



Editorial on “Cannabis and cannabinoids: history, practice and socio-economical inferences of a controversial plant”

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Abstract

With this Editorial article, we introduce the Topical collection on “Cannabis and cannabinoids: history, practice and socio-economical inferences of a controversial plant”, consisting of six review articles published in the *Rendiconti Lincei, Scienze Fisiche e Naturali* between the end of 2020 and the beginning of 2021.

Keywords *Cannabis sativa* · Cannabinoids · Endocannabinoids · Endocannabinoidome

In the last decade, the word “cannabis” has been among the most cited in articles from newspapers, magazines and generalist periodicals. This is not due to the increase in the “recreational” consumption of the preparations of the inflorescences of this plant (the best known of which is marijuana), which remains fairly stable even though it still makes of these preparations the most widespread drug in the young populations of Western countries. The cause of the renewed fame of cannabis is instead linked to the growing debate about the opportunity to decriminalize the therapeutic use

of such preparations, as is already happening in many states of the USA and countries around the world, but also in some Italian regions; or even to legalize their “recreational” use, as occurred in some countries (e.g. The Netherlands, Uruguay and, more recently, Canada), thus assimilating them to substances of potential abuse, such as tobacco and alcohol. In this context, there is some concern among botanists, chemists, pharmacologists and sociologists that precise and detailed information on what cannabis really is and does is only rarely provided to the public and sometimes even to legislative bodies, with the consequence that both often “polarize” on conflicting positions that describe the preparations of this plant as either a panacea for any disease or a source of dreadful dangers for its users. These positions are often “supported” by news, or sometimes fake news, that easily become available in the social media. Additionally, it is frequently ignored that the plant, historically, has many

This peer-reviewed paper belongs to the Topical Collection “Cannabis and Cannabinoids”, originated from the Conference “Cannabis and Cannabinoids: History, Uses, and Socio-Economical Implications of a Controversial Plant” organized by Vincenzo Di Marzo (Coordinator), Gennaro Marino, Jacopo Meldolesi, Daniela Parolaro, and held on December 20, 2019, at the Accademia Nazionale dei Lincei in Rome.

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other uses, and currently offers also new opportunities for its industrial exploitation in the mechanical engineering, food and agricultural sectors.

This topical issue stems from a conference, held at the Accademia dei Lincei in Rome on December 20, 2019, which aimed at providing accurate information, and a forum for discussion, on the past and present use of this millennial plant and its medical and socio-economic implications. The conference was attended by almost 100 participants, who contributed to making of this event an occasion to clarify some controversial issues and an opportunity for a lively discussion on cannabis and cannabinoids. Almost all the speakers of the conference agreed to provide to the Rendiconti Lincei, an article describing the major take-home messages of their presentations. The result is a collection of six review articles on subjects spanning from the history of

studies on this controversial plant and its origin and genetic background, to the discovery of endocannabinoids, the therapeutic exploitation of cannabinoids and the dangers of the indiscriminate use of these natural products as medicines or recreational substances, concluding with the emerging economical opportunities offered by the new industrial uses of cannabis (Fig. 1).

John McPartland, from the University of Vermont in Burlington, USA, provides a thoughtful and thought provoking insight into the evolution of the plant and its phylogenetics as part of the family *Cannabaceae*, which now consists of ten genera. He dwells on the controversial concept of the “two species of cannabis”, by clarifying that *Cannabis* is a monotypic genus consisting of only one species, *Cannabis sativa* L., as shown by DNA “barcode” studies. However, two subspecies are now recognized, whilst the number of

Fig. 1 Pharmaceutical and other industrial uses of *Cannabis sativa*. **a** Inflorescences yielding cannabinoids with therapeutic and recreational properties; **b** Seeds yielding flours and oils with increased nutritional value; **c** Stems yielding strong fibers for the building and textile industries



accepted varieties has increased to six. Prof. McPartland also describes the current knowledge of the evolution of Cannabis, which has been investigated using molecular clock analyses and fossil pollen studies. While the taxonomy of drug-type plants—“Sativa” and “Indica”—can be traced back to Asia, Italy has been at the crossroad of fiber-type plant genotypes (hemp) (McPartland 2020).

Giovanni Appendino, from the Università del Piemonte Orientale, Novara, Italy, instead focuses on the history of cannabinoid research, starting from the identification of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) as the intoxicating constituent of recreational cannabis. He reviews critically the anecdotes, controversies and mistakes that have characterized the early studies in the area, recalling how significant contributions to the elucidation of the chemical structure of the major cannabinoids, which include also cannabidiol and cannabidiol (CBD), were provided by some of the finest organic chemists of their generation, such as Raphael Mechoulam, Roger Adams and the Nobel laureate Alexander Todd. Prof. Appendino also highlights the crucial role that the development of chromatographic methods of purification and of spectroscopic techniques of chemical structure elucidation have played in this field as well as in the progress of organic chemistry in general (Appendino 2020).

Mauro Maccarrone, from the Campus Biomedico in Rome, Italy, instead describes another milestone in cannabinoid research: the discovery of the endocannabinoid system. He emphasises how the chemical complexity of cannabis is mirrored by the complexity of the molecular targets that cannabinoids have in animals, which include, but are not limited to, the cannabinoid receptors, activated by endogenous ligands known as endocannabinoids. Prof. Maccarrone describes the mechanisms through which the endocannabinoid system is regulated in mammalian cells, its physiopathological roles, and its targeting for therapeutic purposes. Finally, he addresses the question of the evolution of cannabinoids and endocannabinoids, showing that the latter compounds, derived from the metabolism of arachidonic acid, were the first to appear in nature, whereas plant cannabinoids took millions of years to mimic the three-dimensional structures of the endocannabinoids, and hence their biological activity (Maccarrone 2020).

Fabiana Piscitelli and Vincenzo Di Marzo, from the Institute of Biomolecular Chemistry of the CNR, in Naples, Italy, and Université Laval, in Quebec City, Canada, focus their article on the multi-faceted pharmacology of cannabinoids, with emphasis on Δ^9 -THC and CBD. They underline the profound differences existing between the pharmacological properties of Δ^9 -THC and those of the other over one-hundred cannabinoids discovered so far in cannabis flowers. Prof. Di Marzo and Dr. Piscitelli point out how the mechanisms of action of CBD

and other non-euphoric cannabinoids are very complex and based on their interaction with several molecular targets, many of which are now considered to be part of an “expanded endocannabinoid system” or “endocannabinoidome”, which also includes several families of endocannabinoid-related lipid mediators. Thus, the pharmacology of cannabinoids can be better explained by the existence of the endocannabinoidome, rather than just the endocannabinoid system (Piscitelli and Di Marzo, 2021).

Daniela Parolaro, from Università dell’Insubria, Busto Arsizio, and Fondazione Zardi-Gori, Milano, Italy, describes the therapeutic as well as toxicological aspects of the use of cannabis and cannabinoids in medicine. She emphasizes how the legalization of cannabis products for recreational and/or medical use implies a new openness of our society to their diffusion, thus calling for a deeper understanding of their clinical benefits and adverse health effects. In particular, Prof. Parolaro describes the efficacy and side effect profiles of cannabinoid-based drugs currently approved for clinical use, mostly to relieve the symptoms of cancer (emesis), AIDS (wasting syndrome), and neurological disorders (multiple sclerosis and epilepsy). She also draws attention to some synthetic cannabinoids, which are several fold more potent and efficacious at activating brain cannabinoid receptors than Δ^9 -THC, and hence potentially more dangerous, particularly as their recreational use in young populations is on the rise (Parolaro, 2021).

Finally, Giuseppe Sorrentino, of the Istituto Sistemi Agricoli e Forestali nel Mediterraneo, and Istituto Protezione Sostenibile delle Piante of the CNR, in Portici, Italy, provides a very comprehensive description of the new non-medicinal industrial uses of different parts of the cannabis plant. These uses range from the exploitation of seeds—by the food and beverage industry, to obtain flour, pasta, pastries and oils—and the stem, whose woody part (canapulo) can be employed in the building sector, and whose more fibrous part (the external layers of the stem) finds new applications in the textile industry. Dr. Sorrentino points out also the agricultural and environmental advantages of the cultivation of cannabis, which has a rapid growth, suppresses other weeds, does not need pesticides as it has no specialized parasites, and improves the physical and chemical fertility of the soil, as well as being considered a climate-friendly crop with respect to climate changes and desertification processes (Sorrentino, 2021).

In summary, we are confident that this topical and multi-disciplinary collection of articles on cannabis and cannabinoids will help to cast some research-originated light on the most obscure—and often too much disputed upon—aspects of these still controversial substances.

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