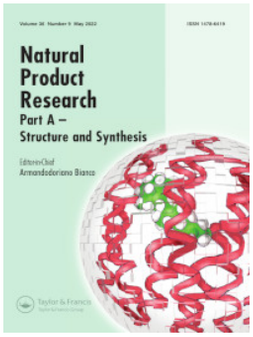

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Conglomeratin: a new antibacterial flavonol derivative from *Macaranga conglomerata* Brenan (Euphorbiaceae)

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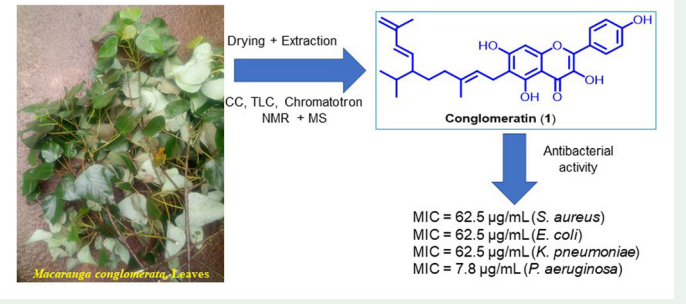
ABSTRACT

A new prenylated kaempferol, conglomeratin (**1**), alongside **7** known compounds including flavonoids (**2** and **3**), ellagic acid derivatives (**4** and **5**), triterpenoids (**6** and **7**), and a coumarin (**8**) were isolated from the leaves (**1 − 5**) and stem bark (**6 − 8**) of *Macaranga conglomerata*. Their structures were elucidated using spectroscopic and spectrometric techniques. The antibacterial assay was performed using disc diffusion method against Gram-positive and Gram-negative microorganisms. Compound **1** was significantly active against *Pseudomonas aeruginosa* ATCC 27853 (MIC = 7.8 µg/mL) and moderately active towards *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 31488 (MIC = 62.5 µg/mL). Compound **2** showed potency against *P. aeruginosa* ATCC 27853 (MIC = 1.0 µg/mL) while **4** and **7** were selective towards *K. pneumoniae* ATCC 31488 (MIC = 7.8 and 1.0 µg/mL, respectively). These findings suggest that prenylation of flavonoids may contribute to improving their broad-spectrum antimicrobial activities.



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1. Introduction

The World Health Organization has identified the rising prevalence of microbial infections, combined with increased antibiotic drug resistance, as one of the most serious

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threats to human health. Bacterial resistance to antibiotics results in high morbidity and mortality in addition to increased hospitalization or treatment time (Singh and Manchanda 2017; Agyepong et al. 2018). Pathogenic bacteria with rising antibiotic resistance include *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus aureus* (Chua and Gubler 2013; WHO. 2017). Due to the resistance developed by these pathogenic microorganisms against the current antibiotics, there is a need to search for new therapeutic agents.

Plants belonging to the family Euphorbiaceae, particularly from the genus *Macaranga*, are well-known sources of prenylated stilbenes and flavonoids (Beutler et al. 1999; 2000; Segun et al. 2021; Vu et al. 2021). The prenyl groups, that is, prenyl, geranyl and farnesyl, improve the lipophilic properties of the molecule, thereby enhancing its affinity to the biological membrane (Barron and Ibrahim 1996; Botta et al. 2005). The genus has recently attracted the attention of researchers due to the existence of prenylated flavonoids with intriguing biological properties, particularly cytotoxicity (Yang et al. 2014; Darmawan et al. 2015; Yang et al. 2015a; Tanjung et al. 2018; Huonga et al. 2019; Mai et al. 2020) with little information reported regarding the antibacterial aspects. *Macaranga conglomerata*, together with three other species in the genus (*M. kilimandscharica*, *M. capensis* and *M. schweinfurthii*), are found in Kenya within $300-2100$ m altitudes (Beentje 1994). *M. conglomerata* is a medium-sized tree (up to 32 m) with a long-stalked inflorescence. Its leaves are slightly pulvinate at the base, held in a drooping position with the incurved margins, and have an oval shape with broadleaf blades (Beentje 1994). *M. conglomerata* is rarely employed in Kenyan traditional medicine, however, other plants in the same genus are used to treat coughing, bilharzia and stomach issues (Kokwaro 1993). We recently provided evidence of the strong antibacterial potency of different parts of *M. conglomerata*, *M. kilimandscharica* and *M. capensis* against 13 bacterial strains expressing multi-drug resistance (MDR) phenotypes (Hashim et al. 2021). Motivated by the previous findings and as part of our ongoing search for new bioactive compounds from Kenya medicinal plants (Nyaboke et al. 2018; Mukavi et al. 2020; Nchiozem-Ngnitedem et al. 2020a, Nchiozem-Ngnitedem et al. 2020b; Omosa et al. 2021), the phytochemical investigation of the leaves and stem bark of *M. conglomerata* was undertaken. We herein report the isolation of a new flavonol derivative alongside 7 known compounds and their antibacterial activities against one Gram-positive (*Staphylococcus aureus* ATCC 25923) and three Gram-negative (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 31488) microorganisms.

2. Results and discussion

Conglomeratin (**1**) was obtained as a yellow solid. Its molecular formula, $C_{30}H_{34}O_6$ (fourteen indices of hydrogen deficiency), was deduced from the deprotonated ion peak observed in the (–)-HRESIMS at *m/z* 489.2271 $[M - H]^-$ (calcd. for $C_{30}H_{33}O_6^-$, 489.2277). Its IR spectrum displayed absorption bands attributable to hydroxyl groups (3317 cm^{-1}) and α,β-unsaturated ketone moiety (1655 cm^{-1}). The UVλ_{max} (372 and 256 nm) and ^{13}C NMR (δ_C 147.8 (C-2), 135.7 (C-3) and 178.3 (C-4) spectra of compound **1** exhibited the signature of C-ring of flavonol framework (Yang et al. 2015b; Le et al.

2021; Nchiozem-Ngnitedem et al. 2021). The NMR spectra of compound **1** also displayed three signals in the aromatic region attributable to that of C-6 (δ_C 112.3) substituted kaempferol moiety similar to 3′-dehydroxysolophenol C (Le et al. 2021) and denticulatain D (Yang et al. 2015b) isolated from *M. denticulata*. Besides the signals observed for the kaempferol core, the ^{1}H and ^{13}C NMR and HSQC spectra also showed signals assigned to a modified geranyl [δ_H 3.21 (2H, m, H-1″), 5.10 (1H, t, $J = 7.3$ Hz, H-2″), 1.79 (2H, m, H-4″), 1.48 (2H, m, H-5″), 1.69 (1H, m, H-6″), 1.44 (1H, m, H-7″), 0.70 (3H, d, $J = 6.8$ Hz, H-8″), 0.73 (3H, d, $J = 6.8$ Hz, H-9″) and 1.65 (3H, s, H-10″); δ_C 22.1 (C-1″), 123.9 (C-2″), 135.6 (C-3″), 38.6 (C-4″), 31.4 (C-5″), 49.8 (C-6″), 33.3 (C-7″), 19.5 (C-8″), 21.2 (C-9″) and 16.1 (C-10″)] and isoprenyl [δ_H 5.24 (1H, dd, $J = 15.9$, 9.5 Hz, H-1‴), 5.82 (1H, d, $J = 15.9$ Hz, H-2‴), 4.65 and 4.60 (2H, br s, H-4‴) and 1.68 (3H, s, H-5‴); δ_C 133.7 (C-1‴), 135.4 (C-2‴), 143.3 (C-3‴), 114.5 (C-4‴) and 18.9 (C-5‴)] units. These signals are typical of a highly prenylated flavonol from the genus *Macaranga*. The large coupling constant ($^{3}J_{\text{H-1‴, H-2‴}} = 15.9$ Hz) indicate the *trans* orientation of the $\Delta^{1'''(2''')}$ olefinic bond. The ^{13}C NMR, HSQC and DEPT spectra showed 30 carbons with different functionalities including 1 α,β-unsaturated carbonyl group, 20 sp^2 and 9 sp^3 hybrid carbons. The interconnectivity of the two aliphatic chains was established from the HMBC cross-peaks observed from H-2‴ (δ_H 5.82) to C-3‴ (δ_C 143.3), C-4‴ (δ_C 114.5), C-5‴ (δ_C 18.9) and C-6″ (δ_C 49.8). The location of the isoprenyl substituent at the said position was further confirmed based on ^{1}H-^{1}H COSY between H-1‴/H-2‴ and H-1‴/H-6″. The transoid conformation of the isoprenyl unit was established as observed in the NOESY spectrum between H-1‴ and H-5‴. Based on these spectral data and by comparison with prenylated flavonoids reported in the literature, compound **1** was systematically named as 6-[(2(*E*),7(*E*))-6-isopropyl-3,9-dimethyldeca-2,7,9-trienyl]kaempferol (trivially named as conglomeratin).

The known compounds (Figure 1) were identified as macaragin (**2**) (Sutthivaiyakit et al. 2002), quercetin (**3**) (Xu et al. 2019), 3,3′,4′-trimethoxyellagic acid (**4**) (Ye et al. 2007), 3,3′-dimethoxyellagic acid (**5**) (De Nkainsa et al. 2020), 3-acetylaleuritolic acid (**6**) (Rumzhum et al. 2012), 2α-hydroxyaleuritolic acid-3-*p*-hydroxybenzoate (**7**) (Chaudhuri et al. 1995) and scopoletin (**8**) (Quynh et al. 2018) as evident from their NMR and HRESIMS spectra.

All isolated compounds were evaluated for their antibacterial activities against 4 bacteria, that is *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 31488. Flavonol derivatives **1 − 3** demonstrated broad-spectrum activities against all the tested bacteria strains (MIC = 1.0 − 500 μg/mL), while compounds **4 − 8** only showed varying degrees of inhibitory activities against *K. pneumoniae* ATCC 31488 (MIC = 1.0 − 500 μg/mL) (Supporting information, Table S2). Among the isolates, compound **1** was mostly active, exhibiting potent and moderate activities (MIC = 7.8 − 62.5 μg/mL) against all tested bacteria. Moreover, compounds **1** (MIC = 7.8 μg/mL) and **2** (MIC = 1.0 μg/mL) were 2 and 16-folds more active, respectively than ciprofloxacin (MIC = 15.6 μg/mL) against Gram-negative *P. aeruginosa* ATCC 27853. Strong activities of compounds **1** and **2** could be attributed to their prenylated nature. It has been reported that prenylation improves the lipophilic properties of the phenolic compounds, which may be important in structure-activity relationship, thereby increasing their

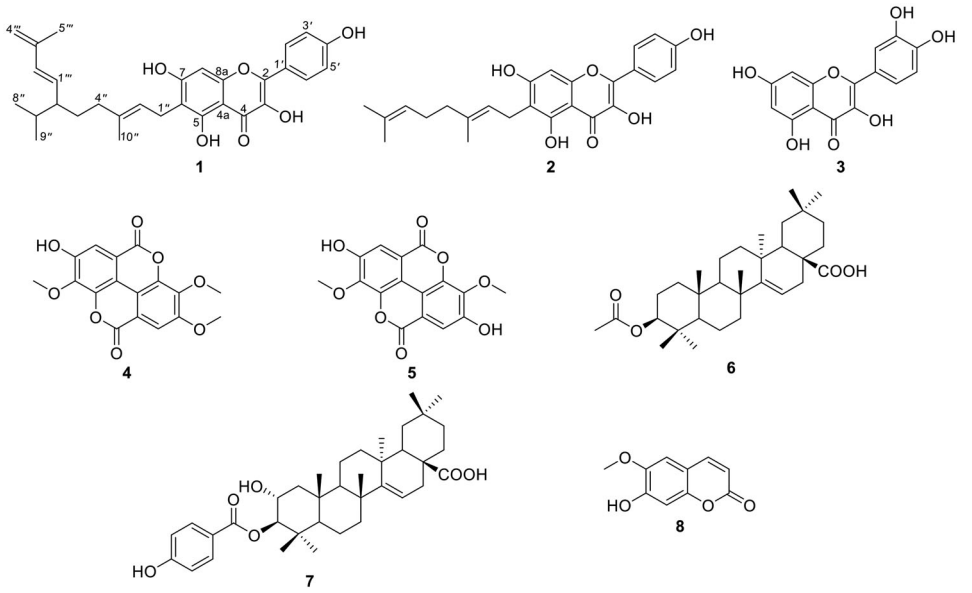

Figure 1. Secondary metabolites isolated from the leaves (**1** – **5**) and stem bark (**6** – **8**) of *M. conglomerata*.

antibacterial activities (Botta et al. 2005; Fukai et al. 2005; Eerdunbayaer et al. 2014; Kı rmızıbekmez et al. 2015). The influence of prenylation can be observed when comparing the MICs values of compounds **1 − 3**, all with flavonol nuclei. Compound **3** (which lack prenylation) was found to have relatively weak/low antibacterial activity (MIC = 500 μg/mL) against all the tested bacteria; therefore, it was considered inactive (Jepkoech et al. 2021). Additionally, Gram-negative *K. pneumoniae* has long been recognized as a possible cause of community-acquired pneumonia. Some of the compounds including **4** (MIC = 7.8 μg/mL) and **7** (MIC = 1.0 μg/mL) displayed strong activity against *K. pneumoniae* ATCC 31488. Interestingly, compound **4** was 2-fold more active than the standard drug, ciprofloxacin providing new lead candidate for optimization against *K. pneumoniae* ATCC 31488.

3. Experimental

3.1. General experimental procedures

NMR spectra were performed on Bruker 400 MHz spectrometer and Bruker Avance III 600 MHz spectrometer using standard pulse sequences and referenced to residual solvent signals. Bruker-Alpha FT-IR spectrometer (SN 100964) with single reflection ATR (cricket, Harrick Scientific) was used in performing the IR analysis. UV absorbance was obtained on Shimadzu UV-1800 UV/Visible Scanning Spectrophotometer (UV − 1800 240 V). Specific rotation was recorded on ADP410 Polarimeter (Bellingham + Stanley Ltd). A Waters Synapt G2 Quadrupole time-of-flight (qTOF) mass spectrometer (MS) connected to a Waters Acquity ultra-performance liquid chromatograph (UPLC) (Waters, Milford, MA, USA) was used for direct infusion high-resolution MS analysis. Electrospray ionization was used in negative mode with a cone voltage of 15 V,

desolvation temperature of 275 °C, desolvation gas at 650 L/h, and the rest of the MS settings optimized for best resolution and sensitivity. Data were acquired by scanning from *m/z* 150 to 1500 *m/z* in resolution mode. A 2 μl injection volume was used to introduce the sample into a flowstream consisting of 40% of 0.1% formic acid in water (solvent A) and 60% acetonitrile containing 0.1% formic acid (solvent B). This solvent conveyed the samples to the High Definition qTOF mass spectrometer which due to its high mass resolution, allows accurate mass elemental composition to be determined. Silica gel (100 − 200 mesh) and Sephadex LH–20 (25–100 μm, Sigma Aldrich) were used for column chromatography. TLC was carried out on pre-coated silica gel 60 plates (0.25 mm; Merck, Darmstadt, Germany). Compounds were visualized under UV light and further sprayed with a solution of H_2SO_4–H_2O (5%, v/v).

3.2. Plant material

Macaranga conglomerata were collected from the Ngangao forest in March 2019 (3°25′ S, 38°20′ E) in Taita-Taveta county, Kenya. The plant was identified by Mr Patrick C. Mutiso, a taxonomist from the Faculty of Science and Technology (FST), University of Nairobi, Kenya, where a voucher specimen HIUON 2019/001 was deposited.

3.3. Extraction and isolation

The air-dried powdered leaves (1.8 Kg) of *M. conglomerata* was macerated in the mixture of CH_2Cl_2/CH_3OH (1:1) (3 × 9 L) at room temperature for three days. The solvents were concentrated under vacuum using a rotary evaporator yielding 200.3 g of crude extract. This extract was fractionated in a column chromatography (CC) using silica gel as an adsorbent eluting with *n*-hexane/CH_2Cl_2 (10:0, 1:1 and 0:10) followed by *n*-hexane/EtOAc (1:1 and 0:10) and finally, CH_2Cl_2/CH_3OH (1:1 and 0:10) to afford seven fractions ($F_{A\text{-}G}$). Size exclusion chromatography on fraction D (20.0 g) with CH_2Cl_2/CH_3OH (1:1) as mobile phase was done to afford five subfractions ($Fr_{D1\text{-}5}$). Subfraction Fr_{D4} (2.4 g) was further purified on a silica gel column and eluted with *n*-hexane in increasing amount of EtOAc to obtain compounds **1** (11.2 mg) and **2** (3.6 mg). Fraction E (15.0 g) was subjected to silica gel CC eluting with *n*-hexane/EtOAc (10:0 to 0:10), resulting in 334 fractions of 100 mL each. The fractions were combined into four main subfractions ($Fr_{E1\text{-}4}$) based on their TLC profiles. Subfraction Fr_{E2} (81.9 mg) was passed through silica gel column chromatography using *n*-hexane/EtOAc (9.5:0.5 to 0:10) as mobile phase to afford compound **4** (5.3 mg). Isocratic elution of subfraction Fr_{E3} (67.8 mg) in a silica gel with *n*-hexane/EtOAc (8.5:1.5) yielded **5** (6.0 mg). Lastly, Fr_{E4} (201.4 mg) was subjected to gel permeation over Sephadex LH-20 CC with CH_2Cl_2/CH_3OH (1:1) as mobile phase to yield **3** (7.3 mg).

The powdered stem bark (3.9 Kg) was macerated in the mixture of CH_2Cl_2/CH_3OH (1:1) (3 × 9 L) at room temperature for three days affording 450.9 g of crude extract after evaporation under reduced pressure. Part of this extract (200.0 g) was subjected to silica gel CC eluting with *n*-hexane/EtOAc (10:0 to 0:10), resulting in 645 fractions of 500 mL each, which were pooled based on their TLC profiles into nine fractions ($F_{A\text{-}I}$).

Fraction F_F (470.1 mg) was loaded onto a silica gel column and eluted with a binary system of *n*-hexane/CH_2Cl_2 (8:2) to afford compound **6** (12.4 mg). Purification of fraction F_H (790.4 mg) using chromatotron with a mixture of *n*-hexane/EtOAc (7:3) as mobile phase resulted in the isolation of compounds **7** (13.8 mg) and **8** (11.2 mg).

Conglomeratin (**1**): Yellow solid, $[\alpha]_D^{25} = +55.8$ (*c* 0.53, MeOH); UV (MeOH)λ_{max} 372 and 256 nm (Supporting information, Figure S1); IR (neat)ν_{max} 3317, 1655, 1450, 1113, 1020 cm^{-1} (Supporting information, Figure S2); ^{1}H-NMR (400 MHz, CD_3OD): δ (ppm) 7.98 (2H, d, $J = 8.4$ Hz, H-2′/6′), 6.79 (2H, d, $J = 8.4$ Hz, H-3′/5′), 6.33 (1H, s, H-8), 5.82 (1H, d, $J = 15.9$ Hz, H-2‴), 5.24 (1H, dd, $J = 15.9$, 9.5 Hz, H-1‴), 5.10 (1H, t, $J = 7.3$ Hz, H-2″), 4.65 and 4.60 (2H, br s, H-4‴), 3.21 (2H, m, H-1″), 1.79 (2H, m, H-4″), 1.69 (1H, m, H-6″), 1.68 (3H, s, H-5‴), 1.65 (3H, s, H-10″), 1.48 (2H, m, H-5″), 1.44 (1H, m, H-7″), 0.73 (3H, d, $J = 6.8$ Hz, H-9″), 0.70 (3H, d, $J = 6.8$ Hz, H-8″); ^{13}C-NMR (100 MHz, CD_3OD): δ (ppm) 178.3 (C-4), 163.6 (C-7), 160.3 (C-4′), 158.2 (C-5), 156.3 (C-8a), 147.8 (C-2), 143.3 (C-3‴), 135.7 (C-3), 135.6 (C-3″), 135.4 (C-2‴), 133.7 (C-1‴), 130.6 (C-2′/6′), 124.1 (C-1′), 123.9 (C-2″), 116.3 (C-3′/5′), 114.5 (C-4‴), 112.3 (C-6), 104.4 (C-4a), 93.6 (C-8), 49.8 (C-6″), 38.6 (C-4″), 33.3 (C-7″), 31.4 (C-5″), 22.1 (C-1″), 21.2 (C-9″), 19.5 (C-8″), 18.9 (C-5‴), 16.1 (C-10″) (Supporting information, Table S1 and Figures S4–S10); HRESIMS *m/z* 489.2271 $[M - H]^-$ (calcd. for $C_{30}H_{33}O_6^-$, 489.2277) (Supporting information, Figure S3).

3.4. In vitro antibacterial assay

Antibacterial activity of isolates (**1**– **8**) and ciprofloxacin (positive control) were evaluated against Gram-positive (*Staphylococcus aureus* ATCC 25923) and Gram-negative (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Klebsiella pneumoniae* ATCC 31488) pathogenic microbes using disc diffusion method in accordance to protocols published (Singh et al. 2018).

4. Conclusion

Overall, 8 compounds, including 1 new flavonol derivative (**1**), were reported from the leaves and stem bark of *Macaranga conglomerata* collected in Ngangao forest, Kenya. Compound **1** with three isoprenyl units demonstrated a broad-spectrum antibacterial activity against all of the tested microorganisms.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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