Project Details	
Project Code	MRCIIAR26Ex Nuetzmann
Title	Decoding the pharmaceutical potential of mistletoe
Research Theme	IIAR
Project Type	Wet lab
Summary	Microbial infections threaten our health and kill millions worldwide. In this project, we will deploy cutting edge biochemistry, genomics, and microbiology to carry out an in-depth characterisation of the natural products of mistletoe and assess their bioactivity against microbial pathogens and biofilms. Our goal is to decode the pharmaceutical potential of a traditional medicinal plant in the treatment of microbial diseases.
Description	Viscum album, commonly known as European Mistletoe, has been used in traditional medicine for centuries and continues to be studied for its diverse pharmacological applications. The natural products of this parasitic plant have shown anti-microbial, anti-cancer, cardiovascular and antidiabetic effects and have been demonstrated to improve the quality of life of cancer patients. In a recent research breakthrough, the giant genome of mistletoe, 30 times larger than the human genome, has been fully assembled, making it now possible to link the natural products of mistletoe to its genetic reservoir of biosynthesis genes and to fully unlock its potential to produce bioactive natural products. In this PhD project, we aim to systematically dissect the metabolic reservoir of mistletoe and to analyse the anti-microbial activity of its metabolites. Our objectives will be: (i) to biochemically characterize the pool of natural products of mistletoe and to uncover its genomic potential for the synthesis of bioactive metabolites, (ii) to link biosynthesis genes to bioactive metabolites and re-constitute metabolic pathways, and (iii) to establish the inhibitory potential of mistletoe extracts, individual metabolites and metabolite combinations on microbial communities. In detail, we will investigate the metabolic profile of mistletoe by liquid and gas chromatography-mass spectrometry (LC-MS and GC-MS). We will collect samples at different times of the year, different growth stages and tissues to collect a comprehensive library of molecules. Identification of novel compounds will be enhanced by a new cutting-edge mass spectrometer with Multistage Mass Spectrometry (MSn) capability at Biosciences Exeter. Metabolic experiments will be accompanied by advanced genome annotation of putative metabolism genes as well as transcriptomics by RNAseq and epigenomics by Cut&Tag to identify candidate metabolite biosynthesis genes. To confirm gene function and reconstitute pathways, key candidate genes will be heterologously expressed and products chemically analysed. Metabolite extracts as well as pure compounds will be tested for their cytotoxic and antimicrobial activity by inhibitory assays against diverse microbes, nematodes and cell lines. A versatile suite of cellular and microbiological assays will be used to assess cytotoxicity in human cell

	lines via LDH release, and antimicrobial activity in both planktonic and biofilm cultures through MIC, MBIC, and MBEC assays under host-mimicking conditions (e.g. cell culture media, 5% CO_2, 37 °C). Resistance potential of lead compounds will be evaluated through serial passage in escalating concentrations. This integrated approach enables scalable screening and provides mechanistic insight into host and microbial responses, supporting translational relevance. Together, this project will advance our understanding of the pharmaceutical potential of an ancient source of medication and will provide an exemplar case for the genomics-driven chemical exploration of plant species with super-sized genomes. The knowledge gained from this project will help to identify novel lead compounds to treat polymicrobial infections. It will offer multidisciplinary training in biochemistry, molecular genetics and microbiology - vital skills for establishing a successful career in medical biology. It will be embedded in a collaboration between the MRC Centre for Medical Mycology, the Biosciences Department in Exeter and the Life Sciences Department at Bath, and will provide access to a world-leading network of scientists. In this project, the prospective student will actively participate in the design of the project, will be encouraged to bring in their own research ideas and drive the direction of the project.
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