In vitro antiplasmodial and cytotoxic activities of sesquiterpene lactones from *Vernonia fimbrillifera* Less. (Asteraceae)

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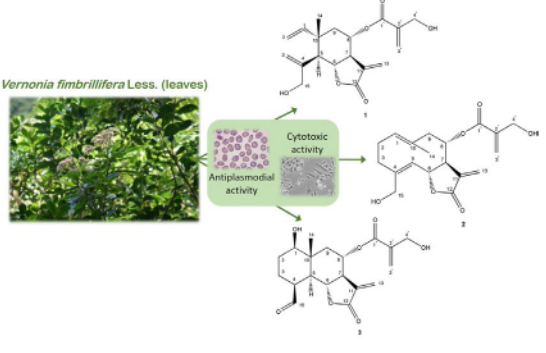
ABSTRACT

Due to the *in vitro* antiplasmodial activity of leaf extracts from *Vernonia fimbrillifera* Less. (Asteraceae), a bioactivity-guided fractionation was carried out. Three sesquiterpene lactones were isolated, namely 8-(4′-hydroxymethacrylate)-dehydromelitensin (**1**), onopordopicrin (**2**) and 8α-[4′-hydroxymethacryloyloxy]-4-epi-sonchucarpolide (**3**). Their structures were elucidated by spectroscopic methods (1D and 2D NMR and MS analyses) and by comparison with published data. The isolated compounds exhibited antiplasmodial activity with IC_{50} values ≤ 5 µg/mL. Cytotoxicity of the compounds against a human cancer cell line (HeLa) and a mouse lung epithelial cell line (MLE12) was assessed to determine selectivity. Compound **3** displayed promising selective antiplasmodial activity (SI > 10).



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1. Introduction

According to the World Health Organization (WHO 2016), malaria caused at least 429 000 deaths globally in 2015. Among these, 70% were children under the age of five and 99% were due to the parasite species *Plasmodium falciparum*. The fight against this major public health problem is threatened by the rapid emergence and spread of parasite strains resistant towards available approved treatments. Urgent efforts are therefore needed to identify new antimalarial drugs. As such, our research groups decided to study Reunion Island as a potential source for the discovery of new antiplasmodial metabolites. This natural patrimony has been identified as a biodiversity hotspot due to its numerous endemic species and its preserved ecosystems (Myers et al. 2000). The National Botanical Conservatory of the Mascarenes indicates that *Vernonia fimbrillifera* Less. is an endemic species from Reunion Island, locally named 'bois de source', which grows in the humid tropical forest (Lavergne and Véra 1989). To the best of our knowledge, neither phytochemical nor pharmacological works have been performed up to now on *V. fimbrillifera*. This study isolated and determined the structure of three antiplasmodial sesquiterpene lactones. Compounds were additionally tested *in vitro* for their cytotoxicity and their selectivity indices were established.

2. Results and discussion

2.1. Chemical composition

An antiplasmodial bioassay-guided fractionation of the CH_2Cl_2 extract from *V. fimbrillifera* leaves was carried out and three compounds (**1–3**) were obtained as active ingredients (Figure 1). Based on their NMR and HR-ESI-MS data and through comparison with those already described in literature, their structures were established as 8-(4′-hydroxymethacrylate)-dehydromelitensin (**1**) (Rustaiyan et al. 1979; Cardona et al. 1989; García et al. 1996), onopordopicrin (**2**) (Lonergan et al. 1992) and 8α-[4′-hydroxymethacryloyloxy]-4-epi-sonchucarpolide (**3**) (Rustaiyan et al. 1986; García et al. 1996).

2.2. Biological activities: antiplasmodial and cytotoxic activities

The three sesquiterpene lactones (**1–3**) isolated from the CH_2Cl_2 extract of *V. fimbrillifera* (leaves) demonstrated *in vitro* antiplasmodial activity with IC_{50} values of 2.96 ± 0.86, 3.37 ± 0.56 and 3.27 ± 1.32 µg/mL (n = 3, see Table S1), respectively, against the 3D7 strain of *P. falciparum*. This study is the first report of such activities concerning **1** and **3**. The

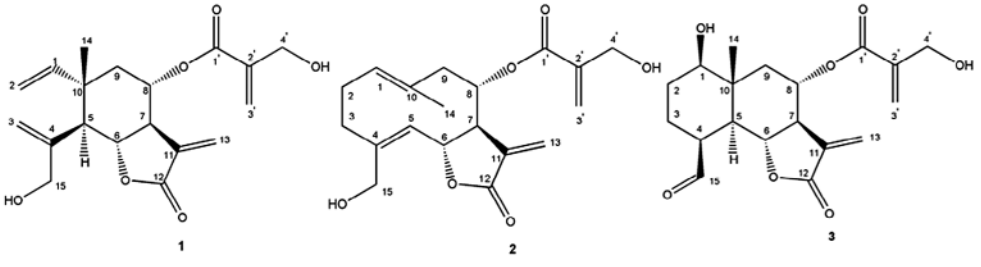

Figure 1. Chemical structures of compounds 1–3.

antiplasmodial activity of **2** has already been described in *Arctium nemorosum* Lej. (Zimmermann et al. 2012). The cytotoxic activity of the compounds was also assessed in order to determine their selectivity. All tested compounds showed cytotoxic activities (ranging from 10.17 ± 0.88 to 35.48 ± 0.15 µg/mL, n = 3) against both mammalian cell lines HeLa and MLE12. As stated in the literature, these compounds have already been found to be cytotoxic (Lonergan et al. 1992; Formisano et al. 2012; Kolli et al. 2012). However, according to WHO guidelines (Pink et al. 2005), compound **3** has a promising selectivity index, being 10 times more potent against *P. falciparum* (Table S1). Several structure–activity relationship studies (Picman 1986; Scotti et al. 2007) have highlighted that α,β-unsaturated ketones seems to be crucial for the biological properties of these compounds due to their particular reactivity (e.g. Michael-type addition) towards free thiol groups. Nevertheless, the higher selectivity of compound **3,** as shown in our work, cannot be easily explained. The presence of an aldehydic moiety on this compound could perhaps contribute to its selectivity, and will be the focus of further studies.

3. Conclusion

To conclude, this study both revealed and confirmed the *in vitro* antiplasmodial and cytotoxic activities of three sesquiterpene lactones isolated from *V. fimbrillifera*. To the best of our knowledge, this is the first report of the antiplasmodial activity and the isolation of compounds **1** and **3** from the *Vernonia* genus. These findings justify that plants of this genus are still to be considered as a rich source of compounds (Dogra and Kumar 2015), particularly sesquiterpene lactones, with potential antiplasmodial activities.

Supplementary Material

Experimental, biological activity data and full NMR data are available online.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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