Updated review of the bioactive compounds isolated from *Plectranthus ecklonii* Benth.

Eva María Domínguez-Martín[1,2], Gabrielle Bangay[1], Ana Margarida Antão[1,3], Epole Ntungwe[1,2], Vera Isca [1,3], Ana María Díaz-Lanza[2], Patrícia Rijo[1,3]

[1] CBIOS - Research Center for Biosciences & Health Technologies, Universidade Lusófona de Humanidades e Tecnologias, Campo Grande 376, 1749-024 Lisboa, Portugal.

[2] Department of Biomedical Sciences, Faculty of Pharmacy, University of Alcalá de Henares, Ctra. A2, Km 33.100 – Campus Universitario, 28805. Alcalá de Henares, Madrid, Spain.

[3] Instituto de Investigação do Medicamento (iMed.ULisboa), Faculdade de Farmácia, Universidade de Lisboa, 1649-003 Lisboa, Portugal.

Introduction

The global figure of cancer cases is set to reach 15 million by 2030, as such, the discovery of novel anti-cancer drugs is imperative. *Plectranthus ecklonii* Benth. (*Lamiaceae*) has widespread ethnobotanical and traditional uses, including in southern Africa to treat listeriosis, tuberculosis-related and respiratory problems and skin diseases [1]. *Plectranthus* species contain many active compounds, including terpenoids, flavonoids and phenolic compounds, known for having multiple biological activities such as anti-inflammatory, antioxidant and antitumour [2]. These properties suggest that *Plectranthus* is a promising genera for the discovery of medicinal compounds and an inspiration for pharmaceutical drug discovery [3,4].

Aims

This work aims to enumerate the abietane diterpene secondary metabolites, isolated to date, from the extracts and fractions of *Plectranthus ecklonii* Benth.. This review focuses on the documented bioactivity of the isolated active compounds, parvifloron D, E, F and sugiol, in order to consider their potential for pharmaceutical development of novel drugs.

P. ecklonii 'Erma', with pink flowers

P. ecklonii 'Tommy', with white flowers

Methods & Materials

The following search terms, *'Plectranthus ecklonii', 'parvifloron D', 'parvifloron E', 'parvifloron F' and 'sugiol',* were used to examine databases, including PubMed, Web of Science and ScienceDirect. Chemical structures were drawn using ChemDraw 19.1.

Results

Abietane diterpenes account for largest number of bioactive terpenes in the Lamiaceae family. Among the 28 compounds isolated from *P. ecklonii*, a total of 4 abietane diterpenes have been identified; Parvifloron D **(1)**, Parvifloron F **(2)**, Parvifloron E **(3)** and Sugiol **(4)**, all showing various biological activity.

ANTIBACTERIAL & ANTIMICROBIAL

- Parvifloron D has demonstrated activity against methicillin- and vancomycin-resistant strains, including *Staphylococcus aureus* and *Enterococcus* species.
- High biological activity was observed when *P. ecklonii* was tested against *Candida* species.
- Parvifloron D and F active against *Listeria monocytogenes, Escherichia coli, Mycobacterium smegmatis*, *Pseudomonas aeruginosa, Enterococcus faecalis* and *Mycobacterium tuberculosis.*

ANTIPLASMODIC

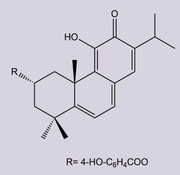
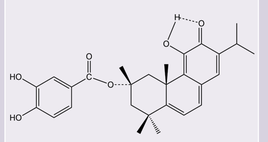
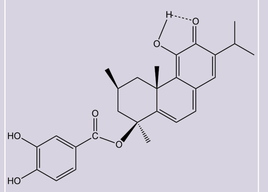
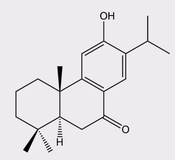
- Parvifloron D and F showed activity in the breakdown of *Listeria monocytogenes* biofilm with an MIC of 15.6 µg/ml and 31.25 µg/ml, respectively.
- Parvifloron F was more effective than quinine and 62% as active as chloroquine, two conventional antimalarials.
- Sugiol showed an IC_{50} between 1.4 µM and 3.4 µM on *Plasmodium falciparum* strains.

ANTIOXIDANT & ANTIINFLAMMATORY

- Sugiol showed significant scavenging activities of DPPH, nitric oxide, superoxide and hydroxyl free radicals and an inhibitory effect of lipid peroxidation.
- Parvifloron D showed antioxidant properties equivalent to hydroxyl butyltoluene but lower than quercetin.
- Sugiol showed effective inhibition of the production of pro-inflammatory cytokines, prointerleukin-1beta IL-1β, tumour necrosis factor alpha and mitogen-activated protein kinases.

ANTI-TUMOUR, CYTOTOXIC & APOPTOSIS

- Sugiol showed activity against human breast, lung, pancreatic and colon cancer cell lines and exhibited a lower IC_{50} value than the classical topoisomerase I inhibitor, camptothecin.
- Parvifloron D was effective against glioma, leukaemia and pancreatic cell lines.
- Parvifloron F demonstrated activity against lung and breast cancer cell lines.
- Parvifloron F showed stronger apoptotic effect on leukaemia cell lines than taxodone.

ABIETANE DITERPENE	IUPAC NAME	STRUCTURE	BIOLOGICAL ACTIVITY
PARVIFLORON D (1)	11-hydroxy-2α-(4-hydroxybenzoyloxy)-abieta-5,7,9(11),13-tetraene-12-one		Antibacterial Antitumor Antimicrobial Antilisteria Ant-inflammatory
PARVIFLORON F (2)	11-hydroxy-2α-(3,4-dihydroxybenzoyloxy)-abieta-5,7,9(11),13-tetraene-12-one		Antiplasmodic Antibacterial Apoptosis Cytotoxic
PARVIFLORON E (3)	11-Hydroxy-19-(3,4-dihydroxybenzoyloxy)-abieta-5,7,9(11),13-tetraene-12-one		Antiplasmodic Anticariogenic
SUGIOL (4)	12-hydroxyabieta-8,11,13-trien-7-one		Antibacterial Antioxidant Antitumour

Conclusions

- Abietane diterpenes from *P. ecklonii* demonstrate an array of important biological activity, with Parvifloron D showing the highest amount of bioactivity.
- Natural compounds isolated from *P. ecklonii* could provide effective treatment for a range of cancers, including lung, colon, breast and pancreatic.
- Parvifloron D has been documented as compromising clinical efficacy in many anti-tumour drugs due to the production of multidrug resistance mechanisms, therefore it is imperative to discover more effective analogues of these naturally-derived compounds.

References

[1] Lukhoba, C.W., Simmonds, M.S.J., & Paton, A.J. (2006). *Plectranthus*: a review of ethnobotanical uses. *Journal of Ethnopharmacology*, *103*(1), 1–24. [2] Garcia, C., Teodósio, C., Oliveira, C., Oliveira, C., Díaz-Lanza, A., Reis, C., Duarte, N. and Rijo, P. (2019). Naturally Occurring Plectranthus-derived Diterpenes with Antitumoral Activities. *Current Pharmaceutical Design*, 24(36), 4207-4236. [3] Sitarek, P., Toma, M., Ntungwe, E., Kowalczyk, T., Skała, E., Wieczfinska, J., Śliwiński, T. and Rijo, P. (2020). Insight the Biological Activities of Selected Abietane Diterpenes Isolated from Plectranthus spp. *Biomolecules*, 10(2), 194. [4] Garcia, C., Ntungwe, E., Rebelo, A., Bessa, C., Stankovic, T., Dinic, J., Díaz-Lanza, A., P. Reis, C., Roberto, A., Pereira, P., Cebola, M., Saraiva, L., Pesic, M., Duarte, N. and Rijo, P. (2019). Parvifloron D from Plectranthus strigosus: Cytotoxicity Screening of Plectranthus spp. Extracts. *Biomolecules*, 9(10), 616.

Acknowledgements

This research was funded by *Fundação para a Ciência e a Tecnologia* (FCT, Portugal), through projects UIDP/04567/2020 and UIDB/04567/2020. E.M.D-M gratefully acknowledges being the recipient of a predoctoral FPU 2019 fellowship from the University of Alcalá de Henares.

6th International Electronic Conference on Medicinal Chemistry
1-30 November 2020

sponsored: MDPI *pharmaceuticals*