frontiers | Frontiers in Natural Products

TYPE Editorial
PUBLISHED 05 January 2024
DOI 10.3389/fntpr.2023.1338469

OPEN ACCESS

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RECEIVED 14 November 2023
ACCEPTED 20 December 2023
PUBLISHED 05 January 2024

CITATION
Caprioglio D, Fasano V, Imperio D and Riveira MJ (2024), Editorial: From chemistry to therapeutics: exploring the universe of cannabinoids and related meroterpenoids.
Front. Nat. Produc. 2:1338469.
doi: 10.3389/fntpr.2023.1338469

Editorial: From chemistry to therapeutics: exploring the universe of cannabinoids and related meroterpenoids

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KEYWORDS

cannabinoids, extraction and isolation protocols, structure-activity relationship, biological evaluation, theranostic, total synthesis

Editorial on the Research Topic
From chemistry to therapeutics: exploring the universe of cannabinoids and related meroterpenoids

Cannabinoids are one of the most important classes of secondary metabolites, among the many natural products derived from plants. There has been a growing interest in the study of cannabinoids and the endocannabinoid system over the past decades. This is partly due to the loosening of legislation and the approval of treatments involving these compounds, but has also occurred as a result of new methodologies being developed and the constant deepening of knowledge regarding this class of natural compounds. With their wide structural complexity and ability to interact with several biological targets of primary significance, cannabinoids are currently one of the most important research trends in global science, which is still in the developmental stages. The Research Topic "*From Chemistry to Therapeutics: Exploring the Universe of Cannabinoids and Related Meroterpenoids*" provided an overview of the latest discoveries in the chemistry and biochemistry of these interesting classes of bioactive compounds, and consists of one original research article and three reviews.

The original article in this Research Topic by Amin et al. focuses on the synthesis and biological profile of the hydroxamate isosteres of acidic cannabinoids. To solve the problem of intrinsic instability toward the decarboxylation of acidic cannabinoids, a synthesis for the hydroxamate derivatives of CBD and Δ^8-THC, potentially also applicable to other cannabinoids, was developed. The biological activity of these two compounds toward several cannabinoid targets was then investigated, revealing promising *in vivo* activity in a murine model of polycystic ovary syndrome (PCOS) associated with obesity. When compared with their carboxylic acid counterparts, both hydroxamates showed substantial positive allosteric modulator activity on CB_1R and acted as antagonists of TRPV-1. The THC derivative, on the other hand, showed agonistic activity on the GPR55 receptor, whereas the CBD derivative was inactive. The *in vivo* activity was investigated on a preclinical model generated by chronically exposing female mice to dihydrotestosterone from weaning onwards, followed by an 18-week high-fat diet (HFD) before the initiation of pharmacological treatments. An HFD caused a corresponding increase in total fat mass in mice, as well as the adiposity index: with either hydroxamate, both parameters

were reduced significantly after 4 weeks of treatment, although THC derivatives resulted in modestly higher reductions. According to the results, cannabinoid hydroxamates have beneficial effects on the metabolic profile of PCOS models, relating to their ability to decrease body weight and improve glucose homeostasis. Providing the first indication that the stability Research Topic of these compounds can be resolved without detriment to their biological profile, this study confirms that cannabinoid hydroxamates can simulate a significant fraction of the biological profile of acidic cannabinoids.

The three review articles published in this Research Topic cover recent advances in different fields, including isolation and purification and diagnostic and theranostic uses, and a monography. In the Review by López-Olmos et al., the key extraction techniques and technologies that have been applied at the industrial scale to *Cannabis sativa* L. are thoroughly examined and compared. Additionally, several aspects of the pretreatment of cannabis plant material and the impact it has on the extraction process are discussed. As a result of its simplicity, the maceration of cannabis plant material in either polar or non-polar liquid organic solvent is the most widely used extraction technique, with ethanol being preferred as the polar solvent and petroleum ether and hexane as non-polar solvents. Other liquid solvents have been reported to have been used to produce cannabinoid formulations for pharmaceuticals and nutritional products, among which vegetable oils are the most popular method, as the final product generally consists of a diluted cannabinoid formulation. Pressurized gases can serve as an alternative to liquid solvents. Although there are many advantages to using pressurized gases, including a lack of solvent residues and easy recovery by thermal gas removal after extraction, they require sophisticated equipment that can operate in severe extraction conditions, which implies high operating and maintenance costs. Additionally, alternative and exotic extraction solvents have been reported, including HFC 134a (1,1,1,2-tetrafluoroethane) refrigerant. The Review also evaluated the performance of alternative extraction methods showing increasing popularity in the cannabinoid extraction industry, including ultrasonic-assisted extraction, microwave-assisted extraction, hydrodynamic cavitation, and pulsed electric field.

The Review paper from Amenta et al. is focused on the derivations of cannabinoids and terpenoids with fluorescent compounds, radiotracers, or photochromic motifs. These molecules may be used *in vitro* and, in some cases, *in vivo* for investigating and exploring the roles of CB_1Rs together with the starting point for the development of CB_1R-targeted drugs. As part of this Review, the authors provided an overview of the pharmacological and imaging tools that are useful for detecting CB_1Rs. Initially, covalent chemical probes incorporating a reactive tag into a CB1R ligand have been discussed. These can be photoaffinity probes, composed of a target-specific ligand and a photoactivatable functional group, or electrophilic probes containing reactive tags that can target nucleophilic amino acids proximal to the binding site of the protein of interest. Moreover, bifunctional probes containing two electrophilic or two photoactivatable moieties (homobifunctional probes) or both (heterobifunctional probes) display the possibility of combining multiple imaging techniques to create a higher spatial resolution. Other types of probes are fluorescently tagged small molecules. These probes have been widely used in the past decade as biological imaging tools as they offer the advantage of allowing real-time monitoring of ligand-receptor interactions with high spatiotemporal precision.

The authors then reported significant progress in the development of positron emission tomography (PET) drugs and tracers for cannabinoid 1 receptor (CB1R) imaging, specifically focusing on PET neuroimaging applications. Additionally, the Review addresses the recent challenges for the development of PET biomarkers, highlighting the important role of PET ligands in studying the pathophysiology of diseases and facilitating drug discovery. In addition to ^{18}F-labeled probes, ^{11}C-labeled radiotracers are taken into consideration, as they show some advantages, considering the shorter half-life of ^{11}C. The radiolabeling was performed by exploiting different approaches, using the [^{11}C]cyanide ion as a labeling agent, [^{11}C]$COCl_2$ to introduce a urea bridge, or *O*-[^{11}C]methylation radiolabeling with [^{11}C]CH_3OTf. The reported structures have a high specific activity, making them potential preclinical and clinical PET agents in animals and humans, indicating the route for promising future developments of new labeled probes.

Last but not least, the Review by Gurgone et al. describes all established synthetic strategies and biological activities discovered for cis-THC, a cannabinoid that is a stereoisomer of the main psychoactive component of *Cannabis sativa*, Δ^9-*trans*-THC. This natural product is found in the same plant as a scalemic mixture, has been less investigated than the *trans*-isomers, and has incorrectly been regarded as a "minor cannabinoid" as its relative abundance can be comparable with that of *trans*-THC in some samples of non-narcotic varieties of cannabis, particularly those rich in CBD. Biological studies on *cis*-THC indicate potential medicinal applications retaining the beneficial effects of the *trans*-isomer. Synthetic approaches range from original preparations based on the acid-promoted condensation between citral and olivetol, before the natural product was even known to occur in nature, to modern efficient and elegant catalytic asymmetric sequences.

The combination of cutting-edge experimental techniques, together with an in-depth analysis of recent scientific literature regarding cannabinoids and related meroterpenoids, make this Research Topic a valuable resource for those interested in the exploration of the fascinating chemical space related to these powerful and intriguing compounds.

Author contributions

DC: Conceptualization, Supervision, Validation, Writing–original draft, Writing–review and editing. VF: Conceptualization, Supervision, Validation, Writing–original draft, Writing–review and editing. DI: Conceptualization, Supervision, Validation, Writing–original draft, Writing–review and editing. MR: Conceptualization, Supervision, Validation, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

10.3389/fntpr.2023.1338469

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