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.

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
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 conglomera*, 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. conglomera* 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. conglomera* 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. conglomera*, *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-Ngitedem et al. 2020a, Nchiozem-Ngitedem et al. 2020b; Omosa et al. 2021), the phytochemical investigation of the leaves and stem bark of *M. conglomera* 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 UV$_{\text{max}}$ (372 and 256 nm) and $^{13}$C NMR ($\delta_{^c}$ 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.
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′-dehydroxyisolphenol 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 1H and 13C NMR and HSQC spectra also showed signals assigned to a modified geranyl [δ_H 3.21 (2H, m, H-1′′′)] and 13C 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′′′ 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°-1H 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) (Suthivaiyakit 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-acetylatedeulcitol (6) (Rumzhum et al. 2012), 2α-hydroxyaleuritolic acid-3-p-hydroxybenzoate (7) (Chaudhuri et al. 2019) 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
antibacterial activities (Botta et al. 2005; Fukai et al. 2005; Eerdunbayaer et al. 2014; Kırırmızibekmez 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 $\text{H}_2\text{SO}_4$–$\text{H}_2\text{O}$ (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$_2$Cl$_2$/CH$_3$OH (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$_2$Cl$_2$ (10:0, 1:1 and 0:10) followed by n-hexane/EtOAc (1:1 and 0:10) and finally, CH$_2$Cl$_2$/CH$_3$OH (1:1 and 0:10) to afford seven fractions (F$_{A-G}$). Size exclusion chromatography on fraction D (20.0 g) with CH$_2$Cl$_2$/CH$_3$OH (1:1) as mobile phase was done to afford five subfractions (FrD1-5). Subfraction FrD4 (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 (FrE1-4) based on their TLC profiles. Subfraction FrE2 (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 FrE3 (67.8 mg) in a silica gel with n-hexane/EtOAc (8:5:1.5) yielded 5 (6.0 mg). Lastly, FrE4 (201.4 mg) was subjected to gel permeation over Sephadex LH-20 CC with CH$_2$Cl$_2$/CH$_3$OH (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$_2$Cl$_2$/CH$_3$OH (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$_{A-I}$).
Fraction FF (470.1 mg) was loaded onto a silica gel column and eluted with a binary system of n-hexane/CH₂Cl₂ (8:2) to afford compound 6 (12.4 mg). Purification of fraction FH (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, [α]D25 = +55.8 (c 0.53, MeOH); UV (MeOH)λmax 3317, 1655, 1450, 1113, 1020 cm⁻¹ (Supporting information, Figure S1); IR (neat)/C23 max 3317, 1655, 1450, 1113, 1020 cm⁻¹ (Supporting information, Figure S2); 1H-NMR (400 MHz, CD3OD): 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’/6’), 5.10 (1H, t, J = 7.3 Hz, H-2’), 4.65 and 4.60 (2H, br s, H-4’/5’/6’), 3.21 (2H, m, H-1’), 1.79 (2H, m, H-4’), 1.69 (1H, m, H-6’), 1.68 (3H, s, H-5’/6’), 1.65 (3H, s, H-10’), 1.48 (2H, m, H-5’/6’), 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”); 13C-NMR (100 MHz, CD3OD): 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’/5’), 135.7 (C-3), 135.6 (C-3’/5’), 135.4 (C-2’/6’), 131.1 (C-1’), 123.9 (C-2’), 116.3 (C-3’/5’), 114.5 (C-4’/5’), 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 C30H33O6, 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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References

Agyepong N, Govinden U, Owusu-Ofori A, Essack SY. 2018. Multidrug-resistant gram-negative bacterial infections in a teaching hospital in Ghana. Antimicrob Resist Infect Control. 7(1):1–8.
Barron D, Ibrahim RK. 1996. Isoprenylated flavonoids—a survey. Phytochemistry. 43(5):921–982.
Beentje HJ. 1994. Kenya trees, shrubs and lianas. 6th ed. Nairobi Kenya: National Museums of Kenya. p. 1–722.
Beutler JA, Jato J, Cragg GM, Boyd MR. 2000. Schweinfurthin D, a cytotoxic stilbene from Macaranga schweinfurthii. Nat Prod Lett. 14(5):399–404.
Beutler JA, McCall KL, Boyd MR. 1999. A novel geranylflavone from Macaranga schweinfurthii. Nat Prod Lett. 13(1):29–32.
Botta B, Vitali A, Menendez P, Misiti D, Monache G. 2005. Prenylated flavonoids, pharmacology and biotechnology. Curr Med Chem. 12(6):713–739.
Chaudhuri SK, Fullas F, Brown DM, Wani MC, Wall ME, Cai L, Mar W, Lee SK, Luo Y, Zaw K, et al. 1995. Isolation and structural elucidation of pentacyclic triterpenoids from Maprounea africana. J Nat Prod. 58(1):1–9.
Chua KB, Gubler DJ. 2013. Perspectives of public health laboratories in emerging infectious diseases. Emerg Microbes Infect. 2(1):1–6.
Darmawan A, Megawati Lotulung PDN, Fajriah S, Primahana G, Meiliawati L. 2015. A new flavonoid derivative as cytotoxic compound isolated from ethyl acetate extract of Macaranga gigantifolia Merr. Leaves. Procedia Chem. 16:53–57.
De Nkainsa A, Fotsos SC, Fusi AA, Francioli K, Alfred TFA, Wansi JD, Désiré DDP, Dongmo AB, Dimo T. 2020. Phytochemical analysis and in vitro antimicrobial screenings of the methanolic stem bark extract and constituents of Parkia bicolor A. Chev. (Leguminosae). Trends Phytochem Res. 4(4):193–200.
Eerdbunbayar Orabi MAA, Aoyama H, Kuroda T, Hatano T. 2014. Structures of new phenolics isolated from licorice, and the effectiveness of licorice phenolics on vancomycin-resistant enterococci. Molecules. 19(9):13027–13041.
Fukai T, Kaitou K, Terada S. 2005. Antimicrobial activity of 2-arylenzofurans from Morus species against methicillin-resistant Staphylococcus aureus. Fitoterapia. 76(7–8):708–711.
Hashim I, Omosa LK, Nchiozem-Ngnitedem V-A, Onyari JM, Maru SM, Guefack M-GF, Mbaveng AT, Kuete V. 2021. Antibacterial activities and phytochemical screening of crude extracts from Kenyan Macaranga species towards MDR phenotypes expressing efflux pumps. Pharmacogn Commun. 11(2):119–126.
Huonga DTM, Vu LTN, The Anh L, Cuc NT, Nhiem NX, Tai BH, Van Kiem P, Litaudon M, Dang Thach T, Van Minh C, et al. 2019. Cytotoxic prenylated flavonoids from the leaves of Macaranga indica. Phytochem Lett. 34:39–42.
Jepkoech C, Omosa LK, Nchiozem-Ngnitedem V-A, Kenanda EO, Guéfack MGF, Mbaveng AT, Kuete V, Heydenreich M. 2021. Antibacterial secondary metabolites from Vernonia auriculifera Hiern (Asteraceae) against MDR phenotypes. Nat Prod Res. 1–4.

Kirmizibekmez H, Uysal GB, Masullo M, Demirci F, Bağıç Y, Kan Y, Piaceinte S. 2015. Prenylated polyphenolic compounds from Glycyrrhiza iconica and their antimicrobial and antioxidant activities. Fitoterapia. 103:289–293.

Kokwaro JO. 1993. Medicinal plants of East Africa. 2nd ed. Nairobi. Kenya: University of Nairobi Press.

Le TNV, Truong BN, Le TP, Litaudon M, Tran DT, Chau VM, Mai HDT, Pham VC. 2021. Cytotoxic phenolic compounds isolated from the fruits of Macaranga denticulata. Nat Prod Res. 35(11):1861–1868.

Mai HDT, Toan TP, Huu GT, Le TN, Oanh VTK, Hang NTM, Thu HT, Chau VM, Litaudon M, Pham VC. 2020. New flavonoid and stilbene derivatives from the fruits of Macaranga balansae. Nat Prod Res. 34(19):2772–2778.

Mukavi J, Omosa LK, Nchiozem-Ngnitedem V-A, Nyaga J, Omole R, Bitchagno GTM, Spiteller M. 2020. Anti-inflammatory norhopanes from the root bark of Fagaropsis angolensis (Engl.) H.M.Gardner. Fitoterapia. 146:104690.

Nchiozem-Ngnitedem V-A, Omosa LK, Bedane KG, Derese S, Brieger L, Strohmann C, Spiteller M. 2020b. Anti-inflammatory steroidal sapogenins and a conjugated chalcone-stilbene from Dracaena usambarensis Engl. Fitoterapia. 146:104717.

Nchiozem-Ngnitedem V-A, Omosa LK, Bedane KG, Derese S, Spiteller M. 2021. Inhibition of proinflammatory cytokine release by flavones and flavanones from the leaves of Dracaena steudneri Engl. Planta Med. 87(3):209–217.

Nchiozem-Ngnitedem V-A, Omosa LK, Derese S, Tane P, Heydenreich M, Spiteller M, Seo EJ, Efferth T. 2020a. Two new flavonoids from Dracaena usambarensis Engl. Phytochem Lett. 36:80–85.

Nyaboke OH, Moraa M, Omosa KL, Mbaveng AT, Nchiozem-Ngnitedem V-A, Masila V, Okemwa E, Heydenreich M, Efferth T, Kuete V. 2018. Cytotoxicity of lupeol from the stem bark of Zanthoxylum gilletii against multi-factorial drug resistant cancer cell lines. Invest Med Chem Pharmacol. 1(1):10.

Omosa LK, Nchiozem-Ngnitedem V-A, Mukavi J, Atieno OB, Nyaboke OH, Hashim I, Obegi MJ, Efferth T, Spiteller M. 2021. Cytotoxic alkaloids from the root of Zanthoxylum paracanthum (mildbr) Kokwaro. Nat Prod Res. 1–8.

Quynth DT, Vu LTN, Huong DTM, Ngan TB, Hue NT, Thach TD, Van Cuong P. 2018. Chemical constituents of MeOH extract from the fruits of Macaranga sampsonii. Vietnam J Chem. 56(5):587–590.

Rumzhum NN, Sohrab MH, Al-Mansur MA, Rahman MS, Hasan CM, Rashid MA. 2012. Secondary metabolites from Jatropha podagrica hook. J Phys Sci. 23(1):29–37.

Segun PA, Ogbole OO, Akinleye TE, Faley TO, Adeniji AJ. 2021. In vitro anti-enteroviral activity of stilbenoids isolated from the leaves of Macaranga barteri. Nat Prod Res. 35(11):1909–1913.

Singh K, Naidoo Y, Mocktar C, Bajnath H. 2018. Biosynthesis of silver nanoparticles using Plumbago auriculata leaf and calyx extracts and evaluation of their antimicrobial activities. Adv Nat Sci: Nanosci Nanotechnol. 9(3):035004.

Singh N, Manchanda V. 2017. Control of multidrug-resistant gram-negative bacteria in low- and middle-income countries-high impact interventions without much resources. Clin Microbiol Infect. 23(4):216–218.

Sutthivaiyakit S, Unganon S, Sutthivaiyakit P, Suksamrarn A. 2002. Diterpenylated and prenylated flavonoids from Macaranga auriculata. Tetrahedron. 58(18):3619–3622.

Tanjug M, Juliawaty LD, Hakim EH, Syah YM. 2018. Flavonoid and stilbene derivatives from Macaranga trichocarpa. Fitoterapia. 126:74–77.

Vu LTN, Anh LT, Cuc NT, Nhiem NX, Tai BH, Van Kiem P, Litaudon M, Thach TD, Van Minh C, Mai HDT, et al. 2021. Prenylated flavonoids and other constituents from Macaranga indica. Nat Prod Res. 35(13):2123–2130.
WHO. 2017. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva.
Xu D, Hu MJ, Wang YQ, Cui YL. 2019. Antioxidant activities of quercetin and its complexes for medicinal application. Molecules. 24(6):1123.
Yang DS, Li ZL, Peng WB, Yang YP, Wang X, Liu KC, Li XL, Xiao WL. 2015a. Three new prenylated flavonoids from Macaranga denticulata and their anticancer effects. Fitoterapia. 103:165–170.
Yang DS, Wei JG, Peng WB, Wang SM, Sun C, Yang YP, Liu KC, Li XL. 2014. Cytotoxic prenylated bibenzyls and flavonoids from Macaranga kurzii. Fitoterapia. 99:261–266.
Yang X, Jiang Y, Yang J, He J, Sun J, Chen F, Zhang M, Yang B. 2015b. Prenylated flavonoids, promising nutraceuticals with impressive biological activities. Trends Food Sci Technol. 44(1):93–104.
Ye G, Peng H, Fan M, Huang CG. 2007. Ellagic acid derivatives from the stem bark of Dipentodon sinicus. Chem Nat Compd. 43(2):125–127.