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Potential antibacterial pharmaceuticals from the flora of Africa

ag0005 **Armelle T. Mbaveng[a,*], Leonidah Kerubo Omosa[b], Gabin T.M. Bitchagno[c,d], Jenifer R.N. Kuete[d], Vaderament-A. Nchiozem-Ngnitedem[b], and Victor Kuete[a]**

aff0005 [a]Department of Biochemistry, Faculty of Science, University of Dschang, Dschang, Cameroon
aff0010 [b]Department of Chemistry, University of Nairobi, Nairobi, Kenya
aff0015 [c]Agrobiosciences, Mohamed IV Polytechnic University, Ben-Guerir, Morocco
aff0020 [d]Department of Chemistry, Faculty of Science, University of Dschang, Dschang, Cameroon
cor1 [*]Corresponding author. e-mail address: armbatsa@yahoo.fr

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Advances in Botanical Research
ISSN 0065-2296, https://doi.org/10.1016/bs.abr.2022.08.021

ab0010 ## Abstract

sp0035 The present chapter highlights the antibacterial potential of nine highly active compounds isolated from the African medicinal plants: 8,8-bis-(dihydroconiferyl)-diferulate, buesgenine, candidone, diospyrone, ferruginin A, isobavachalcone, neobavaisoflavone, neocyclomorusin, and plumbagin. Their botanical source as well as their hypothetical biosynthetic pathways have also been discussed. Regarding their inhibitory potential towards the Gram-negative and Gram-positive bacteria, and mycobacteria, the above phytochemicals constitute potential pharmaceuticals that deserve clinical studies to develop antibacterial drugs to combat bacterial infections involving both drug-sensitive and drug-resistant phenotypes.

Nomenclature

COVID Corona Virus Infection Disease
EPI Efflux Pump Inhibitor
IC_{50} Inhibitory Concentration 50
MBC Minimal Bactericidal Concentration
MRSA Methicillin-resistant *Staphylococcus aureus*
MIC Minimal Inhibitory Concentration
MDR Multidrug-resistant
PAβN Phenylalanine Arginine β-Naphthylamide
WHO World Health Organization

1. Introduction

p0050 Bacterial drug resistance remains a challenging issue globally. This threat arises naturally but misuse and overuse of drugs motivate its development. The World Health Organization (WHO) has pointed out that some pathologies such as pneumonia, tuberculosis, blood poisoning, gonorrhea, and foodborne diseases are becoming difficult to resolve with common health care pipelines. Besides, there is a reemergence of new pathogens with new resistance mechanisms, threatening our management strategies of similar ailments. The current spreading of COVID-19 and Ebola viruses are some instances. The WHO strategies to overcome this scourge include to strengthening surveillance and research on the subject amongst others. Designing and identifying new lead candidates for drug discovery is one of the goals of research in this area. Nature has inspired the progress in drug discovery and continues to enrich libraries of organic chemicals featuring potent impair against pathologies. Plant secondary metabolites or their semisynthetic derivatives have widely been reported to possess a broad spectrum of activities including antibacterial, anticancer, and antiplasmodial activities among others. Regardless of the class of secondary metabolites (alkaloids, flavonoids, terpenoids, miscellaneous), different degrees of activities ranged from significant, moderate to low have been reported (Damen et al., 2019; Demgne et al., 2021; Kuete, 2013; Mbaveng, Damen, et al., 2020; Tamokou, Mbaveng, & Kuete, 2017). Despite intensive research done in the search for new lead compounds, plant-based products have been reported valuable sources of drugs with anti-infective properties. In the two last decades, intensive searches have been carried on with African medicinal plants to discover potential phytochemicals that could serve as lead molecules for new antibacterial drugs. In the present survey, we are reporting on the most promising antibacterial compounds isolated so far from various African medicinal plants. Candidates were sorted out based on the sole records towards bacterial strains with special emphasis on those expressing a multidrug-resistant (MDR) phenotype such as 8,8-bis-(dihydroconiferyl)-diferulate (**1**), buesgenine, candidone, diospyrone, ferruginin A, isobavachalcone, neobavaisoflavone, neocyclomorusin, and plumbagin. Their botanical source as well as their hypothetical biosynthetical pathways was also discussed.

2. The 8,8-bis-(dihydroconiferyl)-diferulate: a ferulic acid derivative

p0055 The 8,8-bis-(dihydroconiferyl)-diferulate (**1**) is the tetramer of ferulic acid derivative. The ferulic acid, a hydroxycinnamic acid, is ubiquitous in the plant kingdom, and occur in a number of vegetable (in seeds and leaves) with particularly high concentrations in popcorn and bamboo shoots (Kumar & Pruthi, 2014; Zhao & Moghadasian, 2008). Ferulic acid is involved in the rigidity of the cell wall and in the formation of other important organic compounds like coniferyl alcohol, vanillin, sinapic, diferulic acid, and curcumin (Kumar & Pruthi, 2014). It has been isolated from was isolated from *Ferula foetida* L. (Apiaceae) and displays a wide variety of biological activities such as antioxidant, anti-inflammatory, antibacterial, antifungal, antiallergic, hepatoprotective, anticarcinogenic, antithrombotic, increased sperm viability, antiviral and vasodilatory actions, metal chelation, modulation of enzyme activity, activation of transcriptional factors, gene expression and signal transduction (Kumar & Pruthi, 2014). It is believed that many of its pharmacological properties can be found in 8,8-bis-(dihydroconiferyl)-diferulate. In fact, 8,8-bis-(dihydroconiferyl)-diferulate had impressive antibacterial and cytotoxic properties (Demgne et al., 2021; Efferth et al., 2021; Mbaveng, Damen, et al., 2020). In effect, the antiproliferative effects of 8,8-bis-(dihydroconiferyl)-diferulate was reported on a large panel of cancer cell lines, including CCRF-CEM (IC_{50}: 1.17 μM) and CEM/ADR5000 (IC_{50}: 3.01 μM) leukemia cells, MDA-MB-231-*pcDNA* (IC_{50}: 4.89 μM) and MDA-MB-231-*BCRP* (IC_{50}: 4.43 μM) breast adenocarcinoma cells, HCT116 $p53^{+/+}$ (IC_{50}: 5.18 μM) and HCT116 $p53^{-/-}$ (IC_{50}: 6.34 μM) colon adenocarcinoma cells, U87MG (IC_{50}: 4.05 μM) and U87MG.Δ*EGFR* (IC_{50}: 4.66 μM) gliobastoma cells, HepG2 (IC_{50}: 5.12 μM) hepatocarcinoma cells, the BRAF-V600E homozygous mutant MaMel-80a (IC_{50}: 1.89 μM) and SKMel-28 (IC_{50}: 4.81 μM) melanoma cells, the BRAF-V600E heterozygous mutant A2058 (IC_{50}: 1.39 μM) and Mel-2a (IC_{50}: 3.26 μM) melanoma cells, the BRAF wildtype MV3 (IC_{50}: 4.14 μM) and SKMel-505 (IC_{50}: 5.21 μM) melanoma cells, the CC531 rat colon adenocarcinoma cells (IC_{50}: 5.27 μM), the B16-F1 (IC_{50}: 3.14 μM) and B16-F10 (IC_{50}: 1.79 μM) murine melanoma cells (Mbaveng, Damen, et al., 2020). In the present section, the antibacterial potential of this compound will be discussed.

2.1 Chemistry of 8,8-bis-(dihydroconiferyl)-diferulate

p0060 8,8-bis-(dihydroconiferyl)-diferulate (**1**) (Fig. 1): Yellowish powder, *m/z* 714, $C_{40}H_{42}O_{12}$ ^{13}C NMR data (DMSO-d_6, 150 MHz): δ_C 131.2 (C-1),

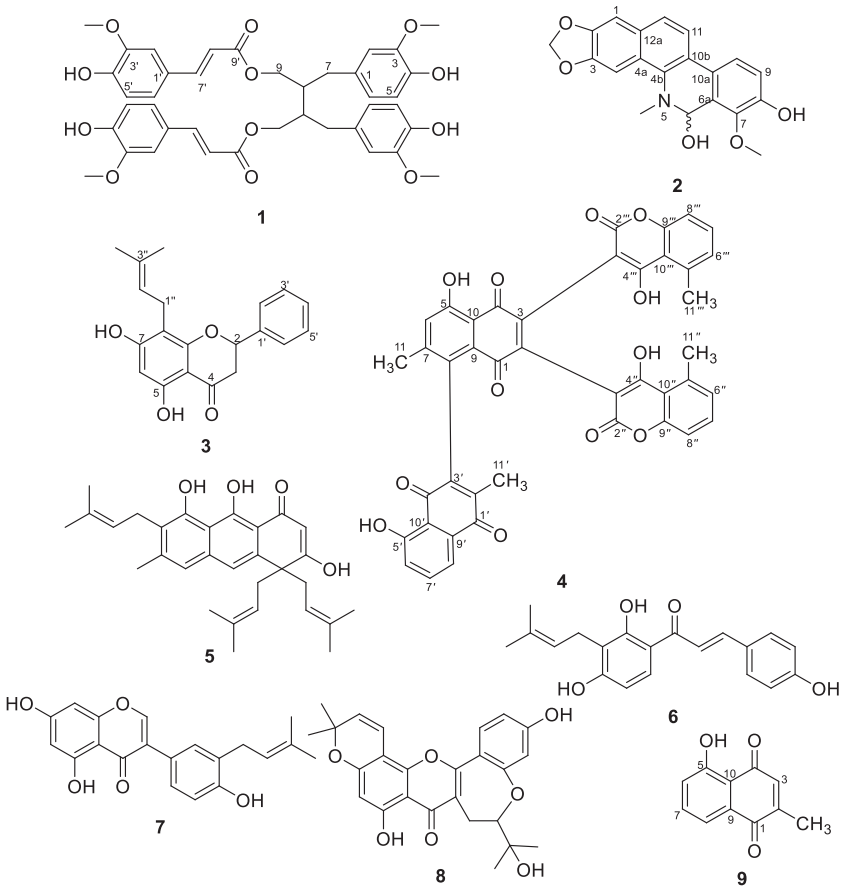


Fig. 1 Chemical structure of potential pharmaceuticals identified in the African medicinal plants. (**1**) 8,8-bis-(dihydroconiferyl)-diferulate; (**2**) buesgenine; (**3**) candidone; (**4**) diospyrone; (**5**) ferruginin A; (**6**) isobavachalcone; (**7**) neobavaisoflavone; (**8**) neocyclomorusin; (**9**) plumbagin.

113.1 (C-2), 147.8 (C-3), 145.1 (C-4), 114.8 (C-5), 111.4 (C-6), 34.2 (C-7), 37.2 (C-8), 64.2 (C-9), 126.0 (C-1′), 111.5 (C-2′), 148.4 (C-3′), 149.8 (C-4′), 115.9 (C-5′), 123.7 (C-6′), 145.6 (C-7′), 115.8 (C-8′), 167.2 (C-9′), 56.1 (3-OCH_3), 55.7 (3′-OCH_3) (Buske, Schmidt, Porzel, & Adam, 1997).

2.2 Botanical source of 8,8-bis-(dihydroconiferyl)-diferulate

p0065 The ferulic acid derivative, 8,8-bis-(dihydroconiferyl)-diferulate has been isolated from the bark and roots of *Antidesma membranaceum* Müll. Arg.

(Phyllanthaceae) (Buske et al., 1997), and from the leaves and bark of *Hypericum roeperianum Schimp.* ex A. Rich (Hypericaceae) (Damen et al., 2020; Demgne et al., 2021; Mbaveng, Damen, et al., 2020).

2.3 Antibacterial activity of 8,8-bis-(dihydroconiferyl)-diferulate against sensitive and multidrug-resistant phenotypes

p0070 In a recent study performed by Demgne and collaborator in 2021, the antibacterial activity of 8,8-bis-(dihydroconiferyl)-diferulate, isolated from the bark of bark of *Hypericum roeperianum* was evaluated on a panel of microorganisms including sensitive and resistant strains of *Klebsiella pneumoniae, Enterobacter aerogenes, Escherichia coli,* and *Providencia stuartii* obtained from the American Type Culture Collection, and the methicillin-resistant strains of *Stphylococcus aureus* (Demgne et al., 2021). The feature of these bacteria was documented by (Badawe et al., 2018; Djeussi et al., 2013; Djeussi, Noumedem, Mihasan, Kuiate, & Kuete, 2020; Djeussi, Noumedem, Ngadjui, & Kuete, 2016; Fankam, Kuiate, & Kuete, 2014; Kuete, Alibert-Franco, et al., 2011; Kuete, Ngameni, Tangmouo, et al., 2010; Kuete, Wabo, et al., 2007; Manekeng et al., 2018; Noumedem et al., 2013; Wamba, Mbaveng, et al., 2018; Wamba, Nayim, et al., 2018). Resistant strains tested included the AcrAB–TolC expressing Enterobacteriaceae such as *Escherichia coli* AG102, *Enterobacter aerogenes* CM64, *Klebsiella pneumoniae* KP55, *Providencia stuartii* PS2636 as well as *Stphylococcus aureus* MRSA3 strains (Davin-Regli et al., 2008; Nikaido, 2009; Wamba, Mbaveng, et al., 2018; Wamba, Nayim, et al., 2018). The authors have applied the microbroth dilution method to determine the minimal inhibitory concentration (MIC) of ferruginin A on these bacteria strains (Mbaveng et al., 2015). They found that outstanding antibacterial activity against Enterobacteria and *Staphylococcus aureus* (MIC ≤ 2 μg/mL) (the classification basis are discussed in Chapters 6–8 of Volume 106) was obtained against all the tested bacteria, including *Escherichia coli* ATCC8729 (MIC of 0.5 μg/mL) and AG102 (MIC of 1 μg/mL), *Klebsiella pneumoniae* ATCC11296 (MIC of 2 μg/mL) and K55 (MIC of 1 μg/mL), *Enterobacter aerogenes* ATCC13048 and CM64 (MIC of 2 μg/mL), *Providencia stuartii* ATCC29916 (MIC of 0.5 μg/mL) and PS2636 (MIC of 1 μg/mL), and *Stphylococcus aureus* strain ATCC25923 (MIC of 2 μg/mL) and MRSA3 (MIC of 0.5 μg/mL) (Demgne et al., 2021). Demgne et al. also demonstrated that 8,8-bis-(dihydroconiferyl)-diferulate generally displayed bacteriostatic activity against the investigated bacteria (Demgne et al., 2021), as the minimal bactericidal concentration (MBC) *vs* minimal inhibitory

concentrations (MBC/MIC) were above 4 (Dzoyem et al., 2012; Eyong et al., 2006; Kuete et al., 2012; Kuete, Ango, et al., 2011; Kuete, Eyong, et al., 2007; Kuete, Fozing, et al., 2009; Kuete, Mbaveng, et al., 2008; Kuete, Metuno, et al., 2007; Kuete, Simo, et al., 2007; Kuete, Wabo, et al., 2007; Kuete, Wansi, et al., 2008). Demgne et al. also compared the activity of 8,8-bis-(dihydroconiferyl)-diferulate with that of the reference drug, chloramphenicol; they found that 8,8-bis-(dihydroconiferyl)-diferulate had better activity than ciprofloxacin on all tested bacteria (Demgne et al., 2021). These are clear indications that 8,8-bis-(dihydroconiferyl)-diferulate is a potential antibacterial against that deserves further investigation to produce a pharmaceutical against bacterial infections including multidrug-resistant phenotypes.

2.4 Antibacterial modes of resistance to 8,8-bis-(dihydroconiferyl)-diferulate

p0075 Demgne et al. have evaluated the role of bacterial efflux pumps, mainly the AcrAB-TolC pumps of the Enterobacteria and MexAB-OprM of *Pseudomonas aeruginosa* on the resistance to 8,8-bis-(dihydroconiferyl)-diferulate (Demgne et al., 2021). The authors tested the compound alone and in combination with the well-known efflux pump inhibitor (EPI), phenylalanine arginine β-naphthylamide (PAβN) (Demgne et al., 2021). They found that in the presence of PAβN, the activity of this compound significantly increased in all tested bacteria, from 4-fold to 16-fold. In the presence of the EPI, outstanding antibacterial activity was recorded in all tested bacteria, with MIC values below 0.125 μg/mL against *Escherichia coli* ATCC8739 and AG102, *Enterobacter aerogenes* ATCC13048 and CM64, *Klebsiella pneumoniae* ATCC11296 and KP55, *Providencia stuartii* ATCC29916 and PS2636 and *Stphylococcus aureus* strain ATCC25923 and MRSA3 strains (Demgne et al., 2021). They concluded that active efflux was the main mode of resistance of Gram-negative bacteria to 8,8-bis-(dihydroconiferyl)-diferulate and that this phytochemical is a powerful antibacterial agent if it is combined with an EPI.

3. Buesgenine: a benzophenanthridine alkaloid

p0080 Benzophenanthridine alkaloids like buesgenine (**2**) have demonstrated activities against a panel of pathogens including drug sensitive and multidrug-resistant showing anti-parasitic activity against *Plasmodium falciparum* (Goodman et al., 2019), antiprotozoal effects against neglected

tropical diseases including *Leishmaniasis* and *Trypanosomasis* (Sandjo et al., 2016), cytotoxic (Sandjo, Kuete, Tchangna, Efferth, & Ngadjui, 2014) and antibacterial activity (Tankeo et al., 2015). This work aims to bring together information regarding the chemistry of buesgenine, its biosynthesis, and total synthesis as well as its antibacterial activity reported to date. Buesgenine has shown significant anti-leukemia properties against CCRF-CEM cell lines with IC_{50} value of 0.24 μM. The compound was moderate to low activity against the other cell lines with IC_{50} ranges of 22–66 μM and has shown a considerable selectivity to normal cell AML12 ($IC_{50} > 106.92$ μM) (Sandjo et al., 2014). Several chemical functions can influence the biological activities of benzophenanthridines including the bulky groups at C-9/C-10, the *N*-methyl positively, an 8-carbonyl, substituent group on the B ring, and a rupture of C-7/C-8 bond (Fuchino et al., 2010).

3.1 Chemistry of buesgenine

p0085 Buesgenine (**2**) is a type II benzophenanthridine alkaloid proper to dihydrobenzo[*c*]phenanthridine skeleton. It can be further located in type II-2 because its C-6/N-5 bond is closed (Han, Yang, Liu, Liu, & Yin, 2016). Buesgenine features a phenol at C-8, an aromatic methoxyl at C-7 and a dioxymethylene group attach at C-2/C-3 positions (Fig. 1). The basic nitrogen bears a methyl group while position 6 is hydroxylated. The compound was trivially named buesgenine after the gross structure (planar structure) unless it exhibits a stereocenter at C-6 (Sandjo et al., 2014). Its stereoconfiguration has never been sold out, that of some related derivatives like 6-hydroxydihydrochelerythrine (8-*O*-methylbuesgenine) as well. However, compound **2** showed a small value of specific rotation (−7). Smaller values of optical rotation are indicative of whether the compound is an impure racemic compound, a scalemic mixture, or a dirty enantiomeric pure compound. Buesgenine could have occurred might as a mixture of both enantiomers since the last step of its biosynthesis involves the hydration (thought to follow a non-enzymatic process) of the imine function.

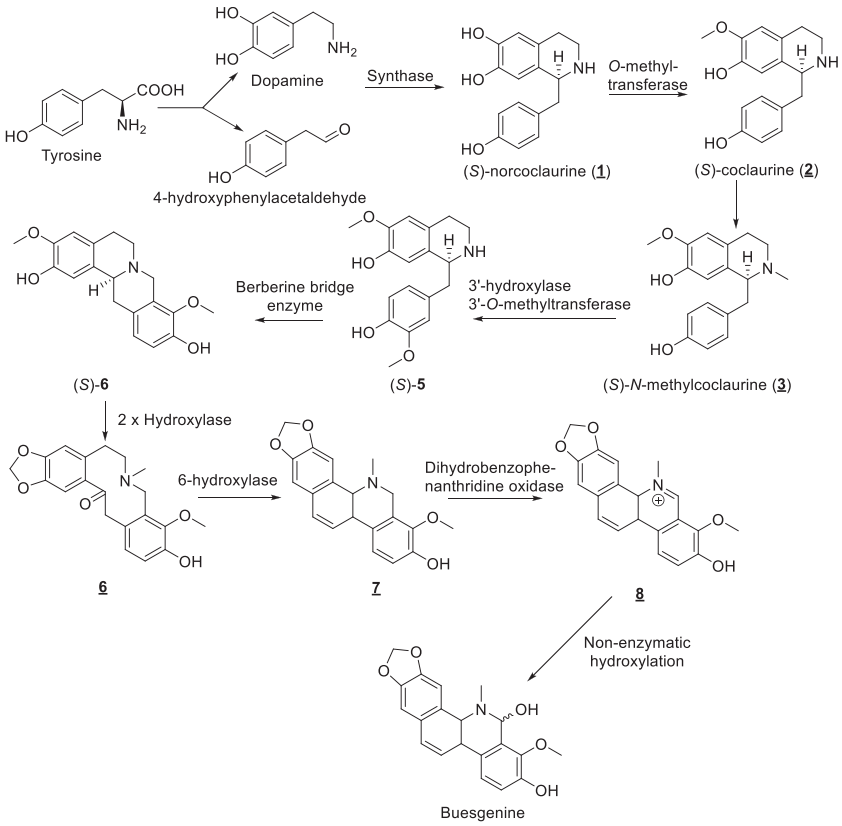
p0090 The ^{1}H and ^{13}C NMR spectra of **2** recorded in pyridine-d_5 on a Brüker DRX-400 MHz with TMS as internal reference by Sandjo et al. display two characteristic doublets of aromatic spins at δ_H/δ_C 8.02 (d, $J = 8.5$ Hz, H-11)/111.0 (C-11), 7.82 (d, $J = 8.4$ Hz, H-10)/120.4 (C-10), 7.62 (d, $J = 8.5$ Hz, H-12)/124.2 (C-12), 7.41 (d, $J = 8.4$ Hz, H-9)/118.3 (C-9) besides two aromatic singlets at δ_H/δ_C 7.89 (s, H-4)/101.7 (C-4) and 7.31

(s, H-1)/105.3 (C-1) and an aliphatic hydroxymethine at δ_H/δ_C 6.54 (s, H-6). The spectrum also discloses signals of different substituents of buesgenine backbone namely the methylenedioxy at δ_H/δ_C 6.04/6.08 (d, J = 1.2 Hz, OCH_2O)/102.0 (OCH_2O), the methoxyl at δ_H/δ_C 4.24 (s, CH_3-O)/62.2 (CH_3-O) and methylamine at δ_H/δ_C 2.77 (s, CH_3-N)/40.6 (CH_3-N). Resonances of quaternary carbons of the molecule are reported at δ_C 150.6 (C-8), 148.8 (C-2), 148.2 (C-3), 146.9 (C-7), 140.1 (C-4b), 131.7 (C-12a), 129.1 (C-10a), 128.2 (C-4a), 124.3 (C-10b) and 124.3 (C-6a) (Sandjo et al., 2014).

3.2 Biosynthesis, natural source, and complete synthesis of buesgenine

p0095 Buesgenine is a chemical constituent exclusively occurring in the plant kingdom of the genus *Zanthoxylum* (or *Fagara*) including *Z. buesgenii* (Sandjo et al., 2014), *F. tessmannii* (Tankeo et al., 2015), *Z. monophylum* (Rodríguez-Guzmán, Fulks, Radwan, Burandt, & Ross, 2011), and *Z. zanthoxyloides* (Goodman et al., 2019).

p0100 The biosynthesis of benzophenanthridine and that of buesgenine has not yet been elucidated. Current empirical observations and hypothetical deductions point its origin to benzylisoquinoline alkaloid. The biosynthesis (Scheme 1) would start with the condensation of dopamine and 4-hydroxyphenylacetaldehyde to yield (*S*)-norcoclaurine (**1**) catalyzed by norcoclaurine synthase, presented as the common precursor of both alkaloid groups. Both reactants are derived from tyrosine following hydroxylation and decarboxylation for dopamine then transamination and decarboxylation for hydroxyphenylacetaldehyde (O'Connor, 2010). Methylation of one hydroxyl group in the intermediate occurs under the catalysis of *S*-adenosyl methionine (SAM)-dependent *O*-methyltransferase to afford (*S*)-coclaurine (**2**), further *N*-methylated to (*S*)-*N*-methylcoclaurine (**3**). The latter is hydroxylated and methylated by *N*-methylcoclaurine 3′-hydroxylase and 3′-hydroxy-*N*-methylcoclaurine 3′-*O*-methyltransferase, respectively, yielding compound **4**, a 3′-methyl analogue of (*S*)-reticuline, transformed to the corresponding 3′-methyl analogue **5** under the catalysis of a flavin-dependent enzyme, berberine bridge enzyme. After the methylenedioxy bridge formation by a hydroxylase, a second enzyme entity converts the resulting intermediate into the intermediate **6**, hydroxylated by a 6-hydroxylase prior to its conversion to compound **7**. Under the influence of a copper-dependent oxidase, dihydrobenzophenanthridine oxidase, the intermediate **7** is turned to **8**. The biological construction of **8** is like the route described in



Scheme 1 Proposed biosynthetic route to buesgenine.

the literature for the biosynthesis of sanguinarine (O'Connor, 2010). Buesgenine could then originate from a non-enzymatic hydroxylation of **8**.

3.3 Antibacterial activity of buesgenine against sensitive and multidrug-resistant phenotypes

p0105 Buesgenine displayed excellent antibacterial activity against *Escherichia coli* AG102 and *Kblebsiella pneumoniae* ATCC11296 with a MIC value of 4 μg/mL as well as a good activity (MIC of 16–32 μg/mL) towards *E. Coli* ATCC10536, *Enterobacter aerogenes* (ATCC13048 and EA294), *K. pneumoniae* K2, *Providencia stuartii* PS2636 and *Pseudomonas aeruginosa* PA01. Interestingly, buesgenine was at least ≥ 4-fold more potent than the standard drug, ciprofloxacin against pathogenic microbes *E. coli* AG102 and *K. pneumoniae* ATCC11296 (Tankeo et al., 2015).

4. Candidone: a flavone

p0110 Flavones are the largest class of flavonoids with 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one) backbone commonly occurring in foods and some yellow or orange fruits and vegetables (Martens & Mithöfer, 2005). They are present in all plant tissues, and the most common are apigenin, luteolin, tangeritin, or chrysin (Martens & Mithöfer, 2005). The flavones subgroups include hydroxylated, O-methylated, C-methylated, isoprenylated or methylenedioxy substituted compounds (Martens & Mithöfer, 2005). They have diverse biological activities such as antimicrobial, antioxidant, anticancer, anti-inflammatory, antiviral, *etc.* Some microbial flavones identified in African medicinal plants or their related synthetic derivatives are 5,7-dihydroxy-3,4-dimethoxyflavone, 3,5,4′-trihydroxy-7 methoxyflavone, 5,7-dihydroxy-3,6,4′-trimethoxyflavone, 5,4′-dihydroxy-3,7-dimethoxyflavone, 5-hydroxy-3,7,4′-trimethoxyflavone, 3,5,6,7,4′-pentamethoxyflavone, 5-hydroxy-2′,3′,4′, 5′-tetramethoxyflavone, 5-hydroxy-7,2′,3′,4′, 5′-pentamethoxyflavone (Omosa et al., 2016), amentoflavone (Mbaveng, Ngameni, et al., 2008), atalantoflavone and 2′-hydroxyatalantoflavone (Mbaveng et al., 2015), gancaonin Q (Kuete, Simo, et al., 2007), cylindricine B (Nago et al., 2021), morelloflavone (Nganou et al., 2019). Antiproliferative flavones identified in the African plants include 3,4′,5-trihydroxy-6″,6″-dimethylpyrano[2,3-*g*]flavone (Kuete, Sandjo, Mbaveng, Zeino, & Efferth, 2015), 5-hydroxy-7,4′ -dimethoxyflavone (Mbaveng et al., 2021), amentoflavone (Kuete, Mbaveng, et al., 2016), artocarpesin and cycloartocarpesin (Kuete, Mbaveng, et al., 2015), atalantoflavone (Kuete, Sandjo, Djeussi, et al., 2014), gancaonin Q (Kuete, Ngameni, et al., 2011), luteolin (Mbaveng, Chi, et al., 2020; Ngaffo et al., 2020). Some naturally occurring anti-inflammatory flavones include 4-hydroxylonchocarpin (Kuete, Noumedem, & Nana, 2013), 3,3′-dimethoxy flavone, and 3,5,6,7,4′-pentamethoxy flavone (Habib et al., 2021), apigenin and apigeninidin (Makanjuola, Ogundaini, Ajonuma, & Dosunmu, 2018), baicalein (Zhang et al., 2021). The present section will be focused on the antibacterial potential of a naturally occurring C-prenylated flavone, candidone, a cytotoxic and antibacterial compound (Blatt et al., 2002; Darzi et al., 2021; Mbaveng et al., 2015). The antiproliferative of candidone was reported towards the human epidermoid (KB) tumor cell line (Blatt et al., 2002). Its cytotoxic effects were reported on HL60 and HL60AR leukemia cells with respective IC_{50} of 38.15 μg/mL and 35.58 μg/mL, MDA-MB231 breast adenocarcinoma cells (IC_{50} of 37.22 μg/mL), HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$ colon adenocarcinoma cells (IC_{50} of 29.44 μg/mL and

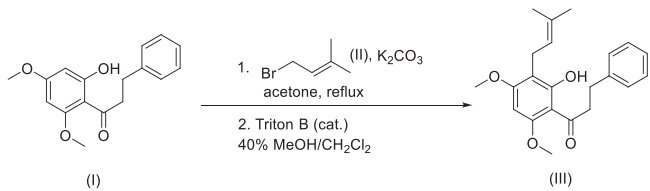
37.62 μg/mL respectively), U87MG and U87MG.Δ*EGFR* gliobastoma cell line (IC_{50} of 27.16 μg/mL and 33.26 μg/mL respectively) (Kuete, Sandjo, Wiench, & Efferth, 2013). The cytotoxicity of this compound cytotoxicity on RAW and HT-29 cell lines was also reported (Ganapaty, Srilakshmi, Thomas, Rajarajeshwari, & Ramakrishna, 2009). Candidone (**3**) was reported as a potent chemosensitizer in MCF7/MX cells (Darzi et al., 2021), inducing cell death mediated by the activation of caspase-3 and -9 and decreased expression of anti-apoptotic proteins, including p65, induced myeloid leukemia cell differentiation protein Mcl-1, B-cell lymphoma 2 (Bcl2), Bcl2-associated agonist of cell death and survivin (Boonyarat et al., 2021). It also inhibited the migration and invasion abilities of HepG2 cells and decreased the levels of proteins associated including phospho-p38 and active matrix metallopeptidase 9 (Boonyarat et al., 2021).

4.1 Natural sources and synthesis of candidone

p0115 Candidone (**3**) (Fig. 1), has been isolated and identified from parts of various medicinal plants. This includes the stems and leaves of *Tephrosia candida* DC. (Fabaceae) (Roy, Mitra, Bhattacharyya, & Adityachaudhury, 1986), the stem bark of *Lonchocarpus aff. fluvialis* (Fabaceae) (Blatt et al., 2002), the fruits of *Derris indica* (Lam.) Bennet (Fabaceae) (Boonyarat et al., 2021; Kurasug, Kukongviriyapan, Prawan, Yenjai, & Kongpetch, 2018), the stem bark of *Pongamia pinnata* (L.) Pierre (Fabaceae) (Carcache, 2003), the roots of *Echinops giganteus* var. lelyi (C. D. Adams) A. Rich. (Asteraceae) (Kuete, Sandjo, et al., 2013). The synthesis scheme below (Scheme 2) was proposed for candidone (Ganguly, Bhattacharyya, Bhattacharyya, & Adityachaudhury, 1988).

4.2 Chemistry of candidone

p0120 Candidone is a naturally occurring C-prenylated Yellowish powder; melting point (mp) 95.1–96.2 C, LR-EI-MS *m/z*: 352.2 [$C_{22}H_{24}O_4$], Rf 1.75/5 (DCM), ^{1}H NMR (C_5D_5N, 400 MHz): 1.67 (3 H, s), 1.72 (3 H, s), 3.00



Scheme 2 Synthesis of candidone.

(1 H, dd, 3.2, 16.3), 3.14 (1 H, dd, 12.4, 16.3), 3.52 (2 H, m), 3.84 (3 H, s), 3.90 (3 H, s), 5.48 (1 H, t, 7.2), 5.57 (1 H, dd, 3.2, 12.4), 6.34 (1 H, s), 7.45 (2 H, br t, 7.6), 7.37 (1 H, br t, 7.4), 7.64 (2 H, br d, 7.4), ^{13}C NMR (C_5D_5N, 100 MHz): 18.4, 22.6, 26.4, 46.6, 56.3, 56.4, 79.6, 90.1, 107.0, 110.5, 124.2, 127.1 (2xC), 129.2, 129.5 (2xC), 131.4, 140.5, 161.7 (2xC), 163.9, 189.4 (Waterman & Mahmoud, 1985).

4.3 Antibacterial activity of candidone against sensitive and multidrug-resistant phenotypes

p0125 In a recent study performed by Mbaveng and collaborators, the antibacterial activity of candidone was evaluated on a panel of microorganisms including sensitive and resistant strains of *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Providencia stuartii,* obtained from the American Type Culture Collection. The resistant strains tested were *Escherichia coli* AG102 and AG100 A_{tet}, *Enterobacter aerogenes* CM64 and EA27, *Klebsiella pneumoniae* KP55, *Providencia stuartii* PS299645, *Enterobacter cloacae* PS299645, BM47, and BM67 as well as the MexAB–OprM in *Pseudomonas aeruginosa* PA124 (Davin-Regli et al., 2008; Nikaido, 2009). Authors have also applied the microbroth dilution method to determine the MIC of candidone on these bacteria strains (Mbaveng et al., 2015). They found that excellent antibacterial activity against Enterobacteria ($2 < \text{MIC} \leq 4\,\mu g/mL$) was obtained against *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC11296, and *Enterobacter cloacae* BM47 strains (Mbaveng et al., 2015). They also reported the very good activity of the compound ($4 < \text{MIC} \leq 8\,\mu g/mL$) against *Escherichia coli* AG102 and *Klebsiella pneumoniae* KP55, as well as its good activity ($8 < \text{MIC} \leq 32\,\mu g/mL$) against *Enterobacter aerogenes* EA27 and *Providencia stuartii* ATCC29916 strains. However, these authors also documented the average activity ($32 < \text{MIC} \leq 64\,\mu g/mL$) of this compound against *Providencia stuartii* PS299645 and weak activity ($64 < \text{MIC} \leq 512\,\mu g/mL$) against *Escherichia coli* AG100Atet, *Enterobacter aerogenes* ATCC 13048 and CM64, and *Enterobacter cloacae* BM67 strains (Mbaveng et al., 2015). Towards the *Pseudomonas aeruginosa* strains, very good activity ($32 < \text{MIC} \leq 128\,\mu g/mL$) was obtained against PA01 strain whilst good activity ($128 < \text{MIC} \leq 256\,\mu g/mL$) was reported against the resistant PA124 strain (Mbaveng et al., 2015). Mbaveng et al. also demonstrated that candidone generally displayed bacteriostatic activity against the investigated bacteria (Mbaveng et al., 2015). Mbaveng et al. also compared the activity of candidone with that of the reference drug, chloramphenicol; they found that candidone had better activity than

chloramphenicol against *Enterobacter aerogenes* EA27 and CM64, *Klebsiella pneumoniae* ATCC 11296 and KP55, and *Enterobacter cloacae* BM47 strains (Mbaveng et al., 2015). In contrast chloramphenicol in return also had a better activity than candidone on *Escherichia coli* AG100, *Enterobacter aerogenes* ATCC 13048, *Providencia stuartii* ATCC29916 and PS299645, *Pseudomonas aeruginosa* PA01, and PA124 strains (Mbaveng et al., 2015).

5. Diospyrone: a binaphthoquinone

p0130 One of the African species *Diospyros canaliculata* De Wildeman belonging to the family Ebenaceae mostly found in Cameroon as well as in other West African countries contains binaphthoquinones as the dominant phytochemicals including diospyrone (**4**). Previous studies on *D. canaliculata* (De Wildeman) revealed tremendous *in vitro* antifungal activity attributed to diospyrone against *Candida albicans* and *Candida krusei* (Tangmouo et al., 2005). This section provides an overview of the current knowledge on diospyrone, with emphasis on findings regarding the antibacterial activity against drug-resistant bacterial species as well the chemistry, and biosynthesis of this naturally occurring compound.

5.1 Natural source and chemistry of diospyrone

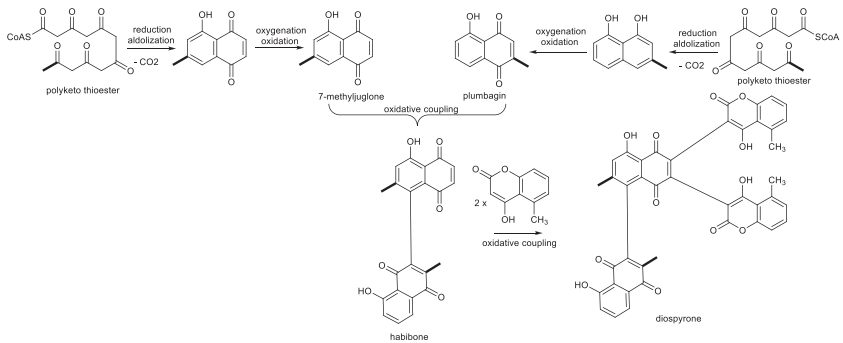
p0135 Diospyrone represents a rare class of binaphthoquinones bearing a 4-hydroxy-5-methylcoumarin-3-yl unit reported in nature. This secondary metabolite was reported for the first time from the stem bark of *Diospyros canaliculata* De Wildeman (Ebenaceae) (Tangmouo et al., 2005). Since then, its isolation has not been reported among plants belonging to the genus *Diospyros,* or in plant kingdom. This binaphthoquinone derivative is an organic compound with a molecular formula of $C_{42}H_{26}O_{12}$ (containing thirty ring double bond equivalents) matching the molecular weight of 723 g/mol. It is highly soluble in organic solvents: acetone and chloroform.

p0140 Diospyrone (**4**) is a yellow amorphous powder; UVλ_{max} (log ε) 213 (2.32), 283 (2.45), 341 (2.53), 390 (2.59), 411 (2.61) nm. IR ν_{max} 2858–3401, 1555–1660; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm): 12.50 (1 H, *s*, HO-5); 7.45 (1 H, *s*, H-6); 2.34 (3 H, *s*, H-11); 7.30 (1 H, *dd*, *J* = 8.0, 1.0 Hz, H-6′); 7.76 (1 H, *t*, *J* = 8.0 Hz, H-7′); 7.66 (1 H, *dd*, *J* = 8.0, 1.0 Hz, H-8′); 1.85 (3 H, *s*, H-11′); 11.95 (1 H, *s*, HO-5′); 7.16 (1 H, *d*, *J* = 8.0 Hz, H-6″); 7.05 (1 H, *d*, *J* = 8.0 Hz, H-6‴); 7.48 (1 H, *t*, *J* = 8.0 Hz, H-7″); 7.39 (1 H, *t*, *J* = 8.0 Hz, H-7‴); 7.10 (1 H, *d*, *J* = 8.0 Hz, H-8″); 7.01 (1 H, *d*, *J* = 8.0 Hz, H-8‴); 2.78 (3 H, *s*, H-11″); 2.64 (3 H, *s*,

H-11′′′). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ (ppm) 183.9 (C, C-1); 184.5 (C, C-1′); 146.5 (C, C-2); 147.7 (C, C-2′); 144.3 (C, C-3); 143.9 (C, C-3′); 189.3 (C, C-4); 190.6 (C, C-4′); 162.8 (C, C-5); 162.2 (C, C-5′); 125.3 (CH, C-6); 124.4 (CH, C-6′); 147.9 (C, C-7′); 137.4 (CH, C-7′); 128.2 (C, C-8); 119.6 (CH, C-8′); 131.8 (C, C-9); 132.9 (C, C-9′); 115.4 (C, C-10); 115.3 (C, C-10′); 20.6 (CH_3, C-11); 13.8 (CH_3, C-11′); 166.4 (C, C-2′′); 165.8 (C, C-2′′′); 100.5 (C, C-3′′); 99.5 (C, C-3′′′); 161.0 (C, C-4′′); 160.6 (C, C-4′′′); 139.2 (C, C-5′′); 138.9 (C, C-5′′′); 128.6 (CH, C-6′′); 128.5 (CH, C-6′′′); 133.5 (CH, C-7′′); 133.0 (CH, C-7′′′); 116.2 (CH, C-8′′); 115.6 (CH, C-8′′′); 155.5 (C, C-9′′); 155.4 (C, C-9′′′); 115.8 (C, C-10′′); 115.5 (C, C-10′′′); 23.5 (CH_3, C-11′′); 23.6 (CH_3, C-11′′′). HR-FABMS *m/z* 723 $[M+H]^+$ (calcd for $[M+H]^+$ $C_{42}H_{26}O_{12}$: 723) (Tangmouo et al., 2005).

5.2 Biosynthesis, natural sources of diospyrone

p0145 A clear look at the molecular structure of diospyrone indicates that it is biosynthetically derived from the convergence of two isomers, plumbagin and 7-methyljuglone to form habibone which can be considered as intermediate in the biosynthesis of diospyrone. The biosynthetic mechanism of plumbagin and 7-methyljuglone like many other naphthoquinones has been elucidated to follow a polyketide pathway (Hou et al., 2018; Hussain, Al-Harrasi, Green, Abbas, & Ahmed, 2015). Like fatty acid biosynthesis, their occurrence arises from the condensation of one molecule of acetyl CoA with five molecules of malonyl CoA in presence of polyketide synthase (PKS) to yield the polyketo thioester. Finally, diospyrone (Fig. 1) may subsequently be formed by chemoselective oxidation coupling between one ring of habibone and two molecules of coumarinyl derivative (Scheme 3).



Scheme 3 Hypothetical biogenetic pathway of diospyrone.

5.3 Antibacterial activity of diospyrone against sensitive and multidrug-resistant phenotypes

p0150 Antibacterial investigation of diospyrone isolated from the stem bark of *D. canaliculata* showed a wide spectrum of activities against six aerobic Gram-positive and Gram-negative bacterial species. Its activity was mainly reported against *Staphylococcus aureus* (MIC value of 9.8 μg/mL), *Streptococcus faecalis* (MIC value of 19.5 μg/mL) (Gram-positive bacteria); and *Escherichia coli* (MIC value of 19.5 μg/mL), *Proteus vulgaris* (MIC value of 312.5 μg/mL), *Klebsiella pneumoniae* (MIC value of 78.1 μg/mL) and *Salmonella typhi* (MIC value of 4.9 μg/mL) (Tangmouo et al., 2005). The MIC values of diospyrone against *S. aureus* and *S. typhi* were comparable with that of gentamycin (positive control) with MICs values of 10 and 5 μg/mL, respectively against the tested bacteria (Tangmouo et al., 2005). On the other hand, diospyrone was also found to display tuberculocidal potency against several strains of *Mycobacterium tuberculosis* including both clinical sensitive and resistant phenotypes. The antimycobacterial effect was recorded against *M. tuberculosis* H37Rv (ATCC 27294) [MIC and MBC value of 2.4 μg/mL], *M. tuberculosis* clinical strains **(**MTCS1) [MIC and MBC values of 2.4 and 4.9 μg/mL, respectively] and *M. tuberculosis* clinical strains (MTCS2) [MIC MBC values of 1.2 and 2.4 μg/mL, respectively] as well as *M. smegmatis* ATCC 700084 [MIC and MBC values of 1.2 and 2.4 μg/mL] (Kuete, Tangmouo, Marion Meyer, & Lall, 2009). In the same line, Kuete et al., also reported the antibacterial activity of this natural binaphthoquinone derivative against several strains of Gram-negative diplococci bacteria, *Neisseria gonorrhoeae* including both clinical sensitive and resistant phenotypes. The MICs values ranged from 1.2 μg/mL (against *N. gonorrhoeae* ATCC 49226) to 19.5 μg/mL [towards *N. gonorrhoeae* clinical strains (NGCS6 (BL+) and NGCS7 (BL+))] (Kuete, Tangmouo, et al., 2009). Interestingly, the MICs values of diospyrone on the hospital strains of *N. gonorrhoeae* (NGCS2 (BL–), NGCS4 (BL–), NGCS5 (BL+), NGCS6 (BL+) and NGCS7 (BL+)) were 2–8–fold greater than that of ciprofloxacin (reference antibiotic), illustrating the interesting antimycobacterial effect of this isolate (Kuete, Tangmouo, et al., 2009). In another study conducted by Kuete and co-workers, this compound was also found to be active on a panel of Gram-negative multidrug resistant (MDR) microorganisms such as *E. coli*, *E. aerogenes*, *E. cloacae*, *K. pneumoniae,* and *P. aeruginosa* with MIC values between 4 and 128 μg/mL against 6/6 (100%) bacteria tested (Kuete, Ngameni, Tangmouo, et al., 2010). When associated with an efflux pump inhibitor phenylalanine

arginine β-naphthylamide (PAβN), the antibacterial activity of diospyrone was substantially enhanced displaying varying MIC values from 0.1 to 64 μg/mL. The potent antibacterial effect of this compound with respect to the MDR phenotypes tested in presence of PAβN would reflect the fact that this compound would have been expelled by the AcrAB-TolC type efflux pumps of the Enterobacteriaceae or MexAB-OprM type of *P. aeruginosa* (Kuete, Ngameni, Tangmouo, et al., 2010).

5.4 Bacterial resistance towards diospyrone

p0155 Efflux pumps, especially ACRAB-TolC in Enterobacteriaceae and MexAB-OprM in *Pseudomonas aeruginosa* have been involved in the resistance of many bacteria to diospyrone (Kuete, Ngameni, Tangmouo, et al., 2010). In effect, when diospyrone was tested in the presence of the efflux pump inhibitor, phenylalanine arginine *β*-naphthylamide (PAβN), the antibacterial activity increased from 2-fold towards *Enterobacter aerogenes* EA298, EA298, EA3, and EA5 to 64-fold against *Escherichia coli* AG100 and *Pseudomonas aeruginosa* PA124. This clearly indicated that efflux pumps were involved in the resistance of bacteria to diopyrone.

6. Ferruginin A: a prenylated anthranol

p0160 Ferruginin A (**5**) belongs to the class of anthranols, also known as anthrols which are the hydroxylated derivatives of anthracene. Their mono-hydroxo derivatives include three isomers namely 1-anthrol, 2-anthrol, and 9-anthrol. The latter exists as a minor tautomer of 9-anthrone. The naturally occurring anthranoids have hundreds of structurally related structures, found in Liliaceae (Aloe, Hawertia, Eremus), Hypericaceae (Hypericum), Polygonaceae (Rheum, Rumex, Polygonum, Fagopyrum, Oxygonum), Rhamnaceae (Rhamnus), Rubiaceae (Galium, Rubia, Morinda), Caesalpiniaceae (Cassia, Gleditschia), Fabaceae (Andira), Verbenaceae (Tectona), and Scrophulariaceae (Digitalis), as well as in Ascomycetes, such as Penicillium and Aspergillus species (Westendorf, 1993). Naturally occurring anthranoids are oxo-, hydroxy-, and hydroxy-oxoderivatives of anthracene (Westendorf, 1993). They are derivatives of 9,10-anthraquinone. Reduction of the anthraquinones leads to anthrones and their tautomeric anthranols, which are also present as dimers (Westendorf, 1993). Anthronoids are generally known for the laxative effect (Westendorf, 1993). However, the α-glucosidase inhibitory activities of anthrols such as harunganols C-F, kenganthranol A, harunganin, as well as

ferruginin A was reported (Johnson et al., 2016). The present chapter will be focused on the antibacterial potential of the prenylated 9-anthanol, ferruginin A. This compound has been shown to possess a panel of biological activities. Ferruginin A was also reported as an anticancer agent and as the Mitogen-Activated Protein Kinase (MAPK) Pathway inhibitor in MCF-7 cells (Sivas, Karaosmanoglu, & Kuete, 2019). It also displayed antifeedant activity against *Spodoptera littoralis, Spodoptera exempta, Heliothis virescens, Heliothis armigera, and Locusta migratoria* (Simmonds, Blaney, Monache, Mac-Quhae, & Marini Bettolo, 1985). Ferruginin A also displayed anti-plasmodial activity against the W2 strain of *Plasmodium falciparum* (Ndjakou Lenta et al., 2007).

6.1 Chemistry of and natural source of Ferruginin A

p0165 Ferruginin A (**5**), $C_{30}H_{36}O4$; orange oil; ^{13}C NMR (400 MHz, DMSO-d_6) δ 192.8 (C-1), 105.9 (C-2), 180.7 (C-3), 51.3 (C-4), 142.6 (C-5), 116.2 (C-6), 137.9 (C-7), 124.5 (C-8), 140.8 (C-9), 123.5(C-10), 155.8 (C-11), 109.7 (C-12), 165.2 (C-13), 112.7 (C-14), 42.3 (C-15, C-15′), 120.2 (C-16, C-16′), 135.2 (C-17, C-17′), 26.6 (C-18, C-18′), 11.6 (C-19 and C-19′), 26.3 (C-20), 119.9 (C-21), 132.0 (C-22), 26.6 (C-23), 11.6 (C-24), 19.8 (C-25) (Nicoletti, Marini-Bettolo, Delle Monache, & Delle Monache, 1982).

p0170 Ferruginin A has been isolated from the berries of *Vismia baccifera* var. *ferruginea* (Kunth) Ewan (Hypericaceae) (Monache, Mc Quhae, Ferrari, & Marini-Bettolo, 1979), from the bark of *Harungana madagascariensis* Lam. ex Poir. (Hypericaceae) (Ndjakou Lenta et al., 2007; Tankeo et al., 2016), from the fruits of *Vismia decipiens* Cham. & Schltdl. (Guttiferae) (Delle Monache, Gonzalez, Delle Monache, & Bettolo, 1980), and from the leaves of *Vismia mexicana* Schltdl. (Guttiferae) (Reyes-Chilpa et al., 2014).

6.2 Antibacterial activity of ferruginin A against sensitive and multidrug-resistant phenotypes

p0175 In a recent study performed by Tankeo and collaborator in 2016, the antibacterial activity of ferruginin A, isolated from the bark of *Harungana madagascariensis* was evaluated on a panel of microorganisms including sensitive and resistant strains of *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli,* and *Providencia stuartii* obtained from the American Type Culture Collection (Tankeo et al., 2016). The resistant strains studied were *Escherichia coli* AG102 and AG100 A_{tet}, *Enterobacter aerogenes* EA294, *Klebsiella pneumoniae* KP2 and KP55, *Providencia stuartii* PS2636 and NAE16, *Enterobacter cloacae* BM67 and

Pseudomonas aeruginosa strain, PA124 (Davin-Regli et al., 2008; Nikaido, 2009). Authors have applied the microbroth dilution method to determine the MIC of ferruginin A on these bacteria strains (Mbaveng et al., 2015). They found that excellent antibacterial activity against Enterobacteria ($2 < \text{MIC} \leq 4\,\mu g/mL$) was obtained against *Escherichia coli* ATCC10536, *Klebsiella pneumoniae* K2, and *Enterobacter cloacae* BM67 strains (Tankeo et al., 2016). They also reported the very good activity of the compound ($4 < \text{MIC} \leq 8\,\mu g/mL$) against *Enterobacter aerogenes* ATCC13048, and EA294, *Klebsiella pneumoniae* KP55. However, these authors also documented the average activity ($32 < \text{MIC} \leq 64\,\mu g/mL$) of this compound against *Escherichia coli* AG102, and *Klebsiella pneumoniae* ATCC11296 strains (Tankeo et al., 2016). Towards the *Pseudomonas aeruginosa* strains, excellent activity ($4 < \text{MIC} \leq 32\,\mu g/mL$) was obtained on the reference PA01 strain whilst good activity ($128 < \text{MIC} \leq 256\,\mu g/mL$) was reported against the resistant PA124 strain (Tankeo et al., 2016). Tankeo et al. also demonstrated that ferruginin A generally displayed bacteriostatic activity against the investigated bacteria (Tankeo et al., 2016). Tankeo et al. also compared the activity of ferruginin A with that of the reference drug, ciprofloxacin; they found that ferruginin A had better activity than ciprofloxacin against *Escherichia coli* AG102, *Enterobacter aerogenes* ATCC13048, and EA94, *Klebsiella pneumoniae* KP2 and KP55, *Enterobacter cloacae* BM67, and *Pseudomonas aeruginosa* PA01 strains (Tankeo et al., 2016). In contrast ciprofloaxin had better activity than ferruginin A in a single case of *Escherichia coli* AG100tet (Tankeo et al., 2016). These are indications that ferruginin A is a potential antibacterial against that deserves further investigation to produce a pharmaceutical against bacterial infections including multidrug-resistant phenotypes.

7. Isobavachalcone

p0180 Chalcones are a class of phenolic compounds characterized by an α,β-unsaturated ketone which is abundant in edible plants and are considered to be the precursors of flavonoids and isoflavonoids (Kuete & Sandjo, 2012). They are endowed with a wide range of pharmacological potencies including antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, cytotoxic, and anti-cancer activities (Efferth, Saeed, et al., 2020; Kuete & Efferth, 2010; Nowakowska, 2007). In effect, Ngameni and collaborators have reported the impressive cytotoxicity of the series of *O*-substituted

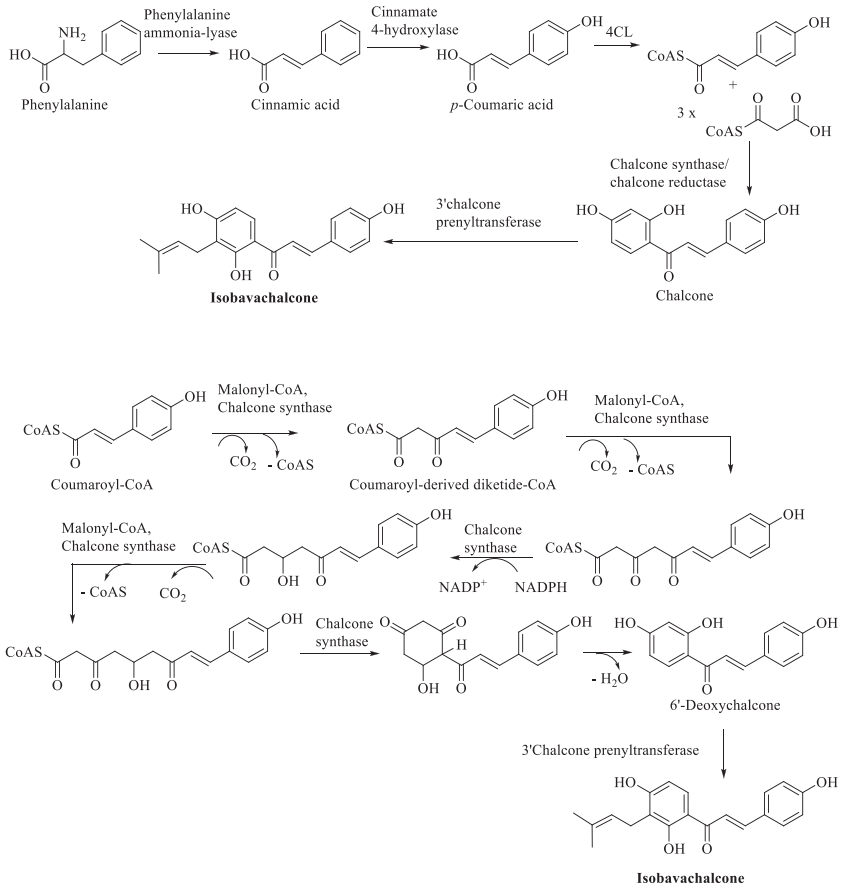
chalcone derivatives bearing an/a allyl-, prenyl- or propargyl-substituent on a panel of drug-sensitive and drug-resistant cancer cell lines such as CCRF-CEM and CEM/ADR5000 leukemia cells, MDA-MB- 231-*BCRP* and MDA-MB-231-*pcDNA* adenocarcinoma, HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$ colon adenocarcinoma, U87. MG and U87. MGΔ*EGFR* gliobastoma cells (Ngameni et al., 2021). Licoagrochalcone A, a chalcone isolated from the twigs of *Dorstenia kameruniana* Engl. (Moraceae) also had a very interesting cytotoxic activity against a wide panel of human cancer cell lines with the IC_{50} values range of 5.16 μM against CCRF-CEM cells to 49.57 μM against MDA-MB- 231-*BCRP* cells (Adem et al., 2018). Several chalcones with very interesting antiproliferative activity on human cancer cell lines were also isolated from African medicinal plants (Efferth, Saeed, et al., 2020; Kuete & Efferth, 2011, 2015; Mbaveng, Kuete, & Efferth, 2017; Nkuété et al., 2015). They include 2′,4′-dihydroxy-6′-methoxychalcone, 4′,6′-dihydroxy-2′,5′-dimethoxychalcone, and 2′,4′,6′-trihydroxy-5′-methoxychalcone identified in several Kenyan medicinal plants (Kuete, Omosa, Midiwo, Karaosmanoğlu, & Sivas, 2019), 4-hydroxylonchocarpin isolated from the leave of *Lonchocarpus bussei* Harms (Fabaceae) and several plants of the genus *Dorstenia* (Adem, Kuete, et al., 2019; Kuete, Ngameni, et al., 2011), cardamomin isolated from *Polygonum limbatum* Meisn. (Polygonaceae) and *Piper capense* L.f. (Piperaceae) (Dzoyem et al., 2012; Kuete, Nkuete, et al., 2014; Mbaveng et al., 2021). Chalcones with antibacterial activity identified in African medicinal plants include isoliquiritigenin isolated from the stem bark of *Trilepisium madagascariense* DC. (Moraceae) (Teke et al., 2011), angusticornin B and bartericin A isolated from the twigs of *Dorstenia angusticornis* Engl. (Moraceae) (Kuete, Simo, et al., 2007), isobavachalcone (**6**), stipulin, 4-hydroxylonchocarpin, and kanzonol C isolated from twigs of *Dorstenia barteri* Bureau (Moraceae) (Kuete et al., 2013; Kuete, Ngameni, Mbaveng, et al., 2010; Mbaveng, Ngameni, et al., 2008), 3′,5′-dihydroxy-1′-methoxychalcone, 1′,5′-dihydroxy-3′-methoxychalcone, 1′,3′-dihydroxy-2′,5′-dimethoxychalcone, 5′-hydroxy-1′,3′-dimethoxychalcone, 1′,3′,5′-trihydroxy-2′-methoxychalcone, and 1,5-diacetate-3′-methoxychalcone identified from various Kenyan plants (Omosa et al., 2016). In an excellent review of the anti-infective and anti-inflammatory activity of chalcones, Nowakowska in 2007 has documented 2,4,6-Trimethoxy-2′-trifluoromethylchalcone, calledmallotophilippens C, D and E, xanthohumol, xanthohumols B and D, dihydroxanthohumol, and 2′-hydroxychalcone as good anti-inflammatory chalcones, as well as 2′,4′-dihydroxychalcone as an interesting antiviral chalcone (Nowakowska, 2007). This compound also

inhibited the Human Immuno-deficiency Virus (HIV) *in vitro via* the inhibition of the HIV reverse transcriptase enzyme clearly indicating that it might be helpful in the treatment of acquired immunodeficiency syndrome (AIDS) (Kuete, Ngameni, Mbaveng, et al., 2010). The antifungal activity of isobavachalcone was also reported on *Cryptococcus neoformans* (ElSohly, Joshi, Nimrod, Walker, & Clark, 2001), *Candida albicans*, *Candida glabrata, Trichophyton rubrum,* and *Microsporum audouinii* (Mbaveng, Ngameni, et al., 2008). In this section, we will emphasize on the antibacterial potential of isobavachalcone against drug-sensitive and drug-resistant bacteria. The natural source, as well as the potential biosynthetic pathway of this compound, will also be discussed. This compound displayed a wide array of biological activities including antibacterial, antifungal, anticancer, anti-reverse transcriptase, antitubercular, and antioxidant (Kuete & Sandjo, 2012).

7.1 Chemistry, biosynthesis and botanical source of isobavachalcone

p0185 Isobavachalcone (**6**): Yellow solid, m.p. 153–154 °C, ^{13}C NMR data ($CDCl_3$): δ 195.7 (CO), 118.5 (C-α), 144.9 (C-β), 127.6 (C-1), 131.7 (C-2, C-6), 116.8 (C-3, C-5), 160.9 (C-4), 116.4 (C-1′), 165.3 (C-2′), 115.1 (C-3′), 162.8 (C-4′), 108.0 (C-5′), 130.3 (C-6′), 3-methylbut-2-enyl: 25.9 (CH_2), 123.3 (CH), 130.7 (C), 17.9 (CH_3), 25.3 (CH_3) (Abegaz, Ngadjui, Dongo, & Tamboue, 1998). Like other chalcones, isobavachacone is a naturally occurring biphenylpropanoid that is a biosynthetic descent of phenylalanine. This amino acid apparently comes from the effect of many enzymes on shikimic acid. The biosynthetic pathway of isobavachalcone proposed by Sugamoto in 2011 is summarized in Scheme 4 (Kuete & Sandjo, 2012; Sugamoto, Matsusita, Matsui, Kurogi, & Matsui, 2011).

p0190 Isobavachlcone is one of the most resourceful active chalcones that has been predominantly isolated from plants of the families Fabaceae and Moraceae. However, its presence in other families has been reported. From the Fabaceae family, isobavachalcone has been isolated from the seeds of *Psoralea corylifolia* L. (Bhalla, Nayak, & Dev, 1968; Tsai, Hsin, & Chen, 1996), from the aerial part of *Anthyllis hermanniae* L. (Pistelli, Spera, Flamini, Mele, & Morelli, 1996), from the roots of *Erythrina burttii* Ball. f. (Yenesew, Midiwo, Guchu, Heydenreich, & Peter, 2002), *Glycyrrhiza glabra* L. (Kobayashi, Noguchi, & Sankawa, 1985), and *Sophora prostrata* Buchanan (Iinuma, Ohyama, & Tanaka, 1995), from the bark of *Erythrina fusca* Lour (Innok, Rukachaisirikul, & Suksamrarn, 2009), the fruits of *Fructus Psoraleae* L. (Qiao et al., 2007), from the tissue culture of *Glycyrrhiza*



Scheme 4 Biosynthetic pathway of isobavachalcone.

uralensis Fisch (Kobayashi et al., 1985); in Moraceae, this chalcone has been isolated from the leaves of *Maclura tinctoria* (L.) D. Don ex Steud. (ElSohly et al., 2001), and *Dorstenia kameruniana* Engler (Abegaz et al., 1998), the twigs of *Dorstenia barteri* Bureau (Mbaveng, Ngameni, et al., 2008), *Dorstenia turbinata* Engl. (Ngameni et al., 2009), *Treculia acuminata* Baill. (Metuno et al., 2008), from the whole plant of *Dorstenia poinsettifolia* var. *angusta* Engl. (Tsopmo et al., 1998), and *Broussonetia papyrifera* L′Hér. ex Vent. (Lee et al., 2001); the compound has also been isolated from the roots of *Hypericum geminiflorum* Hemsl. (Guttiferae) (Chung, Lai, Yen, Wu, & Lin, 1997), the stem bark of *Kadsura ananosma* Kerr (Schisandraceae) (Chen et al., 2006), and from the stem of *Angelica keiskei* koidzumi (Umbelliferae) (Nishimura et al., 2007).

7.2 Antibacterial activity of isobavachalcone against sensitive and multi-drug resistant phenotypes

p0195 The antibacterial effects of isobavachalcone were reported on a wide range of bacteria including Gram-positive and Gram-negative bacteria, as well as mycobacteria. In the work of Kuete and collaborators, this compound inhibited the growth of the drug-sensitive Gram-positive bacteria: *Bacillus cereus, Bacillus megaterium, Bacillus stearothermophilus, Bacillus subtilis, Staphylococcus aureus,* and *Streptococcus faecalis*, the drug-sensitive Gram-negative bacteria: *Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhi, Shigella dysenteriae*, and *Shigella flexneri* with the MIC values varying generally between 4.9 and 39.1 9.8 μg/mL (Mbaveng, Ngameni, et al., 2008). This chalcone also inhibited the growth of *Staphylococcus aureus, Staphylococcus epidermitidis* with the MIC values of 18 μM and 9 μM respectively (Yin, Fan, Wang, Dong, & Yue, 2004). Isobavachalcoe also had bactericidal effects against *Bacillus cereus* and *Staphylococcus aureus* (MIC and MBC of 31.2 μg/mL) (Avila, Smânia Ede, Monache, & Smânia, 2008). Isobavachalcone inhibited the growth of several drug-sensitive and drug-resistant strains of *Neisseria gonorrhoeae*, with MIC values of 0.61–9.76 μg/mL (Kuete, Ngameni, Mbaveng, et al., 2010). The antimycobacterial activity of isobavachalcone was also reported against *Mycobacterium smegmatis* (MIC and MBC of 2.44 μg/mL), against the drug-sensitive *Mycobacterium tuberculosis* H37Rv (MIC of 39.06 μg/mL), and against the clinical strains of *M. tuberculosis* (MIC: 19.53–39.06 μg/mL) (Kuete, Ngameni, Mbaveng, et al., 2010). In a study performed by Kuete and collaborator in 2010, the antibacterial activity of isobavachalcone, was evaluated on a panel of microorganisms including sensitive and resistant strains of *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, and Escherichia coli* obtained from the American Type Culture Collection. The resistant strains investigated were *Escherichia coli* AG100, AG102, AG100A, and AG100 A_{tet}, *Enterobacter aerogenes* CM64, EA3, EA5, EA27, EA289, EA294, and EA298, *Klebsiella pneumoniae* KP55 and KP63, *Enterobacter cloacae* Ec07769 and Ec1194, and *Pseudomonas aeruginosa* PA124. Authors have applied the microbroth dilution method to determine the MIC of candidone on these bacteria strains (Mbaveng et al., 2015). They found that isobavachalcone had very good antibacterial activity against Enterobacteria, compound ($4 < \text{MIC} \leq 8$ μg/mL) against *Enterobacter aerogenes* EA298 strain (Kuete, Ngameni, Tangmouo, et al., 2010). They also reported the good activity ($8 < \text{MIC} \leq 32$ μg/mL) of isobavachalcone against

Escherichia coli, AG100A, *Enterobacter aerogenes* EA294, *Klebsiella pneumoniae* ATCC11296, KP55 and KP63 meanwhile average activity (32 < MIC ≤ 64 μg/mL) of was reported on *Escherichia coli* AG100, *Enterobacter aerogenes* EA5 and *Enterobacter cloacae* Ec1194 strains (Kuete, Ngameni, Tangmouo, et al., 2010). Towards the *Pseudomonas aeruginosa* strains, very good activity (32 < MIC ≤ 128 μg/mL) was obtained on the reference PA01 and PA124 strains (Kuete, Ngameni, Tangmouo, et al., 2010). Kuete et al. also compared the activity of isobavachalcone with that of two reference drugs, chloramphenicol, and norfloxacin; they found that isobavachalcone had better activity than chloramphenicol against *Enterobacter aerogenes* EA289, EA294, EA298, EA27, EA3, and EA5, *Klebsiella pneumoniae* KP55, and Enterobacter *cloacae* Ec07769 strains; they also noted that this compound was more active than norflaxacin against *Enterobacter aerogenes* EA294 and *Enterobacter cloacae* Ec07769 strains (Kuete, Ngameni, Tangmouo, et al., 2010). This was an indication that isobavachalcone is a potential antibacterial compound that deserves further investigation to produce a pharmaceutical against bacterial infections including multidrug-resistant phenotypes.

7.3 Resistance of bacteria to isobavachalcone

p0200 Kuete et al. in 2010 have evaluated the role of bacterial efflux pumps, mainly the AcrAB-TolC pumps of the Enterobacteria and MexAB-OprM of *Pseudomonas aeruginosa* on the resistance to isobavachalcone. Authors have tested the compound alone and in combination with the well-known efflux pump inhibitor (EPI), phenylalanine arginine β-naphthylamide (PAβN) (Kuete, Ngameni, Tangmouo, et al., 2010). They found that in the presence of PAβN, the activity of this compound significantly increased in all tested bacteria. They deduced that active efflux was the main mode of resistance of Gram-negative bacteria to isobavachalcone and that this chalcone is a powerful antibacterial agent if it is combined with an EPI. In effect, when this chalcone was combined with PAβN outstanding activity (MIC ≤ 2 μg/mL) was obtained against *Escherichia coli* ATCC10536, AG100, and AG100A, *Enterobacter aerogenes* EA294 and EA298, *Klebsiella pneumoniae* KP63, *Enterobacter cloacae* Ec1194 strains as well as against the resistant *Pseudomonas aeruginosa* PA124 strain (MIC ≤ 4 μg/mL), whilst excellent activity was recorded against *Klebsiella pneumoniae* ATCC 11296 and KP55, and *Pseudomonas aeruginosa* PA01 (4 < MIC ≤ 32 μg/mL) (Kuete, Ngameni, Tangmouo, et al., 2010).

8. Neobavaisoflavone

p0205 Isoflavonoids are a class of flavonoids sometimes referred to as phytoestrogens including isoflavones, isoflavanones, isoflavans, pterocarpans, rotenoids (Bruneton, 1999). They are derived from the flavonoid biosynthesis pathway *via* liquiritigenin or naringenin (Dhaubhadel, McGarvey, Williams, & Gijzen, 2003). Isoflavonoids such as genistein, daidzein, dihydrodaidzein, *O*-desmethylangolensin, and equol can be quantified in various body fluids (Lampe, 2003). They have a variety of pharmacological activities, with some of them being identified as toxins, including biliatresone which may cause biliary atresia in infants (Lorent et al., 2015). Several biologically active isoflavonoids have been isolated in the tree last in the African medicinal plants (Efferth, Kadioglu, et al., 2021; Kuete & Efferth, 2015; Mbaveng et al., 2017). Their cytotoxic and antibacterial activities were largely documented. Isoflavonoids with prominent antiproliferative activities isolated in the African medicinal plants include seputhecarpan A, seputheisoflavone, seputhecarpan B, seputhecarpan and seputhecarpan D isolated from *Ptycholobium contortum* (N.E.Br.) Brummitt (Fabaceae) (Kuete et al., 2018; Mbaveng et al., 2018; Ngnintedo et al., 2016), neobavaisoflavone, sigmoidin H, isoneorautenol isolated from *Erythrina excelsa* Bak. and *Erythrina senegalensis* DC. (Fabaceae) (Kuete, Sandjo, Kwamou, et al., 2014), sigmoidin I, sophorapterocarpan A, bidwillon A and 6α-hydroxyphaseollidin isolated from *Erythrina sigmoidea* Hua (Fabaceae) (Kuete, Sandjo, Djeussi, et al., 2014), alpinumisoflavone, laburnetin isolated from *Ficus chlamydocarpa* Mildbr. & Burret (Moraceae) (Kuete, Mbaveng, et al., 2016; Kuete, Ngameni, et al., 2008), osajin, 5,7-dihydroxy-4'-methoxy-6,8-diprenylisoflavone isolated from *Ormocarpum kirkii* S. Moore (Fabaceae) (Adem, Mbaveng, et al., 2019). Many antibacterial isoflavonoids were also reported in the African plants. They include 2-hydroxyisoprunetin, 6,7-(2-isopropenyl furo)-5,2,4-trihydroxyisoflavone, cajanin isolated from *Ficus ovata* Vahl (Moraceae) (Kuete, Nana, et al., 2009), alpinumisoflavone, genistein, laburnetin isolated from *F. chlamydocarpa* (Kuete, Ngameni, et al., 2008), neobavaisoflavone and daidzein isolated respectively from *E. Senegalensis* and *Milicia excelsa* (Welw.) CC Berg (Moraceae) (Mbaveng et al., 2015), atalantoflavone, bidwillon A, neocyclomorusin, 6α-hydroxyphaseollidin, neobavaisoflavone (Djeussi et al., 2015), calycosin, biochanin A and prunetin isolated from *Pycnanthus angolensis* (Welw.) Warb. (Myristicaceae) (Kuete, Nono, et al., 2011; Nono et al., 2010). In this section, we will focus on the antibacterial potential of the prenylated isoflavone, neobavaisoflavone (**7**).

8.1 Chemistry and botanical source of neobavaisoflavone

p0210 Neobavaisoflavone (**7**) (Fig. 1). Colorless solid, mp 193.1–194.3 °C, LR-EI-MS m/z: 322.1 [$C_{20}H_{18}O_4$], Degree of purity 98%, ^{1}H NMR (C_5D_5N, 400 MHz): 11.7 (s, OH) 8.49 (d, J = 8.7 Hz, H-5), 8.21 (s, H-2), 7.79 (d, J = 2.2 Hz, H-2′), 7.69 (dd, J = 2.2, 8.2 Hz, H-6′), 7.27 (d, J = 8.2 Hz, H-5′), 7.24 (dd, J = 2.2, 8.7 Hz, H-6), 7.15 (d, J = 2.2 Hz, H-8), 5.72 (m, H-2″), 3.76 (d, J = 7.3 Hz, H-1″), 1.77 (s, H-4″), 1.70 (s, H-5′′) ^{13}C NMR (C_5D_5N, 100 MHz): 176.3 (C-4), 164.5 (C-7), 159.0 (C-8a), 157.1 (C-4′), 152.9 (C-2), 132.4 (C-3′′), 131.6 (C-2′), 129.3 (C-3′), 128.9 (C-6′), 128.7 (C-5), 125.8 (C-3), 124.2 (C-1′), 124.3 (C-2′′), 118.4 (C-4a), 116.3 (C-6), 115.9 (C-5′), 103.5 (C-8), 29.9 (C-1′′), 26.3(C-4′′), 18.3 (C-5′′) (Nkengfack et al., 1994).

p0215 Neobavaisoflavone has been isolated from a few medicinal plants. In effect, the compound was isolated from the seeds of *Psoralea corylifolia* L. (Fabaceae) (Bajwa, Pyare, & Seshadri, 1972), and from the bark and roots of *Erythrina sigmoidea* Hua (Fabaceae) (Djeussi et al., 2015; Nkengfack et al., 1994).

8.2 Antibacterial activity of neobavaisoflavone against sensitive and multidrug-resistant phenotypes

p0220 The antibacterial activity of neobavaisoflavone was first reported against *Staphylococcus aureus* by Nkengfack and co-workers (Nkengfack et al., 1994). Using the agar-streak dilution method, they determined the MIC value of 2.5 μg/mL against *S. aureus*. In an interesting work performed by Djeussi and collaborator in 2015, the antibacterial activity of neobavaisoflavone, isolated from the bark of *Erythrina sigmoidea* was evaluated on a panel of micro-organisms including sensitive and resistant strains of *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Providencia stuartii,* obtained from the American Type Culture (Djeussi et al., 2015). The resistant strains tested included *Escherichia coli* AG100A$_{tet}$ and AG102, *Enterobacter aerogenes* EA289, *Klebsiella pneumoniae* KP55, *Providencia stuartii* NAE16, *Enterobacter cloacae* ECCI69 and *Pseudomonas aeruginosa* PA124 (Davin-Regli et al., 2008; Nikaido, 2009). Authors have applied the microbroth dilution method to determine the MIC of neobavaisoflavone on these bacteria strains (Mbaveng et al., 2015). They found that the very good antibacterial activities against Enterobacteria ($4 < \text{MIC} \leq 8$ μg/mL) were recorded towards *Escherichia coli* ATCC8739, *Enterobacter cloacae* ECCI69, *Klebsiella pneumoniae* KP55 and *Providencia stuartii* NAE16, strainswhilst average activity ($32 < \text{MIC} \leq 64$ μg/mL) was obtained on *Escherichia coli*

AG100Atet (Djeussi et al., 2015). Nontheless, they also noted that this compound was not active (MIC > 512 μg/mL) against *Escherichia coli* AG102, *Enterobacter aerogenes* ATCC13048 and EA289, *Klebsiella pneumoniae* ATCC11296, *Providencia stuartii* ATCC29916, clearly highlighting its selectivity (Djeussi et al., 2015). Towards the *Pseudomonas aeruginosa* strains, excellent activity (4 < MIC ≤ 32 μg/mL) was obtained on the reference PA01 strain whilst good activity (128 < MIC ≤ 256 μg/mL) was reported against the resistant PA124 strain (Djeussi et al., 2015). Djeussi et al. also demonstrated that neobavaisoflavone generally displayed bacteriostatic activity against the investigated bacteria (Djeussi et al., 2015). Djeussi et al. also compared the activity of neobavaisoflavone with that of the reference drug, chloramphenicol; they found that neobavaisoflavone had better activity than chloramphenicol against *Enterobacter cloacae* ECCI69, *Klebsiella pneumoniae* KP55, and *Pseudomonas aeruginosa* PA01 strains (Djeussi et al., 2015). A similar study was performed by Mbaveng et al. (2015) on the same bacterial species as that previously reported above by Djeussi et al. They also applied similar experimental protocols to evaluate the antibacterial activity of neobavaisoflavone against *Escherichia coli* ATCC 8739, AG102 and AG100Atet, *Enterobacter aerogenes* ATCC13048, CM64 and EA27, *Klebsiella pneumoniae* ATCC11296 and KP55, *Providencia stuartii* ATCC29916 and PS299645, *Enterobacter cloacae* BM47 and BM67, and *Pseudomonas aeruginosa* PA01 and PA124 strains (Mbaveng et al., 2015). They recorded the excellent activity (2 < MIC ≤ 4 μg/mL) against *Providencia stuartii* ATCC29916 (MIC of 4 μg/mL *vs* MIC > 512 μg/mL obtained by Djeussi et al.), *Enterobacter cloacae* BM47 strains whilst very good antibacterial activity was obtained in *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC11296 and KP55, *Providencia stuartii* PS299645 strains (Mbaveng et al., 2015). They also obtained good antibacterial activities (8 < MIC ≤ 32 μg/mL) against *Escherichia coli* AG102 and average to weak activities in some of the bacterial strains (Mbaveng et al., 2015). However, these authors found that the compound was active on all tested bacteria contrary to Djeussi et al. These are indications that neobavaisoflavone is a potential antibacterial against that deserve further investigation to produce a pharmaceutical against bacterial infections including multidrug-resistant phenotypes.

9. Neocyclomorusin: a flavone

p0225 Neocyclomorusin or 6,12-dihydroxy-9-(2-hydroxypropan-2-yl)-3,3-dimethyl-8,9-dihydrobenzo[2,3]oxepino[4,5-*b*]pyrano[2,3-*h*]

chromen-7(3 H)-one (**8**) is a naturally occurring flavone with impressive pharmacological potential (Kuete & Efferth, 2015; Mbaveng et al., 2017). This compound has shown antiproliferative activities towards CCRF-CEM and CEM/ADR5000 leukemia cell lines with the respective IC_{50} values of 59.02 μM and 69.98 μM, MDA-MB-231-*pcDNA* breast adenocarcinoma cells (IC_{50}: 78.51 μM), HCT116 ($p53^{+/+}$) colon adenocarcinoma cells (IC_{50}: 75.44 μM), U87MG.Δ*EGFR* glioblastoma cells (IC_{50}: 70.53 μM) (Kuete, Sandjo, Djeussi, et al., 2014). Neocyclomorusin had antibacterial activities on a panel of Gram-negative bacteria including multidrug-resistant phenotypes (Djeussi et al., 2015; Mbaveng et al., 2015). The inhibitory effect of this compound was reported on cholinesterase enzymes, acetylcholinesterase (AChE), and butyrylcholinesterase (BChE) (Kim et al., 2011). Neocyclomorusin had radical scavenging activity with the IC_{50} value of 0.73 mg/mL (Oke-Altuntas et al., 2016). This compound was shown to enhance neuronal cell viability from nitrosative stress-induced cell death within a non-toxic dose range of m 0.16–20 μg/mL (Lee et al., 2012). The inhibitory activity of neocyclomorusin was also reported on β-secretase, an enzyme strongly implicated in the onset of Alzheimer's disease, with the IC_{50} value of 146.1 μM (Cho et al., 2011). This flavone had antiplatelet aggregation effects with the inhibition percentages of adenosine diphosphate, arachidonic acid, and platelet-aggregating factor-induced platelet aggregation of 98.57%, 99.70%, and 99.63% respectively at 100 μM (Liao et al., 2017).

9.1 Chemistry and botanical source of neocyclomorusin

p0230 6,12-dihydroxy-9-(2-hydroxypropan-2-yl)-3,3-dimethyl-8,9-dihydrobenzo [2,3]oxepino[4,5-*b*]pyrano[2,3-*h*]chromen-7(3 H)-one or neocyclomorusin (**8**) (Fig. 1): Yellowish oil, LR-EI-MS *m/z*: 436.1 $[C_{25}H_{24}O_7]^{-+}$, ^{1}H NMR (C_5D_5N, 400 MHz): 13.8 (s, OH-5), 8.25 (d, J = 8.7 Hz, H-2′), 7.13 (dd, J = 2.5, 8.7 Hz, H-3′), 7.14 (d, J = 2.5 Hz, H-5′), 7.02 (d, J = 9.9 Hz, H-1′′), 6.56 (s, H-5), 5.72 (d, J = 9.9 Hz, H-2′′), 4.84 (dd, J = 1.8, 10.0 Hz, H-2′′′), 3.94 (dd, J = 1.8, 16.9 Hz, H-1′′′), 2.96 (dd, J = 10.0, 16.9 Hz, H-1′′′), 1.71 (s, H-5′′′) 1.50 (s, H-5′′, H-4′′), 1.49 (s, H-4′′) ^{13}C NMR (C_5D_5N, 100 MHz): 182.0 (C-4), 164.0 (C-4′), 162.7 (C-5), 162.0 (C-6′), 160.1 (C-7), 158.4 (C-2), 152.4 (C-8a), 131.2 (C-2′), 128.0 (C-2′′), 117.5 (C-3), 115.8 (C-1′′), 114.3 (C-1′), 112.8 (C-3′), 109.2 (C-5′), 104.8 (C-4a), 101.7 (C-8), 100.3 (C-6), 86.3 (C-2′′′), 83.3 (C-3′′′), 78.7 (C-3′′), 28.5 (C-4′′, C-5′′), 26.3 (C-1′′′), 23.1 (C-5′′′), 20.6 (C-4′′′) (Jeong et al., 2009).

p0235 Compound **8** has been isolated from several medicinal plants. It was isolated from the bark of *Erythrina sigmoidea* Hua (Fabaceae) (Kuete, Sandjo, Djeussi, et al., 2014), from the stem leaves of *Lagerstroemia indica* L. (Lythraceae) (Zhang, 2015), from the roots bark of *Milicia excelsa* Welw. C. C. Berg (Moraceae) (Oke-Altuntas et al., 2016), from Cortex Mori Radicis, the root epidermis of *Morus alba* L. (Moraceae) (Lee et al., 2012) and its root barks (Singab, El-Beshbishy, Yonekawa, Nomura, & Fukai, 2005), from the root bark of *Morus australis* Poir. (Moraceae) (Liao et al., 2017), from the root bark of *Morus lhou* L. (Moraceae) (Kim et al., 2011), and from the twigs of *Morus notabilis* C.K. Schneid (Moraceae) (Zhen et al., 2015).

9.2 Antibacterial activity of neocyclomorusin against drug sensitive and multidrug-resistant phenotypes

p0240 The antibacterial activity of neocyclomorusin has been performed through the determination of the inhibitory effects of the compound on test bacteria using the disc diffusion method (Oke-Altuntas et al., 2016). It was found that the compound had inhibitory effects against *Staphylococcus aureus* ATCC 29213 and ATCC25923 with the respective inhibition zone sizes of 7.6 mm and 9 mm(Oke-Altuntas et al., 2016). However, using the disc diffusion method Oke-Altuntas et al. (2016) have not detected the antibacterial activity of this compound on *Escherichia coli*. An in-depth evaluation of the antibacterial potential of neoclycomorusin was performed by Djeussi and collaborator, the antibacterial activity of neobavaisoflavone, isolated from the bark of *Erythrina sigmoidea* was evaluated on a panel of microorganisms including sensitive and resistant strains of *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Providencia stuartii,* obtained from the American Type Culture (Djeussi et al., 2015). The investigated resistant strains were *Escherichia coli* AG100A_{tet} and AG102, *Enterobacter aerogenes* EA289, *Klebsiella pneumoniae* KP55, *Providencia stuartii* NAE16, *Enterobacter cloacae* ECCI69 and *Pseudomonas aeruginosa* PA124 (Davin-Regli et al., 2008; Nikaido, 2009). Authors have applied the microbroth dilution method to determine the MIC of neobavaisoflavone on these bacteria strains (Mbaveng et al., 2015). Unfortunately, they rather observed that the weak antibacterial activities against Enterobacteria ($64 < MIC \leq 512\ \mu g/mL$) were recorded towards the tested bacteria and that the compound was also not active ($MIC > 512\ \mu g/mL$) against *Enterobacter aerogenes* EA289, *Enterobacter cloacae* ECCI69, and *Pseudomonas aeruginosa* PA124 strains (Djeussi et al., 2015).

Djeussi et al. also demonstrated that neobavaisoflavone generally displayed bacteriostatic activity against the investigated bacteria (Djeussi et al., 2015). In a similar study performed by Mbaveng and collaborator (Mbaveng et al., 2015) on the same bacterial species as that previously reported above by Djeussi et al. As well as on many other bacteria, contradictory data were reported. They also applied similar experimental protocols to evaluate the antibacterial activity of neobavaisoflavone against *Escherichia coli* ATCC8739, AG102 and AG100Atet, *Enterobacter aerogenes* ATCC13048, CM64 and EA27, *Klebsiella pneumoniae* ATCC11296 and KP55, *Providencia stuartii* ATCC29916 and PS299645, *Enterobacter cloacae* BM47 and BM67, and *Pseudomonas aeruginosa* PA01 and PA124 strains (Mbaveng et al., 2015). They recorded the excellent activity ($2 < \text{MIC} \leq 4\,\mu g/mL$) against *Klebsiella pneumoniae* ATCC11296 (MIC of 4 μg/mL *vs* MIC of 256 μg/mL obtained by Djeussi et al.) and *Enterobacter cloacae* BM47 strains (Mbaveng et al., 2015). The very good antibacterial activity ($4 < \text{MIC} \leq 8\,\mu g/mL$) of neocyclomorusin was reported by the team of Mbaveng and collaborators against *Escherichia coli* ATCC8739 (MIC of 8 μg/mL *vs* MIC of 256 μg/mL obtained by Djeussi et al.), *Enterobacter aerogenes* ATCC13048 (MIC of 8 μg/mL *vs* MIC of 512 μg/mL obtained by Djeussi et al.), *Klebsiella pneumoniae* KP55 and *Providencia stuartii* ATCC29916 strains (MIC of 4 μg/mL *vs* MIC of 512 μg/mL obtained by Djeussi et al.) (Djeussi et al., 2015; Mbaveng et al., 2015). Besides, good antibacterial activity ($8 < \text{MIC} \leq 32\,\mu g/mL$) was reported by Mbaveng and co-workers against *Escherichia coli* AG102 (MIC of 32 μg/mL *vs* MIC of 128 μg/mL obtained by Djeussi et al.) and AG100Atet, *Enterobacter aerogenes* CM64 and EA27, *Providencia stuartii* PS299645, and *Enterobacter cloacae* BM67 strains (Djeussi et al., 2015; Mbaveng et al., 2015). Towards *Pseudomonas aeruginosa*, excellent activity ($4 < \text{MIC} \leq 32\,\mu g/mL$) was obtained on the reference PA01 strain whilst very good activity ($32 < \text{MIC} \leq 128\,\mu g/mL$) was obtained against the resistant PA124 strain (Mbaveng et al., 2015). These data, especially those documented by the Mbaveng and collaborator's team are indications that neocyclomorusin is a potential antibacterial against that deserve further investigation to produce a pharmaceutical against bacterial infections including multidrug-resistant phenotypes.

10. Plumbagin: a naphthoquinone

p0245 Naphthoquinones are a class of organic compounds structurally related to naphthalene. Naphthoquinones are natural pigments that are

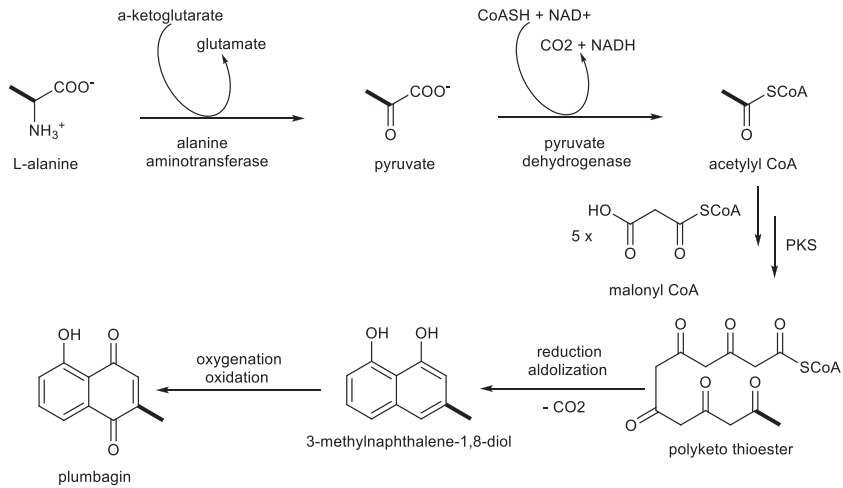
widely distributed in nature and have important biological applications. Their occurrence has been found in various plant families and serves as vital links in the electron transport chains in the metabolic pathway, participating in multiple biological oxidative processes (O'Brien, 1991; Pinto & de Castro, 2009). Naturally occurring naphthoquinones like plumbagin (**9**) have been reported in higher plants especially those belonging to the family Plumbaginaceae (Jetty et al., 2010; Paiva, Lima, Figueiredo, & Kaplan, 2011; Yue, Lin, Wang, Feng, & Sun, 1994), Ancistracladaceae (Bringmann & Feineis, 2001; Bringmann et al., 2008), Ebenaceae (Borges-Argáez, Canche-Chay, Peña-Rodríguez, Said-Fernández, & Molina-Salinas, 2007; Kuete, Tangmouo, et al., 2009), Nepenthaceae (Eilenberg et al., 2010; Rischer, Hamm, & Bringmann, 2002) and Droseraceae (Egan & van der Kooy, 2012; Madhavan, Basnett, Kumar, & Yoganarasimhan, 2008; Zenk, Fürbringer, & Steglich, 1969). The biological activity of naphthoquinones in general and plumbagin is large. Plumbagin has been reported with diverse pharmacological applications including antitumor, antiparasitic, anti-inflammatory and analgesic, antifungal, antidiabetic, neuroprotective, and antiviral. Several scholars have documented the antineoplastic activity of plumbagin against a panel of cancer cell lines (Binoy et al., 2019; Croft, Evans, & Neal, 1985; Kuete, Omosa, et al., 2016; Kuo, Hsu, & Cho, 2006; Mbaveng et al., 2017; Powolny & Singh, 2008). Croft et al., have demonstrated both in *vitro* and in *vivo*, the activity of plumbagin and other electron carriers against *Leishmania donovani* and *Leishmania mexicana amazonensis* (Croft et al., 1985). Dzoyen and co-workers demonstrated the antifungal potency of this natural isolate, against five yeast (*Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Cryptococcus neoformans*,) and five filamentous (*Aspergillus niger*, *Aspergillus flavus*, *Alternaria sp.*, *Cladosporium sp.*, *Geotrichum candidum*, *Fusarium sp,* and *Penicillium sp*) fungi (Dzoyem, Tangmouo, Lontsi, Etoa, & Lohoue, 2007). In another study, plumbagin exhibited antifungal activity against *Alternaria alternata*, *Aspergillus niger*, *Bipolaris oryzae*, *Fusarium oxysporum*, *Phytophthora capsici*, *Rhizoctonia solani*, *Rhizopus stolonifer* var. *stolonifera,* and *Sclerotinia sclerotiorum* (Shin, Lee, & Cha, 2007).

10.1 Chemistry, botanical source, and biosynthesis of plumbagin

p0250 Plumbagin (**9**) is a bicyclic naphthoquinone derivative with a molecular formula $C_{11}H_8O_3$ (m/z 188.1820 g/mol) corresponding to eight rings double bond equivalents. The identification of plumbagin has mainly been

achieved using extensive spectroscopic and spectrometric techniques as well as co-thin layer chromatography (TLC) by comparison of its retention factor with authentic samples. The planar structure of plumbagin is an analogue of vitamin K3 with the only difference being the presence of a hydroxyl substituent in *peri* position in one of the carbonyl groups. Plumbagin is an **o**range to yellow needles, m.p 76–79 °C, yellow amorphous powder; UVλ_{max}: 254 nm. IR (KBr) ν_{max}: 3321–3577 (OH), 1645–1667 (CO), 1609–1611 (Ar C=C) Cm^{-1}. ^{1}H NMR (500 MHz), (CD_3OD): δ (ppm): 7.65 (1 H, dd, J = 8.3, 7.4 Hz, H-6); 7.59 (1 H, d, J = 7.4 Hz, H-7); 7.24 (1 H, d, J = 8.3 Hz, H-9); 6.85 (1 H, q, J = 2.0 Hz, H-3); 2.15 (3 H, d, J = 1.6 Hz, CH_3-2); ^{13}C NMR (125 MHz), CD_3OD: δ (ppm) 192.5 (C, C-4); 184.6 (C, C-1); 161.0 (C, C-10); 149.8 (C, C-2); 136.1 (C, C-6); 135.3 (C, C-3); 132.4 (C, C-8); 123.6 (C, C-5); 118.8 (C, C-7); 115.2 (C, C-9); 15.2 (CH_3, CH_3-2) ESIMS m/z 187.2 $[M\text{-}H]^+$ (calcd for $[M\text{-}H]^+$ $C_{11}H_7O_3$: 187.2). Elemental analysis: C: 70.21; H:4.29; O: 25.51 (Cesari et al., 2013).

p0255 Naphthoquinones like plumbagin have been predominantly reported from plants belonging to three distant families such as Plumbaginaceae, Ebenaceae, and Droseraceae. This biologically active naphthoquinone derivative has also been found in Iradaceae, Drosophyllaceae, and Nepenthaceae families among others. The biosynthesis (Scheme 5) of plumbagin has extensively been studied and examined by different research



Scheme 5 Proposed biosynthetic pathway of plumbagin.

groups. Durand and Zenk reported that plumbagin is one of the naphthoquinones in higher plants shown to be formed according to the acetate pathway which has long been known for the formation of naphthoquinones in fungi (Durand & Zenk, 1971). In 2002, Rischer and co-authors reported labeled L-alanine as the starting amino acid to build up the allelochemical plumbagin (Rischer et al., 2002). As reported by Rischer the biosynthesis pathway of plumbagin starts with an acetyl CoA, that originated from pyruvate catalyzed by the enzyme pyruvate dehydrogenase, which in turn arises from L-alanine in presence of alanine aminotransferase. The third step involves the condensation of one molecule of acetyl CoA with five molecules of malonyl CoA catalyzed by polyketide synthase (PKS) to yield the polyketo thioester which undergoes reduction, aldol condensation, and decarboxylation to form 3-methylnaphthalene-1,8-diol. The last step involves the oxygenation followed by oxidation of 3-methylnaphthalene-1,8-diol to form plumbagin.

10.2 Antibacterial activity of plumbagin against drug sensitive and multidrug-resistant phenotypes

p0260 Plumbagin isolated from *Diospyros* species was evaluated against four Gram – multidrug-resistant (MDR) phenotypes of *Escherichia coli* (ATCC 8739, AG100, AG100A, AG100A$_{Tet}$, and AG102), *Enterobacter aerogenes* (ATCC 13048, EA-CM64, EA27, EA289, EA294 and EA298), *Klebsiella pneumoniae* (ATCC 11296, Kp55, and Kp63) and *Pseudomonas aeruginosa* (PA01 and PA124) (Kuete, Alibert-Franco, et al., 2011). Overall, MICs of plumbagin against the tested microorganisms ranged from 2 mg/L (against *E. coli* AG100A) to 64 mg/L (towards *E. aerogenes* EA-CM64). The best activity was observed against *E. coli* AG100A$_{Tet}$ (MIC of 8 mg/L), AG102 (MIC of 16 mg/L); *E. aerogenes* EA-CM64 (MIC of 64 mg/L), EA289 (MIC of 32 mg/L), EA294 (MIC of 16 mg/L), EA298 (MIC of 16 mg/L) and EA27 (MIC of 32 mg/L); *K. pneumoniae* Kp63 (MIC of 32 mg/L); *P. aeruginosa* PA01 (MIC of 16 mg/L) and PA124 (MIC of 32 mg/L) compared to the standard antibiotic; chloramphenicol, MICs values of 32, 32, 256, > 256, 64, 64, > 256, > 256, 128 and 256 mg/L, respectively (Kuete, Alibert-Franco, et al., 2011). Based on this previous observation, plumbagin which displayed antibacterial effects against all pathogenic bacteria were associated with the efflux pump inhibitor, phenylalanine beta naphthylamide, PAβN, to explore the influence of efflux in its activities (Kuete, Alibert-Franco, et al., 2011; Kuete, Ngameni, Tangmouo, et al., 2010). Interestingly, plumbagin disclosed antibacterial activity against all Gram-negative

bacteria strains with MICs values recorded from 8 to 0.25 mg/L (against *E. coli* AG100A_{Tet}) and from 64 to 8 mg/L (towards *E. aerogenes* EA-CM64) (Kuete, Ngameni, et al., 2011). In another study, plumbagin showed anti-mycobacterial activity against *Mycobacterium smegmatis* ATCC 700084 (MIC of 4.9 mg/L), *M. tuberculosis* H37Rv (ATCC 27294) (MIC of 4.9 mg/L), and good activity towards *M. tuberculosis* clinical strains **(**MTCS1 and MTCS2) (MIC > 39.0 mg/L, each) (Kuete, Tangmouo, et al., 2009). Gonorrhea caused by *Neisseria gonorrhoeae* is a sexually transmitted disease (STD) with different health complications including cervicitis, urethritis, proctitis, and pelvic inflammatory disease. The antigonorrhoeal potency of plumbagin, against *N. gonorrhoeae* strains, revealed selective activity with MICs values ranging from 4.9 to 39.1 μg/mL for plumbagin against 9/10 (90%) tested strains. Interestingly, plumbagin was 2–4-fold more active than gentamicin (standard drug) against NGCS2 (BL-) (MIC of 9.8 μg/mL), NGCS4 (BL-) (MIC of 9.8 μg/mL) and NGCS7 (BL+) (MIC of 19.5 μg/mL) *versus* NGCS2 (BL-) (MIC of 39.1 μg/mL**)**, NGCS4 (BL-) (MIC of 19.5 μg/mL) and NGCS7 (BL+) (MIC of 39.1 μg/mL) for gentamicin. The equipotent activity was recorded for plumbagin and gentamicin towards WHO (BL-) (MIC of 9.8 μg/mL) and NGCS5 (BL+) (MIC of 19.5 μg/mL) (Kuete, Tangmouo, et al., 2009). The naphthoquinone, plumbagin, was also active against both Gram + and Gram – bacteria tested with interesting MIC values ranging from 2 to 64 μg/mL. Furthermore, this naphthoquinone exhibited outstanding to average antibacterial activities against methicillin-resistant *Staphylococcus aureus* MRSA3 **(**MIC of 64 μg/mL), MRSA4 (MIC of 2 μg/mL), MRSA6 (MIC of 2 μg/mL), and MRSA8 (MIC of 2 μg/mL) strains compared to chloramphenicol with the respective MIC values of > 256, 8, 64 and 32 μg/mL (Omosa et al., 2016). Jeyachandran et al. have investigated the *in vitro* antibacterial activity of plumbagin purified from Plumbago zeylanica L. against Gram + and Gram – bacteria using the agar disc diffusion technique. Plumbagin showed inhibition against S. aureus, B. subtilis, E. coli, S. typhi, K. pneumoniae, S. marcescens (MIC < 1 μg/disc), and moderate potency towards P. vulgaris and P. aeruginosa (MIC > 2 μg/disc) (Jeyachandran, Mahesh, Cindrella, Sudhakar, & Pazhanichamy, 2009). Similar results of plumbagin were established by De Paiva et al., against *S. aureus* with MIC of 1.6 μg/mL (de Paiva, Figueiredo, Aragao, & Kaplan, 2003). Yap and co-authors reported the bacteriostatic and bactericidal effects of a commercially available plumbagin against both Gram-positive and Gram-negative pathogenic microbes using the microdilution broth method (Yap, Tan, Tang, Thien, & Chan, 2021). The MICs values of plumbagin

ranged from 0.0078 to 0.125 mg/mL against Gram-positive (*Micrococcus luteus* (ATCC 4698), *Bacillus cereus* (ATCC 14579), methicillin-sensitive *Staphylococcus aureus* (MSSA) (ATCC 25923), MRSA (ATCC 33591), clinical isolates of MRSA) and from 0.0625 to 0.25 mg/mL towards Gram-negative (*Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 10031; ATCC 2146; ATCC 1705), *Pseudomonas aeruginosa* (ATCC 10145), and *Salmonella choleraesuis* (ATCC 10708)) bacteria (Yap et al., 2021). Taraszkiewicz and collaborators studied the antibacterial activity of plumbagin isolated from *Drosera gigantea*, a carnivorous plant against the bacterial fruit tree pathogens, *Pseudomonas syringae* pv. *Syringae* and *P. syringae* pv. *Morsprunorum* (Taraszkiewicz, Jafra, Skrzypczak, Kaminski, & Królicka, 2012). Plumbagin was also documented by Jetty et al., to have antibacterial activity against 10/10 (100%) bacteria tested including six Gram-positive and four Gram-negative bacteria with MIC values in the range of 0.78–3.13 μg/mL (Jetty et al., 2010). Plumbagin showed antibacterial activity with MICs ranging from 10 to 30 μg/mL against P. syringae isolates (Pss-762, Psm2–764, Psm1–782, Ps-791, and Psm1–793). Plumbagin also demonstrated antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Ra$ (MIC of 8 μg/mL), four clinical strains of *M. tuberculosis* (MIC: 0.25–4 μg/mL), *M. chelonei* (MIC of 16 μg/mL), and *M. fortuitum* (MIC of 32 μg/mL), and a broad spectrum of antibacterial potency against 35 bacteria tested. The MICs of plumbagin against Gram-positive and Gram-negative bacteria ranged from $< 4 - 16$ and $16 - 128$ μg/mL, respectively (Dey, Ray, & Hazra, 2014). The activity guided purification of the root extract of *Plumbago indica* for antibacterial application led to the isolation of plumbagin which displayed satisfactory activity against Propionibacterium acnes strains (MIC: 2.1 – 66.5 μg/mL), Staphylococcus aureus (MIC of 16.6 μg/mL), and S. epidermidis (MIC of 0.1 μg/mL) (Kaewbumrung & Panichayupakaranant, 2012). The antibacterial activity of this compound was also noted against S. aureus (MIC of 5 μg/mL) (Nair et al., 2016). Furthermore, plumbagin isolated from *Plumbago zeylanica* L. showed promising activity with MIC range from 4 to 8 μg/mL against MRSA strains (Periasamy, Iswarya, Pavithra, Senthilnathan, & Gnanamani, 2019). In addition to its antibacterial activity, plumbagin showed interaction properties with some antibiotics including ciprofloxacin and piperacillin (Periasamy et al., 2019).

10.3 Bacterial resistance to plumbagin

p0265 Efflux pumps, especially ACRAB-TolC in Enterobacteriaceae and MexAB-OprM in *Pseudomonas aeruginosa* have been involved in the resistance of

many bacteria to plumbagin (Kuete, Alibert-Franco, et al., 2011). In effect, when plumbagin was tested in the presence of the efflux pump inhibitor, phenylalanine arginine β-naphthylamide (PAβN), the antibacterial activity increased from 4-fold towards *Enterobacter aerogenes* ATCC 13048-64-fold against *Escherichia coli* AG100A_{Tet} and *Pseudomonas aeruginosa* PA124. This clearly indicated that efflux pumps were involved in the resistance of bacteria to plumbagin.

11. Conclusion

p0270 In the present chapter, we have documented the impressive antibacterial potential of nine chemicals isolated from various African medicinal plants. They include 8,8-bis-(dihydroconiferyl)-diferulate, buesgenine, candidone, diospyrone, ferruginin A, isobavachalcone, neobavaisoflavone, neocyclomorusin, and plumbagin. Their botanical source as well as their hypothetical biosynthetic pathways were also provided. These compounds are potential pharmaceuticals that deserved further in-depth studies to develop pharmaceuticals to combat bacterial infections including their multi-drug resistance.

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