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Traditional uses of *Cannabis*: An analysis of the CANNUSE database

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ABSTRACT

Ethnopharmacological relevance: Cannabis is one of the most versatile genera in terms of plant use and has been exploited by humans for millennia. Nowadays, *Cannabis* is the centre of many scientific studies, most of them focusing on chemical composition and medicinal values. While new and varied applications are continuously being developed, the knowledge surrounding less common uses of the plant is slowly disappearing.

Aim of the review: We have analysed diversity of global data of *Cannabis* traditional uses, to investigate if certain plant parts are significantly associated with particular *Cannabis* use. We wanted to uncover potential associations between the plant parts used for the treatment of different body systems and ailments.

Materials and methods: We have analysed the extensive database of *Cannabis* traditional uses (CANNUSE). This database contains 2330 data entries of *Cannabis* ethnobotanical uses from over 40 countries across the world. The dataset was divided into five general groups based on the type of use: medicinal, alimentary, psychoactive, fibre and other uses. Given the abundance of human medicinal uses, detailed analysis was done on the subset of 1167 data entries. We analysed the relationship between 16 body system categories and ailments treated with *Cannabis* plant parts. We used a Pearson's chi-square and Fisher's exact test, to determine which *Cannabis* parts are characteristic of treatment for specific ailments.

Results: In this dataset, the majority of reports were represented by medicinal (75.41%), followed by psychoactive (8.35%) and alimentary (7.29%) use. The most commonly used plant parts were leaf (50.51%), seed (15.38%) and inflorescence (11.35%). We found that different *Cannabis* plant parts were significantly associated with different uses; the leaf was typically used for medicinal, seed for alimentary and inflorescence for psychoactive use. Regarding the human medicinal uses, most common were reports for treatments of the digestive system and nutritional disorders (17.66%), nervous system and mental disorders (16.24%), followed by pain and inflammations (12.21%). We found a significant relationship between the use of certain *Cannabis* parts and treatment of ailments and body systems categories; leaf was significantly associated with treatment of two categories: skin and subcutaneous tissue disorders and circulatory system and blood disorders; seed use was associated with musculoskeletal system disorders and traumas; while inflorescence use shows a statistical support for treatment of nervous system and mental disorders.

Conclusion: Several pharmaceutical companies are intensely working on developing new drugs with isolated chemical compounds or crude extracts, almost exclusively from *Cannabis* inflorescences. However, our review revealed that use of leaf or seed in traditional medicine is often more important than use of inflorescence for the treatment of certain ailments. A review of traditional medicine provides a body of knowledge and an initial pathway to identify landraces and plant parts that could have an important role in future medicinal research. We are confident that traditional medicine still has a large potential for modern medicine. As more information on *Cannabis* diversity (genetics, biochemistry, and clinical studies) becomes available, ethnobotanical data are poised to be of much greater significance.

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1. Introduction

Cannabis sativa L. (hereafter *Cannabis*) is one of the most versatile plants known to man and has traditional roots among many cultures around the world. Because of its exceptional phenotypic plasticity, *Cannabis* has played an important role in various aspects of human life.

Even though people have used it for thousands of years, details about *Cannabis* origin are still not well known. Latest studies place its origin in Central Asia, in the NE part of the Tibetan plateau (Kovalchuk et al., 2020; McPartland et al., 2019), however theories of South Asian origin have also been proposed (Linné et al., 1737; Zhang et al., 2018). In addition, more research is needed to determine the possible domestication area of *Cannabis*. The oldest archaeological remains are the seeds discovered in Japan about 10,000 years ago (Kudo et al., 2009), but the exact centre of *Cannabis* domestication is still unknown. Domestication most likely started somewhere in Central Asia (Clarke and Merlin, 2013), but theories of multiregional domestication have also been suggested (Long et al., 2017; McPartland et al., 2019; Vavilov, 1992; Zhang et al., 2018).

A long coexistence of *Cannabis* and people managing it has resulted in its worldwide distribution, alongside a high genetic, morphological, and chemical diversity. This variability has impeded the taxonomic resolution within *Cannabis* genus (Clarke and Merlin, 2013). Two hundred years of attempts have produced numerous interpretations, the genus being composed of either: three (*C. sativa* L., *C. indica* Lam., *C. ruderalis* Janisch.; Hillig, 2005; Clarke and Merlin, 2013; Sawler et al., 2015), two (*C. indica* and *C. sativa*; Clarke and Merlin, 2016) or one species (*C. sativa*; Small and Cronquist, 1976; Small, 2015; McPartland, 2018; Zhang et al., 2018). Currently the most widely accepted theory is that the genus consists of a single species, *C. sativa*, with several subspecies and varieties. Depending on the purpose and chemical composition it is mostly divided into fibre-type (hemp; $<$ 0.3% Δ9-tetrahydrocannabinol (THC)) or drug-type (marijuana or medicinal cannabis; $>$ 0.3% THC) plants (Hurgobin et al., 2021). Drug-type plants are known in the vernacular nomenclature as *''sativa''* and *''indica''* plants based on their CBD/THC ratio. However, this does not always coincide with the taxonomical nomenclature of *C. sativa* and *C. indica* and does not necessarily reflect the common genetic ancestry. For a more detailed review of the taxonomic and popular classification of *Cannabis*, see McPartland and Small (2020) and Small (2015). Since the taxonomy within the genus is still not well resolved and our study does not focus only on one type of plant, we will consider *Cannabis* at the genus level.

Cannabis has a long tradition of use in many cultures around the world. It was traditionally used for medicinal purposes, production of fibres, ropes, textile, and paper, it served as a valuable source of food, and it was an important element in many shamanic rituals (Clarke and Merlin, 2013). Traditional knowledge is the result of centuries of experience and innovations. Practices of indigenous and local communities around the world were passed down from generation to generation and adapted to local culture and environment (Convention on Biological Diversity, 2011). Despite its many uses for millennia, now *Cannabis* is most famous for its psychoactive recreational use. The cannabinoid responsible for its mind-altering effects is Δ-9-tetrahydrocannabinol, better known as THC. It is not clear when and how people first discovered the psychoactive effects of *Cannabis*, but it has probably been used in different ritualistic and religious contexts since the early Palaeolithic period (Clarke and Merlin, 2013). One of the first conclusive evidence of its use in ritual smoking comes from Pamir mountains and dates back 2500 years. The findings of charred seeds, wooden braziers and stones in the Pamirs revealed that *Cannabis* plants were burned intentionally, and chemical analysis suggested high levels of psychoactive chemicals (Ren et al., 2019). Remains from a prehistoric site in China from about the same age also suggest *Cannabis* was used for ritual purposes (Jiang et al., 2016). Recently, ritual use of *Cannabis* was also confirmed at the Judahite Shrine of Arad in Israel, dating to the 8th century BCE (Arie et al., 2020). All these finds reveal that in the past *Cannabis* had an important role in religious rituals. Today, *Cannabis* is the most used recreational drug in the world - an estimated 183 million people were using it in 2014 (UNODC, 2016). In the early 20th century, *Cannabis* became regarded as an illegal drug and its use started to decrease (Pisanti and Bifulco, 2019). However, in the past twenty years, research on *Cannabis* increased and several traditional uses (especially medicinal) have started to gain more attention.

The pharmacological industry's growing interest in *Cannabis* has made it a valuable plant in medical research. Up until now, over 150 cannabinoids and hundreds of other compounds like terpenoids, flavonoids, and alkaloids (with valuable anti-inflammatory, antimicrobial, neuroprotective properties) have been discovered in *Cannabis* (Bonini et al., 2018; Hanuš et al., 2016; Jin et al., 2020). Many traditional medicinal uses of *Cannabis* were already proven and are now medically recognised treatments. It is used for cancer pain and chronic pain management (Blake et al., 2017; Lynch and Ware, 2015), spasticity and pain management associated with multiple sclerosis (Mecha et al., 2020), and inflammation reduction (Perisetti et al., 2020). However, many other uses have been reported in ethnopharmacological surveys but remain to be studied in a broader framework. Several pharmaceutical companies are intensely working on developing new drugs with isolated natural *Cannabis* products, while others are focusing on studying effects of crude extracts from *Cannabis* inflorescence, recently proven superior to the single molecule use in medical treatment (i.e., the entourage effect; Koltai and Namdar, 2020). Despite the deep pharmaceutical inroads, the diversity of *Cannabis* continues to make the research on this plant challenging. Many studies already confirmed differences in chemical profiles between different *Cannabis* landraces and cultivars (Abdollahi et al., 2020; Bueno and Greenbaum, 2021; Eržen et al., 2021; Kornpointner et al., 2021; Li et al., 2020; Nagy et al., 2019; Namdar et al., 2019; Nissen et al., 2010; Novak et al., 2001; Stack et al., 2021). Some of this variation is attributed to the genetic background (Vergara et al., 2019), but the differences are also caused by different growing conditions (Burgel et al., 2020; Saloner and Bernstein, 2021; Wei et al., 2021), and collection period (Kornpointner et al., 2021; Stack et al., 2021). Diversity of material used in clinical trials makes it very difficult to compare the results, because plants with different chemical composition, could be more or less effective for treatment of certain illnesses (Mudge et al., 2019; Namdar et al., 2019). This variation within the plants and plant parts makes standardisation and reproducibility of medicinal products very difficult (Bernstein et al., 2019; Gorelick and Bernstein, 2014). An additional problem in clinical research is the lack of randomized double-blind placebo controlled clinical trials, which are particularly hard to secure when the tested drug is psychoactive, or is considered "miraculous" (Gertsch, 2018; Russo, 2016).

Inflorescences are best-known and almost exclusively used part of *Cannabis* in pharmaceutical industry, even though in the past all plant parts had an important role in traditional medicine (Clarke and Merlin, 2013; Stuart and Smith, 1911). Specific plant parts contain different types and amounts of chemical compounds, and depending on the illness different plant parts and preparations were used (Chopra and Chopra, 1957; Stuart and Smith, 1911). Inflorescences contain the highest density of glandular trichomes, particularly rich in cannabinoids (Livingston et al., 2020), and therefore are the focus of most medicinal studies. Only recently have other plant parts started to gain more attention. In the latest study by Jin et al. (2020), they screened different parts of *Cannabis* and found that inflorescence and leaves are the most abundant source of cannabinoids, mono- and sesquiterpenoids, and flavonoids. However, pharmacologically relevant quantities of triterpenoids and sterols can also be found in roots, stems, and bark. The identification of biochemically active compounds in different plant parts is the basis for development of new medicinal uses (Jin et al., 2020). Nevertheless, a comprehensive review of traditional medicine can also help us identify plant parts and preparations that could potentially be more useful for

treatment of specific illnesses. This traditional knowledge could be the basis for further pharmacological investigation determining key active compounds responsible for the desired medicinal effects.

Apart from well-known psychoactive and medicinal uses, *Cannabis* has played an important role in many other aspects of human life. *Cannabis* fruits (usually referred to as 'seeds'), were probably the first parts of this plant people collected. Throughout Asia, *Cannabis* seeds have represented an important part of human diet and are still consumed in several ways (e.g., raw, roasted, pickled, grinded, parched or pressed for oil) (Clarke and Merlin, 2013). Seeds of non-psychoactive *Cannabis* varieties, commonly known as hemp, contain over 30% of oil, 25% of easily digested protein and are high in dietary fibres, vitamins, minerals, with an optimal ratio of omega-6 to omega-3 fatty acids for human health (Callaway, 2004). *Cannabis* is also known for having one of the strongest and most durable natural fibres, which is why it has long been used in production of clothing, coarse canvas, sackings, twine, rope, fishing nets, rugs, and pulp for paper (Clarke, 2010a, 2010b). *Cannabis* fibres are gaining new uses in sustainable industry as house insulation material, hemp fibre interior panels in automotive industry, animal bedding, nonwoven agricultural fleece, matting, mulch for weed suppression, and erosion control. Furthermore, seeds rich in polyunsaturated fatty acids and proteins have started to gain the popularity as snacks, as well as in oil production (Clarke and Merlin, 2013).

Information on *Cannabis* traditional knowledge is substantial, however there is a strong need to synthesise and standardise these data, since it is scattered among many publication sources. Recently, an online source - the CANNUSE database (http://cannusedb.csic.es) (Balant et al., 2021b) – was released, containing information on *Cannabis* traditional knowledge related to medicinal, alimentary, fibre and other uses from different geographical areas.

In the present study, we analysed the data on traditional *Cannabis* uses included in the CANNUSE database to obtain a general overview of the most common *Cannabis* traditional uses and their diversity. We further investigated if certain plant parts are significantly associated to a particular *Cannabis* use or even treatment of different body systems and ailments.

2. Methodology

2.1. The CANNUSE database content

We have analysed the dataset gathered in the database of *Cannabis* traditional uses – CANNUSE (Balant et al., 2021; https://digital.csic.es/handle/10261/226973?locale=en). The CANNUSE database contains information on literature published in the English language from 1960 until the end of October 2020 comprising of first-hand information obtained through any type of ethnobotanical interviews. The publication search for the database construction was carried out in four major online databases—Scopus, Web of Science, PubMed and Google Scholar, using the following set of keywords and exact terms: *Cannabis* AND ('folk medicine' OR 'traditional medicine' OR 'ethnobotany' OR 'traditional knowledge'). Information obtained from review papers and books was only used when original research papers could not be found. It consists of 2330 entries from 649 publications related to medicinal, alimentary, fibre and other uses from different geographical areas.

For each reference, the following information is provided: type and year of publication, country and region, taxon, vernacular name, and part of the plant (inflorescence, leaf, whole plant, seed, aerial parts, stem, bark, root, twigs and branches, other parts) or plant product (resin, fibre, other products) used. In the database, the term 'seed' refers to the monosperm *Cannabis* fruit, a nut (also called achene) (Naraine et al., 2020). It contains information of the type of use, whether *Cannabis* had animal or human use, and includes modes of preparation and administration, whenever they were provided by the authors. For medicinal use, type of administration (external, internal) is also recorded whenever possible.

The database is divided into five main use categories: medicinal, alimentary, fibre, psychoactive and other uses. Since *Cannabis* is sometimes considered poisonous, with several side effects, an additional category named toxicity is included. The majority of authors also provided vernacular names of *Cannabis,* which can be found next to each use. For more details on data collection and database structure, see Balant et al. (2021b) or the CANNUSE database website (http://cannusedb.csic.es).

2.2. Data analysis

The information included in the CANNUSE database (i.e., 2330 data entries) (Balant et al., 2021a; Table 1 in https://doi.org/10.20350/digitalCSIC/13686) was analysed to obtain a general overview of the most common *Cannabis* uses and their diversity. To investigate the relationship between different uses (i.e., medicinal, alimentary, psychoactive, fibre and other uses) and the plant parts utilised, we analysed the data with Pearson's chi-square test of independence — and Fisher's exact test to calculate the p-values — in XLSTAT 2020.3.1 (Addinsoft, New York, USA). In some references included in the database, plant parts used were not unambiguously specified. Therefore, the analysis of the relationship between plant parts and their uses were performed on a subset of 1725 (74.03%) data entries, where the plant part used was well specified (Balant et al., 2021a; Table 2 in https://doi.org/10.20350/digitalCSIC/13686). Because of low frequencies, reports using whole plant and aerial plant parts were grouped, and less commonly used plant parts (i.e., bark, fibre, root, resin, stem, shoot, twig and branch and other plant parts and products) were grouped under 'other plant parts and products'.

Because of the numerous data entries, a specific analysis of human traditional medicinal uses was done on the subset of 1167 (50.09%) data entries where the plant part used was well specified. Medicinal uses were classified into 16 human body system categories, according to Cook (1995) with minor modifications (Supplementary data Table S1). We tested the relationship between body system categories treated with *Cannabis* and plant parts used (grouped as in the previous step). If the ailment was classified into two categories, it has been considered as two use reports. System categories with less than 30 data entries (i.e., poisoning, pregnancy, birth and puerperal disorders, and sensory system disorders) were grouped together with unclassified ailments under 'other categories and unclassified'. The same analysis was additionally carried out by sub-setting data from two individual countries with over 200 entries (India and Pakistan), to test if the plant parts employed for medicinal use differ between the countries. We also analysed the relationship between specific ailments treated with *Cannabis* and plant parts used. Because only five ailments had over 30 data entries, we chose only those for further statistical analyses. Pearson's chi-square test of independence with 2000 Monte Carlo replicates was performed and p-value was calculated with Fisher's exact test in XLSTAT 2020.3.1. The Pearson's chi-square results were visualized using the function "corrplot" of 'corrplot' package (Wei and Simko, 2017) in R software system 4.0.1 (R Core Team, 2020).

3. Results and discussion

3.1. General overview of the information presented in the CANNUSE database

Traditional uses of *Cannabis* from 41 countries worldwide are represented in the database. The majority of reports come from India (41.76%) and Pakistan (25.89%), two of the countries where the use of *Cannabis* in folk medicine has one of the longest traditions (Chopra and Chopra, 1957; Dymock et al., 1893; Russo, 2005). Unexpectedly, even though there are many documented records of ancient *Cannabis* use in China (Jiang et al., 2006, 2016; Liu et al., 2017; Stuart and Smith, 1911), we found only 12 ethnobotanical papers from this country mentioning

the use of this plant. Cultural changes in China could have a major influence on its use. After the rise of Confucianism, around 200 BCE, ritual, psychoactive and medicinal uses of *Cannabis* started to decline (Touw, 1981), and are nowadays only used for fibre production and consumption of seeds - as snacks and pressed for oil (Clarke and Merlin, 2013). Another possible explanation for the limited reports found from China could be the search strategy carried out to construct the CANNUSE database. Ethnobotanical research is often published in lesser known, often local journals, which are not written in the English language, and the bibliographic search missed those references.

Due to the ambiguous taxonomic status within the genus *Cannabis*, we found eight scientific names within the references included in CANNUSE database. The most frequently employed taxonomic entity was *C. sativa* L. (96.92%), but we also recovered other taxonomic names (in decreasing order) *C. sativa* var. *sativa*, *Cannabis* sp., *C. sativa* var. *indica* (Lam.) E.Small & Cronquist, *C. sativa* subsp. *indica* (Lam.) E.Small & Cronquist, *C. indica* Lam., *C. ruderalis* Janisch., *C. sativa* f. *ruderalis* (Janisch.) Chu, and *Cannabis* spp.

Because *Cannabis* has been used by humans worldwide for thousands of years and for a variety of purposes, we can also find many popular or vernacular names for it. Often it is named differently depending on the use and the plant part used; for example, we can find over 40 names for *Cannabis* in Sanskrit language (Russo, 2005). It is therefore not surprising that the database contains 211 vernacular names. The highest diversity of names was found in references from India (56 vernacular names), South Africa (34) and Pakistan (31). The overall most frequent vernacular name was *bhang* (in 46.22% of references), a prevalent name for *Cannabis* in India. As mentioned before, vernacular names of *Cannabis* do not only change depending on the different countries (or regions within them) but may also depend on the plant part or plant use. In India, for example, the three most common preparations are: *bhang* - dried matured leaves and flowering shoots of female and male plants, *ganja* - dried flowering tops of the cultivated female *Cannabis* plant, and *charas* - the resinous matter collected from the leaves and flowering tops (Chopra and Chopra, 1957). All of them are recorded in the CANNUSE database as vernacular names for *Cannabis*.

The majority of the 2330 entries of the database refer to medicinal use (75.41%), followed by psychoactive (8.35%) and alimentary use (7.29%). Most commonly used plant parts are leaf (50.51%), seed (15.38%) and inflorescence (11.35%). The results of Pearson's chi-square test show, that there is a non-random association between *Cannabis* use categories and plant parts employed ($X^2 = 684.618$; df = 16; $p < 0.0001$) (Supplementary data Table S3). Medicinal reports are significantly associated with the use of leaves, psychoactive reports with inflorescence use and reports of alimentary and other uses with the use of seeds (Fig. 1 and Supplementary data Table S2).

3.2. Medicinal use

Cannabis has been a valuable plant in traditional medicine for thousands of years, so it is not surprising that medicinal use represents the majority of data entries (Fig. 1). According to our analysis, all plant parts have been used for medicinal purposes, but leaf use was reported in over half of data entries (55.76%). The results of Pearson's chi-square and Fisher's exact test show us that different plant parts are not randomly used for medicinal purposes. In fact they show that leaf is strongly associated with medicinal use ($p < 0.0001$) (Supplementary data Table S3). The majority of medicinal uses belong to human medicine, while only 8.54% of them was represented by veterinary use. We recorded 152 entries of 53 ailments treated in animals with the most common being antidiarrhoeal use (9.87%), treatment of dysentery (6.58%), appetite stimulant (4.61%) and treatment of coccidiosis (4.61%).

3.2.1. Human medicinal uses

We analysed 1627 data entries for human medicinal use, which were divided in 16 system categories. The most common ailments belong to digestive system and nutritional disorders (17.66%), nervous system and mental disorders (16.24%), followed by pain and inflammations (12.21%). We recorded *Cannabis* treatments for 210 ailments. The most common uses were sedative (6.02%), analgesic (5.84%), antidiarrhoeal (3.01%), antihaemorrhoidal (2.52%), followed by the use for dysentery (2.27%), wound treatment (2.21%) and as a tonic (2.40%). Some of these uses have already been confirmed by human and/or animal clinical studies, albeit sometimes with contradictory or non-conclusive findings (e.g., Buggy et al., 2003; Maharajan et al., 2020), but many others (i.e., antihaemorrhoidal and wound healing) still need to be verified.

The list of *Cannabis* human medicinal uses is very long, however not all plant parts were similarly used for all treatments. Since different plant parts have different chemical profiles (Burgel et al., 2020; Jin et al., 2020; Nagy et al., 2019; Namdar et al., 2018), they could be more or less effective for the treatment of different illnesses. We analysed the relationship between plant parts used for the treatment of different body systems and ailments, to see if the plant parts are randomly used or an association between them exists. Pearson's chi-square test showed that there is a significant relationship between the two variables ($X^2 = 110.36$, $p = 0.0005$) (Fig. 2 and Supplementary data Table S4).

The leaf was significantly associated with treatment of skin and subcutaneous tissue disorders and circulatory system and blood

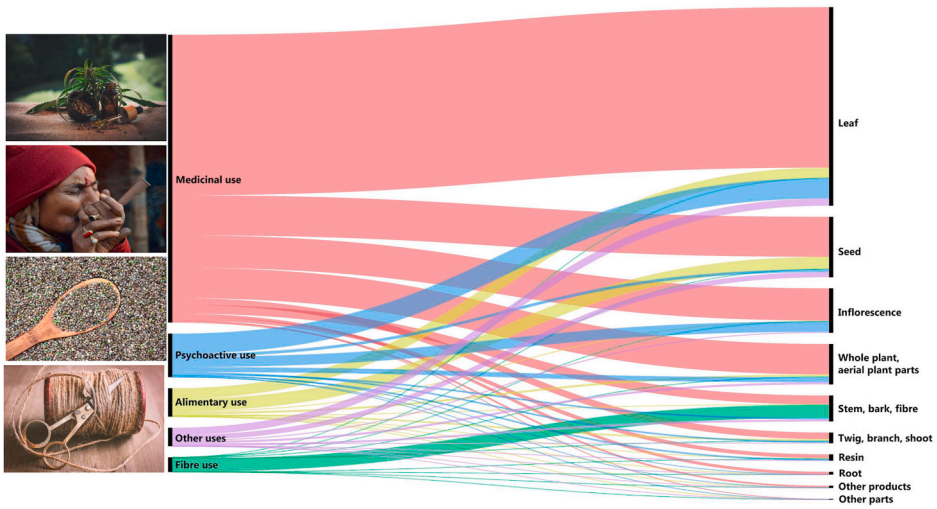

Fig. 1. Different *Cannabis* uses and the plant parts used for each use category. For the medicinal purpose leaves were used in most cases (55.76%), followed by seeds (13.92%) and inflorescences (11.20%). For the psychoactive use leaf use represented majority of reports (44.46%), but inflorescence use is also common (23.85%). In alimentary use, seeds were mostly used (43.59%) and for fibre use, other plant parts (particularly stem, bark, and fibre) were almost exclusively used (93.83%).

disorders. Seed use was associated with musculoskeletal system disorders and traumas, inflorescence with nervous system and mental disorders, while whole plant and aerial plant parts are significantly associated with treatment of pain and inflammation and was often used as tonic and restorative. We also found a significant association between the plant parts used for treatment of different specific ailments (X^2 = 59.447, p = 0.0005) (Fig. 3 and Supplementary data Table S5).

Regarding the analyses of plant part use between countries, most of the results show that reports from India (600 data entries) and Pakistan (548 data entries) yielded similar results as the dataset as a whole. However, we found differences in the plants parts employed for certain body system categories among countries. In the data from India, we found a strong association of leaf use with the treatment of body systems grouped in the category 'other categories and unclassified'. Because this is a very diverse group (poisoning, pregnancy, birth and puerperal disorders, sensory system disorders and unclassified), we cannot assign this relationship to any particular use. Whole plant and aerial plant parts in India were only significantly associated with the use of pain and inflammation treatment and not as a tonic and restorative (Supplementary data Table S6). In Pakistan, seeds were significantly associated with the use of respiratory system disorders and not with musculoskeletal system disorders and traumas, as in other countries. Use of inflorescence in Pakistan was positively associated with treatment of nervous system and mental disorders, but here the relationship was not significant (p = 0.106). The use of other plant parts (especially use of shoots, branches and twigs) was significantly associated with the use as tonic and restorative – this association was not found in the analysis of the rest of the data (Supplementary data Table S7).

These differences between countries could be explained by several factors. Many studies have proven that different landraces and chemovars contain different chemical profiles (Abdollahi et al., 2020; Bueno and Greenbaum, 2021; Eržen et al., 2021; Kornpointner et al., 2021; Li et al., 2020; Nagy et al., 2019; Namdar et al., 2019; Nissen et al., 2010; Novak et al., 2001; Stack et al., 2021), which could be one of the causes for this variation. Detailed analysis of individual countries or regions could help us identify landraces with specific chemical profiles. Currently the dataset obtained from the CANNUSE database only allowed us a detailed analysis of the reports from India and Pakistan, since other countries are still underrepresented. However, the database is currently being updated (Balant et al., 2021b) and can become an important resource for such analysis in the future. Differences in uses between countries can also be caused by other reasons such as local customs, cultural differences and availability of other medicinal plants in the region (Kunwar et al., 2019). Therefore, different traditional uses between countries should be further investigated, through a series of pharmacological and phytochemical studies on local *Cannabis* landraces.

Fig. 2. Frequencies (circle size) and values of adjusted Pearson's chi-square residuals (colour shades) of the plant part use for each body system category. The size of each circle indicates the number of reports for treatment of each system category depending on the plant part used, while the colour shades indicate values of adjusted Pearson's chi-square residuals. The red colour indicates a positive and the blue a negative association between the plant part used and the body system treated. Asterisk indicates a significant positive association between the body system and the plant part used, as calculated with Fischer's exact test (*p < 0.05 and **p < 0.001); LE – leaf, SD – seed, INFL – inflorescence, WP & AP – whole plant and aerial plant parts, OP & P – other plant parts and products (root, resin, twig, branch and shoot, fibre, stem, bark, and other parts). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. Frequencies (circle size) and values of adjusted Pearson's chi-square residuals (colour shades) of the plant use for ailments with over 30 data entries. The size of each circle indicates the number of reports for treatment of each ailment depending on the plant part used, while the colour shades indicate values of adjusted Pearson's chi-square residuals. The red colour indicates a positive and the blue a negative association between the plant part used and the ailment treated. Asterisk indicates a significant positive association between the ailments and the plant part used, as calculated with Fischer's exact test (*p < 0.05 and **p < 0.001); LE – leaf, SD – seed, INFL – inflorescence, WP & AP – whole plant and aerial plant parts, OP & P – other plant parts and products (root, resin, twig, branch and shoot, fibre, stem, bark and other parts). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.2.1.1. Leaves. The leaf was the most used plant part for treatments in all system categories (used in 54.69% of all data entries), but the most numerous records correspond to treatments of the digestive system and nutritional disorders (157 data entries; Fig. 2 and Supplementary data Table S8). *Cannabis* leaves contain a considerable amount of cannabinoids that can interact with cannabinoid receptors in the gastrointestinal tract. Many clinical studies already confirmed their effectiveness for treatment of different gastrointestinal disorders, e.g., inflammatory bowel disease (Goyal et al., 2017; Kienzl et al., 2020; Pellesi et al., 2019; Perisetti et al., 2020; Picardo et al., 2019). Other system categories frequently related with *Cannabis* leaves are nervous system and mental disorders (131 entries), skin and subcutaneous tissue disorders (108), infections and infestations (105) and pain and inflammations (101). Among them, Fischer's exact test showed that the use of leaf was significantly associated with the treatment of skin and subcutaneous tissue disorders ($p < 0.0001$) (Fig. 2 and Supplementary data Table S4). According to our data, typical ailments treated with *Cannabis* leaves are wounds, cuts, skin diseases and sores. In these treatments, leaves are either grinded or crushed and applied externally in a form of juice, paste or powder. The analysis of the relationship between plant parts and specific ailments showed that leaf use is significantly associated with the treatment of wounds ($p = 0.001$) (Fig. 3 and Supplementary data Table S5). A recent study by Jin et al. (2020) found that leaves are rich in cannabinoids, terpenes and sesquiterpenoids, but also contain significant quantities of flavonoids and sterols. They all have anti-inflammatory, anti-bacterial and anti-fungal properties that can promote wound healing and can help with different skin problems (Andre et al., 2016; Kupczyk et al., 2009; Wilkinson and Williamson, 2007; Wright et al., 2005). Another system category with which leaf use is significantly associated was circulatory system and blood disorders ($p = 0.005$) (Fig. 2 and Supplementary data Table S4). According to our analysis, this relationship is almost exclusively related to haemorrhoids treatment (also highly associated with leaf use; $p < 0.0001$) (Fig. 3 and Supplementary data Table S5), where leaves are usually applied externally in a form of paste. No clinical tests have been done so far to verify the antihaemorrhoidal effects of *Cannabis* leaves, but the positive effects could be due to the presence of cannabinoids, terpenes, sesquiterpenoids, flavonoids and sterols in leaves, that have anti-inflammatory and analgesic effects (Gallily et al., 2018; Rabgay et al., 2020).

3.2.1.2. Seeds. Seeds are the second most used *Cannabis* part in human medicine, and they represent 14.46% of data entries. Reports of seed use were most frequent for the treatment of digestive system and nutritional disorders, nervous system and mental disorders, followed by pain and inflammation (51, 32, 30 data entries, respectively) (Supplementary data Table S8). Seeds have been used for treatments of these ailments since the early ages. In Arab medicine they were used (among other) for their antiepileptic, antiemetic, and carminative properties and for soothing neurological pain (Lozano, 2003). In traditional Chinese medicine *Cannabis* seeds were used for constipation and obstinate vomiting (Stuart and Smith, 1911), and still today traditional medicinal practitioners prescribe them for digestive and genitourinary problems (Shou-zhong, 1998). A recent study by Xue et al. (2020) found that they have protective effects on intestinal oxidative damage in mice. Indeed, *Cannabis* seeds are commonly used for a large diversity of ailments, but our analysis showed their use is significantly associated with the treatment of musculoskeletal system disorders and traumas ($p = 0.007$) (Fig. 2 and Supplementary data Table S4). In most cases, seed oil is massaged on the affected part, due to the supposed analgesic, antiarthritic, and antirheumatic effects. Clinical studies have already proved that cannabinoids are useful for treating rheumatic pain (Blake et al., 2006; Malfait et al., 2000), however the specific effect of *Cannabis* seeds – or products derived from seeds – still needs to be tested.

3.2.1.3. Inflorescences. In modern medicine, *Cannabis* female inflorescence is the most used part of the plant (Minghetti et al., 2019) and the main focus of many clinical trials. However, in our data, inflorescence use represented only 11.17% of human medicinal reports. Most numerous reports of the inflorescence use correspond to the treatment of nervous system and mental disorders (Supplementary data Table S8), a relationship showing statistical support ($p = 0.002$) (Fig. 2 and Supplementary data Table S4). Many of these data entries represent the use of inflorescence as a sedative, which also showed a statistically significant association ($p = 0.009$) (Fig. 3 and Supplementary data Table S5). The form of administration for the sedative use was given in less than half of the reports, but when specified, it was either smoked or drunk.

Female *Cannabis* inflorescences contain the highest concentration of different cannabinoids, terpenes and sesquiterpenoids that have proven sedative effects, which many studies already confirmed (Choi et al., 2020; Hazekamp et al., 2010; Mondino et al., 2019; Nuutinen, 2018). Treatment of digestive system and nutritional disorders are the second most common use of *Cannabis* inflorescence (Supplementary data Table S8). The three most common digestive ailments treated with inflorescences are dysentery, diarrhoea, and appetite loss, which were also previously confirmed with clinical trials (Mechoulam and Hanuš, 2001; Pellesi et al., 2019).

Analgesic effects of cannabinoids have also been clinically proven and are effectively used for alleviating chronic pain (Aviram et al., 2020; Blake et al., 2017; Cameron and Hemingway, 2020; Lynch and Ware, 2015). However, our results show that traditionally, inflorescences are less frequently used for treatment of pain and inflammation (24 data entries) and we did not find statistical support for such use (Fig. 2 and Supplementary data Table S4).

3.2.1.4. Whole plant and aerial plant parts. The use of whole *Cannabis* plant or its aerial parts is not very frequent and was recorded only in 11.24% of data entries. Whole plant or its aerial parts were most commonly used for treatment of ailments connected to nervous system and mental disorders. The two most common uses were sedative and stimulant use. We found that these preparations were administered in various ways: in the form of decoction or other types of drinks, by bathing in them, smoking or eating them, or they were externally applied. The association between the use of whole plant and its aerial parts for specific treatments is statistically significant for system categories pain and inflammations ($p = 0.015$; used for its analgesic effects, which is statistically significant ($p = 0.008$)) and tonic and restorative ($p = 0.029$; used for tonic preparations) (Figs. 2 and 3 and Supplementary data Tables S4 and S5). Different *Cannabis* parts have been used in tonic preparations for centuries; seeds were used in Chinese traditional medicine (Stuart and Smith, 1911), and other parts were used in indigenous medicine in India (Chopra and Chopra, 1957), Japan (Olson, 1997), and Jamaica (Comitas, 2011).

3.2.1.5. Other plant parts. The versatility of *Cannabis* for human medicine is well reflected in our results, as we found examples of ailments treated with every part of the plant. Although the uses of leaf, seed, inflorescence, whole plant, and aerial plant parts are prevalent, we also found reports of medicinal uses of roots, twigs, branches, shoots, stems, and bark, as well as plant products such as resin and fibre (8.44% of data entries; grouped in the category 'other plant parts'). Most of these data entries fall to the system categories pain and inflammation, digestive system and nutritional disorders and nervous system and mental disorders (21, 20 and 20 data entries, respectively). Even though uses of these parts are not numerously represented, they should not be overlooked. Fibre, stem, and bark were mostly used for their antirheumatic effects and treatment of skin diseases (both 5 data entries). Twigs, branches, and shoots were used for their analgesic effects (4 data entries). Since resin is most abundant on inflorescences, the use was similar for both plant parts - it was mostly used as a sedative (three data entries). *Cannabis* root has most entries (three) for treatment of menstrual disorders. In the past, *Cannabis* roots have been consumed for various uses, such as treatment of inflammation, fever, gout, arthritis, joint pain, skin burns, hard tumours, postpartum haemorrhage, difficult child labour, sexually transmitted disease, gastrointestinal disorders and infections (Ryz et al., 2017). A recent study by Lima et al. (2021) showed that roots of this plant have anti-inflammatory effects in mice models. In the dataset analysed here we also found reports for fever and cancer treatment, indigestion problems, stomach pain, liver disorders, and antiacid, among others. However, we found no indication for the anti-inflammatory use of *Cannabis* roots.

3.3. Psychoactive use

Psychoactive use of *Cannabis* is probably one of its most famous ones. It has been employed for millennials in many cultures and in many different forms (e.g., smoking dried inflorescences or purified resinous products like *charas* or *hashish*, drinking preparations of fresh leaves called *bhang*, etc.) (Clarke and Merlin, 2013). Knapp et al. (2019) indicate that today *Cannabis* is mostly used recreationally and consumed in different ways, most frequently by smoking. However, in the CANNUSE database, psychoactive use only represents 8.35% of all entries. The relatively low percentage of psychoactive uses does not match with the relevance of *Cannabis* cultivation, commerce, and consumption as a recreative drug, which has an important incidence at the worldwide level and frequently falls in the field of illegal activities. Irrespective of these societal considerations, ethnobotanical reports of *Cannabis* toxic activity, which could be linked to side effects of psychoactive consumption, are not very numerous (see section 3.5.).

In the CANNUSE database we found different methods of *Cannabis* administration for psychoactive use: smoking the leaves, inflorescences or resin preparations with different potency (*charas* or *attar, hashish, ganja,* plant powder) and drinking preparations from *Cannabis* leaves, inflorescences and shoots (*tandai, bhang*). The majority of references for psychoactive use did not specify the administration mode (73.10%), but considering only the reports including this information, it was administered by smoking in 56.6%, drunk in 37.74% and ingested as food in 5.66% of cases. For psychoactive use, the most used part of the plant is leaf (46.44%) followed by inflorescence (23.85%) (Fig. 1 and Supplementary data Table S2). Even though inflorescences are the biggest source of THC and other cannabinoids, they are also present in leaves (Jin et al., 2020). This could explain the common use of leaf in psychoactive purposes. Higher percentage of leaf use could also be explained by the common consumption of the traditional Indian drink *bhang* (also called *bang, thandai, tandai,* etc.) that is enjoyed in many religious and festivity ceremonies, but also drunk for its medicinal effects. Even though the use of inflorescence for psychoactive purposes is less frequently represented in the database than leaves, our analyses indicate that inflorescence is significantly associated with psychoactive, but not with other uses ($p < 0.0001$) (Fig. 1 and Supplementary data Table S3).

3.4. Alimentary use

Nowadays *Cannabis* products are becoming recognised as functional food. Seeds have been recognised as valuable food source, rich in easily digestible proteins, polyunsaturated fatty acid (PUFA), lipids, carbohydrates, and insoluble fibre (Rupasinghe et al., 2020). They have a favourable ratio of omega-6 to omega-3 of PUFA, well suited for human diet and have beneficial effect on the cardiovascular health, cancer, atopic dermatitis conditions and constipation problems, among other issues (Callaway et al., 2005; Cerino et al., 2021; Cheng et al., 2011; Rupasinghe et al., 2020). Seeds are mostly pressed for oil, but also available in many other preparations – from energy bars, pralines and chocolates, flavoured yogurt, hemp flour, baked goods, hemp milk, protein seed powder and seasoning sauce (Cerino et al., 2021; Rupasinghe et al., 2020). Although *Cannabis* seeds and its products are mostly used in today's food industry, *Cannabis* sprouts, leaves and flowers are also eaten raw in juices or in salads. They contain additional bioactive compounds (e.g., polyphenols and cannabinoids) not found, or less abundantly found in seeds (Cerino et al., 2021; Rupasinghe et al., 2020).

In our dataset, *Cannabis* alimentary use comprised 7.29% of all uses (Fig. 1 Supplementary data Table S2); 58.72% of them corresponded to traditional food and 41.28% to traditional drinks. As expected, the most used plant part for alimentary purposes are seeds (43.60%), which also proved to be significantly associated with alimentary use ($p < 0.0001$) (Supplementary data Table S3). Seeds are still considered as a good food source for elderly people throughout Asia because they contain plenty of

easy digestible protein and dietary roughage (Clarke and Merlin, 2013). Our analysis showed that traditionally seeds are most commonly pressed for oil (17.65%) or pickled (14.71%). We also found references of their use in beverages, as a condiment, they are roasted, or processed in flour or curd. Leaves are the second most used plant part for alimentary purposes (37.18%), mostly consumed in traditional beverages (e.g., *bhang*; 60.34%), but also fried, or otherwise included in the dishes.

3.5. Fibre and other uses

Regarding the fibre uses, as expected, the most likely used *Cannabis* parts are fibre, stem, and bark (grouped inside other plant parts and products; $p < 0.0001$), which represent over 90% of data entries in this category (Supplementary data Table S3). *Cannabis* fibres were most often used for making ropes (27.40%) and fabric (24.66%). Even though *Cannabis* used to be a very important fibre plant (Clarke and Merlin, 2013), in the CANNUSE database, fibre use represents only 3.82% of all data entries (Fig. 1 and Supplementary data Table S3). Many ethnobotanical papers included in the database almost exclusively focused on medicinal plants in the area, so the traditional uses of *Cannabis* fibres are probably underrepresented in our results. In the last decades, this use has almost disappeared because of the discovery of synthetic materials, but it remained strong in some areas, like China (Clarke and Merlin, 2013). In recent years it is again being rediscovered due to durability of fibres and sustainable production (Gedik and Avinc, 2020).

Besides the most known and common uses mentioned above, we also recorded *Cannabis* magicoreligious and cosmetic uses, use for firewood and other miscellaneous ones, which together represented 5.13% of all data entries (Fig. 1). Most frequently used parts in these cases are leaves (39.22%) and seeds (27.45%) (Supplementary data Table S2). Magicoreligious use represents 23.14% of reports in the category other uses. Due to the mind-altering purposes, *Cannabis* has been a vital element of many religious ceremonies. In India, *Cannabis* is considered a holy plant, and it is a vital element in many religious rituals, mainly regarding the worship of Lord Shiva. The traditional drink *bhang* is often consumed during Indian festivals like Shivratri and Holi (Chopra and Chopra, 1957). Due to the high content of oil (especially polyunsaturated fatty acids) in seeds, *Cannabis* was also used in traditional cosmetic preparations (16.53%), especially in hair care. A study in 2005 (Callaway et al., 2005) found that the addition of modest amounts of hemp seed oil in everyday diet significantly improved the strength of fingernails and hair thickness. Although *Cannabis* is an herbaceous plant, its stems are also used for firewood or torch wood (13.22%), especially in Pakistan, where 62.5% of records comes from. The other 47.11% of data entries in this category are comprised of miscellaneous uses. Leaves and above-ground parts of *Cannabis* were used in apiculture, pest control and for fish poisoning, while oil made from seeds was used for production of soaps, paints, varnishes and for lightning.

3.6. Potential toxic effects

Even though in many regions of the world *Cannabis* is considered a valuable medicinal plant, it is considered toxic (or toxic if used in excess) in others. There are still opposing opinions about the extent of negative effects of *Cannabis* consumptions between scientists. Results of some studies indicate that long-term consumption of *Cannabis* has harmful effects on developing brain (e.g., neuroanatomic changes, metabolic and neurotransmitter activity, and neuronal activation), especially in people with specific genetic polymorphisms, which indicates that *Cannabis* use can interact with genotype to increase the risk of mental health issues (Hurd et al., 2019). A recent review by Thomas et al. (2014) indicated adverse effects of *Cannabis* on cardiovascular activity (e.g., myocardial infarction, sudden cardiac death, cardiomyopathy, stroke, transient ischemic attack, and *Cannabis* arteritis). Additional adverse effects in other body systems, such as ophthalmological, gastrointestinal, respiratory, immune, and hormonal system were also connected with exposure to high THC concentrations, mainly related with recreational use. However, significant toxicity is infrequent in adults, intoxication symptoms are normally short-lived and do not pose a significant risk of death (Breijyeh et al., 2021; Cabral and Staab, 2005). Regarding our data, only 3.24% of data entries reported toxic effects. They were mostly caused using the inflorescence (42.86%) and leaf (40.82%). We found 45 side effects, the most frequent were hallucination, poisoning, drowsiness, nausea, and vomiting. Only one reference mentioned death.

Many references also stated that *Cannabis* was only considered toxic if used in excess. The importance of the correct dosage and negative consequences of extensive and prolonged abuse of *Cannabis* were well known in traditional medicine (Chopra and Chopra, 1957). We can find records that differentiate between early effects (reviving heat, exhilaration, improvement of complexion, excitement of imagination, appetite increase, aphrodisiac) and late effects of *Cannabis* consumption (refrigerant and sedative effect) in Pharmacographia Indica (Dymock et al., 1893). The authors also warned that prolonged use can cause unwanted negative effects like indigestion, wasting of the body, melancholy, impotence, and dropsy (swelling, accumulation of water). Today we know that cannabinoids display bell-shape dose-response curves (Jamontt et al., 2010; Zuardi et al., 2017), and so the correct dosing is crucial in therapeutic and recreational use to avoid undesired effects. The conflicting evidence of *Cannabis* effects are probably the reason why at the end of 2020 UNDOC Commission followed the WHO recommendation and removed *Cannabis* from the Schedule IV drug list, but it remained listed as a Schedule I drug (UNDOC, 2020).

4. Conclusion

Today, *Cannabis* is mostly associated to recreational use due to its mind-altering effects. However, this is not reflected in the dataset of the CANNUSE database analysed here, where 92% of data entries correspond to non-psychoactive uses. Over two thirds of this data are comprised of *Cannabis* medicinal uses – most of them human medicinal uses – representing treatments for 210 human ailments. Together, our study confirms that *Cannabis* shows a large number and diversity of traditional medicinal uses. The majority of data analysed here come from a determined geographic region (i.e., India and Pakistan), so the results obtained here could be biased towards the uses from those areas. The chemical composition of the plants used in certain regions is expected to vary, therefore the associations between plant parts and medicinal use could also be different in other areas of the world where *Cannabis* is traditionally used. Unfortunately, ethnobotanical papers rarely contain information about the chemical composition, or the cultivars of the plants studied, hence this information was not available. Regardless, describing the specific chemical components and the exact phytochemical pathways responsible for medicinal effects was beyond the scope of this paper. Our aim was to shed light to the less known traditional uses of *Cannabis* and connect them with the use of different plant parts on a global scale. We believe that this study revealed some new potential uses that could be further chemically and pharmacologically explored for potential drug development.

Many pharmaceutical companies are intensely working on developing new drugs with isolated natural products or crude extracts of *Cannabis*, almost exclusively based on inflorescences from commercial varieties. In contrast, references included in the CANNUSE database show that 89% of all traditional medicinal uses are related to other plant parts. *Cannabis* inflorescences are of great importance for drug development because of their high content of cannabinoids. However, other plant parts also contain a diverse composition of valuable secondary metabolites that could make them effective for treatment of a variety of illnesses. In this study, we prove that *Cannabis* parts are not randomly used in the traditional treatment of different body systems and ailments. Instead, our results clearly show that certain plant parts are significantly associated with particular body systems and ailments. Some of these relationships (e.g., inflorescences and treatment of nervous system) have

already been confirmed in previous clinical studies, but others (e.g., leaves for treatment of haemorrhoids; or seeds for treatment of musculoskeletal system disorders and traumas) still need to be further explored. As more information becomes available on *Cannabis* diversity (e.g., genetic, biochemical, and clinical studies) and more comprehensive ethnobotanical dataset is gathered (in terms of geographic regions and local landraces surveyed), the usefulness of the CANNUSE database is poised to be of much greater significance.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2021.114362.

Author contributions

T.G., J.V. and A.G. designed the research, M.B. and M.R. analysed the dataset, and M.B. and D.V. wrote the manuscript; all authors discussed the results and commented on the manuscript.

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