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SHORT COMMUNICATION

Antiplasmodial and antimicrobial activities of *ent*-abietane diterpenoids from the roots of *Suregada zanzibariensis*

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ABSTRACT

The root extract of *Suregada zanzibariensis* Baill. afforded six previously described *ent*-abietane diterpenoids, namely 7-oxo-*ent*-abieta-5(6),8(14),13(15)-trien-16,12-olide (**1**), mangiolide (**2**), 8,14β:11,12α-diepoxy-13(15)-abietane-16,12-olide (**3**), 7β,11β,12β-trihydroxy-*ent*–abieta-8(14),13(15)-diene-16,12-olide (**4**), 8α,14-dihydro-7-oxo-jolkinolide E (**5**), jolkinolide A (**6**), together with 3β-sitosterol (**7**), scopoletin (**8**) and vanillin (**9**). Their structures were deduced through 1D and 2D NMR spectroscopic techniques, and HRESIMS, as well as by comparison of the NMR data with those reported in the literature. The crude extract and compounds **1**–**9** were evaluated for their antiplasmodial, antifungal and antibacterial activities. Mangiolide (**2**) showed strong *in vitro* antiplasmodial activity against chloroquine sensitive (D6) and resistant (W2) strains of *Plasmodium falciparum* with IC_{50} values of 0.79 and 0.87 μg/mL, respectively, while **3** (IC_{50} 1.24 and 1.17 μg/mL) was less active than **2**. Compound **2** also displayed antimicrobial activity against *Cryptococcus neoformans*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE) with IC_{50} values of 1.20, 3.90 and 7.20 μg/mL, respectively.

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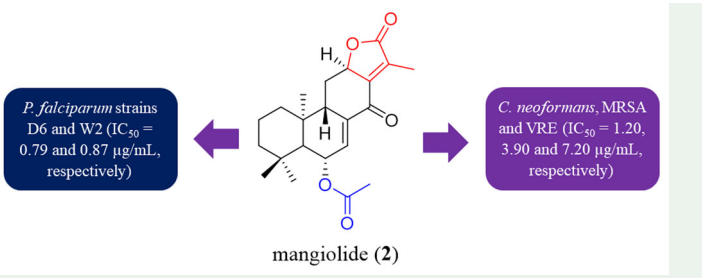

1. Introduction

The genus *Suregada* (Euphorbiaceae) accummulate roughly 40 species found worldwide, including Australia, Southeast Asia and Africa (Yan et al. 2008). *Suregada zanzibariensis*, a plant endemic to East Africa including Kenya has recently attracted the attention of different research group as a source of *ent*-abietane lactones with a large spectra of activities. Previous biological studies on the methanol extract of the leaves demonstrated good antiplasmodial activity (Kigondu et al. 2009), and its essential oil displayed insect repellence activity (Innocent et al. 2010). In another investigation, from the stem bark of *S. zanzibariensis*, Mangisa et al. nicely demonstrated the cytotoxicity and anticancer properties of mangiolide and jolkinolide B against a panel of cancer cell lines (Mangisa et al. 2019). More recently, Kalenga and colleagues showed that *S. zanzibariensis* leaf extract displayed inhibitory effect against herpes simplex virus 2 (HSV-2) and was also found to be toxic on African green monkey kidney (Kalenga et al. 2022). Futhermore, zanzibariolides A and B, two modified abietanolides purified from this extract fails to suppress the release of HSV-2. Despite all these elegant activities, neither the antiplasmodial, nor the antimicrobial effects of the root extract of this endemic plant as well as the phytochemicals have been reported. Hence, through various chromatographic separation techniques, followed by spectroscopic and HRESIMS analysis, six known *ent*-abietane diterpenoids **1** – **6**, together with 3β-sitosterol (**7**), scopoletin (**8**) and vanillin (**9**), were isolated and characterized. The antiplasmodial activity against chloroquine sensitive D6 and resistant W2 strains of *P. falciparum* and antimicrobial potency towards *Cryptococcus neoformans*, MRSA and VRE are reported in this paper.

2. Results and discussion

Phytochemical analysis of *S. zanzibariensis* roots used as a medicinal ingredient by indigenous local communities was undertaken. Systematic fractionation of the roots extract; followed by further purification of subfractions by chromatographic methods (for details see Experimental, Supplementary material), yielded nine secondary metabolites, including *ent*-abietanes (**1**–**6**) and compounds (**7**–**9**) (Figure 1). Their structures were elucidated based on 1D and 2D NMR spectroscopic data and HRESIMS, as well as by comparing those reported in the literature data. Furthermore, the relative configurations around the stereogenic carbons were established based on coupling constants alongside NOESY correlations notably between H-12 and the angular methyl group

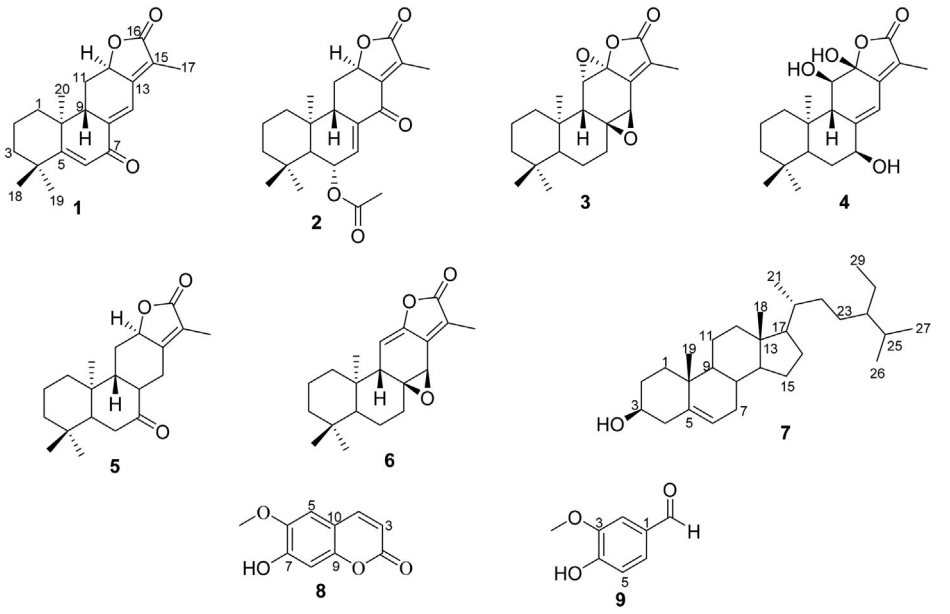

Figure 1. Secondary metabolites purified from the methanol/dichloromethane (1:1) root extract of *Suregada zanzibariensis*.

(CH_3-20). They were identified as 7-oxo-*ent*-abieta-5(6),8(14),13(15)-trien-16,12-olide (**1**) (He et al. 2009), mangiolide (**2**) (Mangisa et al. 2019), 8,14β:11,12α-diepoxy-13(15)-abietane-16,12-olide (**3**) (Gondal et al. 2018), 7β,11β,12β-trihydroxy-*ent*–abieta-8(14),13(15)-diene-16,12-olide (**4**) (Wang et al. 2006), 8α,14-dihydro-7-oxo-jolkinolide E (**5**) (Appendino et al. 2000), jolkinolide A (**6**) (Sutthivaiyakit et al. 2000), β-sitosterol (**7**) (Ayaz et al. 2017), scopoletin (**8**) (Mehul et al. 2011) and vanillin (**9**) (Michalakea et al. 2019). The important features depicted in the ^{1}H-NMR spectrum of **1**, **2** and **5** include the presence of homoallylic splitting observed between the methyl group (CH_3-17) and the oxymethine proton (H-12) in the lactone ring. Such spliting could not be depicted while analyzing the spectroscopic (NMR) data of compounds **3**, **4** and **6** indicating some substitution at C-12 in these compounds. 8,14β:11,12α-Diepoxy-13(15)-abietane-16,12-olide (**3**) appears to have originated from jolkinolide A (**6**) by epoxidation at C-11/C-12, since these two compounds were structurally related. Furthermore, it was found that 2D NMR HMBC correlations of compounds **3** and **5** have not been reported so far. Therefore, we have analyzed their full NMR data (Table S1, Supplementary material), which eventually substantiated the proposed structures. Based on these observations, all isolated compounds, except **2**, are reported from this plant for the first time.

The antiplasmodial and antimicrobial potencies of the crude extract of *S. zanzibariensis* and its isolated compounds **1**–**9** were evaluated against malaria causing parasite *P. falciparum* D6 (chloroquine-sensitive clone) and W2 (chloroquine-resistant clone) strains, as well as fungi and bacteria, notably *C. neoformans*, MRSA and VRE, (Table 1). Among the isolated compounds, diterpene **2** exhibited strong antiplasmodial activity with IC_{50} values of 0.79 μg/mL (SI 4.6) and 0.89 μg/mL (SI 4.2) against D6 and W2 strains, respectively. Additionally, it has been reported to have potent anticancer

Table 1. Antimalarial and antimicrobial activities (IC_{50} values are in μg/mL) of crude extract and compounds **2** and **3** obtained from *Suregada zanzibariensis*.

	P. falciparum					Antimicrobial		
	D6[a]		W2[b]		VERO cells	*C. neoformans*	MRSA	VRE
Extract/compounds	IC_{50}	SI[c]	IC_{50}	SI[c]	IC_{50}	IC_{50}	IC_{50}	IC_{50}
S. zanzibariensis	>47.6	1	>47.6	1	>47.6	>200	>200	>200
2	0.79	4.6	0.89	4.2	3.6	1.20	3.90	7.20
3	1.24	>3.8	1.17	>4.1	>4.76	>20	>20	>20
Chloroquine	0.016	497	0.16	48	>4.76	–	–	–
Artemisinin	0.0056	845	0.003	1697	>4.76	–	–	–
Methicillin	–	–	–	–	–	–	50	>20
Vancomycin	–	–	–	–	–	–	0.73	>20

[a]Chloroquine-sensitive clone; [b]Chloroquine-resistant clone; [c]Selectivity index = IC_{50} VERO cells/IC_{50} *P. falciparum; C. neoformans: Cryptococcus neoformans* ATCC 90113; MRSA: methicillin-resistant *Staphylococcus aureus* ATCC 43300; VRE: Vancomycin-resistant *Enterococcus faecium*.

activity against a panel of selected cancer cell lines though it displayed significant cytotoxicity ($LC_{50} < 10$ μM) (Mangisa et al. 2019) while **3** was less active (IC_{50} 1.24 and 1.17 μg/mL).

The *in vitro* antifungal and antibacterial assays were evaluated against *C. albicans*, *A. fumigatus* and *C. neoformans*, VRE, MRSA, *E. coli*, *P. aeruginosa* and *K. pneumoniae*. All fungi and bacteria tested were found to be inactive against the extract and isolated compounds (IC_{50} >200 and >20 μg/mL, respectively), except **2**, which was active against *C. neoformans* and MRSA, and moderately active against VRE with IC_{50} value of 1.20, 3.90 and 7.20 μg/mL, respectively. In an ealier study, compound **6** (jolkinolide A) at 50 μg/mL was found to be inactive against *Moraxella catarrhalis*, a Gram-negative bacteria responsible for infections of the respiratory system (Sutthivaiyakit et al. 2000).

3. Conclusions

In summary, nine known secondary metabolites were purified from the root extract of *S. sanzibariensis*. The acetylated abietanolide (**2**) displayed both antiplasmodial and antimicrobial activities against *P. falciparum* and MRSA, while **3** only showed selective inhibitory activity against *P. falciparum* strains.

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Disclosure statement

The authors declare no conflict of interest.

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