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REVIEW

The chemistry and biological activities of natural products from Northern African plant families: From Ebenaceae to Solanaceae

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Traditional medicinal practices significantly affect the livelihoods of populations in countries with developing economies. The aim of this survey was to validate the use of traditional medicine within Northern African communities. In this review series, we summarize the ethnobotanical uses of selected plant species from the Northern African flora and attempt to correlate the activities of the isolated bioactive principles with known local uses of the plant species in traditional medicine. The literature is covered for the period 1971 to 2014. Part II of this series focuses on plant families with names beginning with letters E to S, with the ethnobotanical uses of 30 plant species from 17 families compared with the bioactivities of 133 compounds identified.

1 Introduction

The region of Northern Africa covers a surface area of about 8,935,659 km^2, comprising the countries Algeria, Egypt, Libya, Morocco, North Sudan, South Sudan, Tunisia and Western Sahara. This region includes a population of about 198,996,526 people.[1] In Northern Africa, Egypt in particular, the use of plant-derived remedies for handing a wide range of ailments locally, is common practice. Herbal shops are very common even in big cities, despite the presence of modern or Western medicine. Thus, the use of African traditional medicine (ATM) in such societies is often without the need for scientific evidence.[2] This is because before the advent Western medicine, people from the societies of Northern Africa have had a long history of the use of plant-derived medicines, which dates back to the prehistoric Egyptian civilization.[2] In effect, it is documented that the apothecaries of ancient Egypt had been familiar with a catalogue of plant-derived traditional remedies. A wide range of plant parts, including the roots, rhizomes, flowers, leaves, fruits, seeds, and oils in the form of powders, pills, suppositories, creams, pastes, and ointments, or sometimes combinations of these, were commonly used.[3,4] The knowledge of herbal remedies from Ancient Egypt has therefore affected the practice of traditional medicine in the entire Northern Africa and the Middle East.

Northern Africa is mostly desert (the Sahara), covering a surface area of 4,619,260 km^2, which is > 50% of the total area occupied by the region. The rest is made of oases and grasslands, with a few species of trees.[5] Vilà *et al*. have reported the existence of a total of 343 vascular plant species from 69 families non-native to this region.[5] The aforementioned paper reported the existence of alien species, ranging from 143 in Algeria to 60 in Tunisia, a majority originating from the regions around the Mediterranean Sea and North America.[5]

There has been a recent surge of publications on traditional knowledge-based de-replication of bioactive compounds for use in the Western or modern medicine. In addition to the increasing global interest in natural products (NPs), it is recommended traditional medicinal concepts be dealt with in detail, with the view of laying the ground work for further scientific investigations. However, unlike modern medicine, the knowledge on traditional medicine is often handed down the ancestral tree and not often properly documented in pharmacopoeia. In our previous study, emphasis has been laid on establishing documented evidence for the use of plant-derived remedies in ATM practices in North Africa.[6] Earlier studies are attempts to explore the components of African traditional medicines in general, by documenting the current available knowledge on the biological activities of NPs isolated from the African flora (from dispersed data/literature sources). This was with the aim of enhancing drug discovery programs on the continent. A number of NP databases for components of ATM have been developed for use in virtual screening campaigns.[7-10] The pharmacokinetic profiling of NP databases from African flora,[10-13] the most recent being the AfroCancer database, which includes about 400 chemical components of African flora with promising anticancer-like properties,[14] has been established. Several focused reviews on NPs isolated from African medicinal plants, some paying attention to plants from particular countries/regions have been published,[15-20] as well as NPs with interesting biological activities against specific diseases/ailments.[21-23] In all the aforementioned cases, emphasis has been laid on the NPs whose measured biological activities correlate with the use of the plant in ATM, with the aim of validating the use of these plant species in traditional medicine. This survey is a continuation of the investigation of ethnobotanical uses of the plant species from Northern Africa *versus* the bioactivities of the derived NPs. As in the previous study,[6] this survey is presented by plant family and in alphabetical order. Wherever the bioactivities

of the isolated metabolites correlate with the ethnobotanical uses of the plant species, these are highlighted in bold in the Tables. In the current survey, plant families with names beginning with letters E to S are covered.

2 Ebenaceae and Euphorbiaceae

A summary of the medicinal uses and biological activities of the compounds of the Ebenaceae and Euphorbiaceae plant families are shown in Table 1. *Diospyros mesipiliformis* (Ebenaceae) is a tropical and subtropical tree which has several ethnopharmacological applications in Sudanese folk medicine.[24] Different parts of the plants are used to remedy a number of ailments including malaria, pneumonia, syphilis, dermatomycoses, diarrhea, skin infections, toothache and headache. The EtOAc extract of the stem bark of *Diospyros mespiliformis* afforded lupeol (**1**), betulinic acid (**2**), betulin (**3**) and lupeone (**4**), Fig. 1.[25a] These compounds and their semi-synthesized acetate were screened for the inhibition of α-glucosidase enzyme activity as well as against antioxidant activity. Compound **1** and its semi-synthesized acetate, as well as compounds **3** and **4**, displayed significant α-glucosidase inhibitory potential. Mohamed *et al*. also reported a study of *Croton zambesicus* (Euphorbiaceae). The MeOH extract of the dried fruit of this plant yielded compounds **1**, **2** and **3**, in addition to the diterpene ent-kaurane-3β,16β,17-triol (**5**) and vitexin (**6**). Only compound **6** exhibited strong antioxidant activity when screened along with the other compounds from both species. Vitexin is also widely used in increasing cardiac output and reducing total peripheral vascular resistance and coronary resistance.[25b] The roots of *Croton zambesicus* have been implicated in the treatment of malaria and diabetes in Nigeria and in the relief of menstrual pains in Sudan.[26-29] The claims of the therapeutic value of *C. zambesicus* roots are, however, still to be supported by solid scientific evidence.

3 Fabaceae (Leguminosae) and Hypericaceae

A summary of the medicinal uses and biological activities of the compounds of the above plant families above are indicated in Table 2. Plants of the Leguminosae or Fabaceae are known to be rich in prenylated flavonoids,[30,31] alkaloids[32] and triterpenoid saponins.[33] The isolated compounds have shown diverse biological activities and the plant materials have been used to treat a number of diseases and ailments.

The *Tephrosia* species (Fabaceae) from Northern Africa are known to possess dynamic pharmacological activities, e.g. piscicidal, insecticidal and anti-cancer properties.[34] Kassem *et al*. isolated and characterized a new naturally occurring flavonol diglycoside, tamarixetin 3-*O*-β-glucopyranoside-7-*O*-α-rhamnopyranoside (**7**), together with kaempferol 3,7-di-*O*-α–rhamnopyranoside (**8**) and quercetin 3,7-di-*O*–α-rhamnopyranoside (**9)** from the aerial parts of *Tephrosia purpurea*, Fig. 2.[35] Bioassay-guided fractionation of the light petroleum extract, which showed antitumor activity, yielded two bioactive 5-deoxyflavones; pseudosemiglabrin (**10**) and glabratephrin (**11**). *In vitro* screening of pseudosemiglabrin and glabratephrin for cytotoxicity against the human cell lines U251 brain, MCF7 breast and Hepg2 liver carcinoma indicated that both showed cytotoxicity to the Hepg2 hepatic human cell line with IC_{50} values of 0.87 and 4.03 μg/mL, respectively and are inactive against U251 (brain tumor) and the MCF7 (breast carcinoma) cell lines.

Lupinus tassilicus (Fabaceae) is considered to be an endangered herbaceous species endemic to the Saharan desert (in the Algerian region of Tassili). Debitted seeds of this plant are believed to possess antidiabetic properties.[36] The seeds of this plant contain quinolizidine alkaloids; sparteine (**12**) and lupanine (**13**), exhibiting moderate hypoglycemic effects on alloxan-diabetic rats, but not on normal rats.[37] Ainouche *et al*. have also identified epilupinine (**14**) and multiflorine (**15**) as the main alkaloids in the species harvested from Algeria.[38] The presence of alkaloids like lupinine, anagyrine, sparteine and hydroxylupanine makes this plant potentially toxic if consumed in huge amounts, probably because these compounds induce hypoglycemia.[36]

In an attempt to establish a chemotaxonomic classification of *Astragalus caprinus* (Fabaceae) from Tunisia growing under different climatic conditions, Semmar *et al*. have isolated fourteen flavonol glycosides, although only thirteen of the compounds (**16-28**) were fully characterized.[39] The identified chemical structures are shown in Fig. 3, but a link between the ethnobotanical uses of the plant and the biological activities of the derived compounds is still to be established. Zitouna *et al*. also carried out a similar study on *Hedysarum* and *Sulla* species (Fabaceae) and established a genetic diversity relationship between the two genera, for species growing under different climatic conditions in Tunisia Algeria and Morocco.[40] Moreover, nineteen flavonoids and isoflavonoids have been identified or tentatively identified with species from the *Adenocarpus* genus (Leguminosae), harvested in Mediterranean and tropical African regions.[41] These include flavones di-*C*-glycosides, luteolin derivatives, apigenin derivatives, daidsein derivatives, genistein derivatives, kaempferol derivatives and quercetin derivatives. The biological activities of the isolated compounds is yet to be correlated with the uses of the plant species in traditional medicine.

Erythrina lysistemon (Leguminosae), grown in Egypt as an ornamental plant, has been associated with the treatment of infertility in women, stomach pain and gonorrhoea. Three prenylated flavonoid derivatives, 5,7,4'-trihydroxy-8-(3'''-methylbut-2'''-enyl)-6-(2'-hydroxy-3'-methylbut-3''enyl) isoflavone (isoerysenegalensein E) (**31**), 5,7,2'-trihydroxy-4'-methoxy-5'-(3''-methylbut-2''-enyl) isoflavanone (lysisteisoflavanone) (**34**), 5,4'-dihydroxy-6-(3'''-methylbut-2'''-enyl)-2''-hydroxyisopropyl dihydrofurano [4'',5'':8,7] isoflavone (isosenegalensin) (**36**), together with the four known flavonoids abyssinone V-4'-methylether (**29**), alpinumisoflavone (**30**), wighteone (**33**) and burttinone (**35**) were isolated from the stem bark of this plant (Fig. 4).[30] Meanwhile, compounds **32** and **38** were isolated from the Cameroonian species.[42-44] Compounds **35** and **36** were evaluated for anticancer activity. The IC_{50} values for compound **35** were less 50 μM against 43 cell lines with maximum cytotoxicity against colon cancer cell line HCC2998 (IC_{50} = 20 μM), while the IC_{50} values were higher than 50 μM in all the five tested leukemia lines. Compound **36** was significantly less cytotoxic than compound **35** but the IC_{50}'s were a little less 50 μM only against four cell lines, namely, ovarian, non-small cell lung cancer, colon cancer, and renal cancer.[30] Both compounds were nonselective in their action.

The bark of *Erythrina abyssinica* (Leguminosae) has been used to cure cough, skin diseases, ulcers, abdominal pain, liver inflammation, colic, trachoma and elephantiasis; the flowers have been used for the treatment of dysentery and as an abortifacient; the leaves are used for the treatment of peptic ulcers, arthralgia and diarrhea; the roots are being used in preparing remedies for epilepsy, malaria and syphilis, while the fruit is used to cure asthma.[45] The

bioassay-guided fractionation of the alkaloidal fraction of the seeds of *E. abyssinica* yielded erythraline (**39**), erysodine (**40**), erysotrine (**41**), 8-oxoerythraline (**42**), and 11-methoxyerysodine (**43**) on purification, Fig. 3.[32] The crude alkaloidal extract was evaluated for *in vitro* cytotoxicity activity against the cell lines HeLa, Hepg2, HEG-2, HCT116, MCF7 and HFB4. This extract showed potential activity with IC_{50} values of 13.8, 10.1, 8.16, 13.9, 11.4 and 12.2 μg/mL, respectively, against the aforementioned cell lines. The pure compounds, **39**–**43**, were screened for *in vitro* cytotoxicity activity against Hepg2 and this resulted in IC_{50} values of 17.60, 11.80, 15.80, 3.89 and 11.40 μg/mL, respectively. These compounds were also evaluated for cytotoxicity activity against HEP-2 cell line and these gave IC_{50} values of 15.90, 19.90, 21.60, 18.50 and 11.50 mg/mL, respectively. The anti-HIV-1 activity of the alkaloidal fraction, using the methyl thiazol tetrazolium (MTT) method, was evaluated. This resulted in the reduction in the viability of mock-infected MT-4 cells by CC_{50} = 53 μM and achieved 50% protection on MT-4 cells from the HIV-1-induced cytopathogeneticy by $EC_{50} \geq 53$ μM, compared with EFV as positive control (which showed CC_{50} = 45 μM and EC_{50} = 0.003 μM).[32] The cytotoxicity of mock-infected MT cells has been attributed to the presence of isoquinoline-type alkaloids, which inhibit the replication cycle of the HIV-1 virus by adsorption or reverse transcription process,[46] thus disrupting the enzyme interaction with template primers.[47] This confirms that the cytotoxicity and anti-HIV activity of the crude extract is due to the presence of the pure compounds, although the modes of action of the isolated metabolites is still under investigation.

As previously mentioned, plant species from the genus *Tephrosia* exhibit a wide range of pharmacological activities, including piscicidal, insecticidal and anti-cancer properties.[34] The flavone (-)-pseudosemiglabrin, (**10**), has also been purified from the aerial parts of *Tephrosia apollinea* (Leguminosae), harvested in Khartoum, Sudan and tested against nine tumor cell lines.[31] The compound indicated selective cytotoxicity against six cancer cell lines, namely, MCF7 (breast cancer, IC_{50} 18.24 μM), PC3 (human prostate cancer, IC_{50} 6.11 μM), HL-60 (human promyelocytic leukemia, IC_{50} 15.7 μM), K562 (human immortalized myelogenous leukemia, IC_{50} 22.5 μM), U937 (human hystiocytic leukemia, IC_{50} 5.76 μM) and HCT116 (human colorectal tumor, IC_{50} 19.6 μM) cell lines. The compound shows, either moderate or poor cytotoxic effects against HT-29 (human leukemia cell line) and Hepg2 (human hepatic carcinoma) with IC_{50} values 135.12 and >300 μM, respectively. Additionally, this compound was nontoxic to normal fibroblast (CCD-18Co) cells (IC_{50} =327.5 μM). It can be concluded that the compound has shown selective anti-proliferative action against leukemia, prostate, breast and colon cancer cell lines and may be a good starting point for synthetic modifications towards anticancer drug development. In addition, the *in vitro* anticancer properties of compound **10** validate the use of this plant in ATM to treat cancer-related ailment.

Gleditsia species (Leguminosae) have been widely used in traditional medicine, e.g. the thorns of *G. sinensis* are used in China for the treatment of abscesses, scabies and skin diseases, while the mature pods and anomalous fruits are mainly used for treating cerebral stroke (caused by hemorrhage in the brain), headache, cough and asthma. *G. japonica* dried fruits have long been known in oriental medicine as a diuretic and expectorant. *G. caspica* is a tree that is grown in public gardens in Egypt and it is associated with cytotoxic activity.[33] Seven bisdesmosidic triterpenoid saponins named caspicaosides E–K (**44**-**50**), were isolated from the methanolic fruit extract of *G. caspica*, harvested from a public garden in Giza, Egypt. The chemical structures were exhaustively elucidated by 1D and 2D NMR spectroscopy as well as high resolution mass spectrometry and acid hydrolysis. The acylated saponins G–K (**46**-**50**) were screened for their *in vitro* cytotoxicity property against the tumor cell lines HCT116, Hepg2 and MCF7, using the acid phosphatase assay. Significant activity was observed against MCF7 cell line (IC_{50} 1.6 – 2.1 μM), while the other two cell lines were moderately susceptible towards the tested isolates.[33]

Hypericum triquetrifolium (Hypericaceae), endemic in Eastern Europe and the Mediterranean area, has been used in folk medicine for its sedative, antihelminthic, anti-inflammatory, and antiseptic effects.[48] The potential uses of its essential oil and crude extracts as drugs have been reported, mainly in the treatment of burns, gastroenteritis, and as antinociceptive and antioxidant drugs.[49-50] Rouis *et al.* evaluated the essential oils of *Hypericum triquetrifolium* harvested from different localities in Tunisia for their antimicrobial activities, using micro-broth dilution methods against bacterial and fungal strains.[51] In addition, the cytotoxic effects and the antiviral activities of these oils were determined using Vero cell lines and coxsakievirus B3. The results revealed good antibacterial activities against a wide range of bacterial strains, with MIC values varying between 0.39 - 12.50 μg/mL and MBC values between 1.56 - 25.0 μg/mL. In addition, the essential oils exhibited potential antifungal activities, with MIC values ranging between 0.39 μg/mL and 12.50 μg/mL; MFC values ranged between 3.12 μg/mL and 25.00 μg/mL; a considerable anticandidal activity was noted (MIC values comprised between 0.39 μg/mL and 12.50 μg/mL). Although their cytotoxic effect was low (CC_{50} ranged between 0.58 mg/mL and 12.00 mg/mL), the essential oils did not show antiviral activity against coxsakievirus B3. The study confirms the multipurpose medicinal use of this plant in various communities in Tunisia.

4 Labiatae and Lamiaceae

A summary of the medicinal uses and biological activities of the compounds of the plant families above are indicated in Table 3.

Nepeta cataria (Labiatae) is native to Eurasia but has been naturalized in North America and other parts of the globe. Members of *Nepeta* genus are noted for different classes of natural products whose biological activities have been evaluated. Extracts of *N. cataria* in different solvents have been investigated *in vitro* for antioxidant activity and carbohydrate-hydrolyzing enzymes with diabetes mellitus (α-amylase, β-galactosidase, α-glucosidase). The results were positive for the different successive extracts with 70% ethanol, petroleum ether and chloroform extracts showing the most potent inhibitory activities. However, EtOAc and pure ethanol extracts revealed moderate to low reducing activities.[52]

The widespread use of *Marrubium vulgare* (Lamiaceae) in folk medicine, led to the phytochemical investigation of the species and eventually led to the isolation and structural elucidation of furanic diterpenes; marrubiin (**51**) and marrubenol (**52**), Fig. 4.[53] These compounds were tested, *in vitro*, for their antihypertensive activity. The results show that marrubenol was more potent than marrubiin (IC_{50} values were 7.7 ± 1.9 μM and 24 ± 2.3 μM for marrubenol and marrubiin, respectively). Both compounds were much less potent than the standard drug, verapamil: IC_{50} ratios of 199 and 64 were obtained for marrubiin and marrubenol respectively compared to verapamil. The presence of these compounds however justifies the vasorelaxant activity of the aqueous extract of the aerial parts of *M. vulgare*.

Plants of the *Salvia* genus (Lamiaceae) are known to have several secondary metabolites which are implicated in the biological activities of the genus. This includes flavonoids,[54] diterpenoids,[55], tritepenoids and other compounds.[56] From the exudates of *Salvia argentea* var. *aurasiaca* (Lamiaceae), ten new triterpenoids were isolated and their structures elucidated by extensive spectroscopic methods.[57] The compounds include, 11α-methoxyurs-12-ene-1β,3β,15α-triol (**53**), urs-12-ene-1β,3β,11α,15α-tetraol (**54**), 11α-methoxyurs-12-ene-1β,3β-diol (**55**), 1β,3β,15α-trihydroxy-11α-methoxyurs-12-en-28-al (**56**), 1β,3β,15α-trihydroxyurs-12-en-28-al (**57**), urs-12-ene-1β,3β,15α,28-tetraol (**58**), 11α-methoxyurs-12-ene-1β,3β,28-triol (**59**), 13β,28-epoxyurs-12-ene-1β,3β-diol (**60**), urs-12-ene-3β,7β,15α,28-tetraol (**61**) and olean-12-ene-3β,7β,15α,28-tetraol (**62**). These triterpenoids were not screened for any specific biological activity. From this family, *Lavanda stoechas* and *Lavanda multifida* are mostly used in traditional medicine for the treatment of several diseases. *L. stoechas* is used for the remedy of epilepsy and headaches[58] and has analgesic, antiseptic, antispasmodic and antimicrobial properties. *L. multifida* is used to treat rheumatism colds[59] and has anti-inflammatory properties.[60] The validation of these ethnobotanical uses is still under investigation.

5 Meliaceae and Moraceae

A summary of the medicinal uses and biological activities of the compounds of the plant families above are indicated in Table 4.

Khaya senegalensis (Meliaceae) is very popular African folk medicine and its bark is used to treat malaria. A bioassay-guided fractionation of the chloroform extract of the bark of a plant sample collected in Khartoum, Sudan afforded three tetranortriterpenoids (limonoids) of the mexicanolide group, one of which is new, namely, 2,6-dihdroxyfissinolide (**63**) and the other two are known compounds: fissinolide (**64**) and methyl 3β-acetoxy-6-hydroxy-1-oxomeliac-14-enoate (**65**).[61] All three compounds were subjected to antiplasmodial and antileishmanial *in vitro* tests against the chloroquine-resistant strains of *Plasmodium falciparum* and the promstigotes of *Leishmania major*, respectively. Fissinolide (**64**) was moderately active in vitro against *Plasmodium falciparum* (IC_{50} 48 ± 3 μM) and promastigotes of *Leishmania major* (IC_{50} 69 ± 13 μM). Compound **63** exhibited IC_{50} 0.12±0.08 μM against *P. falciparum* and IC_{50} > 0.20 mM against *L. major*. The limonoid **65** exhibited no significant antiprotozoal activity (IC_{50} > 0.20 mM) against either *P. falciparum* or *L. major*.[61]

Among the plants surveyed in the Moraceae in North Africa, the aerial parts of *Dortsenia foetida* is used in Yemen to treat skin diseases.[62] The roots are used in Ethiopia to treat leprosy, liver disease and intestinal worms[63] and in Oman the roots are used as food.[64-65] The extracts of the aerial parts of *Ficus auriculata*, another Moraceae of North Africa, has shown antimicrobial, antioxidant, anti-inflammatory, antidiabetic and hepaproctective properties.[66] The phytochemical investigation of the leaves of *Dorstenia foetida* yielded four new furanocoumarins and one carboxymethyl coumarin derivative, along with six known previously isolated compounds.[65] The known compounds include, psoralen (**66**), bergapten (**67**), isopimpellinin (**68**), phellopterin (**69**), 5-methoxychalepensin (**70**) and turbinatocoumarin (**73**). The new compounds are, 5-(2,3-epoxy-3-methylbutoxy)-chalepensin (**71**), 5-methoxy-3-(3-methyl-2,3-dihydroxybutyl)-psoralen-diacetate (**72**), 5-methoxy-3-[3-(β-D-glucopyranosyloxy)-2-acetyloxy-3-methylbutyl]-psoralen (**74**), 5-(3-methyl-2,3-dihydroxybutyloxy)-3[3-(β-D-glucopyranosyloxy)-2-hydroxy-3-methylbutyl]-psoralen (**75**) and 7-hydroxy-5-methoxy-6-carboxymethyl-3-[3-(β-D-glucopyranosyloxy)-2-hydroxy-3-methylbutyl]-coumarin (**76**). Three new derivatives were obtained from the fraction containing compound **71**: 5-(2,3-dihydroxy-3-methylbutoxy)-chalepensin (**77**), 5-(2-hydroxy-3-methoxy-3-methybutoxy)-chalepensin (**78**) and 5-(3-chloro-2-hydroxy-3-methybutoxy)-chalepensin (**79**). The *n*-heptane and EtOAc extracts of *D. foetida* have antifungal potenetial. Psoralen derivatives have been known to exhibit antifungal activities due to their genotoxic reaction with DNA under the influence of UV-A light.[67-68] The plant extract was tested against the intestinal worms, *Caenorhbditis elegans*. The *n*-heptane extract displayed no anthelminthic activity but instead protected the worms compared to the negative control. The *n*-heptane extract showed significant antibacterial activity against *Bacillus subtilis*, shown by the growth inhibition of 60.5% at a concentration of 100 μg/mL. More polar extracts indicated only slightly higher activity. The *n*-heptane extract also demonstrated cytotoxicity activity against HT29 and PC3 cancer cell lines by a cell growth inhibition of 80% at a concentration of 50 μg/mL. The antimicrobial and cytotoxicity activities of *D. foetida* justify its use in folk medicine.

Eight known compounds were isolated from *Ficus auriculata* collected in Giza, Egypt. The chemical structures elucidated by spectroscopic methods and by comparison with known data.[66] The compounds include betulinic acid (**2**), lupeol (**1**), stigmasterol (**80**), bergapten (**67**), scopoletin (**81**), β-sitosterol-3-O-β-D-glucopyranoside (**82**), myricetin (**83**), and quercetin-3-O-β-D-glucopyranoside (**84**). The leaves and fruit extracts of the plant were screened against a host of bacteria (agar well diffusion method) and they were found effective against gram-positive bacteria (*Staphylococcus aureu*s and *Bacillus aureus)* and gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa)*. The alcohol leaf extract at a dose of 500 mg/kg, showed *in vitro* anti-inflammatory activity using carrageenin-induced rat hind paw oedema model, as well as antioxidant activity. The fruit extract showed higher antioxidant activity than the leaf. Both extracts (fruit and leaves) exhibited moderate hepatoprotective and antidiabetic properties.[66] Thus, the use of this plant in traditional African medicine is supported by the study reported by El-Fishawy and coworkers.

6 Orobanchaceae, Poaceae and Podocarpaceae

A summary of the medicinal uses and biological activities of the compounds of the plant families above are indicated in Table 5.

Koua has reviewed the medicinal uses of *Striga hermonthica* (Orobanchaceae),[69] a ubiquitous parasitic weed of the grain family. Although this plant grows widely in rice, millet or maize farms, it has its benefits. The aqueous extract of this plant has exhibited antioxidant activity and a decoction or infusion of the roots is taken orally in East Africa as an abortifacient and in the treatment of pneumonia.[70] Fungal infections are treated with a decoction of the plant in Northern Nigeria and the flowers are used to prevent conception.[71] The methanol extract of the whole plant exhibited weak activity with IC_{50} 274.8 μg/mL against the plasmodium parasite although the same extract exhibited a higher intrinsic activity (*in vivo*) against chloroquine-sensitive *Plasmodium berghi* with a dose of 400 mg/kg weight of mice.[72] Moreover, *S. Hermonthica* has also shown antitrypanocidal properties against *Trypanosoma cruzi* and *Trypanosoma congolense*[73] as well as antibacterial properties against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans.*[74] The aqueous extract has also shown weak antiheminthic activity against

Rhavaditid nematode and *Caenorhabditis elegans* as well as insecticidal properties.[75]

Eragrostis tef (Poaceae) is one of the ancient grains of the world. It originated in Ethiopia and it is widely used in the Horn of Africa as food. Three types of the grain are known, the white, red and brown. The phytochemistry of the red type has led to the isolation and characterization of seven compounds, namely, β-sitosterol (**85**), β-amyrin-3-*O*-(2'-acetyl-glucoside) (**86**), β-sitosterol-3-*O*-β-D-glucoside (**84**), naringenin (**87**), naringenin-4'-methoxy-7-*O*-α-L-rhamnoside (**88**), eriodictyol-3',7-dimethoxy-4'-*O*-β-D-glucoside (**89**) and isorhamnetin-3-*O*-rhamnoglucoside (**90**).[76] The ethanol extract of the plant indicated anti-hyperlipidaemic and anti-hyperglycaemic properties and the oils from the seeds increased the calcium levels in the blood of rats.[76]

The conifer, *Podocarpus gracilior* (Podocarpaceae), grows in East and Central Africa and many species are resistant to insect attack, therefore, they are important trees. In folk medicine various parts of the tree have been used for the treatment of fevers, asthma, coughs, cholera, distemper, chest pain and veneral diseases.[77a] Three new terpenoids, 2α,16-dihydroxy-4β-carboxy-*O*-β-D-glucopyranosyl-19-nor-totarol (**91**), nagilactone K (**92**), and 15-hydroxy phaseic acid (**93**), along with nine known compounds, were isolated and characterized from the leaves of *Podocarpus gracilior*. The following known compounds were identified by comparison with published spectroscopic data: nagilactone B, nagilactone C, nagilactone D, podolactone B, blumenol C glucoside, *erythro*-4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-*O*-4'-oxyneolignan, *threo*-4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-*O*-4'-oxyneolignan, glochidiobioside, and 20-hydroxyecdysone (**94**). Some of these compounds have been subjected to a chemical proteomics study as a strategy for the molecular target identification of natural bioactive compounds, setting up a method for the research of their molecular targets. A fishing for partners study reveals Hsp70 and PPARγ as potential proteic target of 15-ketoatractyligenin methyl ester, a semi-synthetic ent-kaurane, while studies based on limited proteolysis-mass spectrometry strategy, free cell assays, and pro-apoptotic activity of hardwiickik acid in human monocytes allowed to validate Hsp27 as target for the clerodane diterpene.[77b]

7 Resedaceae, Rhamnaceae and Rutaceae

A summary of the medicinal uses and biological activities of the compounds of the plant families above are indicated in Table 6.

In the survey of the Resedaceae, two species were found: *Oligomeris linifolia*[79] and *Randonia africana*.[80] *R. africana* has been used to cure scorpions' stings. The phytochemical investigation of *O. linifolia* yielded one new flavonol monoglycoside: isorhamnetin-4'-*O*-rhamnopyranoside (**99**), in addition to 10 compounds; β-sitosterol-3-*O*-β-glucopyranoside (**84**), kaempferol-3-*O*-β-glucopyranoside (**95**), kampferol-3,7-di-*O*-β-glucopyranoside (**96**), isorhamnetin (**97**), isorhamnetin-3-*O*-β-glucopyranoside (**98**), adenosine (**100**), *p*-hydroxy benzoic acid (**101**), gallic acid (**102**) and two free sugars; glucose (**103**) and galactose (**104**). The new glycoside, compound **101**, was not tested for any activity. Nine flavonoid glycosides were isolated and characterized from the aerial parts of *R. africana*, namely kaempferol-3-*O*-β-glucopyranoside (**95**), kaempferol-3-*O*-β-glucopyranoside-7-*O*-α-rhamnopyranoside (**105**), 8-hydroxykaempferol 8-methyl ether 3-*O*-β-glucopyranoside-7-*O*-α-rhamnopyranoside (sexangularetin) (**106**), kaempferol-3,7-di-*O*-α-rhamnopyranoside (**107**), kaempferol-3-*O*-β-xylopyranosyl-(1'''→2')-O-α-rhamnopyranoside-7-*O*-α-rhamnopyranoside (sagittatin A) (**108**), quercetin-3,7-di-*O*-α-rhamnopyranoside (**19**), quercetin-3-*O*-β-glucopyranoside-7-*O*-α-rhamnopyranoside (**110**), isorhamnetin-3-*O*-β-glucopyranoside (**98**) and isorhamnetin-3,7-di-*O*-α-rhamnopyranoside (**111**).

Scutia myrtina (Rhamnaceae), which is widely available in India, East Africa and South Africa, is an important medicinal plant. The aerial parts used for the remedy of stomach problems and salpingitis. The roots and leaves of the plant are traditionally used as an antihelmintic.[70] The alcohol extract of the aerial part of the plant possesses antiviral activity.[81] The root bark of *S. myrtina* is used to treat fever and an infusion of the plant is used to treat malaria. In eastern Tanzania, the leaves and root bark of this plant are used for the treatment of bilharziasis, gonorrhea, intestinal worms and fever.[82] The tribal people of Kolli Hills in Tamil Nadu (India) used this plant for the treatment of various types of tumours, inflammation and liver disorders. The plant has been reported to show anti-inflammatory and antimicrobial activity.[83] An alkaloid nitidine with potent antimalarial activity has been isolated from a Kenyan herbal remedy.[84] The ethanol extract of *S. myrtina* has been investigated for its antitumor and antioxidant activity against Ehrlich ascites carcinoma in Swiss albino rats. The results indicate that the extract has potent antitumor and antioxidant properties and justifies the use of this plant in traditional medicine.[85]

Another species of the Rhamnoceae with important medicinal uses in the Mediterranean region is *Rhamnus alaternu*s commonly called "oud el khir" in Tunisia. The *Rhamnus* species have been utilized for the remedy of inflammations, constipation, cancers and asthma.[86] The biological screening of pure compounds and extracts of this plant has shown that it has antiproliferative and antibacterial, antimutagenic, antigenotoxic, antioxidant activities.[87] Further studies investigate the apoptotic effect of extracts (EtOAc and total oligomer flavonoids) from *Rhamnus alaternus* in human K562 leukemia cells and on lipid peroxidation.[88] The results show that total oligomer flavonoids and ethyl acetate extracts induce apoptotic death in human chronic myelogenous leukemia K562 cell line and effectively protected lipid peroxidation with IC_{50} values of 196 and 237 μg/mL, respectively.

Murraya species (Rutaceae) have been used for the remedy of diseases in India, Australia and Africa. A decoction of the leaves has been used to treat bruises, skin diseases, toothache, dysentery and diarrhoea. The leaves have also been used as a tnic, an emmenagouge, a stimulant and an astringent.[89] *Murraya exotica* has been investigated for its potential anticancer, cytotoxic, thrombolytic and antioxidant activities.[90] Two new biscoumarins, bismurrangatin (**112**) and murramarin A (**113**) have isolated and characterized from the vegetative branches of *M. exotica* but they have not been tested for biological activity.

8 Salicaceae, Sapindaceae and Solanaceae

A summary of the medicinal uses and biological activities of the compounds of the plant families above are indicated in Table 7.

The berries of *Solanium distichum* (Solanaceae) are used for the treatment of several chronic diseases. In general, *Solanum* species are known to have steroidal glycoalkaloids which possess many biological properties. They prevent fungal growth[94] and inactivate Herpes simplex virus[95] and has been shown to have molluscicidal activity.[96] The fractionated ethanol extract of the berries of *S. distichum* yielded two steroidal glycoalkaloids,[91] namely; Solanidine 3-O-[α-L-rhamnopyranosyl-(1''→4)-[α-L- rhamnopyranosyl-

(1’→2)]-β-D-glucopyranoside] (**114**) and Solanidine 3-O-[α-L-rhamnopyranosyl-(1’’→4)-β-D-glucopyranoside] (**115**) commonly known as α-chanonine and β_2-chanonine. Their structures were determined by spectroscopic methods and they were not tested for any biological activities.

The leaves of *Salix subserrata* (Synonyms *S. safsaf*) (Salicaceae), while being used as a laxative in human and veterinary medicine has provided a black dye for local mats in Sudan.[97] The roots are used in concoctions that remedy stomach pains, fever and headaches[97] and the leaves are used along with milk to treat patients with rabies.[98] The EtOAc fraction of the extract of the bark of *S. subserrata* yielded catechin (**116**), 1,2-benzenedicarboxylic acid, bis(2-ethylhexyl) ester (**117**), salgenin (**118**), methy 1-hydroxy-6-oxocyclohex-2-enecarboxylate (**119**), and catechol (**120**). The *n*-hexane extract afforded propyl acetate (**121**), β-sitosterol (**85**) and the chloroform fraction of the bark gave β-sitosterol glucopyranoside (**84**). The crude extracts and compounds **116** and **85** were tested by an agar diffusion method for antibacterial (*Escherichia coli, Bacillus magaterium)*, antifungal (*Microbotyrum violaceum*) and antialgal (*Chlorella fusca*) activities.[91] The crude extracts exhibited promising antialgal activity against *Chlorella fusc*a except the EtOAc extract of the leaf but moderate activity against the fungus. All extracts exhibited potential antibacterial activity against *Bacillus megaterium* but the EtOAc extract of both the leaf and bark of *S. subserrata* were inactive against fungal *Microbotyrum violaceum*. Compounds **116** and **85** indicated good activity against *Chlorella fusca* and antibacterial activity against gram-positive bacterium, *Bacillus megaterium* and gram-negative bacterium *Escherichia coli*. The tested compounds only showed moderate antifungal activity against *Microbotyrum violaceum*. A mixture of compounds **118** and **119** also showed good algal and antibacterial properties but moderate antifungal activity against *Microbotyrum violaceum*.[92] These studies underscore the necessity to properly evaluate plants for their biological properties in order to establish a scientific base for their utility in folk medicine. *Dodonea viscosa* (Sapindaceae) is used as used as a medicinal plant worldwide to cure sore throat, cold, fever, rheumatism, diarrhea, ulcers, indigestion, headache, toothache to expel intestinal worm and to soothe itching.[99] The seeds are used in India as fish poison[100] and in East Africa, the roots are eaten by women to activate breast milk and treat dysmenorrheal and irregular menstruation.[99]

The bioassay-guided fractionation of the aerial parts of *D. viscosa* (Sapindaceae) from Egypt resulted in the isolation and identification of three new compounds, including two new clerodane diterpenoids **122** and **123** and a new myo-inositol derivative **124**, along with nine known compounds **125**–**133**.[93] The new compounds were identified as 13,14-dihydroxy-15,16 dimethoxy-(–)-6α-hydroxy-5α, 8α,9α,10α-cleroda-3-en-18-oic acid (**122**), (–)-6α-hydroxy-5α,8α,9α,10α-cleroda-3,13-dien-16,15-olid-18-oic acid. (**123**), 1-L-*O*-methyl-2-acetyl-3-*p*-coumaryl-myo-inositol (**124**), and the known compounds as 1-L-1-*O*-methyl-2-acetyl-3-P-*E*-coumaryl-myo-inositol (**125**), pinocembrin (**126**), isokaemferide (**127**), 6-methoxy isokaemferide (**128**), 5,7-dihydroxy-3,6,4’-trimethoxy flavone (**129**), penduletin (**130**), 5-hydroxy-3,6,7,4’-tetramethoxy flavone (**131**), aliarin (**132**) and 5,7-dihydroxy-3’-(4-hydroxy-3-methylbutyl) 3,6,4'-trimethoxyflavone (**133**). All isolated compounds were screened for antimicrobial activity, *in vitro*, against *Staphylococcus aureus* ATCC 29213, methicillin-resistant *S. aureus* ATCC 33591 (MRS), *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium intracellulare* ATCC 23068, *Candida albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258, *Cryptococcus neoformans* ATCC 90113, and *Aspergillus fumigatus* ATCC 204305 using ciprofloxacin and amphotericin B as positive controls for bacteria and fungi, respectively. All isolated compounds were equally checked for antileishmanial activity, *in vitro*, against a culture of *Leishmania donovani* promastigotes using pentamidine and amphotericin B as a standards. All isolated compounds were investigated for antimalarial activity in vitro against chloroquine sensitive (D6, Sierra Leone) and resistant (W2, Indo China) strains of *Plasmodium falciparum* by measuring plasmodial LDH activity. Chloroquine was used as positive control. The results concluded that compound **130** displayed good antifungal activity against *Cryptococcus neoformans* with an IC_{50} value of 6.11 mg/mL. Compounds **131** and **132** exhibited reasonable antileishmanial activity against *Leishmania donovani* with IC_{50} values of 16.6 and 19.06 mg/mL, respectively.

9 Conclusions

African medicinal plants are an enormous repository of bioactive NPs with a huge potential for drug discovery programs. As an example, previous studies on Central[7,8,15,16] and West Africa,[17-20] have revealed a diversity of NPs with a broad range of biological activities. In the Congo Basin, located in Central Africa, several regions in Cameroon serve as typical biodiversity hotspots, with a strong traditional medicinal background and presence. Cameroon’s diversity spans hotspots from Mount Cameroon to the Dja reserve, along with several important investigations on traditional plants based on their usage in traditional medicine, some of which have been cited in the aforementioned reviews. Madagascar is another hotspot for NP lead discovery on the continent of Africa and will be discussed in detail in our review series focused on the Southern African region.

The results for 30 plant species belonging to 17 families (beginning with letters E to S) from North Africa have been discussed in the current review. This involves 142 compounds with intriguing chemical structures and diverse biological activities. An attempt to correlate the biological activities of the isolated compounds with the uses of the plants in traditional medicine has been carried out. However, such an endeavour could prove to be challenging. One of the reasons may be because the traditional methods (steam baths, boiling, use of total extracts as mixtures, etc.) do not match the typical laboratory extraction methods (isolation in polar or non-polar solvents, separation of fractions, isolation of pure compounds, testing of pure isolated compounds, etc.). A quick look at Tables 1 to 7 clearly shows many discrepancies (with the exception of a few correlations marked in bold). This contributes to reducing the true impact of the “value” of traditional knowledge derived from ATM in the current scenario in natural products research. The present results however show the usefulness of traditional medicine drug discovery programs. This review paper does not claim to be exhaustive, the reason being that its principal objective is to establish a baseline for further investigations of North African flora. Data on plant sources, geographical collection sites, chemical structures of pure compounds as well as their spectroscopic data, were retrieved from literature sources comprising data collected from major international journals on natural products and some available PhD theses, spanning the period 1971 to 2014. The current survey consisted in collecting data from the literature sources, mainly using author queries in major natural product and medicinal chemistry journals. 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, etc. The data was collected on an Excel sheet and analyzed. We further propose to build a searchable database for

compounds isolated from Northern African flora, in order to assist in drug discovery programs on the continent of Africa.

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11 Notes and references

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