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Short communication

Quality requirements for *Cannabis flos* as final product

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Introduction

Cannabis sativa L. is one of the oldest medicinal plants containing a variety of compounds such as terpenoids, flavonoids and cannabinoids. One of the most important cannabinoids are: Δ9-tetrahydrocannabinol (Δ9-THC, THC), cannabinol (CBN), cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), Δ9-tetrahydrocannabivarin (Δ 9-THCV) and cannabidivarin (CBDV) (Pagano et al., 2022). Research studies have shown that cannabinoids are highly efficient, primarily in the treatment of nausea and vomiting and the management of chronic pain. There is a great potential of cannabinoids to be applied for the treatment of many other pathological conditions, such as multiple sclerosis, epilepsy, neurodegenerative diseases (Alzheimer's disease, Parkinson's disease), spinal cord injuries, Tourette's syndrome, hypertension, glaucoma (Montero-Oleas et al., 2020).

Analysis of the original composition of the plant material is necessary in order to determine the phenotype as well as quality control especially for medicinal cannabis used for therapeutic purposes. Of utmost importance are the critical quality attributes which have to be established in order to meet the safety, efficacy and quality standards. For instance, a critical parameter for cannabis flos should be the concentration of cannabinoids in the final product. Since the cannabis industry is young and emerging, there is need for well-developed procedures, guidelines and harmonized monographs for cannabis-derived herbal substances in order to avoid multiple examinations as a result of differences in the national standards.

Therefore, the main aim of this study was to evaluate and distinguish the differences in the requirements for the quality of cannabis flos according to European and German Pharmacopoeia.

EU regulations for *Cannabis flos* quality

The tests and acceptance criteria for Cannabis-derived herbal substances such as flowers (Cannabis flos) or resin (Cannabis resina), usually in their dried form, can be found by the 'herbal substance' definition in Directive 2001/83/EC and in the Ph. Eur. monograph on herbal drugs (EMA, 2021).

Herbal substances are determined by the source plant and the plant part. Both are usually distinguished and specified in individual monographs of the European Pharmacopoeia, or in absence thereof, in the pharmacopoeias currently used officially in the EU Member States (EMA, 2021). In this sense, the tests and acceptance criteria prescribed in Ph. Eur. monograph on herbal drugs are: Definition - which includes statement for the botanical source, plant part used, the geographical sources as well as the conditions under which the herbal substance is obtained; Characters – organoleptic and micro/macroscopic characteristics; Identification – tests which should be specific for the herbal substance and are combination of micro / macroscopical analysis, chromatographic procedures and chemical reactions; Tests - for determination of foreign matter, total ash, ash insoluble in hydrochloric acid, water soluble extractive and extractable matter. Other tests covered in this monograph are particle size and particle size distribution which may affect the dissolution and thus the bioavailability of herbal medicinal products derived from these herbal substances; loss on drying (for non-pharmacopoeial herbal substances, acceptance criteria should be justified by data on the effects of moisture absorption); Contaminants – which include inorganic impurities, toxic (heavy) metals (where justified, sulphated ash/residue on ignition/heavy metals), microbial

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limits (the total count of aerobic micro-organisms, ofyeasts and molds, and the absence of specific bacteria). It is important to be mentioned that the microbial counts should be performed using pharmacopaeial or other validated procedures. Determination of potential mycotoxin contaminations should be in accordance with the pharmacopaeial procedures and acceptance criteria given for aflatoxins (*2.8.18*) and for ochratoxin A (*2.8.22*). When necessary, potential residues for pesticides and fumigation agents should be controlled by suitable validated methods (EMA, 2011).

The last item in the monograph on herbal substances refers to the assay where in case of herbal substances with compounds with known therapeutic activity or with active markers, assays of their content are required with details of the analytical procedure (EMA, 2011).

Since the cannabis plant is capable of producing psychoactive substances such as THC, it is usually legally controlled. Therefore, in the female flowers, and the resin-producing trichomes (plant hairs), THC concentration can reach 20 % or more. For this reason, the international treaties require that the entire plant is controlled under national drug laws (EMCDDA, 2018).

Since there is still no published a monograph for 'Cannabis flos' (or derived preparations or constituents) in Ph. Eur., some EU Member States, like Denmark and Germany, have published monographs in national pharmacopoeias (EMA, 2021).

Regulations for *Cannabis flos* quality in DAB

According to the German Pharmacopoeia (Deutsches Arzneibuch, DAB) there are two published monographs for Cannabis-derived herbal substances: monograph for Cannabis Flos and Cannabis Extract.

The DAB monograph for the quality of the starting material, defines the Cannabis flos as dried shoot tips of the female plants of *Cannabis sativa* L. (Cannabaceae), where is specified that the drug should contain 90-110 % of the labeled cannabinoids, calculated as THC ($C_{21}H_{30}O_2$; Mr 314.5) and CBD ($C_{21}H_{30}O_2$; Mr 314.5), based on the dried drug. Requirements for identity tests include macroscopic and microscopic evaluations as well as thin layer chromatography (2.2.27). It is worth mentioning that there is a difference between the EU regulations and DAB monograph for cannabis flos, where according to the tests for identification of the herbal drugs in the European Pharmacopoeia, possible contamination with pesticides, heavy metals, aflatoxins and microorganisms is practically limited (Manns et al., 2019). Regarding the purity testing, in the DAB monograph is specified that the drug should have external components (2.8.2) not more than 2 percent and not more than 10 percent of drying loss (2.2.32). In this segment it is also included the analysis of the content of cannabinol (max 1%) which should be done by liquid chromatography (2.2.29). When it comes to the determination of the content of the significant cannabinoids, the examination is carried out with liquid chromatography (2.2.29) as well, where according to their quantity, there are three different products defined: cannabis flos with THC content higher that CBD (type I), THC content equal to CBD (type II) and THC content lower than CBD (type III). In the last part of the monograph there is an information on labeling where calculated percentage of the amount of THC and CBD should be indicated on the container.

Conclusion

The quality requirements for cannabis flos in the European and German Pharmacopoeia are similar, although due to the ongoing process of legalization and decriminalization of cannabis for medicinal purposes usage in different EU countries, there is a need for a harmonized monograph.

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