

'Cannabis' ontologies I: Conceptual issues with *Cannabis* and cannabinoids terminology

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Abstract

Objective: Identify a coherent nomenclature for *Cannabis sativa* L. derived products and their analogues.

Design: Research undertaken in parallel to the three-year assessment of *Cannabis* derivatives by the World Health Organisation. The scope is limited to *Cannabis* products intended for human incorporation (internal and topical consumption). Primarily embedded in pharmacognosy, the study incorporates a wide range of scholarly and grey literature, folk knowledge, archives, pharmacopœias, international law, field pharmacy, clinical and herbal medicine data, under a philosophical scrutiny. Generic and *Cannabis*-specific nomenclatural frames are compared to determine the extent to which they coincide or conflict.

Results: All lexica reviewed use weak, ambiguous, or inconsistent terms. There is insufficient scientific basis for terms and concepts related to *Cannabis* at all levels. No sound classification exists: current models conflict by adopting idiosyncratic, partial, outdated, or utilitarian schemes to arrange the extraordinarily numerous and diverse derivatives of the *C. sativa* plant. In law and policy, no clear or unequivocal boundary between *herbal* and *non-herbal* drugs, nor *natural* and *synthetic* cannabinoids was found; current nomenclatures need updates. In science, the botanical *Cannabis* lexicon overlooks parthenocarpy, and wide disagreement remains as to the taxonomy and systematics of the plant; chemical research should address differences in kinds between *synthetic cannabinoids*; pharmacopœias include little information related to *Cannabis*, and disagree on broader classes of herbal medicines, virtually failing to embrace many known *Cannabis* medicines. Since existing products and compounds fail to be categorised in an evidence-based manner, confusions will likely increase as novel cannabinoid compounds, genetic and biotechnological modifications surge.

Conclusions: The lack of clarity is comprehensive: for patients, physicians, and regulators. This study proposes an update of terms at several levels. It points at gaps in morphological descriptions in botany and pharmacognosy and a need for a metaphysical address of cannabinoids. Methods of obtention are identified as a common criterion to distinguish products; the way forward suggests a mutually exclusive nomenclatural pattern based on the smallest common denominator of obtention methods. In the context of a swelling number of *Cannabis* products being consumed (be it via medical prescription, adult-use, 'hemp' foodstuff and cosmetics, or other purposes), this study can assist research, contribute to transparent labelling of products, consumer safety and awareness, pharmacovigilance, medical standards of care, and an update of prevention and harm reduction approaches. It can also better inform regulatory policies surrounding *C. sativa*, its derivatives, and other cannabinoid-containing products.

Keywords

botany, cannabinoids, cannabis, drug control, epistemology, hemp, herbal medicine, nomenclature, pharmacognosy, synthetic cannabinoids

“What’s the use of their having names”, the Gnat said,
“if they won’t answer to them?”

“No use to them”, said Alice; “but it’s useful to the
people that name them, I suppose. If not, why do
things have names at all?”

– Lewis Carroll, *Through the Looking-Glass, and What
Alice Found There*

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Introduction

The World Health Organisation's (WHO) Expert Committee on Drug Dependence (ECDD) is mandated under the International Drug Control Conventions (IDCC) to conduct 'medical, scientific and public health evaluation of substances'. It advises in a manner that is 'determinative as to medical and scientific matters', on 'whether or not the substances assessed should be placed under international control' (ECDD, 2018; Riboulet-Zemouli, 2018; World Health Organisation, 2015). In 2015, the ECDD started a series of assessments of 'cannabis-related drugs'. Despite significant efforts, goodwill, and resources, obstacles prevented the Experts from providing a fully clear, complete, and methodologically sound assessment. Among the barriers, a significant one relates to the 'specific provisions and terms used in the [IDCC]' (Room, 2013) and in particular the way *Cannabis* and its derived products are referenced. Primarily relied on at the national level, the nomenclature of the IDCC aggregates pharmaceutically distinct products under the same labels that correspond to abstract concepts rather than to classes of products found in real life. In science, the botanical 'cannabis confusions' (McPartland, 2018; McPartland and Guy, 2017; Watts, 2006) in the taxonomic ranking of the plant are echoed by unclear morphological designations of 'cannabis' and 'cannabis resin' in pharmacy, all within the context of a complex pharmacological activity. Aware of that lack of conceptual and terminological consistency, the ECDD included, in its outcome recommendations sent to the United Nations (UN) Secretary-General in 2019, elements suggesting a renewed, modernised, clarified terminology for 'cannabis drugs' in the IDCC.

Beyond international organisations, unscientific or connotated epithets such as 'marijuana' continue to be used, including in policy or research papers, without proper justification. The terms 'industrial cannabis', 'industrial hemp', and 'hemp' remain commonly employed as synonyms. However, in some parts of the world, 'cannabis industry' refers to companies undertaking activities related to adult-uses of *Cannabis* products (e.g. for recreational purposes). In contrast, in others, it applies only to fibre-related industries. The most studied active phytoconstituent of *Cannabis* is interchangeably called 'THC', 'delta-9-THC', and 'dronabinol', although these terms correspond to different chemical entities. Many other impractical terminological habits arise from the use of similar words to designate products that are essentially different and have no comparison in terms of pharmacological effects. The 'fibres' which compose the stems of *Cannabis* plants, used to produce paper,

clothing, or concrete, are often confused with 'protein fibres' obtained from seeds. The word 'oil' refers to the non-psychoactive fatty oil obtained from seeds (popularly called 'hemp seed oil', 'hemp oil', or 'cannabis seed oil'). Yet, it is also used to denote some preparations of extracted/concentrated active compounds ('hash oil', 'butane honey oil', 'cannabis oil', 'Rick Simpson Oil', etc.; see Chandra et al., 2017; Krawitz et al., 2018; Szendrei, 1997). The current increase in innovation and diversification in production, distribution, and transformation of 'cannabis' into medical, pharmaceutical, nutraceuticals, food, cosmetic, and adult-use products will only accentuate that tendency to confusion.

Jurisdictions around the world are increasingly reviewing policies on medicine-related or adult-use 'cannabis products', or on derivatives of *Cannabis* for which purposes are not related to psychoactivity ('hemp'). The analysis of cannabinoid content is useful, but not sufficient to distinguish types of products: a traditional 'hashish' and an oromucosal spray can indeed have similar thresholds. Policies are expected to be grounded in consensual customs, conventions, and standards, when not directly based on substantial science. Nevertheless, the potential bias implied by weak lexica, a non-scientific nomenclature, and numerous sociocultural terminological variants, might hinder efficient decisions in the field of *Cannabis* policymaking. The need to establish definitions, categories, limits, and boundaries between the different products, preparations, and substances derived from *Cannabis* has only become more urgent after the WHO's assessment. Beyond the IDCC, other standards of reference should allow for a better understanding of the subject matter over which regulators are starting to work. In continuation of the multidisciplinary work undertaken by the ECDD, a comprehensive public health approach guided by evidence, urges. This study reviews the scope, basis, and limitations of the nomenclatures and semantics currently used as references in the legal and public health debate on *Cannabis*, parsing their relevance and their gaps and discussing approaches towards possible updates.

Materials and methods

The problematisation and design of the study emerged during discussions held at the UN Commission on narcotic drugs meetings from 2014 onwards. A common conclusion was shared by patients, physicians, pharmacists, pharmacologists, toxicologists, chemists, biologists, botanists, UN and WHO staff, national or local health authorities, diplomats, parliamentarians, lawyers, traditional healers, farmers, and people crafting *C. sativa* derivatives in various contexts, from all

corners of the world: difficulties in understanding one another due to critical linguistic inconsistencies with ‘cannabis-specific’ terms, and the extreme challenge to overcome this stalemate from a single science, discipline, field, or focus.

The initial workstream, which sought to propose an evidence-based nomenclature of *Cannabis* products, turned out to be insoluble before a first address of existing terms and concepts from the perspectives of the philosophies of science and language. Ontology, both traditionally as a metaphysical address of the nature and essence of ‘things’ and, in its modern understanding, as an applied discipline of knowledge management (Merrill, 2011) provided methodological guidance in this regard. ‘The big task for the new “ontology”’ as Smith (2003) notes, ‘derives from what we might call the Tower of Babel problem. Different groups of data- and knowledge-base system designers have their own idiosyncratic terms and concepts by means of which they build frameworks for information representation’ (158). The assessments of the ECDD, progressively unfolding, emphasised this problem (see Krawitz et al., 2018). Their work (data collection, preliminary documentation, meeting outcomes) served as the basis to identify areas where ‘cannabis’ ontologies and terminologies seemed inconsistent, insufficient, or lacking scientific background. Complementary research identified existing nomenclatures for *C. sativa* derivatives within international legal instruments and documentation from a wide range of institutions. These sources were also consulted concerning non-*Cannabis* herbal drugs (i.e. phytopharmaceuticals). Phytopharmaceutical nomenclatures and herbal drugs categorification criteria were searched in manuals and guides of herbal pharmacy, herbal medical practice, and pharmacognosy. Research was undertaken at Biblioteca de Catalunya, Jardí Botànic, and CRAI of the Universitat de Barcelona (Barcelona, Spain), Conservatoire et Jardin Botanique de Genève, Faculté de Médecine of the Université de Genève, Archives of the League of Nations, Libraries of the UN and of the WHO (Geneva, Switzerland), Dag Hammarskjöld Library (New York, USA, remotely), the library of the UN Office on Drugs and Crime (UNODC) (Vienna, Austria), and at the Académie Nationale de Médecine, Académie de Pharmacie, Académie des sciences, Muséum National d’Histoire Naturelle and Université de Paris (France). References used in the 2019–2020 courses of the universities visited were favoured. Drug codifying compendia and other relevant references were also consulted at this stage.

Searches were then performed in a corpus of pharmacopœias from 26 different jurisdictions (identified in WHO, 2013a, 2013b, 2018a), detailed in Table 1.

Except where indicated otherwise, all abbreviations of pharmacopœias used along the article refer to the latest edition consulted, as referenced in Table 1. The first stream of queries focused on whether pharmacopœias included *C. sativa* phytopharmaceuticals or other derivatives, and if so, how they were categorised. A second stream searched for general frameworks categorising phytopharmaceuticals in notices, monographs, and glossaries, and for other categorisation patterns emerging from individual monographs.

Literature searches were carried out up to 1 October 2019, in ProQuest, PubMed®, PMI, and Scopus™ using database-specific search strategies and appropriate keywords, truncation, symbols, and reference index terms, as appropriate. In addition, Google, DuckDuckGo, Archive.org, Google Scholar, and ResearchGate were employed to hand search additional articles and references. The door to serendipity stayed open.

The ‘Discussion’ section introduces neologisms: supplementary Appendix I exposes the methods followed to craft them.

There were several limitations in the research. The main limitation is contained in substance in the axis of research: the unsuitable, or nonexistent language and terminology for ‘cannabis’ derivatives. False cognates and other similar words relating to different concepts or different objects were overwhelmingly found between different authors or references, imposing the use of a vocabulary proper to the article as a manner of distinguishability (e.g. the use of *phytopharmaceuticals*, instead of *herbal drugs* whose meaning varies importantly among regions and areas of expertise). Another significant limitation is rooted in the Western embed of international pharmaceutical and medical standards; those could only partially be balanced due to language limitations.

A self-imposed limitation consisted in excluding from the scope of the article those products of *C. sativa* for which the purpose of use is not related to incorporation (internal or external consumption). *C. sativa* is a plant also used for the production of fibre, processed into paper, clothing, biocomposite materials, etc. These products are often processed in a manner that renders them unsuitable for incorporation, although they can be consumed (e.g. clothes are worn, paper is used, but not incorporated). Relying on the criteria of exemption by purpose present in the IDCC (i.e. products for which the purpose of use is not in relation to its potential psychoactive properties are exempt from drug control, see Riboulet-Zemouli, 2019) the products whose purpose is not that of human incorporation are excluded from the scope of this study. Because the products that can be incorporated are still numerous, the specific downstream criteria of

Table 1. Pharmacopoeias consulted.

Legally-binding pharmacopoeial references consulted.					
Jurisdiction concerned	Vernacular name / English name	Abbreviation	Previous editions (date)	Last edition (date)	
Argentina	<i>Farmacopea Argentina</i> / Argentinian Pharmacopoeia	FA	n/a	7th (2013) ¹	
Brazil	<i>Farmacopéia Brasileira</i> / Brazilian Pharmacopoeia	FB	5th (2010)	6th (2019) ²	
China	中华人民共和国药典 / Pharmacopoeia of the People's Republic of China	Ch.P	7th (2000)9th (2010)	10th (2015) ³	
Egypt	Egyptian Pharmacopoeia	Ph.Eg.	n/a	3rd (1984) ⁴	
France	<i>Pharmacopée Française</i> / French Pharmacopoeia	Ph.Fr.	n/a	11th (2012) ⁵	
Germany	<i>Deutsches Arzneibuch</i> / German Commission E's Monographs	DAB	n/a	10th (1991) ⁶	
Greece	<i>Ελληνική Φαρμακοποία</i> / Hellenic Pharmacopoeia	Ph.Gr.	n/a	5th (1998) ⁷	
India	Indian Pharmacopoeia	IP	6th (2010)	8th (2018) ⁸	
Indonesia	<i>Farmakope Indonesia</i> / Indonesian Pharmacopoeia	Ph.Indo.	n/a	2nd (1972) ⁹	
Japan	第十七改正日本薬局方 / Japanese Pharmacopoeia	JP	16th (2011)	17th (2016) ¹⁰	
Mexico	<i>Farmacopea Mexicana</i> / Mexican Pharmacopoeia	n/a	n/a	5th (1925) ¹¹	
	<i>Farmacopea Herbolaria de los Estados Unidos Mexicanos</i> / Herbal Pharmacopoeia of the United Mexican States	FHEUM	n/a	2nd (2013) ¹²	
The Netherlands	Analytical Monograph Cannabis Flos (flowers / granulated)	n/a	n/a	7.1 (2014) ¹³	
Pan-European	<i>Pharmacopoeia Europaea</i> / European Pharmacopoeia	Ph.Eur.	8th (2014)	9th (2016) ¹⁴	
Poland	<i>Farmakopea Polska</i> / Polish Pharmacopoeia	Ph.Pl.	n/a	5th (1993) ¹⁵	
Romania	<i>Farmacopeea Română</i> / Romanian Pharmacopoeia	FR	n/a	10th (1993) ¹⁶	
Russian Federation	Государственная фармакопея Российской Федерации / State Pharmacopoeia of the Russian Federation	SPRF	n/a	13th (2015) ¹⁷	
Spain	<i>Farmacopea Española</i> / Spanish Pharmacopoeia	n/a	5th (1865) ¹⁸	8th (1930) ¹⁹	
	<i>Real Farmacopea Española</i> / Royal Spanish Pharmacopoeia	RFE	n/a	5th (2015) ²⁰	
Switzerland	<i>Pharmacopoeia Helvetica</i> / Swiss Pharmacopoeia	Ph.Helv.	n/a	11th (2017) ²¹ 11.3 (2019) ²²	

(continued)

Table 1. Continued

Legally-binding pharmacopœial references consulted.				
Jurisdiction concerned	Vernacular name / English name	Abbreviation	Previous editions (date)	Last edition (date)
United Kingdom	British Pharmacopœia	BP	(1914) ²³ (1968) ²⁴ (2009) ²⁵	(2017) ²⁶
United States of America	United States Pharmacopœia	USP	n/a	42nd (2019) ²⁷
Vietnam	<i>Dược điển Việt Nam</i> / Pharmacopœia of Vietnam	VP	n/a	3rd (2002) ²⁸
Non- or partially legally-binding pharmacopœial references, and other compendia of reference consulted.				
Area concerned	Name	Abbreviation	Date	
African continent	African Herbal Pharmacopœia	AfrHP	2010 ²⁹	
African continent	African Pharmacopœia	AfrP	1986 ³⁰	
African continent (North-Western)	Médecine arabe ancienne et savoirs populaires: La pharmacopée marocaine traditionnelle	n/a	1997 ³¹	
African continent (Western)	Medicinal plants in tropical West Africa	n/a	1986 ³²	
India	West African Herbal Pharmacopœia	WAHP	2013 ³³	
India	Ayurvedic Pharmacopœia of India	IPA	1989 ³⁴	
International	The International Pharmacopœia	Ph.Int.	2018 ³⁵	
Taiwan	Martindale: the complete drug reference		2005 ³⁶	
United Kingdom	The illustration of common medicinal plants in Taiwan		2009 ³⁷	
United Kingdom	British Herbal Pharmacopœia	BHP	1996 ³⁸	
United States of America	American Herbal Pharmacopœia (monograph on <i>Cannabis</i> spp.)	USHP	2014 ³⁹	

Pharmacopœias underlined are those legally in force at the date of redaction of this article. References: ¹ Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, 2013; ² Agência Nacional de Vigilância Sanitária, 2019; ³ Chinese Pharmacopœia Commission, 2015; ⁴ Permanent Commission of the Egyptian Pharmacopœia, 1984; ⁵ Agence nationale de sécurité du médicament et des produits de santé, 2017; ⁶ Blumenthal et al., 1998; ⁷ Трощак and Бульчик, 1998; ⁸ Indian Pharmacopœia Commission, 2018; ⁹ Departemen Kesehatan Republik Indonesia, 1972; ¹⁰ Ministry of Health, Labour and Welfare, 2016; ¹¹ Unión Nacional de Farmacéuticos Científico-Cooperativa, 1925; ¹² Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, 2013; ¹³ Ministerie van Volksgezondheid and Welfare, 2016; ¹⁴ European Directorate for the Quality of Medicines, 2016; ¹⁵ Komisji Farmakopei Polskiej, 1993; ¹⁶ Institutul pentru Controlul de stat al Medicamentului și Cercetări Farmaceutice, 1993; ¹⁷ Министерство здравоохранения Российской Федерации, 2015; ¹⁸ Real Academia de Medicina de Madrid, 1865; ¹⁹ Real Academia Nacional de Medicina, 1930; ²⁰ Agencia Española de Medicamentos y Productos Sanitarios, 2011; ²¹ Swiss Agency for Therapeutic Products, 2012, ²² 2019; ²³ General Council of Medical Education and Registration of the United Kingdom, 1914; ²⁴ General Medical Council, 1968; ²⁵ Medicines and Healthcare products Regulatory Agency, 2009, ²⁶ 2017; ²⁷ United States Pharmacopœial Convention, 2019; ²⁸ Công Hòa Xã Hội Chủ Nghĩa Việt Nam, 2002; ²⁹ Brendler et al., 2010; ³⁰ Organisation of African Unity, 1986; ³¹ Bellakhdar, 1997; ³² Oliver-Bever, 1986; ³³ Organisation Ouest-Africaine de la Santé, 2013; ³⁴ Ministry of Health and Family Welfare of India, 1989; ³⁵ World Health Organisation, 2018b; ³⁶ Sweetman, 2005; ³⁷ Huang et al., 2009; ³⁸ Willoughby et al., 1996; ³⁹ Upton et al., 2014.

the route of administration (which often vary among consumers, sometimes overlapping for the same product; and which are difficult to assess in a context of partial illegality) have been ignored, and left for further studies.

The IDCC, a set of treaties almost universally ratified, has shaped national laws, regulate research, and impose thorough obligations to Member States. Hence, the IDCC has been used as the paradigmatic point of departure for the study; however, all other classification criteria or existing *Cannabis*-related nomenclatures reviewed were given a comparable weight, and addressed with a similar approach, in an attempt to unearth a denominator.

The length of the article reflects the over three years of research involved in its production. The plan reflects the incremental aspect in which unfolded the research: it explores, from the most simple to the most sophisticated products, the limitations of existing terminology, why these limitations are rooted, beyond the terms, in conceptual confusions; the conclusion discusses lessons to be drawn, in view of possible new evidence-based terminologies to be proposed.

Results

The Home Medical Encyclopedia defines ‘cannabis’ as ‘[a]ny of the numerous psychoactive preparations derived from the hemp plant *Cannabis sativa* (such as hashish and marijuana)’ (American Medical Association, 1989: 230). Although commonly accepted, this is the perfect example of a circular definition: it explains the term ‘cannabis’ using this same word in the text of its definition (Kripke, 1980: 67–70, 1982). This ‘two cannabises’ approach is symptomatic of a fundamentally dichotomous vision of the word, used

daily to designate two conceptually different concepts: either a plant genus, ‘*Cannabis*’, or a series of (mind-altering) products from that plant, ‘cannabis’ (Cherney and Small, 2016; Small, 2017: 1–5). This double-edged meaning affects and complicates the understanding of both ‘*Cannabis*’ as a plant and ‘cannabis’ as a product.

Polysemic acceptances of this word are profuse, worldwide, including in law. Legislations relating to ‘*Cannabis*’ and/or ‘cannabis’ often follow the codification of the IDCC (UNODC, 2013), particularly the Single Convention on Narcotic Drugs of 1961 as amended in 1972 (C61) and the Convention on Psychotropic Substances of 1971 (C71). This latter treaty does not directly mention ‘cannabis’; it comprises only pure compounds and includes dronabinol (ECDD, 2019: 41–44) as well as its stereochemical variants and isomers. Dronabinol is the international non-proprietary name (INN) for the (–)-trans stereoisomer of the delta-9 isomer of tetrahydrocannabinol (THC). Two confusions often arise (Figure 1): while the INN seems to only designate (–)-trans-delta-9-tetrahydrocannabinol, some references like United States Pharmacopœia (USP), recognise as dronabinol all four enantiomers of delta-9-tetrahydrocannabinol. For others, the word *dronabinol* is understood as referring only to delta-9-tetrahydrocannabinol obtained *ex vivo*. According to WHO, however, ‘dronabinol’ corresponds to (–)-trans-delta-9-THC, either obtained *in vivo* or *ex vivo* (ECDD, 2018: 33).

The C61, on its side, includes four occurrences of the word in its Article 1 on definitions (UNODC, 2013: 24–26):

- a. ‘Cannabis plant’ that is ‘any plant of the genus *Cannabis*’ (art. 1[c]),

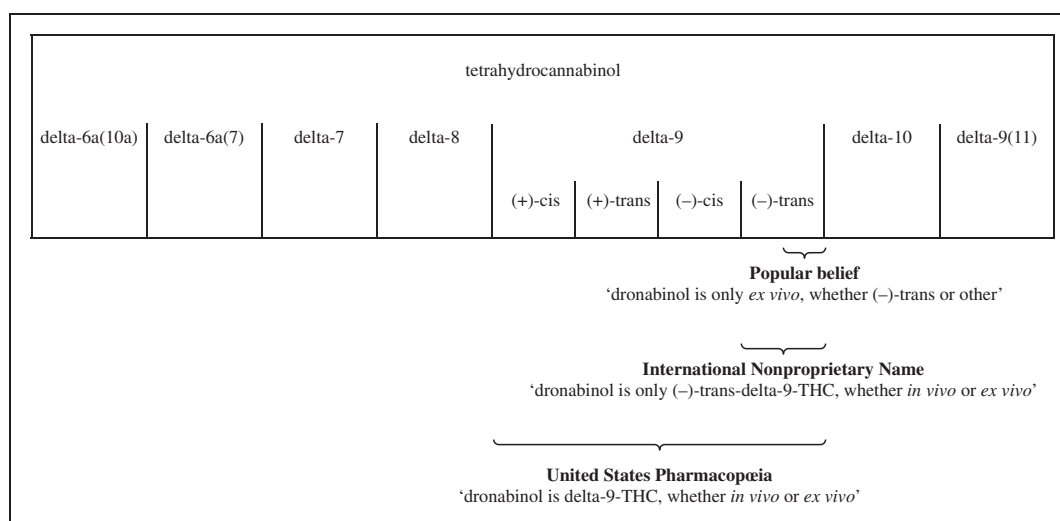


Figure 1. Conflicting ontologies: dronabinol and THC. THC: tetrahydrocannabinol.

- b. ‘Cannabis’, defined as ‘the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted, by whatever name they may be designated’ (art. 1[b]). The Commentary on the C61 treaty, prepared by the office of the UN Secretary-General (hereinafter called *Commentary*, see UN, 1973), explains that ‘the term “cannabis” [...] covers all tops including those which are not yet dried, as well as those of the male plants’ (UN, 1973: 2 §1).
- c. ‘Cannabis resin’ defined as ‘the separated resin, whether crude or purified, obtained from the cannabis plant’ (art. 1[d]). The Commentary further explains (UN, 1973: 5 §3) that ‘resin, however, becomes “cannabis resin” only when it is “separated” from the plant; without such separation, it remains a part of the cannabis plant, and if in the top part, of “canna bis”’.
- d. ‘Extracts and tinctures of cannabis’, for which no definition is provided.

The C61 treaty is a delicate equilibrium between the labour of merging several previous international legal instruments into a new, single text, and the geopolitical developments of the postwar era (Jelsma et al., 2014; Krawitz et al., 2018: 6–11; Riboulet-Zemouli, 2018). The limited knowledge of the active constituents of the plant at the time contributed such imprecise language. A background paper to ECDD’s 2012 meeting explains: ‘in the half-century since the 1961 Convention was adopted, there has been considerable developments in the terminology used’ (Room, 2013). Today the efficiency of this nomenclature, used globally for several decades, seems to be backed by weak evidence. It is, however, representative of a trend in regulatory terminological shortcuts, as well as in the legal polysemy of the very word *cannabis*. C61 defines drugs as ‘any of the substances in Schedules I and II, whether natural or synthetic’ (art.1(j)). Only ‘cannabis’, ‘cannabis resin’, and ‘extracts and tinctures of cannabis’ are listed in these Schedules (UN, 1961: 239). Consequently, ‘cannabis plant’ is not seen as a drug as per the C61 regulations.

‘Cannabis’ as a plant

Beyond the ancient uses of the word ‘cannabis’ to refer to this particular plant, modern science legitimises the word with Linnæus (1753: 1027; see also and Watts, 2006) describing a monogeneric plant under this name. At the higher family level, its belonging to *Cannabaceae* is nowadays generally accepted (McPartland, 2018; Stevens, 2001a onwards, 2001b onwards; Watts, 2006). However, although unrivalled

at the genus level, the systematic classification of *Cannabis* at lower taxonomic levels continues to be an essential subject of controversy (Chopra and Chopra, 1957; Clarke and Merlin, 2013; Lynch et al., 2016; McPartland, 2018; Small, 2017; Stevens, 2001a onwards; Yang et al., 2013). Contemporary findings tend to show *C. sativa* as the only monospecific expression of the genus *Cannabis*; the rich genetic diversity responsible for the numerous *types* of *C. sativa* would be expressed at a lower level (in the taxonomic ranks of subspecies, variety, forma, or cultivar, see Lynch et al., 2016; McPartland, 2018). While no consensus arises, none of the findings matches the traditional distinction between drug-type and fibre-type *Cannabis* mimicked in folk language by the use of terms such as ‘marijuana’ and ‘hemp’. Hazekamp et al. (2010) even state that such a ‘distinction between the two types may have limited relevance for medicinal research’ (1037). Genetic diversity happening below the species rank reflects substantial variabilities of *C. sativa* crops, which might explain the reported use of ‘drug-type’ varieties for the obtention of fibres, and vice versa (Clarke and Merlin, 2013; Lynch et al., 2016; Szendrei, 1997). The UNODC (2009) finds:

Chemical and morphological distinctions by which Cannabis has been divided into these subspecies are often not readily discernible, appear to be environmentally modifiable, and vary in a continuous fashion. For most purposes, it suffices to apply the name Cannabis sativa to all Cannabis plants encountered. (7)

‘Cannabis’ as phytopharmaceuticals

Surprisingly, evidence-based definitions of the word ‘cannabis’ understood as a series of products obtained from the *C. sativa* plant are absent from scientific literature. Besides the living plant, the word is also used to refer to one of the products of the harvest of *C. sativa* plants, a particular botanical part used for human consumption in relation to a sought-after pharmacological activity. This ‘cannabis’ is often referred to as *buds*, *flowers*, *inflorescences*, *bracts*, *heads*, or *tops*.

Additionally, an important number of extracts or transformed derivatives of the *C. sativa* plant, at different stages of elaboration, are commonly referred to as ‘cannabis’. In the 1950s, the *Multilingual list of narcotic drugs under international control* (UN, 1958: 13–14) defined ‘cannabis’ as both raw herbal parts, and more elaborate products such as confections, beverages, and preparations. Sixty years later, the WHO also considered a number of prepared, compounded, or elaborate products, mostly traditional ones, under the agenda item ‘cannabis’ rather than under that of ‘extracts

and tinctures of cannabis' (Cannazza and Citti, 2018a: 5, 2018b).

The C61 recognises differences between *simple* botanical 'cannabis', the processed 'cannabis resin', and 'extracts and tinctures of cannabis'. However, no clear distinction between the two latter entities is mentioned in the Convention, the processes to obtain one or the other are sometimes similar (Table 2); the entities 'cannabis', 'cannabis resin', and 'extract and tinctures' are sometimes considered interchangeably (UN, 1973: 2 §5) even though they are listed in different Schedules and eventually subject to a distinct policy régime.

In literature, neither simple 'cannabis' nor elaborate products are defined in a better way. In other international instruments, *Cannabis* and its derivatives are present under limited functional appellations, not always reconcilable with the ones used in the IDCC. For example, the World Trade Organisation's Harmonised Tariff System contemplates a category (No. 1302.19) titled 'Cannabis flower/*Cannabis* extract' (Krawitz et al., 2018: 20).

Defining the basic botanical 'cannabis product'. Scientifically identifying the 'buds', 'tops', 'ganja', 'heads', or 'flowers' is not an easy task, and consensus lacks on their precise botanical designation. *C. sativa* is an annual dioecious (although sometimes monoecious or hermaphrodite) flowering herb (Clarke, 1981; Evans, 2009) producing geniculate achenes as fruits (Evans, 2009; Upton et al., 2014: 8). Reproduction occurs through wind-dispersed pollen liberated from the flowers of *staminate* (i.e. male) plants (Chandra et al., 2017; Small and Antle, 2003). Chopra and Chopra (1957) described the parts of *C. sativa* used for the production of drugs as 'flowers, leaves (and the resinous matter derived therefrom), fruit, young twigs, and bark of the stem'. Twenty-three years later, Kimura and Okamoto found that traces of active compounds were present at all stages of the plant's life, in both staminate and *pistillate* (i.e. female) *C. sativa*, although mainly 'contained in the parts in prosperous growth, and especially concentrated at the bractlet in the period when the seeds are at the peak of ripening' (Kimura and Okamoto, 1970). They refer interchangeably to these botanical parts, containing the most active phytochemicals, as pistillate 'tops', 'flowers', 'inflorescences', or 'fruits'. More accurately, the active ingredients (mostly phytocannabinoids, terpenoids, phenols) are biosynthesised inside the multicellular, glandular heads of epidermal multiseriate stalk trichomes (Chandra et al., 2017; Clarke, 1981; ECDD, 2018; Evans, 2009: 525–527, 553–557; Flemming et al., 2007: 8; Frank, 2018; Happyana et al., 2013; Heinrich et al., 2017: 18, 149–150; Turner et al., 1981). While these epidermal glandular trichomes (EGT) are also

present in a much lesser extent on leaves, stem, and other parts of the plants (explaining the results of Kimura and Okamoto, 1970; see also Turner et al., 1981), their dense concentration around the reproductive parts of pistillate plants (the so-called 'buds' or 'heads') is a major factor in the choice of the parts to harvest and transform for psychoactive purposes. Hence, the most common and well-characterised phytoconstituents are found only in trace amounts outside of the EGT found on the leaves, flowers, and fruits (Jin et al., 2020).

'Flowers' is the name for the preferred harvested parts bearing phytopharmaceutical ingredients and is the most commonly encountered designation in the literature as well as references like USHP, Ph.Helv, UNODC (2009), or in the various ECDD (2018, 2019) reports. C61 accepts both flowering and fruiting tops in its definition but excludes seeds, which, however, are sometimes referred to as fruits, such as in Pharmacopœia of the People's Republic of China (Ch.P) and Japanese Pharmacopœia (JP) (Chinese Pharmacopoeia Commission, 2015; Ministry of Health, Labour and Welfare, 2016).

Numerous references use imaginative formulations to mean that flowers have seeds, without directly verbalising 'seeded flowers'. This would indeed oppose the basics of botany where seeded flowers are not an option. As early as 1894 it was noted that the materials used for the production of a local extract in India were 'flower heads, which are now full of seed, discarding the coarser leaves' (Indian Hemp Drugs Commission, 1894). 123 years later, a paper describes the botanical parts harvested for their psychoactivity, in Nepal, as the 'mature seeded female inflorescences' (Clarke, 2007). Creative alternatives, such as *buds*, *bractlets*, *calyxes* (Frank, 2018), '*bracts which surround the ovaries*' (Dewick, 2012), or *seedless floral clusters* were found, reflecting a lack of consensus around the designation of these parts. The sentence describing the frontispiece photograph of *Cannabis and Health* (Graham, 1976: III) achieves the feat of referring to the same specimen simultaneously as a 'fresh flowering top' and a 'developing fruit'. These curious phraseologies can be explained by the fact that, in traditional outdoor cultivation, staminate and hermaphrodite plants can occur in the field, thus resulting in the pollination of some flowers, and their transformation into fruits bearing seeds (Chopra and Chopra, 1957; Clarke, 2007). *C. sativa* farmers have developed strategies to avoid this and reduce the presence of seeds in harvestable crops, mostly by impeding pollination. Chopra and Chopra (1957) noted that an important operation of India's 1950's *C. sativa* farmers consisted of going 'through the field cutting down all staminate plants' for 'preventing seed formation'. Hamayun and

Shinwari (2004) explain that the early flowering stage of pistillate flowers allows for easy removal from the fields. They note that ‘even the young fruit of the female cannabis plant’ is used for the production of psychoactive products. The plants resulting from crops where such sexual selection has taken place are known as ‘sinsemilla’ (Clarke and Merlin, 2013; ECDD, 2018: 18), derived from Spanish *sin semilla*, literally meaning ‘without seed’. The UNODC (2009) explains:

Cannabis with the highest level of THC is comprised exclusively of the female flower heads (“buds”) that remain unfertilized throughout maturity and which, consequently, contain no seeds. The production of sinsemilla requires identifying the female plants and ensuring that they are not exposed to pollen. (11)

‘Ganja’, the traditional word used in many parts of the globe to refer to psychoactive *C. sativa* tops, was described by the UN (1958) as ‘the prototype of the pharmacopœial cannabis or “Indian hemp”, defined as the flowering tops of the pistillate plants of *Cannabis sativa* L. (sometimes required to be unfertilised)’ (13).

The consideration of buds as flowers conflicts with the repeated mentions of a seemingly needed *maturity* of flowers to be harvestable. Flowers do not ripen: they wilt (senescence) and turn into fruits which, on their turn, do mature. Literature repeatedly suggests that the optimal moments for the harvest of seeds, and of content rich in cannabinoids, occur simultaneously. Dewick (2012: 120) explains that ‘resin is produced from the time flowers first appear until the seeds reach maturity’, as confirmed by Clarke (1981: 12). Kimura and Okamoto (1970) go in the same direction: although they do not refer to the word fruit, they distinguish ‘bractlet’ from ‘flowers’, the former appearing chronologically after the latter. They explain that bractlets bear a higher concentration of cannabinoids two months after analysing the staminate flowers, which are known to appear slightly before pistillate flowers and to have a maximum life duration of three weeks (Small and Antle, 2003). These observations could mean that pistillate flowers would survive five weeks or more after their staminate counterparts have lost the ability to pollinate them. That would be an unprecedented form of dioecism in the *Plantae* kingdom, with the only known seeded flowers ever, and where male and female iterations would enter flowering at different periods.

From a different angle, yet fully aligned with modern botanical sciences, considering ‘bud’ not as bractlets, flowers, or inflorescences, but as *fruits* or *infructescences*, might be insightful. In the past defined

as ‘structures bearing seeds’, fruits are currently described in a more sensible way as ‘matured pistil or ovary of the flower, with or without accessory structures’ (Blumenthal et al., 1998: 59) or as ‘a derivative of the gynoecium or whatever extracarpellary part it may be united with during the fruiting stage’ (Esau, 1977: 430; Scagel et al., 1967: 559). Botanical sciences do contemplate the development of fruits from unfertilised female flowers, a mechanism termed ‘parthenocarpy’ and widely spread among dicots (supplementary Appendix II).

These observations suggest that the *basic* ‘cannabis product’ might not be composed of flowers, but fruits – more precisely, parthenocarpic fruits. Because *C. sativa* naturally has both abilities to produce seeded and seedless fruits, the genus would be more accurately classified as a ‘facultative parthenocarpic plant’ (Koltunov et al., 2002), and when some seeds remain in an otherwise seedless *Cannabis* ‘top’ it would be called a ‘*partially* parthenocarpic infructescence’.

The phenomenon of parthenocarpy in *C. sativa* and possible reasons for its oversight in literature are discussed and illustrated in supplementary Appendix II. In this study, the expression ‘parthenocarpic fruits’, or ‘parthenocarpic infructescence of *C. sativa*’ (which can be abbreviated as ‘pioC’), is therefore preferred to ‘inflorescence’, ‘top’, ‘bract’, or other terms, when referring to the mature seedless reproductive parts of pistillate *C. sativa* plants.

Defining products derived from the Cannabis plant. In popular and folk lexica of extracts, tinctures, resins, and other derivatives of *C. sativa* for human consumption (except pioC themselves), a seemingly standard corpus of terms is used globally (Backes, 2014; Cannazza and Citti, 2018a, 2018b; Chambers, 2019; Daniulaityte et al., 2017; Jaffe, 1995: 982–989; Ministry of Health and Family Welfare of India, 1989; Nicoletti Motta, 2018; Oliver-Bever, 1986; UN, 1958; UNODC, 2009; World Health Organisation, 2016; Závřelová, 2017) although it refers to different concepts, depending on sources, area, and time. No universally accepted terminology is used, but some terms recur. For instance, while the word ‘hashish’ in Morocco refers to the living plant from which resin is extracted (Bellakhdar, 1997: 233), the Encyclopedia of Drugs and Alcohol explains it is ‘the Arabic word for a particular form of *Cannabis sativa*...the resin derived principally from the flowers, bracts and young leaves’ (Jaffe, 1995: 541). For Oliver-Bever (1986: 78) it is a ‘purified alcoholic extract’ and for the UNODC (2009: 16) hashish consists of ‘resinous secretions of the plant, produced in glandular trichomes’. The Martindale explains that the word ‘is often applied to the resin, although in some countries, *hashish* is applied to any

Table 2. Nomenclature of methods of obtention of *Cannabis* products in the 1961 Convention on narcotic drugs.

Starting material	Method of obtention	Resulting drug
cannabis plant	Production (I(t))	cannabis
cannabis plant	Production (I(t)) Separation (I(c))	cannabis resin
cannabis	Manufacture (I(t)) Extraction (I(b))	
	Manufacture (I(t))	extracts and tinctures
cannabis plant	Manufacture (I(t))	
cannabis resin	Manufacture (I(t))	
crude cannabis resin	Manufacture (Art. I(t), I(j))	refined cannabis resin
not a scheduled drug (e.g., <i>in vitro</i> synthesis)	Manufacture (Art. I(t), I(j))	cannabis resin
	Manufacture (Art. I(t), I(j))	extracts and tinctures

The products in bold are those defined as 'drugs' in the Convention (Art. I(j)), as of 2020.

Table 3. Ontological conflicts: 'extracts and tinctures of cannabis' according to different authors of the pre-review documentation used at the 40th ECDD meeting.

Chemistry	Pharmacology	Toxicology	Therapeutic use	Epidemiology
Cannabis tinctures	Cannabis tinctures	Cannabis extracts, tinctures, oils and tea	Cannabis Sativa Extract	Extracts and tinctures
Cannabis extracts	Cannabis oils			
Cannabis oils				
Aqueous extracts	Aqueous extracts		n/a	n/a
n/a	Hemp seed oil		Hemp seed, 'Evening Primrose Oils'	n/a
Nabiximols / cannabidiol in preparation with other cannabis-related ingredients	Nabiximols n/a	Nabiximols n/a	Nabiximols Oral-mucosal cannabinoid extract	Nabiximols
n/a	n/a	Cannabis resin	n/a	n/a

Adapted from Krawitz et al., 2018.

cannabis preparation' (Sweetman, 2005: 1666). Many *C. sativa* products linked to traditional medical practice or entheogenic uses, still partially undocumented (Abbott, 2014; Abdool, 2013; Bellakhdar, 1997: 232–234; Kutesa, 2018) are victims of similar terminological confusions. Another example is the inappropriate use of the word 'oil' (Daniulaityte et al., 2017; Szendrei, 1997; WHO, 2016) to describe all sorts of products very distinct from the common understanding of 'oil', mostly limited to fatty oils and essential oils. Although a lot of these 'cannabis'-specific terms seem universally

known and used, they have no consistent, nor universal definition.

Generally, folk distinctions between 'resin' and 'extracts' recur (Nicoletti Motta, 2018; Satchel, s.d). Resin is often described as the product of a simple and often traditional extraction process. The Encyclopedia of Drugs and Alcohol sees hashish as 'a concentrated resin containing increased amounts of Δ^9 -THC', 'derived principally from the flowers, bracts, and young leaves of the female hemp plant', and that 'contains cannabinoids' (Jaffe, 1995: 429, 541). Some

products like *rosin*, *dry sift*, or *bubble hash* are alternatively referred to as either a form of hashish or as extracts (Cannazza and Citti, 2018a, 2018b; Medicaljane, s.d). This confusion is absent from another widely used approach, which distinguishes products in two complementary categories based on the use of solvent during the extraction process, or not (Zavřelová, 2017; see also supplementary Appendix III).

Defining resin. Because ‘cannabis’ is defined in C61 as tops of *C. sativa* ‘from which the resin has not been extracted’, it is suggested that extraction is the method of obtention of ‘resin’ from ‘cannabis’. Such definition corresponds to ‘manufacture’ in Article 1(n): ‘all processes, other than production, by which drugs may be obtained [including] refining as well as the transformation of drugs into other drugs’. Additionally, Article 1 (d) explains that resin is ‘separated’ from *C. sativa*, which conflicts with Article 1(t) for which this operation is ‘production’ (‘the separation of [...] cannabis and cannabis resin from the plants from which they are obtained’). ‘Resin’ can therefore, under the Convention, be obtained by extraction, by manufacture, and by separation, as outlined in Table 2.

An additional detail about ‘resin’ is its state of being either ‘crude or purified’. The Commentary notes: ‘the separated resin is “cannabis resin” not only when it is “purified”, but also in its “crude” state, i.e. when it is still mixed with other parts of the plant’ (UN, 1973: 5 §3). The concept of *purification* is invoked to mean the elimination of residual botanical elements. It relates to the processes of *refining* described in Article 1(n) as being ‘manufacture’. Production and manufacturing are the two genuine ‘operations by which “drugs” [...] are obtained’ (UN, 1973: 15 §2). However, a more complex set of terminology, summarised in Table 2, is used to refer to the processes of elaboration of *C. sativa* and piC derivatives. Boundaries in C61 are unclear and leave a margin for bias and errors of interpretations. Because a different régime of control under the IDCC is currently applied to these products, this may have non-negligible legal implications.

Besides the language of the IDCC, the word *resin* is widely used to describe complex mixtures of phytochemicals secreted by plants (Evans, 2009: 298). Bone’s *Principles of herbal pharmacology* (2013) explains the polysemy of the word resin:

The term is used in several contexts. When certain plants are damaged, either by incision or naturally due to the action of animals or the environment, they secrete a viscous fluid that soon hardens... Such resins are often associated with essential oils (oleoresins), with gums (gum resins) or with oil and gum (oleo-gum resins). Their resin components, which mainly

comprise diterpenes known as resin acids, resin alcohols and resin phenols, are soluble in alcohol and ether but are insoluble in water and hexane. In another context, the term ‘resin’ (or occasionally ‘resinoid’) means the part of the plant that is soluble in ether or alcohol... These resins are chemically diverse and can contain resin acids, pyrones, lignans, esters and glycosides amongst others. (38)

Plants generally biosynthesise their phenols, terpenes, and terpenoids in specific glands. These are the classes of organic compounds to which phytocannabinoids are associated with, also including a large number of aromatic molecules. These secreting glands are mainly located inside the plants’ organs like in conifers (Kutchan et al., 2015: 1132–1135, 1147–1148) but can sometimes appear externally, like in EGT in the case of *C. sativa* plants (Evans, 2009: 298) and others (Chrispeels and Sadava, 1994: 345; Swiss Agency for Therapeutic Products, 2012: 134).

The WHO ECDD (2018: 18) considers that ‘resin’ originates from ‘resinous secretions’ of the plant’s EGT which contain, in addition to numerous phenols and terpenoids, dronabinol and other phytocannabinoids. Analytical explorations of the exudate secreted by EGT show the most present components numerically are terpenoids, phytocannabinoids, hydrocarbons, sugars, nitrogenous compounds, phenols, and flavonoids, with fatty, simple and amino acids, ketones, esters, lactones, aldehydes present in a much less significant yield. These substances ‘have all been identified as a constituent of some preparation of *Cannabis*: herbal plant material, whole extracts, and chromatographic fractions, or illicit material such as hashish’ (Hazeekamp et al., 2010: 1038–1039).

All of these compounds correspond to those described as characteristics of plant resins in literature. They are obtained by the secretion from a plant’s glands and are all known for their ether soluble properties (Clarke, 1981; Evans, 2009: 525–527, 557; Happyana et al., 2013). In other words, all acceptations of ‘resin’ (glandular origin, composition, solubility in alcohol) match with the material contained in *C. sativa* trichomes’ glandular heads. The systematic and substantial yield of aromatic metabolites in addition to phytocannabinoids suggests *oleoresin* might be a more accurate term than *resin* to describe the ether soluble separable content from EGTs.

It is generally assumed that the authors of the C61 agreed to use ‘resin’ in the absence of more advanced knowledge about its chemical composition, as a way to ensure dronabinol, by then unidentified, would fall under control in all circumstances. The assumption that the active compound(s) of *C. sativa* were included in resin is reflected in the Commentary, which refers,

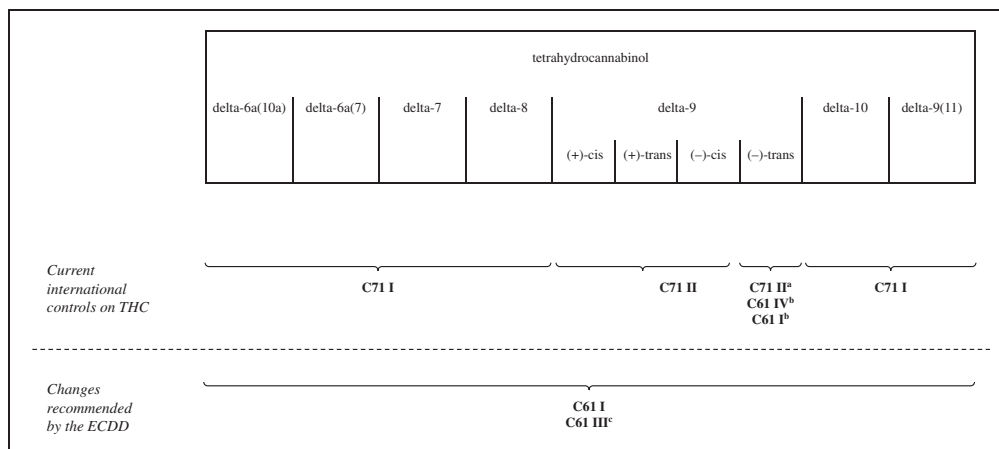


Figure 2. Conflicting ontologies of dronabinol and THC: impact on international control. C61 I: Schedule I of the 1961 Single Convention; C61 III: Schedule III of the 1961 Single Convention; C61 IV: Schedule IV of the 1961 Single Convention; C71 I: Schedule I of the 1971 Convention; C71 II: Schedule II of the 1971 Convention; THC: tetrahydrocannabinol. ^aOnly when ‘from synthetic origin’ (INCB, 2019: 8); ^bOnly when obtained from *C. sativa* (INCB, 2019: 8); ^cOnly for some preparations for medical use (ECDD, 2019: 55).

for instance, to the ‘pharmacologically strongly active resin’ (UN, 1973: 2 §1). Pure THC/dronabinol itself was eventually placed in the schedules of another IDCC treaty: the C71. Interestingly, countries’ authorities have been encouraged by the International Narcotics Control Board (INCB) to consider dronabinol of *synthetic origin* under the régime of C71, while dronabinol derived from the *C. sativa* plant would be considered under C61 rules (INCB, 2019: 8). A gross inconsistency (see Figures 1 and 2) which has been proposed a solution in the ECDD (2019: 45–47, 49–50) recommendations: placing all dronabinol-related isomers and stereoisomers within the same Schedule.

Notably, since 1961, the chemical composition of *C. sativa* oleoresin has been figured out: it was found to be exceptionally diverse and variable (Baram et al., 2019), with components interacting and interplaying above and beyond their individual pharmacological activity (Ben-Shabat et al., 1998; Rather et al., 2013; Russo, 2011). This dramatically influences the oleoresin’s overall therapeutic effects far beyond that of dronabinol, dependent on ‘complex interaction between molecules and multiple targets’ (Atakan, 2012; Baker et al., 2000; Baram et al., 2019; Russo, 2011) – a phenomenon which is typical of herbal medicines (Rather et al., 2013), called ‘cooperative effect’ or ‘entourage effect’ (Ben-Shabat et al., 1998; Oña and Bouso, 2019). This entourage effect results in *C. sativa* drugs binding to different neuronal targets, an effect in turn called ‘polypharmacology’ (Gertsch, 2011; Oña and Bouso, 2019).

In other words, ‘cannabis resin’ in IDCC as well as folk language, relates to a single concept: the sum of all

ingredients contained in the material separated from the glands of the epidermal capitate trichomes from *C. sativa* plants. In *Water is not H₂O*, Weisberg (2006) warns that there are not always ‘a straightforward connection between scientific kinds and the natural kinds recognised by ordinary language users’ (337). Similarly it can be stated that *resin is not THC*, refraining from amalgamating ‘cannabis resin’ with THC/dronabinol (or any other single cannabinoid or simplified composition) as an epistemological precondition.

Defining extracts. A changing nomenclature at the level of the IDCC. ‘Extracts and tinctures of cannabis’, although present in the Schedules of C61 since its inception (UN, 1961: 239) are nowhere defined in the Treaty. No additional information is provided in the Commentary. To document the ECDD assessment of that particular category of *Cannabis* products, the WHO tasked five teams of authors to draft reports on, respectively, the chemistry, pharmacology, toxicology, therapeutic use, and epidemiology of the products (Krawitz et al., 2018: 17–22). The five documents result in different understandings of the products covered (or not) by this category, as presented in Table 3.

The word ‘extraction’ derives from Latin *extrahō/extrahere*, formed by the lemmas *ex-* (‘out of’) and *trahō* (‘to pull’, ‘raw’, ‘drag’), meaning together: to withdraw, drag-out, remove. Popular meaning covered by the word ‘extraction’ is often that of a process consisting in ‘the separation of a substance from a matrix’ (Wikipedia, s.d). *Separation* is defined in the *Encyclopedia of Separation Sciences* as a ‘process of

any scale by which the components of a mixture are separated from each other without substantial chemical modification' (Wilson, 2000: VIII); in this approach, 'extraction' is seen as a subset of 'separation', and defined as 'the process of moving one or more compounds from one phase to another'. (Wilson, 2000: 1372). The concept of separation also seems to correspond to all four methods of obtention used in C61 (see Table 2). Products can also involve actual separation without properly extracting: an illustration is the preparation of traditional 'dry' *hashish* where trichome heads are separated from the rest of the plant, but where the glands' external layers are not broken to liberate (extract) the oleoresin contained in the cavity of the trichome's head.

Associated with 'extraction' in C61, the word *tincture* seems to denote with common understanding likewise with etymology. A tincture is indeed generally a mixture, a dilution of a herbal matrix in alcohol. This process increases the mass of the original matrix by diluting it in a solvent, in apparent divergence from the extracts produced by separation which inevitably involve a reduction in the mass or volume of the final material compared to the starting matrix.

In order for the ECDD (2018, 2019: 2–3, 34–36) to review *C. sativa*, the WHO collected data, using the nomenclature of C61 as terms of reference (Riboulet-Zemouli and Krawitz, 2019: 4). This explains why products known for their total absence of similarity with dronabinol or other phytocannabinoids' effects were de facto included. 'Hemp oil' and 'essential oil' were indeed considered in the scope of the review (WHO, 2016) aside products such as 'CO₂ oil', 'butane hash oil, propane hash oil and solvent extracts', 'wax', 'budder', 'live resin', 'shatter', 'taffy', 'distillate', 'pie crust/honeycomb', 'caviar', 'jelly hash', 'rosin', 'edibles', 'e-liquids' (Cannazza and Citti, 2018b: 5–7). On the other hand, the ECDD (2019) noted that 'some preparations with high Δ^9 -THC concentrations are produced in such a way that they are not captured within the definition of an extract or tincture' (35).

The results of the ECDD assessments suggested editing the Schedules of the C61 to replace the terminology *extracts and tinctures* with that of *preparations*. In the Convention's Article 1(s), preparations are defined as any 'mixture, solid or liquid, containing a drug' and subject to the same dispositions as the drug they contain. Such a move makes the definition more accurate by covering processes other than extraction/separation, such as dilution (mixing, compounding, composition, emulsion) or concentration (further mechanical or chemical processing). It would also provide a consistent division of *C. sativa* derivatives in three clear categories able to match evidence-based definitions:

- a. 'Cannabis' as *pioC* and other botanical material of minor importance,
- b. 'Cannabis resin' as the raw, unprocessed oleoresin separated from EGTs,
- c. 'Preparations of cannabis' as those products obtained by further processing (a) or (b).

C. sativa derivatives, defined as drugs in the IDCC (i.e. products whose 'medical use continues to be indispensable for the relief of pain and suffering', UN, 1961: Preamble), also correspond to the definition of a 'medical product' laid out in BP (Medicine and Healthcare products Regulatory Agency, 2017: I-22):

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings and/or animals; or
- (b) any substance or combination of substances that may be used in or administered to human beings and/or animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

This definition eventually captures several purposes of use: the supervised therapeutic (a *C. sativa* product prescribed by a physician), the conscious or unconscious auto-therapeutic (self-medicated uses), but it also encompasses so-called *recreational* purposes of use (adult-use) as well as other purposes of consumption such as the entheogenic (spiritual), nutraceutical, or cosmetic. Even though pharmacopœias are only partial standardisation references, thought mostly for the first of these purposes of consumption, their contents can provide useful guidance when mapping existing *C. sativa* phytopharmaceuticals, for whatever their purpose of use may be.

Historical nomenclatures of Cannabis in pharmacopœias. *C. sativa* was considered a *valuable drug* (i.e. essential drug) at the moment of the first *International conference on the unification of formulæ of potent medicaments* held at Brussels in 1906, which resulted in an Agreement seen as an early basis for the harmonisation of pharmacopœias, and later for The International Pharmacopœia (Ph.Int.) (WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2008: 6). Remarkably, *C. sativa* drugs were not included in the first harmonised list because too little of their phytoconstituents were known (Power, 1903: 9). In contrast, the second conference, and Agreement, of September 1925 (*International Agreement revising the Agreement signed at Brussels, 29 November 1906, on the Unification of Pharmacopœial Formulas for Potent Drugs*, see: *Seconde conférence internationale pour*

l'unification de la formule des médicaments héroïques, 1925a, 1926; Indian Med Gaz, 1932) did incorporate three *C. sativa*-based 'formulæ' (Real Academia Nacional de Medicina, 1930: 897–905; Seconde conférence internationale pour l'unification de la formule des médicaments héroïques, 1925b): *Cannabis indica herba* (raw plant), *Extractum cannabis indicae* and *Tinctura cannabis indicae*. The proceedings of the conference show that prior to 1925, *extractum cannabis* was found in the pharmacopœias of at least 10 countries (detailed in Table 4), and that *Cannabis tinctura* were present in very diverse formulations in all countries reviewed except in the Austrian, Belgian, and Dutch pharmacopœias (General Council of Medical Education and Registration of the United Kingdom, 1914; Seconde conférence internationale pour l'unification de la formule des médicaments héroïques, 1925a, 1926). After the entry into force of the Agreement in 1929, monographs of internationally standardised formulations were progressively included in most national pharmacopœias. While the 1865 edition of the Spanish pharmacopœia only included 'Cañamo – *Cannabis sativa* L.' as a crude drug, pointing at the seeds as the preferred material for formulations (Real Academia de Medicina de Madrid, 1865: 25), the 1930 revision harmonises on the Agreement's standard by adding *extractum* (Real Academia Nacional de Medicina, 1930: 335) and *tinctura* (Real Academia Nacional de Medicina, 1930: 857). In the UK, the British Pharmacopœia Commission followed in 1932, although with some changes (Cartwright, 2015: 50–51; Indian Med Gaz, 1932). It is safe to assume that C61 partially inherited this nomenclature.

Conversely, in the 1950s, the body within the recently created WHO with a similar mandate to that of the ECDD today (Danenberg et al., 2013) stated that 'there is no justification for the medical use of cannabis preparations' (in 1952 and 1953), adding that 'there should also be extension of the effort towards the abolition of cannabis from all legitimate medical practice' (in 1954), and that 'Cannabis and its preparations are practically obsolete and there is no justification for their medical use' in 1960 (Riboulet-Zemouli, 2018: 37–39). The records of their meetings on *Cannabis* feature cherry-picked documentation, and no trace of methodology seems to have been used to reach these conclusions. After receiving the first draft of C61, 'the Committee was pleased to note the decision... to place cannabis drugs together with diacetylmorphine (heroin)... in the list of prohibited drugs' although it seems that such decision had not been consulted with them as, in the next paragraph, the Experts 'expressed the view that [they] would welcome an opportunity to consider, and give advice on, substances that might be placed in that schedule' (WHO Expert Committee on Drugs

Liabile to Produce Addiction, 1956: 3–4). Once the Convention was in force, they continued in 1965, and again in 1968, to declare that 'medical need' for *C. sativa* drugs 'no longer exist'. The placement of *C. sativa*-related medicines in the Schedules of C61 which involve the most stringent controls, obviously 'with insufficient scientific support to substantiate those classifications' (Committee on Economic, Social and Cultural Rights, 2020: 15), but also the subsequent withdrawal of *Cannabis* drugs from pharmacopœias and pharmacy shelves, was undoubtedly influenced by these statements.

Monographs on *Cannabis* disappeared from BP in 1932, and 10 years later from USP (Giancaspro et al., 2016). Nonetheless, the UN (1958: 111) still reports, in the 1950s, *C. sativa* pharmaceuticals in at least 16 legally binding pharmacopœias, on all continents. With the entry into force of the C61 in 1964, these phytopharmaceuticals started to disappear from pharmacopœias as well as from mainstream medical practice, following the gradual decline in the use of phytomedicines in modern healthcare along the latter 20th century (see Table 4, and Chandra et al., 2017).

At the time of writing this article, *C. sativa* phytopharmaceuticals were almost totally absent from pharmacopœias worldwide, even in jurisdictions where it was allowed for medical prescription. In Asia, Ch.P and JP include monographs of *C. sativa* fruits (raising questions with regards to pioCs), while in North America, USP has two monographs on dronabinol. In Europe, German Commission E's monographs (DAB) and Swiss Pharmacopœia reincluded in 2019 monographs of *Cannabis* parthenocarpic infructescences (although titled '*Cannabis flos*' [flower], see Swiss Agency for Therapeutic Products, 2019: 115, 263–266). Besides the mere presence of *Cannabis* or not in pharmacopœias, the way medical products of herbal origin are addressed and classified provides useful guidance on how to approach *C. sativa* derivatives.

Pharmacopœial nomenclatures of phytopharmaceuticals. All current pharmacopœias reviewed contemplated phytopharmaceuticals, in individual monographs, in general notices/appendices, or both. One pattern of categorification for plant-based medication was found recurrent from the 1865 edition of the Spanish pharmacopœia onwards to the latest edition of European Pharmacopœia (Ph.Eur). It is based on the observation of the physical consistency of phytopharmaceuticals, divided between:

- solid/dry (*extracta sicca*),
- semisolid/soft (*extracta spissa*) or
- fluid/liquid extracts (*extracta fluida*).

The latest editions of Argentina's, Brazil's, Ph.Eur., Russia's State Pharmacopœia of the Russian Federation (SPRF), and Spain's pharmacopœia consistently use this model. Others like Herbal Pharmacopœia of Mexico (FHEUM), Indian Pharmacopœia (IP), JP, and French Pharmacopœia (Ph.Fr.) occasionally refer to these terms without systematising them. Most pharmacopœias consider tinctures (*tincturæ*) distinct from *extracta*, while others such as Argentinian Pharmacopœia and Ph.Eur. consider *tincturæ* a subset of *extracta fluida*. Pharmacopœial monographs however never mention that other alcohols like glycerol, propylene glycol, or polyethylene glycol are increasingly replacing ethanol in the preparations of *tincturæ* (Schulz et al., 2004: 11). Ph.Eur. separates *oleoresina* (oleoresins), defined as 'semi-solid extracts composed of a resin in solution in an essential and/or fatty oil . . . obtained by evaporation of the solvent(s)', from *extracta spissa* that it defines as 'semi-solid preparations obtained by evaporation or partial evaporation of the solvent'.

In the 2000s, new models of classification were introduced to complement the traditional one (Gaedcke and Steinhoff, 2003: 4–7, 26). One of these newer models divides phytopharmaceuticals between drugs that are genuine extractable matter, termed 'native extracts', and drugs that contain added ingredients (whether active compounds or excipients) with regard to the starting botanical material, termed 'non-native' (European Directorate for the Quality of Medicines, 2016: 6519, 6521; Gaedcke and Steinhoff, 2003: 6–7). In 1988, Menßen (Gaedcke and Steinhoff, 2003: 26–27) proposed to distinguish between 'primary extracts' and 'refined extracts' as the refinement process (also referred to as *purification* or *enrichment*) produces phytopharmaceuticals with a reduced spectrum of constituents.

Another complementary model pushed forward by Ph.Eur. is that of ordering phytopharmaceuticals according to content standardisation criteria, distinguishing them according to the level of precise knowledge of their composition in active compounds. According to this model rapidly expanding, phytopharmaceuticals are either 'standardised extracts', 'quantified extracts', or 'other extracts' (European Directorate for the Quality of Medicines, 2016: 25–26). Ph.Eur. explains:

Standardised extracts are adjusted to a defined content of one or more constituents with known therapeutic activity. This is achieved by adjustment of the extract with inert excipients or by blending batches of the extract. Quantified extracts are adjusted to one or more active markers, the content of which is controlled within a limited, specified range. Adjustments are made

by blending batches of the extract. Other extracts are not adjusted to a particular content of constituents. (European Directorate for the Quality of Medicines, 2016: 6515–6516, 6519)

This latter standardisation-based distinction is currently included in BP, DAB, Brazilian Pharmacopœia, Ph. Eur., and Royal Spanish Pharmacopœia (RFE). Evans (2009: 72) cites nabiximols (the generic name for a formulation of dronabinol and cannabidiol (CBD), of which a well known marketed example is Sativex[®]) as an example of standardised *C. sativa* drug.

Ch.P., FHEUM, FP, Romanian Pharmacopœia (FR), IP, JP, Egyptian Pharmacopœia, Ph.Fr., Hellenic (Greek) Pharmacopœia, Polish Pharmacopœia, SPRF, USP, and Pharmacopœia of Vietnam (VP) adopted *sui generis* approaches, often in complement to one of the above patterns. Ch.P. references none of the previous models: instead, it separates crude drugs from preparations, which are subdivided into 26 specific formulations (e.g. pills, powders, granules, concentrated decoctions, plasters, ointments, etc.). In the same spirit, JP regards 'crude drugs' (including drugs of herbal, animal, or mineral origin), only distinguishing between 'whole', 'cut', or 'powdered' crude drugs (Ministry of Health, Labour and Welfare, 2016: 1, 5–6). It classifies crude drugs simultaneously in eight subcategories: 'extracts' (corresponding to both *extracta sicca* and *spissa*), 'fluid extracts', 'tinctures', 'spirits', 'infusions or decoctions', 'teabags', 'aromatic waters', and 'pills' (Ministry of Health, Labour and Welfare, 2016: 21–23). FHEUM separates 'vegetal drugs', 'trituated herbs', 'teas', 'tinctures and extracts', and 'essential oils' (Comisión Permanente de la Farmacopea de los Estados Unidos Mexicanos, 2013: 7–8). IP distinguishes 'crude herbs' and 'processed herbs' (covering either intermediary or traditional preparations), 'botanical extracts' which includes fluid, powdered, and semisolid extracts, separates the 'tinctures', and presents 'herbal formulations' as readily available products for consumers, and potentially for non-medical uses (e.g. food supplement, nutraceutical, cosmetic, see Indian Pharmacopoeia Commission, 2018: 3725–3729). Numerous references such as Ph.Eg, Ph.Indo, Ph.Pl, FR, and VP use long lists of traditional formulations (e.g. elixirs, ointment, potion, granulate, powder, suppository, syrups, etc.), with a rationale mostly reliant on historical addition of marketed formulations types rather than on the intrinsic physical characteristics of the products. USP makes mention of 'herbals', 'crude products of plant origin', as well as 'botanical-containing products' without further definition, nor consistent use throughout the different pharmacopœial monographs. A different detailed scheme of categorification was found in the

Table 4. Presence of *C. sativa* pharmaceuticals in pharmacopœias, 1925–2020; non-exhaustive.

\\	<i>Cannabis</i>	<i>Cannabis extractum</i>	<i>Cannabis tincturæ</i>	<i>Cannabis flos (fructus)</i>	<i>Cannabis fructus (semen)</i>	Dronabinol
1925	Undocumented	Austria ^{a,c} Belgium ^{a,c} France ^{a,c} Hungary ^{a,c} Italy ^{a,c} Japan ^{a,c} Mexico ^e Netherlands ^{a,c} Switzerland ^{a,c} UK ^a USA ^{a,b} (<i>extractum fluidum</i>)	France ^{b,c} Hungary ^{b,c} Italy ^{b,c} Japan ^b Switzerland ^{b,c} UK ^b USA ^b	Mexico ^e	Mexico ^f	n/a
1958	Argentina ^d Belgium ^d Brazil ^d China ^d Egypt ^d Finland ^d France ^d India ^d Italy ^d Netherlands ^d Portugal ^d Romania ^d Spain ^d Switzerland ^d USSR ^d Venezuela ^d	Undocumented	Undocumented	Undocumented	Undocumented	n/a
2020	Undocumented	Undocumented	Undocumented	Germany ^g Netherlands ^h Ph.Helv ⁱ	ChP/JP ^k	USP ^l

^a Seconde conférence internationale. . . , 1925a: 48; ^b Seconde conférence internationale. . . , 1925a: 49; ^c Seconde conférence internationale. . . , 1926; ^d United Nations, 1958: 111; ^e Unión Nacional de Farmacéuticos Científico-Cooperativa, 1925: 406–407; ^f Unión Nacional de Farmacéuticos Científico-Cooperativa, 1925: 163; ^g Swiss Agency for Therapeutic Products, 2019: 115; ^h Ministerie van Volksgezondheid Welzijn en Sport, 2019; ⁱ Swiss Agency for Therapeutic Products, 2019: 263–266; ^j Chinese Pharmacopœia Commission, 2015: 93; ^k Ministry of Health, Labour and Welfare, 2016: 1876; ^l United States Pharmacopœial Convention, 2019.

former USSR pharmacopœia (USSRSP, see Shikov et al., 2014) in force until 2007. Phytopharmaceuticals were distinguished between ‘medicinal plant’, ‘summarised non-refined (or galenic) formulations’ (which includes infusions, decoctions, tinctures, concentrated extractions, and elixirs), ‘novo-galenic formulations’ (herbal material mixed with non-herbal ingredients), ‘combined phyto-preparations’ (mixtures of only herbal ingredients), and ‘active pharmaceutical ingredients’ (APIs).

Finally, among the non- or partially legally binding pharmacopœias reviewed (Table 1), Ph.Int. did not contemplate herbal medicines at all, while others such as British Herbal Pharmacopœia, Ayurvedic Pharmacopœia of India, USHP, and African Herbal

Pharmacopœia did not rely on any orderly meta-category for phytopharmaceuticals.

Other kinds of medical products of herbal origin were found in a number of pharmacopœias, particularly those following Ph.Eur. standards. Some of these eventually correspond to *C. sativa*-derived phytopharmaceuticals, such as:

- Essential oils, termed *atherolea* (European Directorate for the Quality of Medicines, 2016: 814–815),
- Teas, *plantæ ad ptisanam*, and instant herbal teas, *preparationes celeres ad ptisanam* (European Directorate for the Quality of Medicines, 2016: 820),
- Products obtained from organisms with recombinant deoxyribonucleic acid (rDNA) biotechnologies,

Table 5. Ontological conflicts in the pharmacopoeial classification of phytopharmaceuticals: comparison between different models and the classification of *C. sativa* phytopharmaceuticals in international law.

	T&CM ^a	EU ^b	Ph.Eur ^c	BP ^d	USSRSP ^e	USP ^f	IP ^g	C61 ^h
Raw / crude drug	Herbs	Herbal substances	Herbal drugs	Herbal drugs	Medicinal plants	Herbals	Crude herbs	Canna bis resin
Inter-mediary drug	Herbal materials	Herbal preparations	Herbal drugs	Herbal drugs	Summarised non-refined (or galenic) formulation	Crude products of plant origin	Processed herbs	Canna bis resin
	Herbal preparations	Herbal preparations	Herbal drug extracts	Herbal drug extract				
Finished drug (Eventually standardised)	Finished herbal products	Herbal preparations	Herbal drug preparations / Pharmaceutical preparations	Herbal drug preparations	Novo-galenic formulations Combined phyto-preparations APIs	Botanical-containing products	Herbal formulations	Extracts and tinctures / preparations
		Herbal preparations	Herbal drug preparations / Pharmaceutical preparations	Herbal drug preparations				

^a World Health Organisation, 2004, 2011; ^b European Commission, 2001; ^c European Directorate for the Quality of Medicines, 2016; ^d Medicines and Healthcare products Regulatory Agency, 2017; ^e Shikov et al., 2014; ^f United States Pharmacopoeial Convention, 2019; ^g Indian Pharmacopoeia Commission, 2018; ^h Riboulet-Zemouli, 2018.

producta ab arte ADN recombinandorum (European Directorate for the Quality of Medicines, 2016: 6526–6528)

- Products of fermentation, *producta ab fermentatione* (European Directorate for the Quality of Medicines, 2016: 5909–5910),
- Vegetable fatty oils, *olea herbaria* (European Directorate for the Quality of Medicines, 2016: 848–850).

European regulatory nomenclature of phytopharmaceuticals. Alternatively, the European Union (EU) in its *Community code relating to medicinal products for human use* (European Commission, 2001) considers a simplified approach where all phytopharmaceuticals are termed ‘herbal medicinal products’ and subdivided between *substances* and *preparations*:

Herbal medicinal products: Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations,

Herbal substances: All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author),

Herbal preparations: Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Even so, this model is not particularly relied upon in pharmacopœias, as shown in Table 5.

Nomenclature of Traditional & Complementary Medicine (T&CM) by the WHO. Unrelated to *C. sativa*, to the ECDD and to its mandate under the IDCC, the T&CM unit of WHO classifies phytopharmaceuticals according to their pharmacological properties, while staying consistent with the processes of obtention that are often firmly embedded into traditional processing methods (Abbott, 2014; Bellakhdar, 1997; Kutesa, 2018; World Health Organisation, 2011). Their approach distinguishes phytopharmaceuticals

according to processing stages (World Health Organisation, 2011: 129–130):

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products:

- *Herbs* include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.
- *Herbal materials* are either whole plants or parts of medicinal plants in the crude state. They include herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.
- *Herbal preparations* are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.
- *Finished herbal products* consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

The definition of ‘herbs’ provided by WHO seems to correspond to EU’s ‘herbal substance’, while EU’s ‘herbal preparations’ include WHO’s ‘herbal materials’, ‘herbal preparations’, and ‘finished herbal products’ (Table 5). The T&CM classification proposed by WHO seems more detailed than EU’s, even though some products could fall under the scope of two of the proposed categories. For instance, a product can match both ‘stir-baking with honey, alcoholic beverages or other materials’ (*herbal materials*) and ‘steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials’ (*herbal preparations*). Regrettably, the WHO T&CM model has not been more followed in pharmacopœias than EU’s.

Often, the same wording is used to encompass different definitions. BP adopted a dichotomous approach to phytopharmaceuticals: on the one hand, it fully follows Ph.Eur. considering ‘herbal drugs’ as non-

processed material while it labels processed herbs as ‘herbal drug extracts’ and ‘herbal drug preparation’ for the further homogenised – and eventually standardised – phytopharmaceuticals (Medicines and Healthcare products Regulatory Agency, 2017: I-17, VII-A837). On the other hand, BP maintains in parallel a monograph for what is called ‘processed herbal drugs’, corresponding to those phytopharmaceuticals obtained via traditional processing methods’ (Medicines and Healthcare products Regulatory Agency, 2017: IV-43–49).

Defining an upper limit to phytomedicine. The only consensus that seems to be shared is that of excluding from the category of phytopharmaceutical some finished products that, however, originate from plant material: those herbal derivatives to which non-herbal active compounds have been added. BP (Medicines and Healthcare products Regulatory Agency, 2017: I-22), in a similar fashion to that of DAB and RFE, the EU with the supra category ‘herbal medicinal products’ or the WHO T&CM with ‘herbal medicines’, groups as phytopharmaceuticals only those drugs:

- exclusively containing as active ingredients one or more herbal drugs,
- exclusively containing as active ingredients one or more herbal drug preparations,
- exclusively containing as active ingredients one or more such herbal drugs in combination with one or more such herbal drug preparations.

WHO (2011) specifies that ‘products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal’ (130). Consequently, herbal-based products containing non-herbal active compounds, or containing non-herbal compounds as excipients, are not regarded as phytotherapy. Gaedcke and Steinhoff (2003: 1) explain that because phytopharmaceuticals ‘are always mixtures of a number of substances’, a medicinal plant (entirely or by parts) is considered as a single active ingredient regardless of the composition (Gaedcke and Steinhoff, 2003; Rather et al., 2013). Besides their multiple constituents, phytopharmaceuticals, working in a synergical ‘entourage’ fashion, are viewed as one single *substance* (Atakan, 2012).

Also, fully isolated compounds or ‘refined extracts’ (Gaedcke and Steinhoff, 2003: 2–7) obtained from botanical material are not regarded as phytopharmaceuticals. These are rather considered as common APIs for the formulation of conventional pharmaceutical preparations. As an example, in the USSRSP model (Table 5) ‘combined phyto-preparations’ would be

considered phytopharmaceuticals, while ‘standardised extracts’ and ‘novo-galenic formulations’ would fall out of this category.

‘Others’: Non-phyto cannabinoid pharmaceuticals, non-Cannabis cannabinoid phytopharmaceuticals, etc

The uppermost limitation of the scope of phytomedicine on which pharmacopœias rely is not complete, as it would not exclude one particular (and diverse) corpus of compounds commonly referred to as *synthetic cannabinoids*. This broad category encompasses some ‘synthetic’ molecules that can be derived from plant material, without being mixed with non-herbal compounds; hence, pharmacopœial models currently de facto embrace some ‘synthetic cannabinoids’ as phytomedicines, which is problematic.

Alonso (1998) explains that botanical materials can, in addition to their use as a source of active compounds, be utilised as non-active starting materials in laboratory processes in order to obtain compounds that were not genuinely present in the plant. Halfway between natural compounds and molecules designed fully in vitro, these drugs have been referred to as *semi-naturals* (Feher and Schmidt, 2003) or more recently as *semisynthetics* (Cragg and Newman, 2013; Jones et al., 2006). Mathur and Hoskins (2017) describe them as ‘generally produced by transforming starting materials from natural sources into final products via chemical reactions’, clarifying that these reactions consist in the ‘rearrangement of chemical entities or structural isomers of naturally occurring products in order to generate new molecules’. Chrispeels and Sadava (1994) mention the example of saponins which are structurally ‘so much like human steroids that saponins are used as the starting material for synthesizing steroids used for making birth control pills’ (136).

At the API level, in order to explore the implications for *C. sativa* medicines, a safe analogy can be established with the extensively studied *Papaver somniferum* L. from which originate naturally occurring opioids (i.e. opiates). Six primary natural secondary metabolites are biosynthesised in *P. somniferum*: morphine, codeine, thebaine, papaverine, noscapine, and narceine. Semisynthetic opioids, in comparison, are those obtained by human intervention over the chemical structure of these compounds: diacetylmorphine (heroin) is a well-known example of semisynthetic opioid obtained from morphine (Novak et al., 2000; Solimini et al., 2018); oxycodone is a semisynthetic derivative of thebaine (Cortazzo et al., 2013: 502; Elkader and Sproule, 2005). In what concerns *C. sativa*, semisynthetics consist of derivatives from naturally obtained phytocannabinoid molecules

(Fahrenholtz et al., 1967), having undergone modifications of some of their pharmacophores with significant binding affinity to brain receptors (Bow and Rimoldi, 2016; Razdan and Zitko, 1969; Shevyrin et al., 2016). It is generally accepted that structural modifications corresponding to the natural pathways of cannabinoids biosynthesis and degradation within the *C. sativa* plant (e.g. decarboxylation, see Baram et al., 2019; Caspi et al., 2017; Hanuš et al., 2016) are not considered products of semisynthesis. However, the product of a semisynthesis can be another, different naturally occurring compound (as in the example of human steroids mentioned). For instance, the process to transform cannabidiol (CBD) into dronabinol, because it does not occur in vivo (not corresponding to the natural biosynthetic pathways of *C. sativa*, see Caspi et al., 2017) but is possible in vitro (ECDD, 2018: 13; Merrick et al., 2016), is considered a semisynthesis.

Importantly, semisynthetic compounds should not be confused with the second subset of *synthetic cannabinoids*, the naturally occurring ones obtained only by synthesis in vitro. In the case of opioids, morphine can either be extracted from *P. somniferum* or created by full chemical synthesis (Gates and Tschudi, 1956; Mechoulam and Hanuš, 2000; Novak et al., 2000). The same goes with molecules structurally identical to naturally occurring phytocannabinoids such as dronabinol or *cannabidiol* (CBD is the INN of (–)-CBD, whether natural or synthetic) that are designed in vitro without involving initial plant material (Adam Ametovski and Lupton, 2019; Mechoulam and Gaoni, 1965; Petržilka et al., 1967; Razdan et al., 1974; Trost and Dogra, 2007). Analytically indistinguishable, fully synthesised in vitro phytocannabinoids and naturally obtained in vivo phytocannabinoids were not distinguished by the ECDD which considers them in all points pharmacologically identical (ECDD, 2019: 54–55; Riboulet-Zemouli and Krawitz, 2019).

Yet another class of compounds termed ‘synthetic cannabinoids’ is that of *synthetic analogues*, also (mostly) obtained via laboratory synthesis without *C. sativa* botanical ingredients. The resulting substances, however, are not phytocannabinoids found in the environment but novel compounds, mimicking their pharmacological effects without being derived from, nor directly relatable to them. Firman et al. (2019) find that out of the ‘223 compounds identified, a mere ten...bear structural relation to THC’. Examples of synthetic cannabinoid analogues are *nabilone* (Blanchard and Ryan, 1977a, 1977b; Flemming et al., 2007: 22–23) or the HU- and JWH-type components found in ‘spice’ (National Institute on Drug Abuse, 2018; Seely et al., 2012), while fentanyl and methadone are well-known synthetic opioid analogues.

Synthetic cannabinoid analogues have been extensively studied, resulting in the invention of a wide array of substances. A proposal of a classification system for cannabinoids (Shevyrin et al., 2016) found few compounds structurally related to *C. sativa* phytocannabinoids – HU-210 and dextranabinol, for instance – and termed them ‘classical cannabinoids’. Shevyrin et al. identified numerous other groups of synthetic compounds with no direct structural relationship to the plant’s phytoconstituents: nonclassical and hybrid synthetic cannabinoid analogues, naphthoylindoles, phenylacetylindoles, benzoylindoles, naphthylmethylindoles, diarylpyrazoles, 3-naphthoylpyrroles, synthetic endocannabinoid analogues, etc. To distinguish these molecules from naturally occurring phytocannabinoids obtained in vitro and from semisynthetics, the expression ‘synthetic analogues’ (Biernat, 2018; European Monitoring Centre for Drugs and Drug Addiction, 2017; Flemming et al., 2007; Luo et al., 2019; Pop, 1999; Shevyrin et al., 2016; Trost and Dogra, 2007) has been proposed. However, the confusing use of the phraseology ‘synthetic cannabinoids’ continues (Bonn-Miller et al., 2018; Carvalho et al., 2017; ECDD, 2019: 19–25; Fattore and Fratta, 2011; National Institute on Drug Abuse, 2018; Pop, 1999; Reekie et al., 2018; Seely et al., 2012). Some authors placed ‘semisynthetics’ as a subset of ‘analogues’ (Bow and Rimoldi, 2016) making the case of the inexistence of both semisynthetics and analogues in a natural environment – the only difference being the use of botanical *C. sativa* material to obtain the former, not the latter. Nevertheless, some compounds existing in nature can be obtained by the semisynthesis process of chemically altering starting botanical material containing phytocannabinoids, when these alterations are different from those of the natural biosynthetic pathways of the plant. This is illustrated by cases such as the transformation of CBD into dronabinol: both compounds are found in nature, but such transformation has not been reported in natural environments – there is limited evidence that CBD can be processed into some compounds defined thus far as metabolites of dronabinol (Huestis, 2007) in an *in vitro* environment simulating gastric acids (Bonn-Miller et al., 2017; Grotenhermen et al., 2017; Merrick et al., 2016; White, 2018:10–11), but no confirmation of conversion in animal or human models has been reported (Crippa et al., 2020; ECDD, 2018: 13; Grotenhermen et al., 2017; White, 2018: 10–11; Wray et al., 2017).

The criterion of similarity in the molecular structure of compounds is not always related to the final pharmacological effect, organoleptic properties, the consistency of the product, or to other characteristics, and it is not yet entirely mapped at this time. Hence, if that variable is discarded, a double dichotomous distinction

stands out: occurrence in nature versus novelty of the compound; obtention from the transformation of *C. sativa* material versus that of other material. This allows for cannabinoid APIs to be arranged in four meta-categories:

- *In vivo* phytocannabinoids: naturally occurring compounds, derived:
 - from *C. sativa* plant material (e.g. dronabinol present in EGTs),
 - from other plant genera (e.g. (–)-cis-perrottetinene present in some plants of the genus *Radula*; see Gertsch, 2018),
- *In vitro* phytocannabinoids: the same naturally occurring compounds as above, obtained by full ‘chemical synthesis’,
- Synthetic cannabinoid analogues (e.g. nabilone, HU-210, dextrabinol): non-naturally occurring compounds, obtained by full chemical synthesis,
- Semisynthetic cannabinoids:
 - Semisynthetic phytocannabinoids, i.e. naturally occurring compounds, derived from *C. sativa* plant material, obtained by partial chemical synthesis different than those of the plant’s natural phytocannabinoid biosynthetic pathways (e.g. CBD transformed into dronabinol),
 - Semisynthetic cannabinoid analogues, i.e. non-naturally occurring compounds, derived from *C. sativa* plant material, obtained by partial chemical synthesis (e.g. the (+)-enantiomer of CBD, not found in natural environments).

An additional layer of complexity is brought by modern biotechnologies and also relates to the method of obtention used (Sirikantaramas et al., 2007). Serious questioning of the traditional Aristotelian breach between nature and artefacts (Bhushan, 2006; Cragg and Newman, 2013; Feher and Schmidt, 2003; Schummer, 2002) arise while innovations such as gene editing, genome mining, and combinatorial biosynthesis (e.g. rDNA) thrive. What were thought to be ‘fundamental differences between combinatorial synthesis and biosynthesis’ (Feher and Schmidt, 2003) are being overcome, also for *C. sativa*. Already, cannabinoid compounds, just like opioids (Galanie et al., 2015) can be obtained from the design of heterologous expression of biosynthetic pathways, such as in genetically modified (GM) organisms (Carvalho et al., 2017; Luo et al., 2019; Siddiqui et al., 2012; Sirikantaramas et al., 2007). Both naturally occurring and novel cannabinoids were obtained by Luo et al. (2019) from genetically engineered yeasts, a feat achieved by introducing selected *C. sativa* genes in *Saccharomyces cerevisiae* using rDNA technologies. Different classes of GM organisms, including GM

C. sativa plants (Berahmand et al., 2016; Feeney and Punja, 2003; Sayre et al., 2019) are currently being engineered to produce different yields or ratios of various cannabinoid compounds. All the four meta-categories of cannabinoids listed above can, or will likely soon, be obtainable via genetically engineered organisms, complicating the distinction between the natural and the artificial. This is echoed in pharmacopœial nomenclatures, increasingly tending to distinguish drugs obtained via organisms having been genetically recombined, adding them special requirements such as PhEur (monograph 0784).

Noteworthy, GM in *C. sativa* can also be unrelated to the biosynthetic mechanisms of the plant. GM can indeed be limited to specific characters, such as resistance to pests, salinity and drought, or tolerance to herbicides or insecticides (Catacora-Vargas, 2011: 10–11, 85–86) which in theory do not alter, or affect only indirectly, the production of phytocannabinoids within EGTs. A distinction is therefore needed between a GM which alters the plant’s biosynthetic pathways and a GM which does not.

Finally, if this was not a complex enough panorama, cannabinoids are naturally produced by other living organisms. Beyond *Cannabis*, other plant genera naturally biosynthesise cannabinoid compounds (Gertsch, 2018; Hanuš et al., 2016). Beyond the *Plantae* kingdom, *Homo sapiens* also produce ‘endocannabinoids’ (Hanusš et al., 2016; Huestis, 2007; Pacioni et al., 2015; Shevyrin et al., 2016) and a series of living organisms (Hanusš et al., 2016) are found to produce their own endogenous cannabinoid substances, similar or not to those known to be biosynthesised in *H. sapiens* or *C. sativa* (e.g. *anandamide* is naturally secreted in humans and in *black truffle* fungi, see Pacioni et al., 2015).

Discussion

This study is the first to examine the interrelation between different nomenclatures of natural and artificial drugs containing cannabinoids, and between these and the products available nowadays. The study finds mostly confusing terminology, where four salient troubling aspects (which sometimes overlap) recur: terms comprising various distinct ‘relata’ (a *relatum* is the thing or entity to which a word relates and which it designates); terms whose relata vary according to context, time, or geography; terms inherited from socially constructed, utilitarian, non-science-based language; terms overly specific to a defined field of scientific research.

Terminologies used for synthetic cannabinoids represent useful frameworks for research but are limited in their potential applications outside of the biochemical sectors. Nomenclatures used in international law rely

on broad, utilitarian categories that expand, beyond the products targeted for control, to other similar peripheral products, even if they are not relevant to drug control criteria. This is the case for *pioC*, controlled as ‘fruiting tops’ alongside ‘flowering tops’ from either male, female, hermaphrodite, and monoecious plants, although they might contain insignificant amounts of phytocannabinoids. It is also the case for dronabinol, the ‘main psychoactive substance in the cannabis plant’ (ECDD, 2019: 45): while only dronabinol, the (–)-trans enantiomer of the delta-9 isomer of THC, is a target for public health scrutiny, the three other stereochemical variants, as well as the six other delta isomers of THC are grouped with dronabinol as *tetrahydrocannabinols* – as a collateral damage – besides the fact that the ECDD (2018) recognised dronabinol ‘is the only [stereochemical variant] that occurs naturally in the cannabis plant’ and that ‘the limited information on the pharmacology of [its] stereochemical variants... suggests that they have little activity’ (33–34). It conflicts, also, with the statement that ‘there are no reports that the THC isomers... induce physical dependence, or that they are being abused or are likely to be abused so as to constitute a public health or social problem’ and ‘there are no reported medical or veterinary uses of these isomers’ (ECDD, 2019: 49).

Way forward: A non-conflicting framework for the nomenclature of ‘cannabis’ products

Besides approximations and scientific inconsistencies, the four-tiered ontology used in C61 is consistent. It can be interpreted as an incremental and mutually exclusive scheme composed of: ‘cannabis plant’ (the living or freshly harvested plant, staminate and pistillate iterations), ‘cannabis’ (*pioCs* and inflorescences of the former), ‘cannabis resin’ (material separated from EGT found on one of the former), and ‘preparations’ (or ‘extracts and tinctures’ any processed drug derived from either one of the former). Consistency is reached at the expense of clear *relata*, at least concerning the last three categories, which include everything *other* than what is in the previous category. Such a categorisation does not carry any practical pharmaceutical information, since it aggregates products of all kinds. It also leaves room for conflicting interpretations: some products are virtually included within this ontological class (because they are prepared from ‘cannabis’ or ‘cannabis plant’) even though they do not comply with the criteria for international drug control (e.g. essential oils, or non-medical cosmetics containing CBD). The IDCC corrects this ontological conflict applying a different, transversal criterion: that of the purpose of use (Riboulet-Zemouli, 2019). As *C. sativa*

products, and their methods of obtention, become increasingly more diverse, the four-tiered categorification of C61 will continue to lose relevance.

While the first two categories, ‘cannabis plant’ and ‘cannabis’ (starting materials, see Table 2) can be easily further defined by modern botanical research, elements are missing to distinguish products within the last two categories, ‘cannabis resin’ and ‘preparations’ (see Table 5). The uniquely complex phytochemical composition of *C. sativa*, the variability in patterns and routes of administration, and the still uncaptured phytopharmacological mechanisms of action of *C. sativa* products render insufficient the analytical identification of the composition in phytocannabinoids. It suggests the need for complementary elements of differentiation between products. This study finds that a consideration of the ‘methods of obtention’ (i.e. transformation, processing, and formulation of the products) in addition to the very composition of the final product, might be insightful. Alas, the four terms present in the C61 treaty to describe obtention processes (‘production’, ‘manufacture’, ‘separation’, and ‘extraction’) are used interchangeably (Table 2) and do not convey additional information about the pharmacognosy of the drugs. In popular culture, the most solid distinction criterion – which relates to the methods of obtention – is a dichotomy discriminating the addition of foreign matter (solvent extraction) to the thermomechanical processing of the plant’s EGTs (solventless extraction). Such additional determinant, complementing the four-tiered basis provided by C61, could help tweak a method of differentiation between products.

The criterion relying on the addition or not of eluents (i.e. solvents), although useful, does not provide full coverage of the potential products obtained: within the two subgroups, variations in techniques and resulting products often happen (see supplementary Appendix III). Lu and Luthria (2014: 5, 12) inform that ‘postharvest storage and processing (such as grinding and drying) influence the quantity of phenolic phytochemicals’ and of phytocannabinoids. Concerning the processing methods based on the addition of foreign matter, all basic and widely used techniques to extract and isolate natural biocompounds are reported for obtaining *C. sativa* derivatives (supplementary Appendix III provides details of these techniques). A series of other secondary methods of extraction exist, likely to be increasingly used in the future. Minor changes in extraction parameters have shown to result in significant chemical and pharmacological differences between final products (for instance cannabinoidless essential oils and high-dronabinol ‘concentrates’ which can both be obtained by distillation). Solventless extraction or processing techniques, although less numerous, also showed substantial

variability; additionally, many of these are embedded in traditional folk knowledge and intangible assets, still fully or partially undocumented (Abbott, 2014; Abdool, 2013; Bellakhdar, 1997: 232–234; Clarke, 2007; Kutesa, 2018). Variables such as the size of filter pores, the amount of pressure exerted, the temperature, or the type of movement applied are also determinative in characterising the final product (Devi and Khanam, 2018; Hamayun and Shinwari, 2004; Upton et al., 2014; supplementary Appendix IV). With or without eluent, all extraction or processing techniques report different thresholds of acid or decarboxylated phytocannabinoids depending on trivial variations in parameters along the process.

Laying out in detail the processes of obtention of drugs is a core objective of pharmacopœias. Nevertheless, even going more in-depth than the IDCC, neither the monographs related to *Cannabis* nor general nomenclature for phytopharmaceuticals provided any thorough pattern for an orderly, non-overlapping and non-arbitrary classification of *C. sativa* derivatives. Pharmacopœias either focus on precise traditional formulations, like in Ch.P and FHEUM, falling short of including all known products (and in particular the most recent ones, e.g. liquid mixtures for electrical vaporisation devices), or they rely, like Ph.Eur., on wide-ranging categories that would include, in the case of *C. sativa*, an heterogeneous array of products with different pharmacological effects (varying concentrations, different formulations, different routes of administration).

Ph.Eur's *extracta sicca*, *extracta spissa*, *extracta fluida*, *oleoresina*, *tincturæ*, *atherolea*, *olea herbaria*, *plantæ ad ptisanam*, *præparationes celeres ad ptisanam*, *producta ab fermentatione*, and *producta ab arte ADN recombinandorum* are relevant to *Cannabis*, but insufficient. The derivative of *C. sativa* called 'rosin', obtained via a solventless extraction process relying on heat and pressure; 'butane hash oil', obtained by percolation of dry pioC using pressurised butane as eluent (Beal, 2019); and 'supercritical CO₂ oil' (Naz et al., 2017; Omar et al., 2013) have a similar consistency. They could be considered as *extracta spissa* although their composition and methods of obtention vary greatly; they could also be seen as *oleoresina*. Another preparation reported already in 1848 (Mechoulam and Hanuš, 2000) and nowadays known as 'Rick Simpson oil' or *full ethanol-extracted cannabis oil*, obtained by maceration of pioC in alcohols followed by partial or total evaporation (mechanically or via distillation), could be viewed either as *tincturæ*, *extracta spissa*, or *oleoresina*. 'Dry sift' or 'dry sieve' (Beal, 2019, Daniulaityte et al., 2017), a type of 'hashish' obtained via repeated microfiltrations of ground dry pioCs, without involving the use of solvent, is another

illustration. The process results in a fine dry powder almost entirely made of capitate heads of EGTs. As such, it corresponds to *extracta sicca*. However, under very light pressure and heat (e.g. from fingers) it immediately takes the consistency of an *extracta spissa* or *oleoresina*, since EGTs' external layers (cuticles) break and liberate the content of the glands, which then stick together (Graham, 1976: 6; Nicoletti Motta, 2018). The UNODC (2009) talks about a resinous secretion that 'appears as loose or pressed sticky powder, depending on the method of production' (16). Two pharmacopœial categories, *oleoresina* and *extracta spissa*, likely apply to these four very different products that have (or can have under certain thermophysical conditions) a consistency in appearance similar. Among all these products, many are popularly referred to as 'oils' although none correspond to the pharmacopœial category of herbal fatty oils *olea herbaria*.

Not only the method of obtention seem to be a common *blind spot* in IDCC and pharmacopœial nomenclatures (notably, with the exception of WHO T&CM's), but this criterion is also a determinative element of a drug's pharmacological effect, since 'preparations with different therapeutic properties can be made from the same herbal material, depending on the manufacturing process employed' (Schulz et al., 2004: 5). The fitness of a phytopharmaceutical to one route of administration or another also relates to the processes involved to prepare it (European Directorate for the Quality of Medicines, 2016: 6519; Gaedcke and Steinhoff, 2003).

From harvest to the last stage of product formulation, processes of obtention are of singular relevance in the case of *C. sativa* phytopharmaceuticals, regarding the large variety of pharmacologically active secondary metabolites present in the plant as well as the complex molecular interactions involved. The presence and yield of flavonoids, phytocannabinoids, and other terpenoids can be subject to variations depending on the method employed. In this regard, *C. sativa* derivatives appear to be chemically unstable since straightforward factors (temperature, time, humidity, light) target degradation or other types of chemical reactions. Variations dramatically affecting the pharmacological properties of a product can be induced by basic thermomechanical stimuli (Agarwal et al., 2018; Naz et al., 2017), for instance, heating at 200°C for seven minutes (Verhoeckx et al., 2006) or ageing (Fairbairn, 1976: 15; Mechoulam and Hanuš, 2000; Zamengo et al., 2019). This is the case when phytocannabinoids, obtained in acidic form when separated from the plant (Happyana et al., 2013; Kimura and Okamoto, 1970; Perrotin-Brunel et al., 2010, 2011, Pertwee, 2006) decarboxylate into compounds with enhanced

psychopharmacological effects (Reekie et al., 2018; Verhoeckx et al., 2006).

From many perspectives, the most compelling evidence suggests the ‘method of obtention’ is a common, and overlooked criterion in classification systems that fail to overarch *C. sativa* products. Significantly, this study shows that, if the identification of different methods of extraction, separation, fractionation, isolation, purification, refinement and concentration (terms somehow used interchangeably) and of crucial parameters within those processes, might not per se provide all sufficient information on *C. sativa* products, it seems likely to provide a consistent and useful complement of information on the characteristics and properties of *C. sativa* products, to achieve a thinner, more precise cartography of them. The variabilities could be used to frame the lowest taxon of ‘products’, the smallest common denominator, in such hypothetical classification.

A metachemistry of cannabinoids (and beyond)

The very same methods which are used to extract or separate phytopharmaceutical material from *C. sativa* are also sometimes employed to transform botanical *C. sativa* material into ‘semisynthetic’ ingredients. Moreover, these same techniques can also be used to process GM *C. sativa* material, and even biotechnologically crafted EGT containing non-natural cannabinoid analogues. Borrow limitations between herbal drugs and non-herbal drugs could lead to even greater confusion in the future. Such reversibility and porosity between *natural* and *unnatural* cannabinoid-containing products was determinative for including ‘synthetic’ products in the scope of this study: limiting the study only to *natural* herbal drugs would have required preexisting boundaries that neither the IDCC nor the pharmaceutical references provided for.

Historically, the myriad of new cannabinoid molecules discovered in the last decades (Firman et al., 2019; Shevyrin et al., 2016) have been termed ‘synthetic cannabinoids’ by opposition to ‘phytocannabinoids’, the naturally occurring cannabinoids found in *Cannabis* plants. While the word ‘phytocannabinoid’ links to an unambiguous and delimited *relatum*, the expression ‘synthetic cannabinoids’ is given by ostentation rather than by description. Eighty years ago, Adams et al. (1940) were the first to synthesise a cannabinoid compound *ex vivo*: the phytocannabinoid CBN (see Mechoulam and Hanuš, 2000; Pertwee, 2006). The first compounds to be named ‘synthetic cannabinoid’ in the 1960s were all closely related to the molecules found in *C. sativa*, either phytocannabinoids obtained *in vitro* or closely related byproducts, obtained during attempts to synthesise and describe

naturally occurring phytocannabinoids (Bow and Rimoldi, 2016; Fahrenholtz et al., 1967; Mechoulam and Gaoni, 1965; Mechoulam and Hanuš, 2000; Pertwee, 2006; Petrzilka et al., 1967; Razdan and Zitko, 1969). Hence their definition by the negative insofar they were, by then, the only non-natural, not wholly-phyto cannabinoids. With the years, dozens of new structurally heterogeneous compounds were described, obtained via varying synthesis routes, using different starting materials, and resulting in an increasingly diverse class of molecular structures within what continued to be a single ontological entity: *synthetic cannabinoids*, encompassing each time more different *relata*.

A compressive arrangement of those ‘synthetic agonists active at cannabinoid CB1 and CB2 receptors’ (Firman et al., 2019) is still to be found. Shevyrin et al. (2016) made insightful proposals (classifying these substances in six groups: ‘classical’, ‘nonclassical’, ‘hybrid cannabinoids’, ‘aminoalkylindoles’, ‘eicosanoids’, and ‘other cannabinoids’), and Biernat (2018) proposed three categories (‘cannabinoids derived directly from cannabis’, ‘synthetic versions of cannabinoids found in cannabis’, and ‘compounds that are similar to cannabinoids found in cannabis’), among others. It appears however that the six-tiered categories continue to rely on a definition by ostentation, grouping under *others* a variety of structurally diverse molecules. The suggestion made by Biernat falls in a similar stalemate with the class ‘compounds that are similar to cannabinoids found in cannabis’, probably too heterogeneous, encompassing novel artificial analogues, semisynthetics, endocannabinoids, and any *other* cannabinoid.

Beyond their ability to bind to the human endocannabinoid receptor system, what brings together cannabinoid compounds is the difficulty in classifying them rightly. Relying solely on their chemical structure might not be the best approach, as, again, the category *other* will always exist and potentially grow as an increased number of substances may be found to have some interaction with CB1 or CB2 (it is already the case for non-cannabinoid phytoconstituents (Gertsch et al., 2010) and for paracetamol (Klinger-Gratz et al., 2018), suggesting the need for a real metaphysical address of the endocannabinoid system). Heretofore, the lemma *cannabinoid* itself has not been discussed. Basis of all neologisms in chemistry, the word ‘cannabinoid’ is nonetheless much more a neuro-pharmacological term than a chemical one. From its etymology – appeared in the 1940s (Google Books Ngram Viewer, s.d) built as a derivative of ‘cannabis’ to which was added the suffix *-oid* derived from classical Greek *εἶδος*, *eidos*: ‘kind’, ‘form’, ‘type’, ‘likeness’ – it designates substances that are *of the cannabis*

kind, that relate, that are similar to ‘cannabis’, from a wholly subjective, empirical point of view. The *relatum* associated with ‘cannabinoid’ does not necessarily imply a structural resemblance at the molecular level, but rather a similarity in terms of the overall pharmacological effects observed, deemed akin to those produced by botanical *Cannabis* products. Dewick (2012) makes an enlightening statement:

Natural products structures are usually quite complex, some exceedingly so, and fully systematic nomenclature becomes impracticable. Names are thus typically based on so-called trivial nomenclature, in which the discoverer of the natural product exerts their right to name the compound. (3)

Driven beyond epistemology, Bachelard (1966) deepens the reflection on chemical nomenclatures, addressing the metaphysics of chemistry (or as Nordmann, 2006 puts it, *metachemistry*), suggesting a ‘rationalised’ use of scientific language ‘which takes *substance* to be a category of the understanding’ (Nordmann, 2006: 348–350) rather conceptual. This approach considers that the term ‘substance... designates the stability of an assemblage’, or what gathers together ‘a multiplicity of agents into a stable and coherent whole’. Naming in chemistry is perhaps the most challenging contemporary classification playground – or, as Schummer (2002) resumed it ‘imagine the tremendous efforts that were necessary to distinguish carefully between millions of substances today, most of them being white powders indistinguishable to the naked eye’.

Because advancements in chemistry make language continuously drift away from compounds, the need to ‘define and stress the differences between terms that may appear to be synonyms’ (Santaló and Casado, 2016: 39) becomes pressing, particularly for the class (es) of ‘synthetic cannabinoids’, neither stable nor consistent. Such demand is outstanding, not only because of the need for accurate language to match understanding, but also in terms of the strong ethical concerns which arise from the debates around the uses of *Cannabis* products (Zarhin et al., 2019) presently amplified in the context of moral and epistemological upheaval driven by two ongoing parallel revolution(s): the *Cannabis* policy reforms one, and the biotechnological one (Perron-Welch, 2019).

Extrapolations from other well-known classes of psychoactive phytoconstituents and their analogues do not seem to provide comprehensive solutions. For instance, cannabinoids differ from opioids on at least three levels: hundreds of different phytocannabinoids have been identified in *C. sativa* plants (while only a dozen of *phyto-opioids* are known); the human body naturally produces endogenous cannabinoids;

cannabinoids are also naturally secreted by other living organisms (whether plant, animal, or fungus). This latter point is subject, again, to further scrutiny of the metaphysics of animal endocannabinoid systems. Besides come the novel, human-conceived cannabinoid compounds, raising the absolute list of cannabinoids kinds (or taxa), but also virtually the complexity of their systematics, above that of opioids, and most other well-studied classes of molecules.

A bioethical nomenclature for cannabinoid compounds. The exploration of a new classification of cannabinoid substances, in a bioethical rather than purely biochemical fashion, might be a solution. In the same fashion that the methods of obtention of *C. sativa* derivatives which bring additional analytical information on the composition of a product, a bioethical nomenclature of compounds does not per se conflict with nomenclatures arranged according to chemical structures. It could very well be a complementary tool, in line with Bhushan’s (2006) suggestion to overcome the difficulties in classifying chemical substances by using ‘a kind for every occasion’ on the basis that ‘kinds are real but particular to the occasion of the individuals who choose to work with them, their choices of models and strategies, and what happens to function best in the environment in question’ (327–328). In this direction, kinds, or nomenclatures, used by chemists, might not be the best approach for an environment of law and public health policy, or for clinical contexts.

As exposed, a pattern in four classes of cannabinoids showed two main axes useful to start discriminating compounds: occurrence in nature or not, and obtention from *C. sativa* material or not.

The first axis, regarding the prevalence of a compound in natural environments, appears to be easily divisible in two clear mutually exclusive groups: one comprises novel and artificial substances, not present in nature, that could be labelled as human inventions. A comparison can be done with the artificial analogues of nicotine: initially defined under a chemical nomenclature as *chloronicotinyls*, they have been renamed *neonicotinoids* by Tomizawa and Yamamoto (1993: 97–98) and Sheets (2002) adding the prefix *νέος* (*néos*: ‘new’, ‘young’) to ‘nicotine’ followed by the suffix *-oid*. Likewise, the group of cannabinoid compounds not present in nature could be grouped under the term *neocannabinoids*. The second group would include cannabinoids occurring in nature (either in raw state, such as dronabinol, or as secondary metabolites processed by a living organism, like THC-COOH; see Huestis, 2007), whether they are derived from living organisms or obtained by processes of human-made synthetic chemistry reproducing the natural biosynthesis pathways of a living organism. These include phytocannabinoids,

human endocannabinoids, as well as naturally occurring endogenous cannabinoid substances found in other living, genetically unmodified organisms. Medical and scientific terminologies often articulate the prefix *neo-* in opposition to *paleo-* (derived from *παλαιός*, *palaiós*: ‘old’, ‘ancient’); as such, this second group, mutually exclusive with the previous one, could be termed *paleocannabinoids*.

The second axis relies on the methods of obtention. The first level of opposition is found between substances derived from living organisms (the mechanism called *biosynthesis*), whether GM or not, and substances derived from an inert material, *in vitro*, via different laboratory processes (traditionally called ‘synthesis’ or ‘chemical synthesis’). The use of the word ‘synthesis’ alone, as a synonym of ‘chemical synthesis’, sometimes *in vitro*, sometimes *ex vivo*, is exceptionally confusing: ‘synthesis’ derives from *σύνθεσις* (*súnthesis*: ‘arrangement’, ‘putting together’, ‘composition’, ‘combination’) and is the generic, general term to refer to any obtention of a complex chemical compound from simpler precursors, whether in living organisms or not. The Oxford Dictionary of Biology defines synthesis as ‘the formation of chemical compounds from more simple compounds’ (Martin and Hine, 2015: 577).

In order to avoid using ‘synthesis’, ‘laboratory synthesis’, or ‘chemical synthesis’ to oppose ‘biosynthesis’, the neologism *poesyntesis* is suggested. It is created from *ποιέω*, *poieō*: ‘to make’, ‘produce’, ‘create’, ‘compose’, ‘bring into existence’; arranged for phonetic and legibility purposes according to lemmas formed with the same prefix, like *poetry*. ‘Poesynthesis’ would aggregate all those molecules obtained via *in vitro* synthesis; it would complement and oppose ‘biosynthesis’ referring only to molecules obtained in laboratory chemical synthesis processes. A cannabinoid obtained *in vitro* would accordingly be called *poesyntetic cannabinoid*.

Looking at the holdups, this axis deserves a more complex than a dual approach, in particular in the context of the surge of gene editing technologies targeting and altering biosynthesis pathways. While both paleocannabinoids and neocannabinoids can be poesyntetic, neocannabinoids can, by definition, not be derived from natural biosynthesis. Or can they? Luo et al. (2019), among others, have shown that neocannabinoids can be obtained through a biosynthesis altered by biotechnological means. This suggests the need for a subdivision within biosynthesis, discriminating GM from non-GM biosynthesis. To distinguish between natural biosynthesis and biosynthesis induced artificially (sometimes called ‘synthetic biology’ [sic] in the context of policy, see Perron-Welch, 2019), the use of lemmas inspired in ancient Greek can again bring terminological clarity. Cannabinoids which are obtained by processes of biosynthesis not naturally

occurring, having been induced by biotechnological genetic modifications, could be termed *dysbiosynthetic cannabinoids* as per the prefix *δυσ-* (*dus*: ‘disordered’, ‘difficult’, ‘abnormal’) to the existing ‘biosynthesis’ (formed with *βίος*, *bios*: ‘life’). By opposition, the prefix *εὖ-* (*eû*: ‘true’, ‘real’) could form the terms *eubiosynthesis* and *eubiosynthetic cannabinoids* to cover compounds obtained entirely by natural biosynthesis in unmodified environments, and their natural metabolites. Figure 3 details the interrelation between the terms proposed.

Figure 3 shows that the only of these neologisms covering an *unnamed ontology* is ‘dysbiosynthesis’. It is also worth noting that the proposed set of terms loses the ability to directly designate what corresponds to ‘*ex vivo*’, which would need to be described as *non-eubiosynthetic*.

Stretching the model to try it, these five terms can be combined in a double-entry table (Table 6), resulting in virtually six classes of cannabinoids: *eubiosynthetic paleocannabinoids*, *eubiosynthetic neocannabinoids*, *dysbiosynthetic paleocannabinoids*, *dysbiosynthetic neocannabinoids*, *poesyntetic paleocannabinoids*, and *poesyntetic neocannabinoids* (individual definitions can be found in supplementary Appendix IV). As seen earlier, the second of these categories, which combines *neocannabinoid* with *eubiosynthesis*, is antithetical and inexpressible. Nonetheless, the five remaining categories offer a coherent nomenclatural basis. At the crossroads of biological and ethical considerations, this five-tiered categorification model is compatible with existing classes of cannabinoids. For instance, phytocannabinoids from *C. sativa* and endocannabinoids from *H. sapiens* are two subdivisions of eubiosynthetic paleocannabinoids. In what relates to *C. sativa*, we can observe that the plant is a source of cannabinoids in all five classes: beyond the ‘classical’ phytocannabinoids from

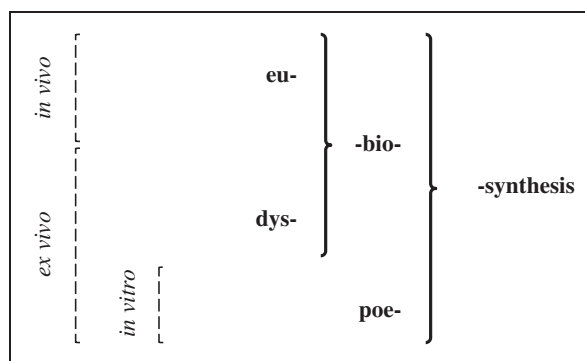


Figure 3. Graphic representation of the neologisms proposed for the distinction of different types of synthesis, and hierarchy between them.

C. sativa (eubiosynthetic paleocannabinoids), both dysbiosynthetic paleocannabinoids and dysbiosynthetic neocannabinoids are obtainable from GM *C. sativa*. Finally, poesynthetic paleocannabinoids and poesynthetic neocannabinoids can also be obtained, in particular via semisynthesis, with *C. sativa* infructescences or oleoresin as starting material.

Unexplored in this study, further subdivisions relying on the same method and scheme could be contemplated: for instance *eumycosynthesis* to distinguish naturally occurring anandamide in truffles from the *dysmycosynthesis* of GM yeasts, or *euphytosynthetic* and *dysphytosynthetic cannabinoids*.

Admittedly this model presents limitations on at least two levels. First is the classic philosophical problem of induction and extrapolation of classes, or their ability to be projective and normative (see The Kripkenstein Paradox and the Private World, 2011). Despite the split nature versus artefacts represented by the dichotomy ‘phytocannabinoids vs synthetic cannabinoids’ being offered an alternative solution in the model proposed with the use of *paleocannabinoids*, ‘[broadening] the notion of natural kind so that it now comes to mean naturally occurring things and those identical to them’, Bhushan (2006) illustrates why projective and normative limitations matter:

A compound that is synthesized first and later discovered to occur naturally... For example, around 1985 the compound now called buckminsterfullerene was prepared synthetically. This is a 60-carbon compound in which the carbons are at the vertices of five- and six-membered rings positioned like those inscribed on the surface of a soccer ball. Subsequently, buckminsterfullerene was found to be a component of soot, including ancient samples of soot. (332–333)

Most philosophical approaches to science prefer to ‘conclude that the category of natural kind is suspect to begin with’ (Bhushan, 2006: 333) and explore other ways of classifying compounds. A useful conceptual instrument to relativise *natural kinds* while keeping aware of ‘what the world really is and the highly cultural ways in which we shape it’ (Latour, 1990: 77) is the notion of ‘trajectory’ in the collective historicity of an ontological entity in chemistry, thought by Bachelard (1966: 66–74) updated by Latour (1990, 2000) and explained by Nordmann (2006: 354–355):

As soon as one lets “time put its mark on substance”, the hypothetical character of persistence drops out, and the old debate of realists versus anti-realists becomes obsolete. It is replaced by the question of how

substance is instituted and how its reality becomes physically, socially, consciously realized over the course of time... In other words, substances become increasingly reliable or stable actors in experimental and technological interactions, i.e., as the situations are defined and become defined in which they will assert themselves in certain ways. The trajectory is, therefore, graphed in reference to two variables: The time that passes as the work of science goes on, and a scale that registers the increasing specificity of the characteristics with which the substance becomes identified.

Figure 4 shows a tentative *representation* of the trajectory of the collective ontological evolution of what is called *poesynthetic neocannabinoids* in this study.

Since the phytoconstituents contained in the plant have quite exhaustively been screened, the possibility that, in the future, neocannabinoids could be found to be occurring naturally is unlikely – but still possible anecdotally – a rather common impasse in induction and extrapolation, that the *Kripkenstein* paradox (Kripke, 1982) illustrates. The division *paleo-* versus *neo-* is relevant from the ethical, public health, and regulatory perspectives, undoubtedly useful in the case of *Cannabis* research. It conveniently adds value in various fields, for this particular moment in time and state of scientific knowledge.

Even today, chemists lack a full understanding of most molecular structures, and certain models in use may in fact prove to be wrong. Yet they can meaningfully talk about these molecules and assert that they are speaking of a particular one, when the molecule they have in mind may not be the same after the model becomes revised. (The Kripkenstein Paradox and the Private World, 2011: 6)

The second limitation arises in the hypothesis of various successive synthesis processes. Assuming a compound which goes through different pathways of synthesis outlined in Table 6: the model proposed would likely only apply for the naming of the final substance obtained; information on the first steps of synthesis – that might have been relevant to characterise the final obtention from the bioethical perspective – would therefore not be contained in the final naming. This dilemma is particularly salient with the example of human secondary cannabinoid metabolites (e.g. THC-COOH, a degradation of dronabinol obtained after consumption by *Homo sapiens*), naturally produced via eubiosynthetic pathways inside the human body (Huestis, 2007). As long as phytocannabinoids from *C. sativa* are consumed, the resulting human metabolites fall under the class of *eubiosynthetic paleocannabinoids*: they have undergone twice the same kind of

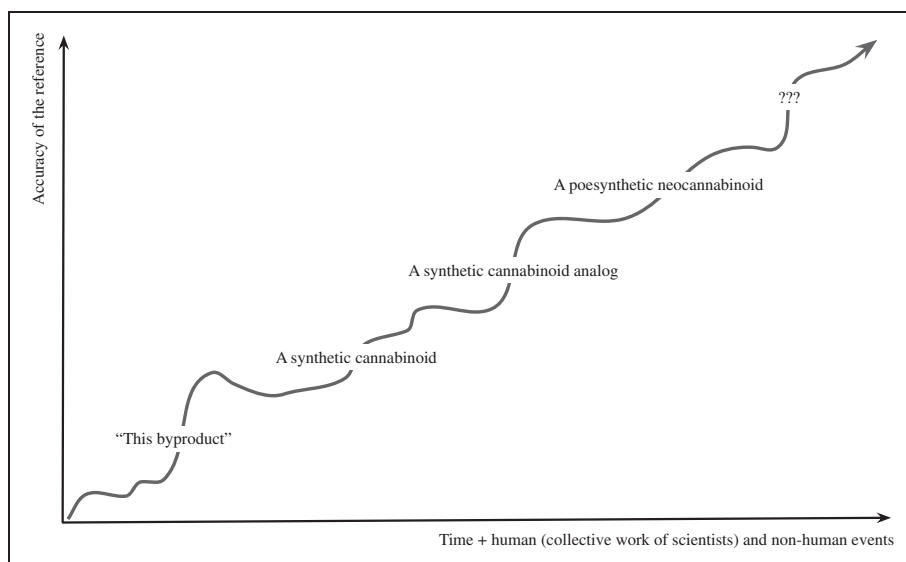


Figure 4. Trajectory of the ontological representation of a 'poesynthetic neocannabinoid'. Source: Adapted from Latour (1990: 68, 2000: 256) and Nordmann (2006: 355).

Table 6. Proposed bioethical nomenclature for cannabinoid compounds.

	Synthesis		
	Biosynthesis		Poesynthesis <i>In vitro</i> chemical synthesis
	Eubiosynthesis True <i>in vivo</i> biosynthesis	Dysbiosynthesis Modified biosynthesis	
Paleocannabinoids Naturally occurring compounds	Eubiosynthetic paleocannabinoids	Dysbiosynthetic paleocannabinoids	Poesynthetic paleocannabinoids
	Phytocannabinoids from <i>C. sativa</i>	Phytocannabinoids from <i>C. sativa</i> with genetically modified cannabinoid biosynthetic pathways	Phytocannabinoids obtained by <i>in vitro</i> synthesis differing from natural biosynthetic pathways, with <i>C. sativa</i> as starting material (= semisynthesis)
	Phytocannabinoids from other plant genera	Phytocannabinoids from other living organisms genetically modified to produce phytocannabinoids	Phytocannabinoids obtained by full <i>in vitro</i> synthesis
	Endocannabinoids from <i>H. sapiens</i>		Endocannabinoids obtained by full <i>in vitro</i> synthesis
Neocannabinoids Novel / artificial compounds	n/a	Dysbiosynthetic neocannabinoids	Poesynthetic neocannabinoids
		Cannabinoid analogues from <i>C. sativa</i> with genetically modified cannabinoid biosynthetic pathways	Cannabinoid analogues obtained by <i>in vitro</i> synthesis, with <i>C. sativa</i> as starting material (= semisynthesis)
		Cannabinoid analogues from other living organisms genetically modified to produce phytocannabinoids	Cannabinoid analogues obtained by full <i>in vitro</i> synthesis

Examples are displayed in dotted boxes, inside each case of the table. Examples involving *C. sativa* are underlined.

synthesis pathways. If, however, the phytocannabinoids consumed by a human (assuming a non-GM human) are *dysbiosynthetic* (for instance, dronabinol obtained from GM yeasts), the resulting compound will be obtained by true biosynthesis, and therefore

termed *eubiosynthetic paleocannabinoid*. It will be similar in all points to the metabolites obtained after the consumption of 'natural' dronabinol separated from *C. sativa*, bringing back the question of primacy of biochemical structures. This second limitation is

problematic insofar the nomenclature proposed wishes to prioritise a bioethical classification of compounds, thus avoiding the traditional metachemical essentialism, we have seen, deeply questionable nowadays.

Besides these issues, this model of representation provides enhanced clarity. It is just one proposed step ahead in the trajectory of advancement in the collective representation of the realities of our world. A salient feature of this classification is its close relatability with the classes of *C. sativa* derivatives identified earlier, which are also characterised by their ‘method of obtention’ as a differentiating factor.

Conclusion

Beyond the results of the assessments conducted by WHO, which change some language but mainly suggest the need for a broader, more thought-through assessment of the different nomenclatures currently used, resolving the confusions in naming ‘cannabis products’ is urgently needed since derivatives continue to diversify. Not only is sound nomenclatures missing for *C. sativa* and cannabinoids, but it is also absent for other phytopharmaceuticals. The lack of clarified, unified, and internationally recognised terminology is salient in herbal medicine and pharmacy generally. Applying to phytomedicine as a whole the exercise of ‘drawing a trajectory’ might result in a flat curve, where time and efforts progress much faster than the accuracy of ontological representations used – at least during the major part of the past Century and the current one. This study locates *C. sativa* and ‘medicinal plants’ as a whole at a relatively low epistemological standing.

More skilful addresses of the philosophical concerns laid out in this paper than those of the author would considerably help – metaphysicians and epidemiologists could bring enlightenment by addressing the endocannabinoid system. The ongoing developments in science and biotechnologies should be closely monitored to capture the extent of actual and future possible products. In parallel, a new look at the basis is needed, in chemistry but also in botany, with studies of the morphology, histology, and cytology of *pioCs* and *EGT* urging.

Over and above this evolving landscape, this study shows that it is possible to stress patterns that can serve to establish evidence-based nomenclatures where they are missing. The method of obtention, best criterion found to distinguish between the myriad of derivatives of *C. sativa*, is also determinative in establishing a practical, bioethical distinction scheme between isolated cannabinoid APIs. It could be used to refine a nomenclatural classification, in combination with the morphological categorification of extracts and formulations used in pharmacopœias, with the route

of administration, and with the absolute or relative content in some identified active compounds. Future attempts to adequately, accurately nomenclature cannabinoid-containing products should consider, in addition to morphology and content analysis, already used, the methods of obtention. These three variables can be articulated in a system allowing a proper identification process for virtually all cannabinoid-containing products. Without the illusion of reaching a *one size fits all* nor universally acceptable nomenclature of ‘cannabis products’, such a process could at least allow a diversion from current confusions and cross-purposes talk, in a domain where misinterpretations can have important legal, social, or health-related consequences. *Cannabis ontologies II*, a follow-up to the present study (in press) that favours the contemporary understanding of ontology as an *applied information science*, pushes forwards a proposal of non-conflicting nomenclature for *Cannabis* and cannabinoid products, based on a ‘smallest common denominator single product signature’ generated through an identification key.

Beyond the advancement of scientific knowledge and correct understanding of a topic immersed in multiple disciplines and scientific corpora, the development of clearer ontologies for *C. sativa* products and cannabinoids can have direct applications in numerous domains: bioinformatics, cheminformatics, ethnobotany, ethnopharmacology, phytochemistry or pharmacovigilance and ADR monitoring (see also Abdool, 2013: 15). It can influence the interpretation of ChP and JP *Cannabis fructus* monographs. It can assist and support the work of documentation, preservation, and transmission of both the genetic and cultural diversities and heritage attached to *C. sativa* and its derivatives. It would be desirable that such a revised nomenclatural ‘cannabis’ background be considered in the various ongoing standardisation and policymaking workstreams: the potential to clarify ambiguous terms and help translate into regulations the complex reality contemplated is non-negligible. Obviously, it can help in guiding physicians’ practice for *C. sativa* or cannabinoid therapeutic treatments, but is also a tool for doctors to make better choices in the field of prevention of dependence and use disorders, as well as for harm reduction practitioners; it can assist the design of accurate product labelling, and consumer information (European Directorate for the Quality of Medicines, 2016: 6520; Gaedcke and Steinhoff, 2003: 31–36; World Health Organisation, 2004). The study contains elements that, if popularised, may contribute to enlightening public scrutiny and debate over *Cannabis* and certain of its controversial products (marketed, or yet to come), thus enhancing the fundamental ‘right to participate in, and to enjoy the benefits of scientific

progress and its applications' (Committee on Economic, Social and Cultural Rights, 2020), for instance in biology, medicine, food sciences, or agriculture.

Accepting that language is 'not a question about correctness, but rather assertion' (Kripke, 1982; The Kripkenstein Paradox and the Private World, 2011), it is worth remembering Camus (1970) for whom 'naming an object inaccurately means adding to the unhappiness of this world' (238). With this in mind, the most important contribution of this article may not be assessing 'cannabis' language, but perhaps asserting the need – and means – for the awakening of evidence-based 'cannabis' terminologies and nomenclatures.

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Supplemental material

Supplemental material for this article is available online.

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APPENDICES SUPPLEMENTAL MATERIAL

Additional references not listed in the article are indicated as footnotes.

Appendix I. Materials and Methods with regard to neologisms

For the creation of novel language in the article, a set of terminological criteria initially followed were those suggested by Julià i Berruezo¹: (a) internationalism, (b) genuineness, (c) terminological tradition in the language concerned, and (d) potential for consensus among both experts and users of the term. All original language proposed was selected because either no word existed, or the existing terms were found inconsistent or used with multiple and diverging meanings.

Botanical, biomedical and biochemical elements, but also epistemological concepts, are traditionally named according to ancient Greek lemmas. To match criterion (c), it has been the preferred language in the design of newly introduced terms instead of a modern English basis, probably the best approach to criterion (a) as well.

For criterion (b), initial etymological query searches were made in the Online Etymology Dictionary (etymonline.com) and Wiktionary (wiktionary.org) in English, aided by four indexes of commonly used Greek lemmas (lexicon of Utah State University's Mark Damen: usu.edu/markdamen/Wordpower/handouts/gkaffix.pdf, Oakton's Gerardo Herrera's *List of medical roots, suffixes and prefixes*: cju-matt.webs.com/List%20of%20medical%20roots,%20suffixes%20and%20prefixes.pdf, the *List of Greek and Latin roots in English*: oakton.edu/user/3/gherrera/Greek%20and%20Latin%20Roots%20in%20English/greek_and_latin_roots.pdf, and the glossary of medical roots, prefixes and suffixes of Wikipedia, en.wikipedia.org/wiki/List_of_medical_roots_suffix

es_and_prefixes). This resulted in a long list of potential terms. The last step consisted of consulting the Perseus Digital Library 4.0 (perseus.tufts.edu/hopper) and the Classical Hub LSJ (lsj.gr/wiki/Main_Page) – both providing for searches into lexica of reference: two English-classical Greek (Liddell, Scott, Jones. *Ancient Greek Lexicon*; Liddell and Scott, *An Intermediate Greek-English Lexicon*) and one French-classical Greek (Bailly. *Dictionnaire grec-français*). Findings were finally double-checked in Spanish using the online Diccionario Griego-Español (dge.cchs.csic.es/xdge).

The final neologisms chosen were selected, keeping in mind the needed balance between criteria (b) and (d). Additionally, the words were selected according to the strength of their etymological rationale, expected ease of understanding among diverse publics, intuitive non-similarity between the terms introduced (and between them and previously existing ones), as well as an attention to the aesthetics of words – even complex words.

For instance, the term *poesyntesis* has been preferred to *anthroposynthesis* (formed with the prefix ἄνθρωπος-, *ánthrōpos*: 'humankind', 'human', 'humanity'). *Anthroposynthesis* is less genuine and might therefore have been more easily misunderstood: for instance, with other words formed with the prefix *anthropo-*, or understood as 'synthesis of/in/resulting in/involving human beings' – instead of 'synthesis performed *ex vivo* by human beings' which is the correct definition. The word is also longer and more grammatically complex than *poesyntesis*, hence less practical to employ and translate.

¹ Julià i Berruezo MA (2013) Criteris terminològics en ciències de la vida i de la salut. In: Sánchez Ferriz MA (ed.) *La Terminologia en les ciències de la vida, en la química i en el món educatiu*. Barcelona: Societat Catalana de Terminologia, pp.23–31. (See p. 28)

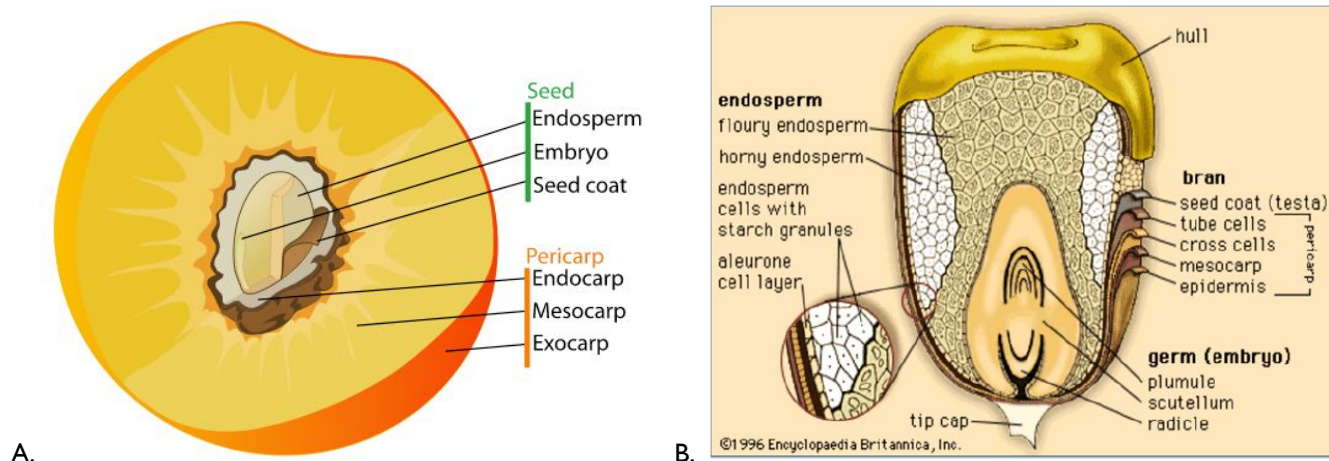
Appendix II. About *Cannabis* and parthenocarpy

The mechanism of ‘parthenocarpy’ was first described (and named) more than a Century ago by Noll (1902; Gustafson, 1942). Widely spread among dicots (Vazart, 1955; Frankel and Galun, 1977; Dhatt and Kaur, 2016; Joldersma and Liu, 2018; Picarella and Mazzucato, 2019), Gustafson has described in-depth these counter-intuitive *parthenocarpic fruits* in 1942, referring to them as seedless fruits ‘produced without pollination or other stimulation’ (Gustafson, 1942). A more recent definition describes ‘developing fruits from unfertilised ovaries; the resulting fruit is, therefore, usually seedless’ (Stern, 1997) Parthenocarpy is described as ‘the development of fruits without fertilisation’ (Scagel et al., 1967; Weier et al., 1970; Esau, 1977). Literature shows (Weier et al., 1970: 307; Stern, 1997: 408) that there are several kinds of biological mechanisms able to provoke the development of seedless fruits, and only those which are the result of the absence of fertilisation stimuli on female eggs are referred to as parthenocarpic. Because *C. sativa* naturally has both abilities to produce seeded and seedless fruits, according to Koltunow et al. (2002) the genus would be more precisely classified as a ‘facultative parthenocarpic plant’.

It is not surprising that research related to *cannabis* missed this element: parthenocarpy is a counterintuitive biological mechanism often subject to confusion, even among experts. Although, in cucumber like any other dicot, parthenocarpy is a phenomenon bound to fruits, the respected Frankel and Galun (1977) incoherently use ‘parthenocarpic flowers’ when discussing seedless cucumbers. USHP (Upton et al., 2014) mentions *C. sativa* ‘female inflorescence with senesced reddish-brown styles and

stigmas, an indicator of inflorescence maturity’ but senesced inflorescences, i.e. flowers brought to maturity, is nowadays considered as the very definition of a fruit (Scagel et al., 1967; Weier et al., 1970; Esau, 1977; Stern, 1997). The very floral cluster involved, the inflorescence, is a compact agglomerate of flowers, turning into an infructescence, compact agglomerate of fruits, complicating observation.

On another level, ChP refers to the *C. sativa* seeds in its monograph with the confusing title ‘*Cannabis Fructus* (火麻仁, Huomaren), Hemp seed’ as ‘the dried ripe fruit of *Cannabis sativa* L.’ from which ‘foreign matter and pericarp’ (Chinese Pharmacopoeia Commission, 2015: 93) have been removed. This description is, however, the one that appeared the closest to botanical rationale, since *C. sativa* seed is indeed a part of the fruit, contained inside the pericarp, external part of the fruit. *C. sativa* fruit pericarp is present both in seeded and parthenocarpic fruits. Like in other achenes, the pericarp is a thin layer hardly distinguishable from the seed coat (see figure II-1 below, and Esau, 1977). It is likely to be a more precise designation of what has been called bracts, bractlets, etc. In JP’s similar monograph for ‘Hemp Fruit, *Cannabis fructus*, マシニン’ it is outlined that ‘when perform the test of foreign matter ... Hemp Fruit does not contain bract’. Interestingly, the guide of medicinal plants edited by Taiwan department of health seems to accredit the thesis by distinguishing the fruit from the seed, explaining that ‘the fruit has anesthetic effects.’ (Huang et al., 2009: 141).

Figure II-1. Markers of fruit morphology.

A: Morphology of a drupe fruit, where seed coat and pericarp are visible. License: public domain (Source: Wikimedia). B: Morphology of an achene fruit (*Zea mays*), showing the seed coat almost merged with the pericarp. License: © 1996 Encyclopaedia Britannica, Inc.

To support or infirm the claim of *sinsemilla buds* being parthenocarpic infructescences instead of inflorescences, morphological and phenological studies reflecting the later stages of flowering and fructification of the genus are missing. Prior research has critically focused either on early growth development phases² or on plants grown for purposes not related to psychoactivity where the preferred harvestable parts are stem fibers or seeded fruits³ (Frankel and Galun, 1977: 157–159). Yet, an epiphenomenal expression characteristic of parthenocarpy, observed in *C. sativa* *sinsemilla* buds, is orientative: the presence of aborted ovules, sometimes termed *pseudo-embryos*, referred to as ‘empty, partly developed seed’ by Gustafson (1942: 6000) and reported in numerous parthenocarpic fruits such as avocados and *Tamarix dioica* (Gustafson,

1942: 617, 625), tomatoes⁴, bananas⁵, and others (Vazart, 1955: 436–438). Figure II-2 presents an example of *pseudo-embryo* observed in parthenocarpic infructescences of *C. sativa*.

There is no reason why *Cannabis* would make an exception to established biological mechanisms. Therefore, and unless future histological or cytological studies disconfirm it, it should be advised to consider the mature seedless reproductive parts of pistillate *C. sativa* plants as ‘parthenocarpic infructescence of *C. sativa*’ (abbreviated *pioC*) / ‘parthenocarpic fruits’ instead of ‘inflorescence’ / ‘flowers’. In the eventuality of some seeded fruits remaining within a *pioC*, as shown in figures II-2 (H and I) and II-3 below, the designation would be ‘partially parthenocarpic infructescence’.

² Spitzer-Rimon B, Duchin S, Bernstein N and Kamenetsky R (2019) Architecture and Florogenesis in Female *Cannabis sativa* Plants. *Front Plant Sci* 2019;10:350. DOI:10.3389/fpls.2019.00350

³ Mishchenko S, Mokher J, Laiko I, Burbulis N, Kyrchenko H and Dudukova S (2017) Phenological growth stages of hemp (*Cannabis sativa* L.): codification and description according to the BBCH scale. *Zemės ūkio mokslai* 2017;24(2):31–35. DOI:10.6001/zemesukiomokslai.v24i2.3496 Available at: maleidykla.lt/ojs/index.php/zemesukiomokslai/article/view/3496

⁴ Goetz M, Hooper LC, Johnson SD, Rodrigues JCM, Vivian-Smith A and Koltunow AM (2007) Expression of Aberrant Forms of AUXIN RESPONSE FACTOR8 Stimulates Parthenocarpy in Arabidopsis and Tomato. *Plant Physiology* 2007;145(2):351–366. DOI:10.1104/pp.107.104174

⁵ Sardos J, Rouard M, Hueber Y, Cenci A, Hyma KE, and Van den Houwe I, et al. (2016) A Genome-Wide Association Study on the Seedless Phenotype in Banana (*Musa* spp.) Reveals the Potential of a Selected Panel to Detect Candidate Genes in a Vegetatively Propagated Crop. *PLoS ONE* 2016;11(5):e0154448. DOI:10.1371/journal.pone.0154448

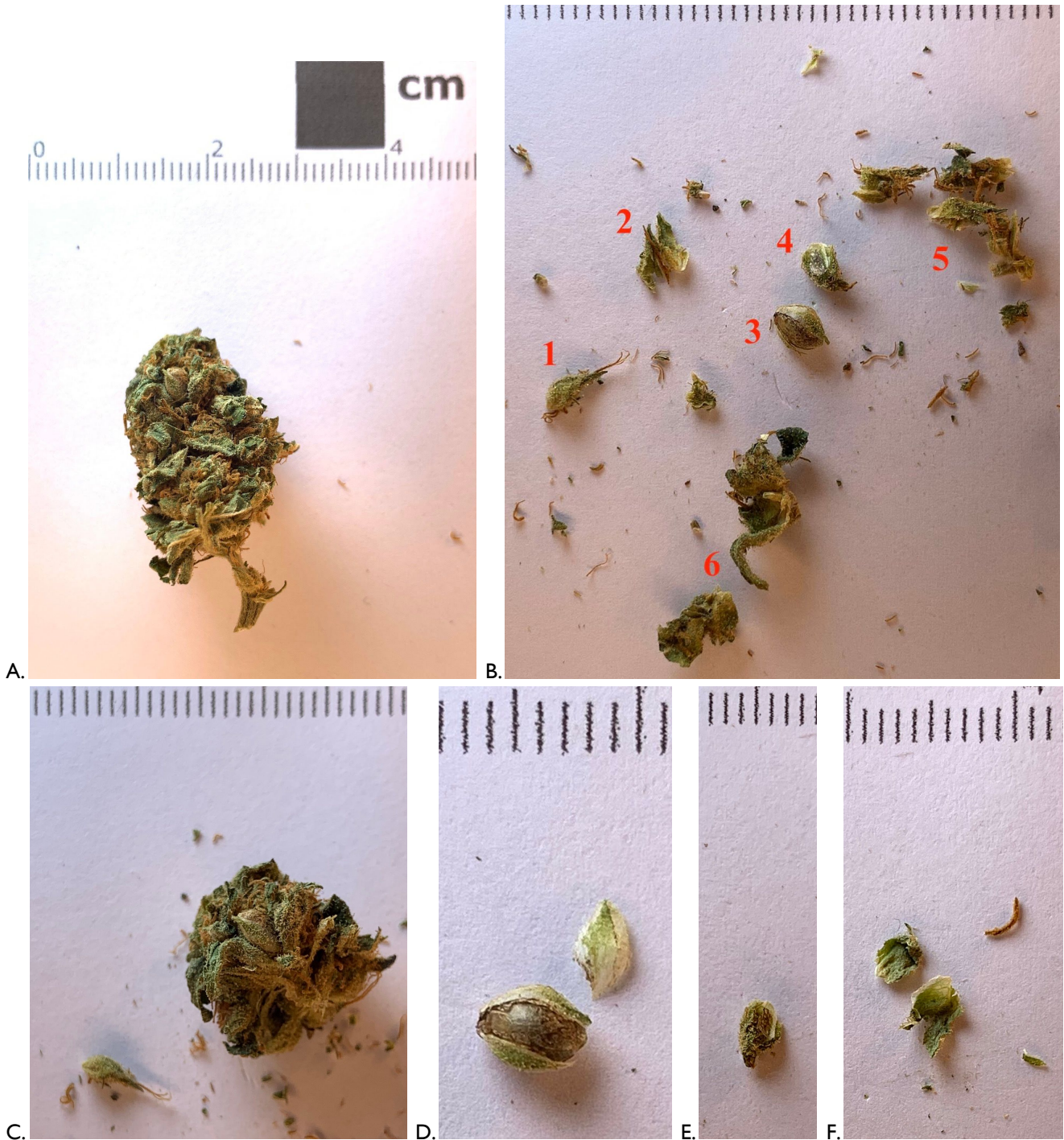
Figure II-2. Observation of different fruits and pseudo-embryos in parthenocarpic infructescences of *Cannabis*.



A: 1. Parthenocarpic fruits of a *C. sativa*; 2. Pseudo-embryos from the same infructescence; and for comparison, 3. Mature seeds from seeded fruits of *C. sativa* (from a different plant) and 4. Immature seeds from the same plant. B: Close-up on the seeds shown in image A-3. C: Close-up on the seeds shown in image A-4. D: 1. A parthenocarpic fruit; 2. A pseudo-embryo isolated from a different

parthenocarpic fruit. E: The pericarp from the parthenocarpic fruit shown in image D-I after having been opened and separated into two bracteoles, leaving visible an empty cavity and the unpollinated, dry, and undeveloped pseudo-embryo (indicated with the arrow). F: Close-up on the pseudo-embryo shown in image D-2 (left) and the pseudo-embryo separated from the fruit of image E (right). G: Close-up on the same pseudo-embryos, turned upside down. A-G: Scale in millimeters. H: Partially parthenocarpic infructescence of a *C. sativa* comminuted. Central part of the image: a dark piece of pericarp and tegument from a comminuted seeded fruit. Upper right part: one of the seedless fruit, separated from the rest of the infructescence during comminution. Scale: approx. 1:2. I: The pericarp from the parthenocarpic fruit isolated in A, after opening and separation into two bracteoles, leaving visible the pseudo-embryo (upper right side). Scale: approx. 1:4.

Figure II-3. Comparison of seeded and seedless fruits in a partially parthenocarpic infructescence of *Cannabis*.



A: Dry, partially parthenocarpic infructescence, where a seed can be observed on the surface. B: The same infructescence, broken down, showing parthenocarpic fruits (1, 2, 4, 5) one of which open (2), apparently empty; a regular fruit with apparent seed (3) and a cluster of dry leaves (6). C: Close-up of a cross-section cut of the infructescence before being comminuted; an untied parthenocarpic fruit is visible on the bottom left side; the seeded fruit is visible on the infructescence. D: Detail of the regular fruit once untied from its cluster; the seed is still partially covered with the pericarp although a piece of it has detached. E: Detail of one of the parthenocarpic fruits. F: The same fruit opened in half, is entirely empty and shows no apparent pseudo-embryo.

Appendix III. Review of extraction methods used with *Cannabis*

A large variety of methods can be applied for the extraction of phytoconstituents from *C. sativa*. It is important to note that, throughout the world, there is an important number of products still derived from *C. sativa* according to traditional techniques and know-hows. Most of them rely on the methods of obtention partially if not entirely undocumented, and should be paid closer attention – in full respect of the rights, cultures and consent of local communities (Bellakhdar, 1997: 232–234; Abdool, 2013; Abbott, 2014; Kutesa, 2018). Whether traditional or not, the methods of obtention of *Cannabis* derivatives are often subdivided in two groups: ‘solvent extractions’ (relying on the addition of foreign matter) and ‘solventless extractions’ (purely thermomechanical).

In respect to these processing based on the addition of foreign matter, the Encyclopedia of Separation Sciences (Wilson, 2000) agrees with reviewers^{6,7} on twelve basic and widely used techniques to extract and isolate natural biocompounds, all of which are reported for the obtention of *C. sativa* derivatives as well. They comprise :

- maceration either in dedicated eluents or in edible preparations like fatty oils or honey^{8,9} (Cannazza and Citti, 2018a, 2018b; Beal, 2019),
- decoction and infusion (Cannazza and Citti, 2018a, 2018b; Baratta et al., 2019),
- percolation (Devi and Khanam, 2018),

- hydrodistillation or steam distillation (Naz et al., 2017; Cannazza and Citti, 2018a, 2018b),
- reflux extraction¹⁰,
- ‘Soxhlet extraction’ (Devi and Khanam, 2018),
- pressurised liquid extraction¹¹,
- ‘supercritical fluid extraction’^{8,11,12} (see also Perrotin-Brunel et al., 2010; Omar et al., 2013),
- ‘ultrasound-assisted extraction’ (sonication^{8,13}, see also Omar et al., 2013; Devi and Khanam, 2018),
- ‘microwave-assisted extraction’⁸,
- ‘pulsed electric field’ extraction^{13,14}, and
- ‘enzyme-assisted extraction’¹¹ (see also Agarwal et al., 2018).

Other methods of extraction are used to a lesser extent but could likely be increasingly used in the future. They include:

- gas-phase extraction techniques (e.g. vacuum-related extractions, sublimation, field flow fractionation, and series of separations relying on supercritical eluents or subcritical water),
- complex liquid phase methods (chromatography, on-line fractionation, winterisation, flocculation, etc.),

⁶ Azmir J, Zaidul ISM, Rahman MM, Sharif KM, Mohamed A, Sahena F, Jahurul MHA, Ghafoor K, Norulaini NAN and Omar AKM (2013) Techniques for extraction of bioactive compounds from plant materials: A review. *J Food Eng* 2013; **117**(4):426–436. DOI:10.1016/j.jfoodeng.2013.01.014. Available at:

www.sciencedirect.com/science/article/pii/S0260877413000277

⁷ Zhang QW, Lin LG and Ye WC (2018) Techniques for extraction and isolation of natural products: a comprehensive review. *Chin Med* 2018; **13**(1):20. DOI:10.1186/s13020-018-0177-x

⁸ Brighenti V, Pellati F, Steinbach M, Maran D and Benvenuti S (2017) Development of a new extraction technique and HPLC method for the analysis of non-psychoactive cannabinoids in fibre-type *Cannabis sativa* L. (hemp). *J Pharm Biomed Anal* 2017; **143**:228–236. DOI:10.1016/j.jpba.2017.05.049

⁹ Namdar D, Mazuz M, Ion A and Koltai H (2018) Variation in the compositions of cannabinoid and terpenoids in *Cannabis sativa* derived from inflorescence position along the stem and extraction methods. *Ind Crops Prod* 2018; **113**:376–382. DOI:10.1016/j.indcrop.2018.01.060

¹⁰ Candy L, Bassil S, Rigal L, Simon V and Raynaud C (2017) Thermo-mechano-chemical extraction of hydroxycinnamic acids from industrial hemp by-products using a twin-screw extruder. *Ind Crops Prod* 2017; **109**:335–345. DOI:10.1016/j.indcrop.2017.08.044

¹¹ Kitrytė V, Bagdonaitė D and Rimantas Venskutonis P (2018) Biorefining of industrial hemp (*Cannabis sativa* L.) threshing residues into cannabinoid and antioxidant fractions by supercritical carbon dioxide, pressurized liquid and enzyme-assisted extractions. *Food Chem* 2018; **267**:420–429. DOI:10.1016/j.foodchem.2017.09.080

¹² Grijó DR, Bidoia DL, Nakamura CV, Osorio IV and Cardozo-Filho L (2019) Analysis of the Antitumor Activity of Bioactive Compounds of Cannabis Flowers Extracted by Green Solvents. *J Supercrit Fluid* 2019; **149**:20–25. DOI:10.1016/j.supflu.2019.03.012

¹³ Teh SS, Niven BE, Bekhit AEDA, Carne A and Birch EJ (2014) The Use of Microwave and Pulsed Electric Field as a Pretreatment Step in Ultrasonic Extraction of Polyphenols from Defatted Hemp Seed Cake (*Cannabis sativa*) Using Response Surface Methodology. *Food Bioprocess Tech* 2014; **7**(11):3064–3076. DOI:10.1007/s11947-014-1313-y

¹⁴ Haji-Moradkhani A, Rezaei R and Moghimi M (2019) Optimization of pulsed electric field-assisted oil extraction from cannabis seeds. *J Food Process Eng* 2019; **42**(4):e13028. DOI:10.1111/jfpe.13028

- the use of the previous methods for the nano- and micro-encapsulation of compounds^{15,16}.

These techniques can vary according to the type of eluent used and thermomechanical parameters; they can also sometimes be combined one with another (Lu and Luthria, 2014), eventually obtaining chemically and pharmacologically different products. This is the case for supercritical CO₂ extraction, a well studied method by which can be obtained products almost fully devoid from cannabinoids such as volatile essential oil¹⁷ or fatty oils from seeds (known as *hemp seed oil*)¹⁸, but that can also be used to obtain an oleoresin rich in phytocannabinoids (Omar et al., 2013), depending on a series of parameters^{10,12} (see also Omar et al., 2013; Lu and Luthria, 2014).

Solventless extraction or processing techniques are not less numerous. An ACS symposium presentation notes that 'postharvest storage and processing (such as grinding and drying) can influence the quantity of phenolic phytochemicals' (Lu and Luthria, 2014: 5, 12) including phytocannabinoids whose quality (acid or decarboxylated form) can change as well. Variation in the drying process are characteristic of different traditional extraction methods: Northern African *C. sativa* farmers often sieve the dry, previously harvested full plants, while the traditional Nepali method obtains 'temple balls' by hand rubbing fresh, living *C. sativa* plants directly in the field, (Fairbairn, 1976: 6; Clarke, 2007; Backes, 2014: 128; Cannazza and Citti, 2018a: 17) suggesting different thresholds of acid and decarboxylated phytocannabinoids between the two products. Filtration and its variables (size of the filter pores, pressure exerted, temperature, movement applied) are also determinative elements in the characteristics of the

final product (Hamayun and Shinwari, 2004; Upton et al., 2014; Devi and Khanam, 2018).

Modern Western methods have been added, such as induced thermic drying (hot or cold wind flow, drying in microwave or vacuum oven, freeze drying, etc.)⁹ as well as other complex solventless processing of phytopharmaceuticals like treatments with ultrasound or electromagnetic waves (e.g., pulsed electric field). Simple or more elaborate physico-mechanical processing methods can be combined between themselves. These parameters can also be used in combination with solvent processing methods.

¹⁵ Soh SH and Lee LY (2019) Microencapsulation and Nanoencapsulation Using Supercritical Fluid (SCF) Techniques. *Pharmaceutics* 2019;11(1):21.

DOI:10.3390/pharmaceutics11010021

¹⁶ Suganya V and Anuradha V (2017) Microencapsulation and Nanoencapsulation: A Review. *Int J Pharm Clin Res* 2017;9(3):233–239. DOI:10.25258/ijpcr.v9i3.8324

¹⁷ Da Porto C, Decorti D and Natolino A (2014) Separation of aroma compounds from industrial hemp inflorescences (*Cannabis sativa* L.) by supercritical CO₂ extraction and on-line fractionation. *Ind Crops Prod* 2014;58:99–103.

DOI:10.1016/j.indcrop.2014.03.042

¹⁸ Aladić K (2015) Cold Pressing and Supercritical CO₂ Extraction of Hemp (*Cannabis sativa*) Seed Oil. *Chem Biochem Eng Q* 2015;28(4):481–490. DOI:10.15255/cabeq.2013.1895

Appendix IV. Glossary of neologisms and terms recommended

Table IV-I. Glossary of terms.

Proposed term	Definition	Etymology or origin	Similar terms
Biosynthesis	Formation of chemical compounds from more simple compounds in living organisms. <i>Can be either eubiosynthesis or dysbiosynthesis.</i>	Classical Greek prefix βίος, <i>bios</i> : 'life' added to the word 'synthesis'.	- Biosynthesis
Cannabis fruit	Matured extracarpellary structure of the <i>Cannabis sativa</i> plant. <i>Can be either seeded (regular) or seedless (parthenocarpic).</i>	<i>Cannabis sativa</i> : Linnæus, 1753; McPartland; 2018. Fruit: Scagel et al., 1967: 559; Esau, 1977: 430; Blumenthal et al., 1998: 59.	- Bractlets - Bracts - Buds - 'Cannabis' - Flower - Ganja
Cannabis parthenocarpic fruit / parthenocarpic infructescence	Mature fruit without seed, produced without pollination, fertilisation or other stimulation. Harvestable part of <i>C. sativa</i> , which contains phytocannabinoids. <i>While seeded fruits favour the production of seeds, the absence of seed can make parthenocarpic fruits redirect their energy to the production of organic compounds, resulting in increased yield of phytoconstituents (flesh, flavour and fragrances for most food fruits like bananas, oleoresin and fragrances for C. sativa).</i>	Parthenocarpy: Noll, 1902; Gustafson, 1942; Appendix II.	- Heads - Inflorescences - Marijuana - Seedless floral clusters - Sensi - Sinsemilla - Tops
Cannabis oleoresin	Ethersoluble material contained inside, or separated from, the capitate glands of epidermal trichomes of <i>C. sativa</i> plants, regardless of texture and composition.	Pharmacopœias.	- BHO - Budder - Cannabis extract - Cannabis oil - Cannabis resin - Concentrate - Dry sift - FECO - Hashish - Rosin - Sauce - Shatter - Temple ball
Dysbiosynthesis	Formation of chemical compounds from more simple compounds <i>ex vivo</i> , in living organisms with biosynthetic pathways altered via genetic engineering. A synthesis process relying on the alteration by humans (via genetic engineering in particular) of natural biosynthetic pathways in order to have them synthesize compounds that would not be obtained under natural unmodified conditions. <i>Refers only to the process of obtention, not to the mere occurrence of the compound in a natural environment. Indeed, this process can also result in compounds found naturally in the environment.</i>	Prefix δυσ-, <i>dys</i> -'disordered', 'bad', 'difficult', 'abnormal', added to 'biosynthesis'. <i>The opposition dysbiosynthesis / eubiosynthesis allows for a subdivision of biosynthesis into coherent subgroups. It relies on the dichotomy between the uses of prefixes dys- and eu- as in, for instance, dysbiosis / eubiosis, or dystopia / utopia.</i>	- Altered biosynthesis - CRISPR synthesis - GMO synthesis - Synthetic biology
Dysbiosynthetic cannabinoid	Cannabinoid obtained by dysbiosynthesis.		- GMO cannabinoids

Table IV-I. Glossary of terms (continued).

Proposed term	Definition	Etymology or origin	Similar terms
Eubiosynthesis	Formation of chemical compounds from more simple compounds <i>in vivo</i> .	Prefix εὖ-, εὐ-: 'true', 'well', 'real' added to 'biosynthesis'.	- Biosynthesis - Natural synthesis
Eubiosynthetic cannabinoid	Cannabinoid obtained by eubiosynthesis.		- Natural cannabinoids
Incorporation	Any use that results in the penetration of part or the entirety of a product inside the body, either via external (topical) or internal use.	From late Latin <i>incorporatio</i> , formed with <i>in-</i> and <i>corpus</i> , literally 'within body', 'inside flesh'.	- Consumption - Internal & topical - Use
Neocannabinoid	Cannabinoid compound not present in nature. <i>Neocannabinoids can only be obtained by dysbiosynthesis or poesyntesis.</i>	From Classical Greek νέος, <i>néos</i> : 'new', 'young', added to the root 'cannabis' and followed by the <i>-oid</i> ('of the kind').	- Artificial cannabinoid - Cannabinoid analogue - New cannabinoid - NPS - Synthetic cannabinoid
Paleocannabinoid	Cannabinoid compound occurring in nature, either raw or as processed metabolites. <i>Paleocannabinoids are usually obtained by eubiosynthesis, but can also be obtained via dysbiosynthesis or poesyntesis. Paleocannabinoids include phytocannabinoids, human endocannabinoids, as well as other naturally-occurring endogenous cannabinoid substances from any possible living organism.</i>	Similarly to <i>neocannabinoid</i> , but formed with the prefix <i>paleo-</i> derived from παλαιός, <i>palaiós</i> : 'old', 'ancient.'	- Natural cannabinoid - 'Phyto and endocannabinoids'
Phytopharmaceutical	Any herbal medicine. Any medicines based on plant material, except finished preparations of single isolated phytoconstituent, semisynthetics and mixtures with non-herbal active compounds.		- Botanical extract - Extract and tinctures - Full-spectrum product - Herbal drug - Herbal extract - Herbal galenic preparation - Herbal material - Herbal medicinal products - Herbal medicine - Herbal preparation - Herbal substance - Herbal therapy - Medicinal plant - Phyto-preparations - Processed herbs - Whole plant product
Poesynthesis	Formation of chemical compounds from more simple compounds, <i>ex vivo</i> and <i>in vitro</i> .	Prefix ποιέω, <i>poieō</i> : 'to make', 'produce', 'create', 'compose', 'bring into existence', added to 'synthesis'.	- Chemical synthesis - Human-made synthesis
Poesynthetic cannabinoid	Cannabinoid obtained via poesyntesis.	<i>The word is arranged for phonetic and legibility purposes according to lemmas formed with the same prefix, such as 'poetry'.</i>	- <i>In vitro</i> synthesis - Laboratory synthesis - Synthesis
Semisynthesis	In the case of <i>C. sativa</i> : Formation of chemical compounds <i>ex vivo</i> and <i>in vitro</i> from <i>C. sativa</i> starting material.		
Synthesis	'Formation of chemical compounds from more simple compounds' <i>Can be either biosynthesis or poesyntesis.</i>	Definition: Martin et al., 2015: 577. Derives from σύνθεσις, <i>súnthesis</i> : 'arrangement', 'putting together', 'composition', 'combination'.	