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Phytochemical investigation of *Eremophila* spp.

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Abstract

Four species of the Australian endemic genus *Eremophila* have been phytochemically investigated as part of a large interdisciplinary project aiming at identifying bioactive natural products. This led to isolation of a series of new caryophyllane sesquiterpenoids and known flavonoids from *E. spathulata*, serrulatanes and flavonoids from *E.* sp. *Kennedy Range* aff. *Compacta BB105*, serrulatanes diterpenoids from *E. denticulata* and benzoylated iridoid glycosides, feruloylated iridoid glycosides and lignans from *E. pantonii*.

Background

Eremophila is a genus comprising approximately 230 species endemic to Australia, and it has played an important role for medicinal and ceremonial purposes for the Australian Aboriginal people. Currently more than 200 natural products have been isolated from *Eremophila*, most of them being sesqui- and diterpenoids [1].

Methods

HPLC

Semi-preparative HPLC was initially used to fractionate the crude extract, and analytical HPLC or HPLC-PDA-SPE was used to further fractionate or purify the collected fractions (**Figure 1**).

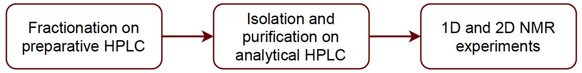

Figure 2: Flow chart of the experimental work

NMR

Structures of the isolated compounds were elucidated by extensive analysis of 1D and 2D NMR experiments. ^{1}H-NMR, HSQC, COSY and HMBC provided structural information, whereas ROESY was used to determine the relative configuration of the molecule (**Figure 2**).

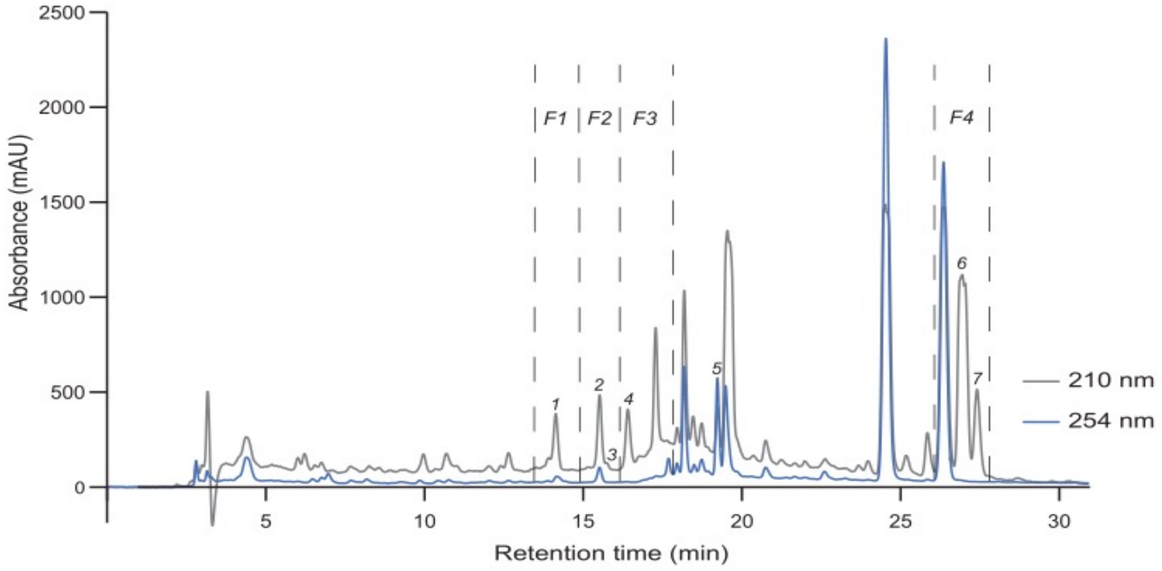

Figure 2: Chromatogram of crude of *E. spathulata* extract with semipreparative-scale fractions as well as the seven isolated compounds indicated

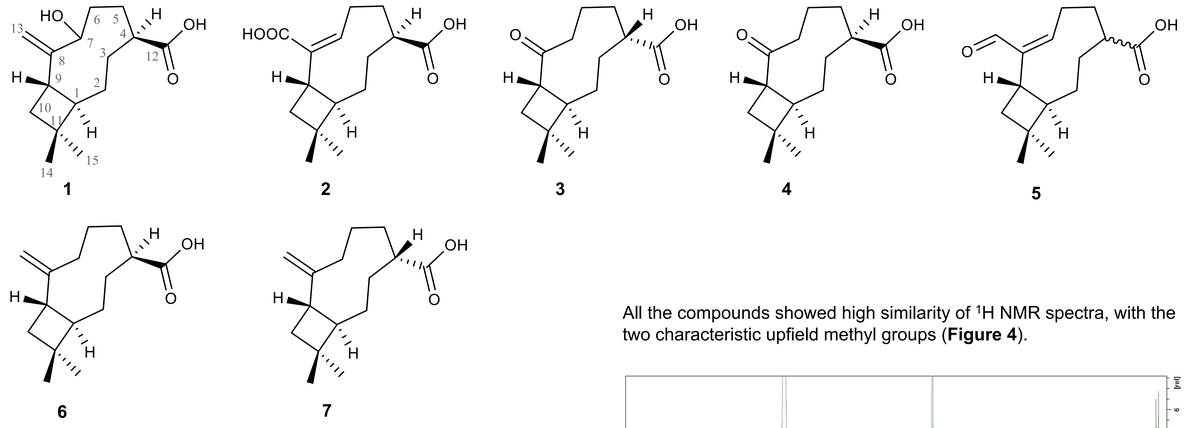

Figure 3: The seven isolated sesquiterpenoids from *E. spathulata*

Results

Isolation of compounds

Semi-preparative HPLC led to isolation of compound **5**, and furthermore four fractions were collected. Fractions 1, 2 and 3 were further fractionated by analytical-scale HPLC leading to isolation of compounds **1**, **2**, **3**, and **4**. Fraction 4 was trapped on HPLC-PDA-SPE which led to the isolation of compounds **6** and **7** (**Figure 3**).

Structure elucidation

Structure elucidation of the seven compounds revealed 5 new compounds and 2 compounds which have been previously reported - however without spectral data (**Figure 3**). All of the seven compounds are sesquiterpenoids and they belong to the class caryophyllanes, which is characterized by a fused bicyclic ring system of dimethylcyclobutane and cyclononane [2].

Highly oxygenated flavonoids were isolated from both *E. spathulata* and *E.* sp. *Kennedy Range* aff. *Compacta BB105, other types of serrulatanes diterpenoids were isolated from both E.denticulata and E.* sp. *Kennedy Range* aff. *Compacta BB105* and benzoylated iridoid glycosides, feruloylated iridoid glycosides and lignans from *E. pantonii*.

All the compounds showed high similarity of ^{1}H NMR spectra, with the two characteristic upfield methyl groups (**Figure 4**).

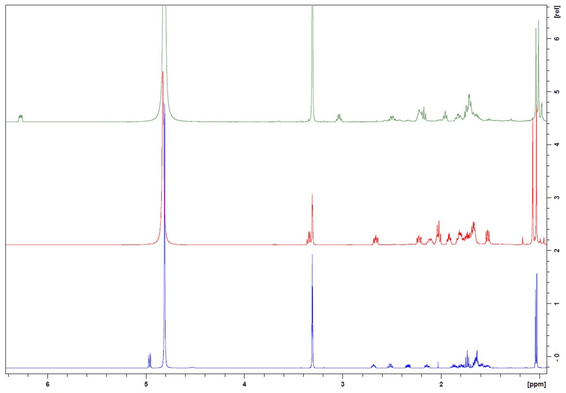

Figure 4: Overlay of ^{1}H NMR spectrum of compound **2** (green), compound **4** (red), and compound **6** (blue),

References

[1] Singab, A. N., Youssef, F. S., Ashour, M. L. & Wink, M. The genus *Eremophila* (Scrophulariaceae): an ethnobotanical, biological and phytochemical review: *Eremophila*: ethnobotany, biology & chemistry. *J Pharm Pharmacol* **2015**, *65*, 1239-1279.

[2] Di Sotto, A. *et al.* Chemopreventive potential of caryophyllane sesquiterpenes: An overview of preliminary evidence. *Cancers* **2020**,*12*, 3034.