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Foreword

Cannabis and Cannabinoids

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The cannabis plant has been used in traditional medicine for thousands of years. However, its use as medicine has not been rigorously assessed due to legislated restrictions in many jurisdictions. The recent relaxation of several of the legal controls has seen medicinal cannabis return to the pharmacy. As such, there has been a considerable resurgence in scientific interest in medicinal cannabis, the endocannabinoid system, and many aspects of cannabinoid chemistry. We are delighted to publish this special issue on 'Cannabis and Cannabinoids' which highlights some of the latest scientific evidence in this continually expanding and important field of research.

This issue opens with a primer review contributed by one of our Guest Editors, Peter Duggan (CSIRO).[1] The article provides a concise overview of the chemistry of cannabis and cannabinoids. It is a comprehensive and up-to-date summary that will be particularly useful for newcomers to the field. It covers topics from the history of the cannabis plant and its chemistry, including its constituents, the pharmacology associated with cannabinoids and cannabinomimetics, and a range of targeted disease areas. This is an important contribution that will serve as a useful resource for some time.

Dylan Marsh and Scott Smid (University of Adelaide) contribute a review that surveys the hundreds of unique phytocannabinoids found in the cannabis plant.[2] There is a particular emphasis on phytochemical diversity and bioactivity – principally as neuroprotective agents. Specifically, the emergent phytocannabinoid research describing the inhibition of aggregation and misfolding of proteins relevant to Alzheimer's disease may afford new strategies for the treatment of a variety of dementias.

Michael Collins (National Measurement Institute, Sydney) reviews the history and challenges posed by the emergence of synthetic cannabinomimetics as recreational drugs.[3] Over the past two decades there has been a plethora of synthetic cannabinomimetics reported to be present in herbal smoking blends, which are commonly produced in clandestine laboratories. The biological evaluation of these cannabinomimetics is very limited or in many cases non-existent. This leads to potentially severe consequences for human health and as a result the production and sale of many synthetic cannabinomimetics has been criminalised. As these illicit drugs continue to evolve, they present new challenges to forensic chemistry laboratories where there is a continual need to identify and detect new cannabinoid analogues.

Hendra Gunosewoyo et al. (Curtin University) review the development of photoactivatable, electrophilic and fluorescent ligands used in the imaging of cannabinoid receptors.[4] Existing photoactivatable and electrophilic probes are covered, then a wide range of fluorescent conjugates are considered. The latter have been assessed for their ability to bind to cannabinoid receptors as well as their potential for cellular imaging. Finally, bifunctional probes containing either fluorophores or electrophilic tags, which are becoming more prevalent in the literature, are described. The imaging of cannabinoid receptors is becoming increasingly important for understanding receptor pharmacology

Peter obtained his B.Sc. (Hon) from Flinders University and Ph.D. from the Research School of Chemistry, ANU, working under the guidance of Professor A. L. J. Beckwith. After post-doctoral work at Columbia University (NYC) and the University of Cambridge, he took up academic positions, first at James Cook University, then at Monash University. In 2004, he 'stepped across the road' to CSIRO Clayton, where he is currently Senior Principal Research Scientist and Leader of the Bioorganic Chemistry Team. Peter is also Adjunct Professor in the College of Science and Engineering at Flinders University. Over the last decade, Peter has become increasingly involved in commercial research with botanical extracts and has established CSIRO's Botanical Extracts Laboratory. In this secure facility, research work with local companies is undertaken, involving the analysis, processing, and formulation of plant extracts, including those derived from medicinal cannabis.

Michael obtained his Ph.D. in organic chemistry from UNSW, followed by positions at ANSTO, the CEA-Service Hospitalier Frédéric Joliot Life Sciences group in France, and the Johns Hopkins Medical Institutes in Baltimore, USA. In 1996, he was awarded a Fogerty Fellowship based at the NIH National Institute of Drug Abuse (NIDA) USA. He then moved back to Sydney to Royal Prince Alfred Hospital as a Principal Hospital Scientist. In 2006, he took up a position at the University of Sydney in which he is currently Professor of Medicinal Chemistry and Academic Director of the Drug Discovery Initiative. Michael leads extensive discovery programs focused on various bioactive molecules relevant to brain disease. In addition, his use of positron emission tomography (PET) also allows not only the rational design of more effective treatments but the ability to evaluate drug efficacy and monitor disease progression in humans.

and in aiding drug discovery efforts, and this review will be a valuable resource for those working in these fields.

Andrea Vernall et al. (University of Otago) describe their efforts in the development of selective cannabinoid type-2 receptor agonists.[5] Such compounds have gained interest as potential therapeutics for the treatment of pain and inflammatory conditions. The authors have designed chromenopyrazole-based cannabinoid type-2 receptor-selective agonists that bear short peptides. The varying physicochemical properties obtained with this class of molecule can likely access different receptor populations and thereby assist in providing a better understanding of the role of cannabinoid type-2 receptors in pain and inflammation.

Giancarlo Pascali et al. (Prince of Wales Hospital, Sydney) provide details on the development of a putative cannabinoid type-2 receptor PET radiopharmaceutical.[6] The compound is based on a naphthyridine scaffold that was radiolabelled with fluorine-18 using microfluidic technology. The pharmacological characterisation of this radiopharmaceutical was based on in vitro autoradiography and in vivo microPET imaging in $SOD1^{G93A}$ mice, a model of amyotrophic lateral sclerosis, to assess the levels of cannabinoid type-2 receptor expression in symptomatic and asymptomatic animals. Their analysis revealed a higher uptake in the symptomatic mice, although studies of whole-body distribution, metabolism, and interspecies differences is required to assess the potential for translation to the clinic.

Peter Galettis et al. (University of Newcastle) present a validated isocratic HPLC method for the detection and quantification of 17 phytocannabinoids.[7] The method can be used with either plant material or oil extracts. The ability to simply and rapidly assess phytocannabinoid levels in such samples is becoming increasingly important when one considers the expansion in the number of cannabis clinical studies. A knowledge of the exact phytocannabinoid composition in trial drug preparations is vital so that doses can be standardised between patients. In addition, the distribution of minor cannabinoids in such samples is also of great interest as information about the biological activity of these cannabis constituents continues to come to light. The reported analytical method is fast, reproducible, and reliable and can be easily transferred to other laboratories in which cannabinoid analyses are performed.

Monika Doblin et al. (La Trobe University) report on a pilot study aimed at examining secondary metabolite variations between male and female unisexual flowers of the dioecious plant genus *Cannabis*.[8] Targeted analysis of 14 phytocannabinoids using certified reference standards showed a higher total phytocannabinoid content in female flowers compared with the male flowers. A phytocannabinoid-specific accurate-mass MS^n fragmentation spectral library was developed, and untargeted metabolic analyses revealed several differentially abundant metabolites associated with sexual phenotype. The developments described in this article have the potential to improve small molecule compound annotation and accelerate the understanding of the metabolic variation underlying the phenotypic diversity in cannabis.

Mary-Jane McCarthy et al. (Institute of Environmental Science and Research, Wellington) outline the emergence of 'Green Fairies' in the New Zealand black market.[9] These people are responsible for marketing home-made cannabis products for medicinal use, in response to frustrations over restrictions to the access of prescribed cannabinoid medicines. An LC-MS/MS method was developed to assess 100 'Green Fairy' samples for cannabinoid content. Analysis of these samples revealed a wide range of cannabinoid concentrations, often in variance with the specifications provided by the suppliers, and a lack of consistency in cannabinoid ratios in products said to have been produced from the same cultivar. This contrasts with little variation in the relative amounts of the major cannabinoids, THC and CBD, being observed when authentic samples of the named cultivars were analysed. This work highlights a common problem with black market cannabis products – you do not know what you are buying and wide variations in cannabinoid ratios and levels are often encountered in these products!

This special issue reflects both the quality and diversity of 'Cannabis and Cannabinoids' research being undertaken across Australia and New Zealand, and we acknowledge the significant efforts from all contributors to make this timely issue possible.

Conflicts of Interest

The authors declare no conflicts of interest.

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