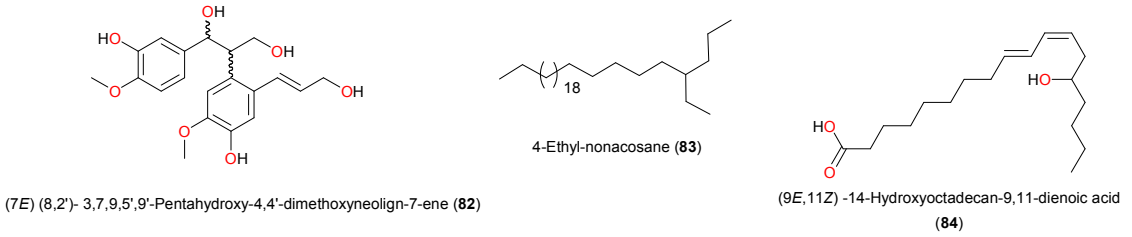


Fig. 8: Chemical structures **82** to **84**.

Table 1: Bioactivity of derived flavonoids *versus* ethnobotanical uses of plant species

Compounds	Plant species (Country)	Family	Ethnobotanical use	Measured Activity	References
Piliostigmol (**1**), 6,8-di-*C*-methylquercetin-3,3',7-trimethyl ether (**2**), 6,8-di-*C*-methylquercetin-3,3'-dimethyl ether (**3**), 3',6,8,-tri-*C*-methylquercetin-3,7-dimethyl ether (**4**), 6-*C*-methylquercetin-3-methyl ether (**5**), 6,8-di-*C*-methylkaempferol-3- methyl ether (**6**) and 6-*C*-methylquercetin-3,3',7-trimethyl ether (**7**)	*Piliostigma reticulatum* (South Africa)	Caesalpiniaceae	**Leprosy**, **smallpox**, **coughs**, ulcer, heart pain, gingivitis, snake bite, **dysentery**, **fever**, **wounds**	**Antimicrobial** activity	Babajide *et al.*,[41]
Flavokawain (**8**), cardamomin (**9**), alpinetin (**10**) and pinocembrin (**11**)	*Combretum apiculatum* (South Africa)	Combretaceae	**Abdominal** disorders, backache, **bacterial infections**	**Antimicrobial** activity	Eloff *et al.*,[48]
5-Hydroxy-7,4'-dimethoxyflavone (**12**), quercetin 5,3'-dimethylether (**13**), rhamnazin (**14**), rhamnocitrin (**15**), genkwanin (**16**), apigenin (**17**) and kaempferol (**18**)	*Combretum erythrophyllum* (South Africa)				
Catechin (**19**)	*Euclea divinorum* (Zimbabwe)	Ebenaceae	Diarrhoea, convulsions, **cancer**, skin diseases and gonorrhoea	**Cytotoxicity** activity	Mebe *et al.*,[52]
Epicatechin (**20**)	*Euclea undulata* (South Africa)	Ebenaceae	**Diabetes**	**Hypoglycaemic** activity	Deutschländer *et al.*,[54]
4,7,2'-Trihydroxy-4'-methoxyisoflavanol (**21**), 5,7,3',4'-tetrahydroxy-5'-(2-epoxy-3-methylbutyl)isoflavanone (**22**), 5,7,2',4'-tetrahydroxy-8,5'-di(γ,γ-dimethylallyl)-flavanone (**23**), 5,7,3'-trihydroxy-4'-methoxy-5' γ,γ-dimethylallylisoflavanone (**24**), 5,7,2'-trihydroxy-4'-methoxy-6,5'-di(γ,γ-dimethylallyl)-isoflavanone (**25**), 5,7,2',4'-tetrahydroxy-8,3'-di(γ,γ-dimethylallyl)-isoflavanone (**26**), derrone (**27**) and bolusanthols A to C (**28** to **30**)	*Bolusanthus speciosus* (Botswana)	Fabaceae	**Emetic**, **abdominal pains**, ornamental tree	**Antibacterial** activity	Bojase *et al.*,[58,59]
5,7,3',5",7",4"'-Hexahydroxy (4'-O-3"')-biflavone (**31**), **(-)**-epicatechin (**20**), epiafzelechin (**32**), dihydrokaempferol (**33**), quercetin (**34**), luteolin (**35**), dihydroquercetin-3'-*O*-glucoside (**36**), daidzein (**37**) and genistein (**38**)	*Vangueria infausta* (Botswana)	Rubiaceae	**Malaria**, **wounds**, menstrual and uterine problems, and genital swelling among others	**Antiplasmodial** and **antimicrobial** activity	Mbukwa *et al.*,[62]
Epiafzelechin (**33**)	*Ficus lutea* (South Africa)		Treatment of **diabetes**.	**Hypoglycaemic** activity.	Olaokun *et al.*[63]

3,5,7-Trihydroxy-4'-methoxyflavone (**39**), 5,7,4'-trihydroxy-3, 6-dimethoxyflavone (**40**), 5,7-dihydroxy-3,6,4'-trimethoxyflavone (**41**), 5-hydroxy -3,7,4'-trimethoxyflavone (**42**) and 3,4',5,7-tetrahydroxy flavone (kaempferol) (**18**)	*Dodonaea viscosa* (South Africa)	Sapindaceae	**Sore throat**, **wounds**, fever, piles, fever, malaria, angina, cold, arthritis, sinusitis flu, and **boils**, skin diseases of the head and face	**Antibacterial** and antioxidant activity	Teffo *et al.*,[66]
7, 3'-Dihydroxy-4'-methoxy-5'-γ,γ-dimethylallylisoflavone (Erylatissin A) (**43**), 7,5'-Dihydroxy-6",6"-dimethyl-4",5"-dehydropyrano[2",3":4',5']isoflavone (erylatissin B) (**44**), (−)-7, 3'-Dihydroxy-4'-methoxy-5'-γ,γ-dimethylallylflavanone (Erylatissin C) (**45**), 7,4'- dihydroxyisoflavone (daidzein) (**37**), 7, 4'-dihydroxy-3'- γ, γ-dimethylallylflavanone (abyssinone II) (**46**), 7, 3'- dihydroxy-4'-methoxyisoflavone (calycosin) (**47**), 7, 4'-dihydroxy-3'- γ,γ-dimethylallyl isoflavone(neobavaisoflavone) (**48**), 3,9-dihydroxy-10- γ, γ -dimethylallylpterocarpan (phaseollidin) (**49**), 3,6a-dihydroxy-9-methoxy-10- γ, γ- dimethylallylpterocarpan (cristacarpin) (**50**), 4,2',4'-trihydroxy-3'- γ,γ-dimethylallylchalcone (**51**), 5,7, 4'-trihydroxyisoflavone (genistein) (**38**), 4, 2',4'-trihydroxychalcone (**52**), 3,9-dihydroxypterocarpan (demethylmedicarpin) (**53**)	*Erythrina latissima* (Botswana)	Fabaceae-Papilionoideae	Dressing open **wounds**	**Antibacterial**, antifungal and radical scavenging activity	Chacha *et al.*,[68]
Davidigenin (**54**)	*Mascarenhasia arborescens* (Madagascar)	Apocynaceae	Intestinal disorders, intestinal **spasms** and diarrhoea	**Antispasmodic** and antioxidant activities	Désiré *et al.*,[85]

Table 2: Bioactivity of derived quinones *versus* ethnobotanical uses of plant species

Isolated metabolites	**Plant species (Country)**	**Family**	**Ethnobotanical use**	**Measured activity**	**References**
Isopinnatal (**55**)	*Kigelia pinnata* (Zimbabwe)	Bignoniaceae	**Skin cancer**	**Cytotoxic activity**	Jackson *et al.*,[86]
Shinanolone (**56**), 7-methyljuglone (**57**) and diospyrin (**58**)	*Euclea natalensis*	Ebenaceae	Toothache, **chest complaints** and headache	**Antimycobacterial** activty	Bapela *et al.*,[88]
Aloeresin A (**59**), aloesin (**60**), aloin A (**61**) and aloin B (**62**)	*Aloe ferox* (South Africa)	Xanthorrhoeaceae	The plant possesses laxative and cathartic effects	Not tested	Kanama *et al.*,[89]

Table 3: Bioactivity of other derived compounds versus ethnobotanical uses of plant species

Isolated metabolites	Plant species (Country)	Family	Ethnobotanical use	Measured activity	References
Scopoletin (**63**)	*Artemisia afra* (South Africa)	Asteraceae	In southern Africa it is used to treat **coughs**, colds, diabetes, malaria, sore throat, **asthma**, headache, dental care, gout and intestinal worms.	**Antimicrobial** properties	More *et al*., [92] Van Vyk and Gerick[93]
2-Butanoyl-4-prenyl-1-methoxy phloroglucinol (**64**), 2-(2-methylpropanoyl)-4-prenylphloroglucinol (**65**), 2-(2-methyl- butanoyl)-4-prenylphloroglucinol (**66**)	*Helichrysum paronychioides* (Botswana)	Asteraceae	Constipation, **coughs** and analgesic	**antibacterial**, antifungal, antiviral and antioxidant activities	Mutanyatta-Comar *et al*.,[94]
Helihumulone (**67**)	*Helichrysum cymosum* (South Africa)	Asteraceae	Respiratory ailments and **wound infections, malaria**	**antimicrobial** and **antimalarial** activity	van Vuuren *et al.*,[101]
Drimenin or 5, 10-Dihydro-6, 7-dimethyl-4*H*-benzo [5, 6] cyclohepta [1, 2-*b*]-furan (**68**)	*Warburgia salutaris* (South Africa)	Canellaceae	Yeast, fungal, **bacterial** and protozoal infections, expectorant and smoked for **coughs** and **colds**	**Antimicrobial** activity	Mohanlall *et al.*,[103]
5-(Hydroxy methyl)furan-2(5*H*)-one (**69**) and 5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (**70**)	*Knowltonia vesicatoria* (South Africa)	Ranunculaceae	**Tuberculosis**	**Antimycobacterial** activity	Labuschagné *et al.*,[104]
Combretastatin B5 (**71**)	*Combretum woodii* (South Africa)	Combretaceae	Treatment of **syphilis**, **abdominal pains**, conjunctivitis, **diarrhoea** and **toothache**, among other ailments	**Antimicrobial** activities**.**	Eloff *et al*.,[108]
Goudotianone 1 (**72**), goudotianone 2 (**73**), 1,3,7-trihydroxy-2-isoprenylxanthone (**74**)	*Garcinia goudotiana* (Madagascar)	Clusiaceae	**Antiparasitic**, **antitussive** and **antimicrobial** properties	**Antimicrobial** and cytotoxic activity	Mahamodo *et al.*,[109]
Uguenenazole (**75**) and uguenenonamide (**76**)	*Vepris uguenensis*	Rutaceae	**Malaria**	**Antimalarial** activity	Cheplogoi *et al.*,[110]
Lippialactone (**77**)	*Lippia javanica* (South Africa)	Verbenaceae	Influenza, measles, rashes, stomach problems, **headaches**.	**Antiplasmodial** activity	Ludere *et al.*,[114]

Cassinidin A (**80**) and cassinidin B (**81**)	*Cassia abbreviate* (Botswana)	Caesalpinioideae	Bilharzias, skin diseases, **cough**, pneumonia, fever, **gonorrhea**, abdominal pains, headaches and snakebites, water fever and heart diseases, **dysentery**, **diarrhea**, severe abdominal pain and **toothache**, oral and vaginal **candidiasis** particularly in HIV/AIDS patients	**Antibacterial** and **antifungal** activity	Erasto *et al.*,[123,125]
Combretastatin B5 (**71**)	*Combretum woodii* (South Africa)	Combretaceae	**Syphilis**, **abdominal pains**, conjunctivitis, **diarrhoea** and **toothache**	**Antibacterial** activity	Eloff *et al.*,[128]
(7*E*) (8,2')- 3,7,9,5',9'-Pentahydroxy-4,4'-dimethoxyneolign-7-ene (**76**) and (9*E*,11*Z*) 14-hydroxyoctadecan-9,11-dienoic acid (**82**)	*Erythrina lysistemon* (Botswana)	Leguminosae	Antiviral, anticancer and cytotoxic activities	Anti-microbial and antifungal activities	Juma *et al.*,[129]
4-Ethyl-nonacosane (**83**)	*Lippia javanica* (Mozambique)	Verbenaceae	Influenza, measles, rashes, malaria, stomach problems, fever, colds, **cough**, headaches	**Antitubercular** and anti-HIV activity	Mujovo *et al.*,[132]