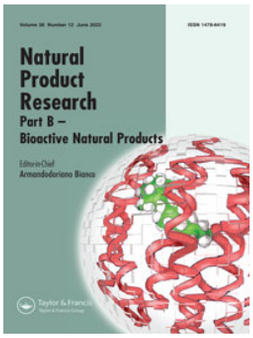

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SHORT COMMUNICATION

Antibacterial secondary metabolites from *Vernonia auriculifera* Hiern (Asteraceae) against MDR phenotypes

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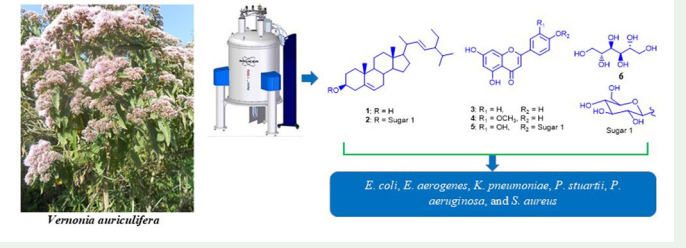
ABSTRACT

Purification of the aerial parts of *Vernonia auriculifera* Hiern afforded steroids (**1–2**), flavonoids (**3–5**), and polyalcohol (**6**). Their structures were determined using spectral evidences as well as by comparison with reported data. Iodonitrotetrazolium chloride (INT) colorimetric assay was used to assess the antibacterial activity of the extract and isolates against 13 pathogenic strains. The crude extract showed strong antibacterial activity (MIC $<$ 100 µg/mL) against the tested bacterial strains. When combined with an efflux pump inhibitor phenylalanine beta naphthylamide (PAβN), the inhibition potency of the extract was substantially enhanced with the lowest MIC value at 4 µg/mL. Compounds **5** and **6** showed moderate activity (MIC $<$ 100 µg/mL) against 12/13 (92.3%), and 8/13 (61.5%) bacterial strains, respectively. A minimal bactericidal concentration (MBC)/minimal inhibitory concentration (MIC) ratio $\leq$ 4 indicated their bactericidal effect against *Escherichia coli*, *Enterbacter aerogenes*, *Klebsiella pneumoniae*, *Providencia stuartii*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.



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1. Introduction

Microbial agents continue to develop enormous resistance mechanisms thwarting the effectiveness of drugs, not sparing even the newly discovered ones (Zahin et al. 2010). Medicinal plants are increasingly attracting attention among researchers since they have been indicated to possess bioactive phytochemicals with effective properties against antimicrobial agents.

Vernonia auriculifera Hiern (Asteraceae family) possess a wide range of applications in traditional medicine. In Uganda, the root infusion of *V. auriculifera* is used to cure malaria (Zahin et al. 2010). The leaves of *V. auriculifera* are used to treat toothache in Cameroon and Ethiopia (Toyang and Verpoorte 2013). Based on previous studies, a number of *Vernonia* species have elaborated mainly the presence of terpenes, diterpenes, flavonoids, and sesquiterpene lactones (Toyang and Verpoorte 2013; Antonio et al. 2015). The latter have been documented as the chemotaxonomic markers of this family (Moujir et al. 2020). Previous phytochemical and antimicrobial study on *V. auriculifera* carried out by Kiplimo et al (2011) led to the isolation eight pentacyclic compounds with moderate level of antibacterial activity (Kiplimo et al. 2011). In this study the antibacterial activity of the ethanolic extract, steroids, flavonoids, and sugar alcohol is reported against a panel of multi-drug resistant (MDR) microorganisms.

2. Results and discussion

Phytochemical study of aerial parts of *V. auriculifera* yielded six (6) known secondary metabolites identify as stigmasterol (**1**), stigmasterol-3-*O*-β-D-glucopyranoside (**2**) (Nchiozem-Ngnitedem et al. 2020), apigenin (**3**) (Kumar et al. 2018), diosmetin (**4**) (Kumar et al. 2018), luteolin-4′-*O*-β-D glucoside (**5**) (Kumar et al. 2018), and D-mannitol (**6**) (Venditti et al. 2016), Figure 1. The structures of the isolates were determined based on spectroscopic (NMR) methods as well as by comparison with similar data previously documented.

The antibacterial study of the crude extract as well as the isolated compounds was evaluated against thirteen (13) microorganisms including Gram-negative (*Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Providencia stuartii*), and Gram-positive (*Staphylococcus aureus*) bacterial strains (Table S1, Supplementary Material). The ethanolic extract displayed antibacterial activity towards 13/13 (100%) of tested bacterial strains with good activity (MIC $<$ 100 μg/mL)

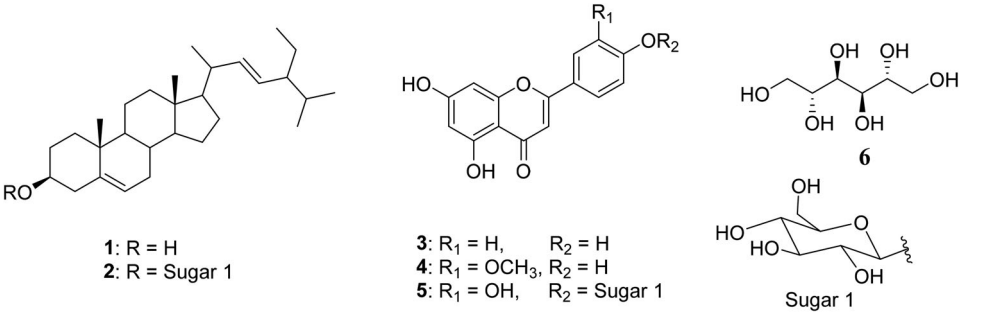

Figure 1. Structures of isolates obtained from the aerial part of *V. auriculifera*.

(Kuete and Efferth 2010; Bitchagno et al. 2015). Among the isolated compounds, flavonoid glycoside (**5**) was the most active showing moderate activity (Kuete and Efferth 2010) against 12/13 (92.3%) tested bacterial strains (Table S2, Supplementary Material). Alditol (**6**) displayed similar level of activity towards 8/13 (61.5%) tested bacterial strains with MIC $< 100\,\mu g/mL$. The other isolates (**1–4**) demonstrated MIC $> 100\,\mu g/mL$, therefore were considered as inactive (Kuete and Efferth 2010). Ciprofloxacin, a reference antibiotic displayed moderate activity against 10/13 (76.9%) tested bacterial strains but had low activity (MIC $> 100\,\mu g/mL$) against *K. pneumoniae* strains. A bactericidal effect with MBC/MIC ratio ≤ 4 was noted for the most active isolates (**5** and **6**) indicating their lethal effect. Efflux pumps have been shown to decrease the intracellular concentration of antibiotics and consequently their activity (Van et al. 2012). The pathogens used in this work are known for their ability to express efflux pumps to a high degree (Kuete et al. 2010). However, these pathogenic bacteria were highly susceptible to the crude extract, and the standard drug ciprofloxacin in the presence of the efflux pump inhibitor, phenylalanine beta naphthylamide, PAβN (Table S2, Supplementary Material). The results showed that, the observed MICs values of *V. auriculifera* aerial parts extract, and ciprofloxacin in the presence of PAβN were significantly enhanced in most cases displaying MICs between 1–16, and 1–4 μg/mL, respectively. Additionally, the low activity (MIC or MBC $>512\,\mu g/mL$) of some secondary metabolites can be explained by the fact that bacterial strains used in this study were multidrug resistance (MDR) phenotypes overexpressing efflux pumps (Kuete 2010). Overall, this study is in good agreement with previous report carried out by Kiplimo and collaborators which showed the synergism effect of isolates in the matrix for strong antibacterial activity (Kiplimo et al. 2011).

3. Conclusion

Five (5) compounds were isolated from the aerial parts of *V. auriculifera*. The crude extract displayed strong antibacterial activity against the tested bacterial strains compared to the isolated compounds, and ciprofloxacin. Overall, the results showed that, *V. auriculifera* could be a potential source of phytodrugs for the control of MDR bacterial infections.

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Disclosure statement

The authors declare that they have no competing interest.

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