Increasing Delta-9-Tetrahydrocannabinol (Δ-9-THC) Content in Herbal Cannabis Over Time: Systematic Review and Meta-Analysis

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Abstract: *Aim*: The objective of this meta-analysis is to assess the data regarding changes in herbal cannabis potency over time (from 1970 to 2009).

Methods: Systematic searches of 17 electronic scientific databases identified studies on this topic, within which 21 case series studies satisfied our inclusion criteria of reporting the mean tetrahydrocannabinol (THC) value per number of samples per year. No language, publication date, publication type or status restrictions were imposed. The study selection and data extraction processes were performed independently but uniformly by two authors, included screening, determination of eligibility and inclusion of the eligible studies in the systematic review, and a meta-analysis of the results on THC content in herbal cannabis samples. We considered papers and not monographic scientific publications, rejecting all studies that were not focused on the subject of this review.

Results: Meta-analysis by year was performed on 21 studies containing 75 total mean THC observations from 1979 to 2009 using the random effects model. The results revealed much variability between studies. Further, there was a significant correlation between year and mean THC in herbal cannabis. The combined data indicated the correlation between year and mean THC in herbal cannabis, revealing a temporal trend of increasing potency (5% above the mean THC value in the Poisson regression analysis).

Conclusions: The results of the analysis suggest that there has been a recent and consistent increase in cannabis potency worldwide.

Keywords: Cannabis, marijuana, tetrahydrocannabinol, drug potency, drug efficacy, trend, THC content, THC concentration, meta-analysis.

INTRODUCTION

The cannabis market is the largest illicit drug market in terms of the global spread of cultivation, volume of production and number of consumers [1].

There is great interest in the subject, sometimes linked with apprehension about increasing drug potency and its effects on human health, as revealed by newspapers [2-5], government reports [6, 7], and scientific publications [8-11] despite the scarce availability of reliable data; existing information on cannabis is fragmented, non-standardized and not always based on scientific evidence.

Published data concerning the diffusion of high potency cannabis varieties and the level of increase in potency are poor worldwide; further, new and successful cultivation methods – which allow selection, cloning and the stimulation of the best plant varieties – exist in the drug market alongside imported, traditional and low psychotropic subspecies [12]. There is variability within and between publications with regards to the sourcing, sampling and analytical approaches to herbal cannabis.

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Herbal cannabis consists of the dried flowering, fruiting tops and leaves of the cannabis plant [13]. The aim of this meta-analysis is to summarize published results concerning the Δ-9-tetrahydrocannabinol (THC) content of cannabis[1] in order to determine the temporal trend in mean THC content over the period 1970 - 2009.

METHODS

The systematic review and meta-analysis shown here are new on this topic, even if a narrative review of nine publications has been published previously [14].

The sources used for guidance were the Cochrane Handbook [15] and the PRISMA guidelines [16].

[1]The *World Drug Report 2007,* United Nations Office on Drugs and Crime (available on http://www.unodc.org/unodc/en/data-and-analysis/WDR-2007.html) states that cannabis is produced for different end products:

- **Cannabis herb** comprises the flowering tops and leaves of the plant, which are smoked like tobacco using a variety of techniques. Depending on the region, cannabis herb is known under many different names, including 'marijuana, 'ganja', 'dagga', etc. A very potent form of cannabis herb is sinsemilla, the flowering tops of the unpollinated female plants.
- **Cannabis resin** consists of the secretions of the plant emitted in the flowering phase of its development. Depending on the region, cannabis resin is known as 'hashish' or as 'charas', etc.
- **Cannabis oil** (hashish oil) is an oily mixture resulting from extraction or distillation of the THC-rich parts of the cannabis plant.

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Literature search – A systematic literature search was carried out by consulting 17 electronic scientific databases including MEDLINE, TOXLINE, SCOPUS, The Cochrane Library, Web of Science, Directory of Open Access Journal; electronic editorial networks such as BMJ, Blackwell, Elsevier, Karger, Nature Publishing Group, Springer; electronic distributors such as OVID Journals and Swetswise; and governmental websites such as the UNODC (United Nations Office on Drugs and Crime) and the EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). Additional searches included bibliographies of retrieved papers and direct contact with experts (Mahmoud Elsohly, USA; Emanuela Licata, Italy) who provided data on the number of samples seized per year and the mean THC content per year.

Inclusion criteria – We considered all studies that included quantification and recording of the THC content in herbal cannabis samples found on the illicit as well as on the licit drug market. No language, publication date, publication type or status restrictions were imposed. We also used the PICOS approach [2] to select studies according to the objective of this review to provide evidence about the increasing Δ-9-(THC) [3] content in herbal cannabis.

Herbal cannabis samples with a known THC content were the population of interest; there were no limits on plant variety, geographic origin, cultivation methods (i.e. outdoor or indoor; cloning or pollination), plant stage at harvesting, type or conservation status of the sample at the time of chemical analysis, or modes of sourcing samples (i.e. seized or freely sold).

Study selection – This process (see the flow diagram in Fig. **1**) was performed independently but uniformly by two authors, and included screening, determination of eligibility and inclusion of the eligible studies in the systematic review, and meta-analysis of the results on THC content in herbal cannabis samples.

We considered papers and not monographic scientific publications, rejecting all studies that were not focused on the subject of this review, such as those concerning the toxic effects of cannabinoids on humans and animals, synthetic cannabinoids and their pharmacological properties, genetic features of the cannabis plant, social issues and drug policy on cannabis.

We also excluded studies that completely or partially lacked clear data, such as articles that reported the THC content not clearly attributable to the herbal form of cannabis (including experimental cultivation) or that presented results together as a range of different concentrations or periods of time.

No divergent opinions in including or excluding studies were encountered between the reviewers, resulting in 21 studies that were eligible for the systematic review and meta-analysis.

Data extraction – This process was performed by two reviewers independently, resolving disagreement by discussion. Repetitions of data from serial publications were rejected, retaining the last update. Two authors were contacted for further information. All the eligible, included studies were written in the English language.

The following information was extracted from each included article and summarized:

- characteristics of the publication such as authors, study design, year and type of publication, first and second objectives, results and conclusion of the report;
- details of the study such as duration and place of conducting the research, number of samples, mean percentage and standard deviation of THC (or THC content per sample) per year, features of samples (age, geographic and cultivation origin, mode of sourcing, aspect, cannabis variety), features of chemical analyses (sampling, method, technique).

Meta and Trend Analysis – We meta-analyzed the results of the included studies by year to take into account the evident temporal trend in the mean % of THC. Given the heterogeneity between studies we adopted a random effects model [17]. We used the I^2 statistic to quantify the degree of heterogeneity among studies [18]. I^2 values of 50% or more indicate a substantial level of heterogeneity. Meta-regression using year as the covariate was performed to assess whether a temporal trend could explain the heterogeneity. To quantify the trend a Poisson regression was performed.

RESULTS AND DISCUSSION

All the included studies [19-39] shown in the table below (Table **1**) were written in English and presented data on the THC content found in herbal cannabis samples in different years, depending on the date of the study.

Most were for an isolated geographic area and period of time and do not describe relevant information about the features (i.e. conservation status and age of the sample) of the analyzed herbal cannabis samples. The percentage of studies reporting the relevant sample details is shown in the bar chart (Fig. **2**) that portrays, for example: 13% of the included studies specify the origin of the sample, 8% do not; 11% indicates the mode of sample acquisition, 10% do not.

For published evidence on the temporal trend in potency, we carried out a meta-analysis of the extracted herbal cannabis data from studies in which the standard deviation around the mean THC value per year was available. Meta-analysis was performed by year on 75 total mean THC observations from 1970 to 2009 using the random effect model. Meta-regression was performed on the same dataset, using year as the covariate.

The results revealed great variability within studies (I^2 = 99.91%) and a significant association (from the meta-regression) (p value < 0.0001) between the mean THC in herbal cannabis and year (coef. 0.214; 95% CI = 0.163–0.266). A summary of the results from the meta-analysis and relative 95% CI per year are shown in Table **2** and Fig. (**3**).

[2]The PICOS (acronym of *Population, Interventions, Comparator, Outcomes, Study Design*) is a structured approach for framing relevant and precise questions, which are often complex and time-consuming, that can be answered in a systematic review.

[3]Systematic (IUPAC) name: (−)-(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol. Abbreviation: THC. Formula: $C_{21}H_{30}O_2$.

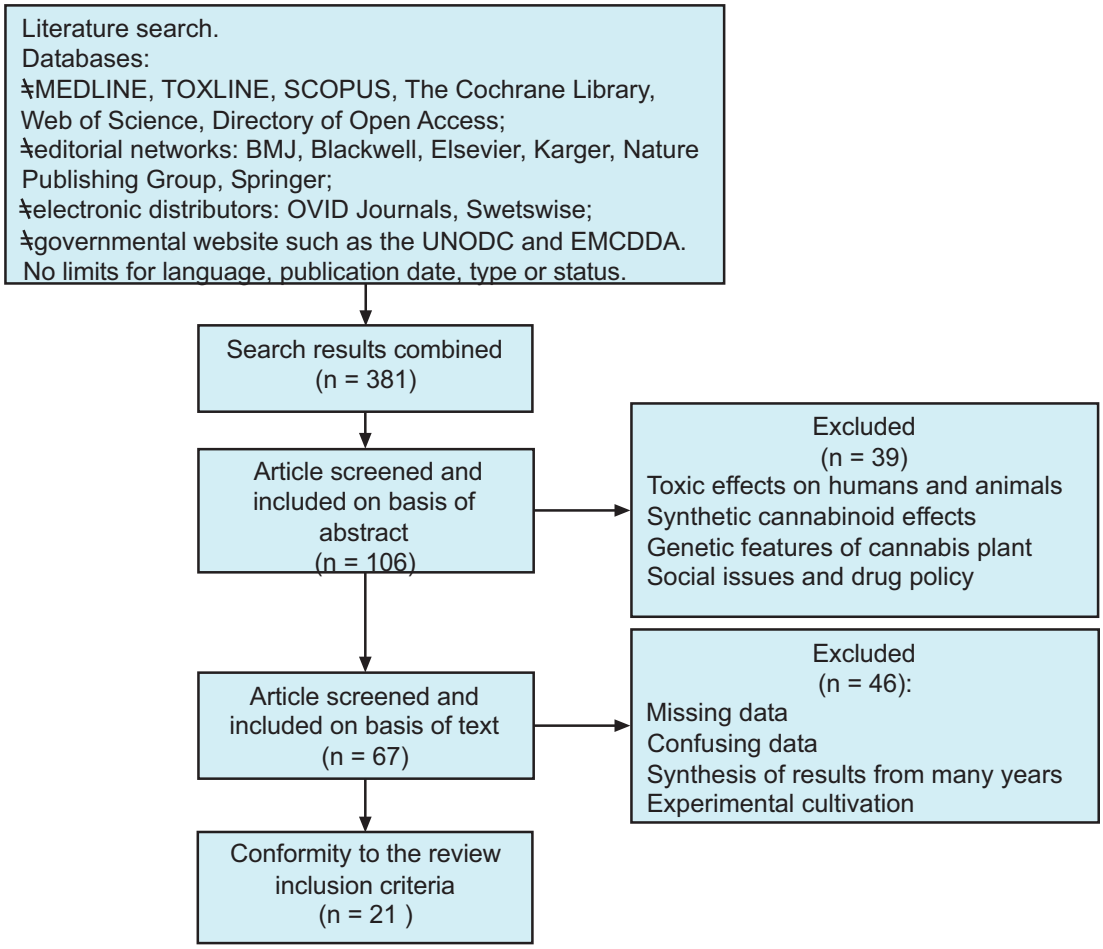

Fig. (1). Flow diagram of study selection process concerning the THC content found in in herbal cannabis samples in a period of time.

The combined data from the 21 included studies indicated an increasing temporal trend in potency (Fig. **4**); the Poisson regression suggested an average increase in the mean THC value of 4.694% (95% CI 3.129–6.283). Of course, this is just an indication of the overall increase, but it is clear (from Fig. **4**) that this rise in mean THC seems to have been more rapid in the last decade.

Analysis of the trend (Tables **3** and **4**; Fig. **4**) according to geographical zone indicated a smaller increase in Europe (2.799%, 95% CI 1.157–4.467; significant at p = 0.001) compared to the rest of the world, almost totally represented by the U.S. (5.279%, 95% CI 3.590–6.996), but this may reflect the fact that the data from Europe started with a higher mean THC.

The European studies indicated a very high mean THC level in recent years with little variability around this mean, especially in The Netherlands; the cannabis potency phenomenon was, on the other hand, characterized by minor fluctuations and relative stability from 1975 to 1989 in other European countries such as Great Britain and Ireland; data from Greece and Denmark, although scarce, revealed a constantly low mean THC value while Italy, particularly the northern part, showed a clear increasing temporal trend.

No other information concerning Europe was obtained from the publications fulfilling the eligibility criteria for the present review; it must also be noted that the cannabis reports on governmental websites are the responsibility of single research groups in each country.

With regard to the rest of the countries (particularly U.S.A.), an evident rise in the mean THC content in herbal cannabis seizure samples from 1997 to 2009, with large variability around this mean value, was reported by the Mississippi University Project [40].

The results of this systematic review suggest that the herbal cannabis market is changing worldwide towards an increasing level of THC content. Further, this increase is not constant and does not exceed 5% globally. According to some [41] it would be right to admit a doubling of potency over the years, possibly due to the increased availability of intensively grown indoor herbal cannabis, but not that cannabis is 25 times stronger than it was a decade ago [4].

On the other hand it should be considered that data from the included studies could present an underestimation of the true mean THC value of commercial herbal cannabis because of the freshness and age of samples from harvesting, their composition before chemical analysis, and the sampling method for the analysis. It is actually well known that the THC content in cannabis can vary in relation to environmental factors such as light, temperature and the humidity during plant growth and sample storage, as well as being influenced by genetic features [42-45].

Table 1. ID and Characteristics of Included Articles (n= 21); in All Cases the Design was Observational (Case Series) and the Language was English

ID	Authors	Year	Journals with Impact Factor	Other Publication/Other Type of Journals
1	Bertol E and Mari F [a]	1980		Bulletin on Narcotics
2	Baker PB *et al.* [b]	1980		Bulletin on Narcotics
3	Baker PB *et al.* [c]	1982		Bulletin on Narcotics
4	Felby S and Nielsen E [d]	1985		Bulletin on Narcotics
5	Pitts JE *et al.* [e]	1990	J Pharmacol	
6	Kaa E [f]	1989	Z Rechtsmed	
7	Stefanidou M *et al.* [g]	2000	Chem Pharm Bull	
8	Pijlman FT *et al.* [h]	2005	Addiction Biology	
9	Marshman JA *et al.* [i]	1976		Bulletin on Narcotics
10	ElSohly MA ∗ [j]	2009		Marijuana Potency Monitoring Project. Report 104
11	Potter DJ *et al.* [k]	2008	J Forensic Sci	
12	Bone C and Waldron SJ [l]	1997		Bulletin on Narcotics
13	- [m]	2005		EMCDDA Statistical Bulletin
14	- [n]	2006		EMCDDA Statistical Bulletin
15	- [o]	2007		EMCDDA Statistical Bulletin
16	- [p]	2008		EMCDDA Statistical Bulletin
17	- [q]	2009		EMCDDA Statistical Bulletin
18	Lopez de Oliveira *et al.* [r]	2008	Forensic Toxicol	
19	Stefanidou M *et al.* [s]	1998	Forensic Science Intern	
20	Chiesa EP and Rondina RV [t]	1973	J Pharm Pharmac	
21	Licata M *et al.* ∗ [u]	2005		Ann Ist Super Sanità

∗ = Data updated in 2010 directly from the authors of the original article.

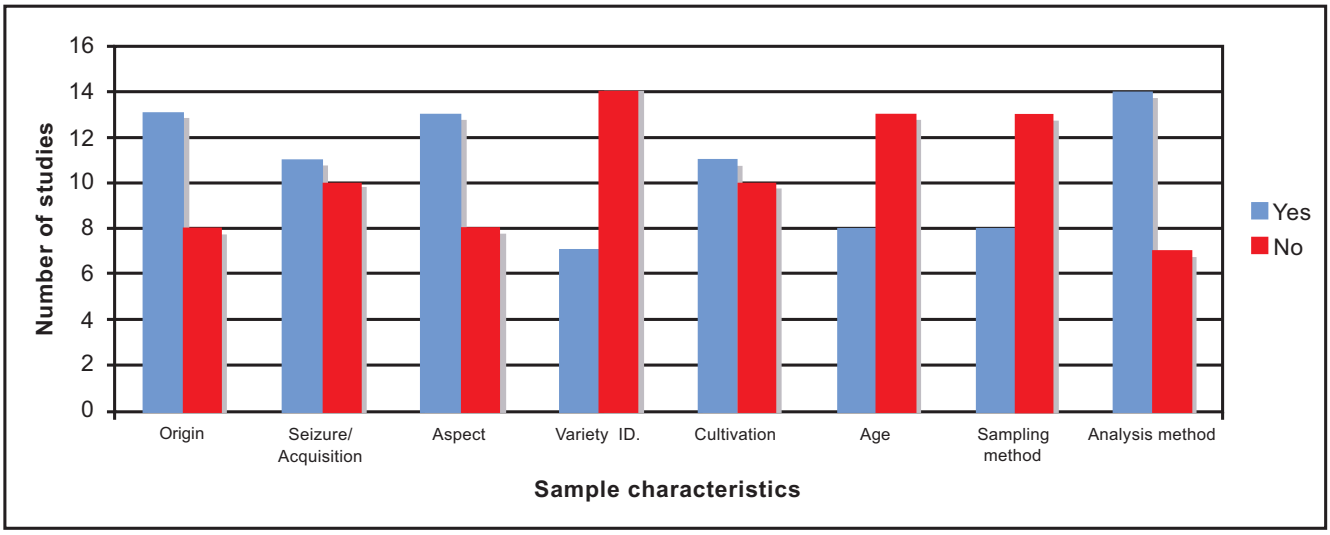

Fig. (2). Bar chart of samples features reported in percentage into the included studies.

The mean THC value could be limited due to the peculiarities of cannabis samples and to methodological differences between laboratories, even though the analytical techniques are the same worldwide, involving gas or liquid chromatography eventually coupled with mass spectrometry [46, 47].

[a] [19]; [b] [20]; [c] [21]; [d] [22]; [e] [23]; [f] [24]; [g] [25]; [h] [26]; [i] [27]; [j] [28]; [k] [29]; [l] [30]; [m] [31]; [n] [32]; [o] [33]; [p] [34]; [q] [35]; [r] [36]; [s] [37]; [t] [38]; [u] [39].

Table 2. Results of Meta-Analysis on 75 Mean THC Observations from Studies in which the Standard Deviation Around the Mean THC Value Per Year was Available

Year Reported	Mean THC Content Per Year	95% IC	Weight of Studies	Number of Studies	Number of Samples
1970	0,93	0,615 - 1,245	1,36	1	28
1971	2,22	1,345 - 3,095	1,34	1	15
1972	1,17	0,753 – 1,587	1,35	1	34
1973	1,436	0,175 – 2,697	2,67	2	37
1974	1,27	0,949 – 1,591	1,36	1	67
1975	2,113	0,346 - 4,571	2,7	2	130
1976	2,371	0,322 – 4,42	4,04	3	150
1977	0,66	0,527 – 0,793	1,36	1	138
1978	2,408	0,281 – 4,534	2,71	2	212
1979	2,042	0,997 – 3,087	4,07	3	366
1980	3,149	0,955 – 5,343	2,7	2	197
1981	3,567	1,01 – 6,124	2,7	2	300
1982	3,04	2,832 – 3,248	1,36	1	486
1983	2,396	0,74 – 4,053	2,72	2	1283
1984	4,751	1,822 – 7,679	2,69	2	1099
1985	3,412	1,893 – 4,932	2,64	2	1563
1986	3,435	1,191 – 5,678	2,71	2	1569
1987	3,025	2,631 – 3,42	2,7	2	1701
1988	2,552	0,583 – 4,521	4,07	3	2234
1989	3,897	2,193 – 5,601	2,71	2	1321
1990	3,35	3,191 – 3,509	1,36	1	1263
1991	3	2,892 - 3,108	1,36	1	2507
1992	3,1	3,017 – 3,183	1,36	1	3540
1993	3,29	3,203 – 3,377	1,36	1	3353
1994	3,48	3,398 – 3,563	1,36	1	3278
1995	3,74	3,678 – 3,802	1,36	1	4732
1996	2,885	0,546 – 5,225	2,71	2	2457
1997	4,53	4,396 – 4,664	1,36	1	2455
1998	3,058	0,351 – 5,766	2,71	2	2293
1999	3,274	0,738 – 5,81	2,71	2	2671
2000	6,265	4,058 – 8,472	3,95	3	3225
2001	6,047	2,24 – 9,854	4,07	3	2884
2002	9,543	4,005 – 15,081	4,06	3	2596
2003	12,043	5,159 – 18,927	3,41	3	2636
2004	12,422	4,645 – 20,2	3,87	3	2760
2005	8,862	5,206 – 12,517	2,6	2	2985
2006	7,51	7,299 – 7,721	2,49	2	2870
2007	6,958	2,562 – 11,354	4,03	3	3118
2008	8,625	8,389 – 8,861	2,64	2	2752
2009	9,75	7,956 – 11,544	1,29	1	82

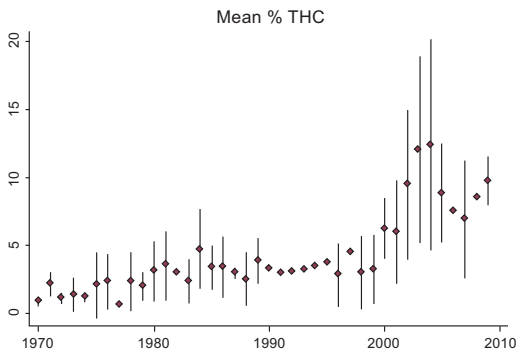

Fig. (3). Per-year meta-analysis graph showing the mean THC value with 95% CI.

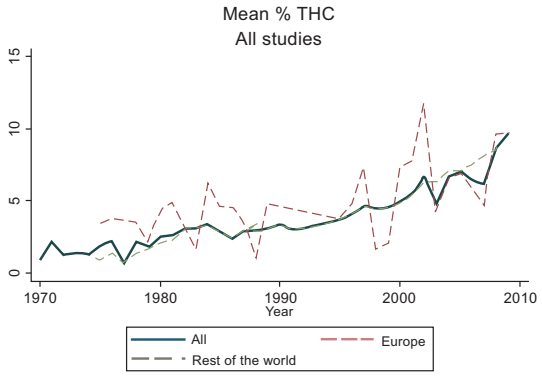

Fig. (4). Time trend of the mean THC value for all samples and disaggregated by zone.

Table 3. Data from All Included Studies Used for Time Trend Analysis

All Studies				
Place	**Authors**	**Year**	**Mean %THC**	**Samples**
USA	El Sohly	1970	0,930	28
USA	El Sohly	1971	2,220	15
USA	El Sohly	1972	1,170	34
USA + Argentine	Chiesa *et al*. + El Sohly	1973	1,383	61
USA	El Sohly	1974	1,270	67
USA + UK	El Sohly + Baker *et al*. (1)	1975	1,855	130
USA + Jamaica + UK	El Sohly + Marshman *et al*. + Baker *et al*.	1976	2,196	150
USA	El Sohly	1977	0,660	138
USA + UK	El Sohly + Baker *et al*. (1)	1978	2,210	212
USA + UK + Italy	El Sohly + Baker *et al*. (2) + Bertol *et al*.	1979	1,841	366
USA + UK	El Sohly + Baker *et al*. (2)	1980	2,560	197
USA + UK	El Sohly + Baker *et al*. (2)	1981	2,647	300
USA	El Sohly	1982	3,040	486
USA + Denmark	El Sohly + Felby *et al*.	1983	3,140	1283
USA + UK + IR	El Sohly + Pittis *et al*.	1984	3,400	1099
USA + UK + IR	El Sohly + Pittis *et al*.	1985	2,884	1563
USA + UK + IR	El Sohly + Pittis *et al*.	1986	2,390	1569
USA + UK + IR	El Sohly + Pittis *et al*.	1987	2,948	1701
USA + UK + IR + Denmark	El Sohly	1988	2,864	2234
USA + UK + IR	El Sohly + Pittis *et al*.	1989	3,125	1321
USA	El Sohly	1990	3,350	1263
USA	El Sohly	1991	3,000	2507
USA	El Sohly	1992	3,100	3540
USA	El Sohly	1993	3,290	3353
USA	El Sohly	1994	3,480	3278
USA + UK	El Sohly + Bone *et al*.	1995	3,740	4802
USA + UK + Greece	El Sohly + Bone *et al*. + Stefanidou *et al*.	1996	4,102	2532
USA + UK	El Sohly + Bone *et al*.	1997	4,694	2595
USA + Greece	El Sohly + Stefanidou *et al*.	1998	4,394	2293
USA + Italy	El Sohly + Licata *et al*.	1999	4,536	2671
USA + Italy + The Netherlands	El Sohly + Licata *et al*. + Pijlman *et al*.	2000	4,954	3225
USA + Italy + The Netherlands	El Sohly + Licata *et al*. + Pijlman *et al*.	2001	5,469	2884
USA + Italy + The Netherlands	El Sohly + Licata *et al*. + Pijlman *et al*.	2002	6,767	2596
Usa + Europe + Italy + The Netherlands	El Sohly + EMCDDA + Licata *et al*. + Pijlman *et al*.	2003	4,680	8748
Usa + Europe + Italy + The Netherlands	El Sohly + EMCDDA + Licata *et al*. + Pijlman *et al*.	2004	6,775	6080
USA + Europe + Italy + UK	El Sohly + EMCDDA + Licata *et al*. + Potter *et al*.	2005	7,048	6416
USA + Europe + Italy	El Sohly + EMCDDA + Licata *et al*.	2006	6,512	6902
USA + Europe + Brazil + Italy	El Sohly + EMCDDA + Lopez *et al*. + Licat *et al*.	2007	6,174	6810
USA + Italy	El Sohly + Licata *et al*.	2008	8,632	2752
Italy	Licata *et al*.	2009	9,750	82

Table 4. Data from European Studies Used for Time Trend Analysis

Europe				
Place	**Authors**	**Year**	**Mean %THC**	**Samples**
UK	Baker, *et al*. (1)	1975	3,400	50
UK	Baker, *et al*. (1)	1976	3,800	50
UK	Baker, *et al*. (1)	1978	3,500	86
UK + Italy	Baker, *et al*. (2) + Bertol *et al*.	1979	2,099	146
UK	Baker, *et al*. (2)	1980	4,300	44
UK	Baker, *et al*. (2)	1981	4,900	41
Denmark	Felby, *et al*.	1983	1,550	76
UK + IR	Pittis, *et al*.	1984	6,300	33
UK + IR	Pittis, *et al*.	1985	4,500	23
UK + IR	Pittis, *et al*.	1986	4,600	55
UK + IR	Pittis, *et al*.	1987	3,500	24
UK + IR + Denmark	Pittis *et al*. + Kaa *et al*.	1988	1,024	444
UK + IR	Pittis, *et al*.	1989	4,800	49
UK	Bone *et al*.	1995	3,766	70
UK + Greece	Bone *et al*. + Stefanidou *et al*.	1996	4,793	111
UK	Bone *et al*.	1997	7,566	140
Greece	Stefanidou, *et al*.	1998	1,667	30
Italy	Licata *et al*.	1999	1,962	14
Italy + The Netherlands	Licata *et al*. + Pijlman *et al*.	2000	7,314	111
Italy + The Netherlands	Licata *et al*. + Pijlman *et al*.	2001	7,748	188
Italy + The Netherlands	Licata *et al*. + Pijlman *et al*.	2002	11,778	204
Europe + Italy + The Netherlands	EMCDDA + Licata *et al*. + Pijlman *et al*.	2003	4,040	6251
Europe + Italy + The Netherlands	EMCDDA + Licata *et al*. + Pijlman *et al*.	2004	6,538	3472
Europe + UK + Italy	EMCDDA + Licata *et al*. + Potter *et al*.	2005	6,944	3465
Europe + Italy	EMCDDA + Licata *et al*.	2006	5,807	4046
Europe + Italy	EMCDDA + Licata *et al*.	2007	4,581	3738
Italy	Licata *et al*.	2008	9,563	64
Italy	Licata *et al*.	2009	9,750	82

To overcome the methodological limits for cannabis samples, recommendations for the standardization of analytical procedures have recently been proposed by United Nations Office on Drugs and Crime [48]. We also hope for an alignment of the interested nations with regular monitoring of the cannabis market to enable constant tracking of the THC temporal trend in accordance with validated guidelines on sample classification, storage, sampling and analytical methods, and the data required from the analyses.

Systematic reviews and the meta-analysis of data from heterogeneous case series studies can be complex. On the other hand they are useful to outline the shape of a phenomenon, as in the case of cannabis, concerning an increasing temporal trend in the potency of this drug.

Key Learning Objectives:

- The cannabis market is the largest illicit drug market in terms of the global spread of cultivation, the volume of production and the number of consumers.
- The amount of the main active constituent of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), naturally depends on the influence that factors such as genotype, plant age and environment have on the biosynthesis of cannabinoids.
- The herbal form of cannabis (i.e. flowering tops and leaves of the plant, which are smoked like tobacco) is traditionally known to have a lower level of Δ^9-THC (very rarely exceeding 5%) in comparison with other resin-type cannabis preparations such as hashish (generally up to 20%) and hash oil (sometimes even above 50%).
- Significantly higher THC concentrations in herbal cannabis were recently documented in the literature.
- The availability of a more THC-concentrated form of herbal cannabis could cause an increase in the total amount of THC consumed, with foreseeable consequences for public health.

Future Research Questions:

- The herbal cannabis market is changing toward an increasing tetrahydrocannabinol (THC) content, although published international data concerning the diffusion of such potent varieties and the level of increase in potency are poor: existing information on cannabis is fragmented, non-standardized and not always based on scientific evidence.
- Continuous, worldwide tracking of herbal cannabis's THC level in accordance with validated guidelines on sampling, sample classification, storage and analytical methods, and the data obtained from analysis, could allow countries interested in the monitoring of the cannabis market to pool their resources to greater effect.
- Clear information about drug potency could be useful for societal and political decisions relating to public health (i.e. health educational programmes for youth, prevention campaigns, prohibition measurements) and also for judicial verdicts concerning illegal traffic and for criminalistics.
- Scientific investigations on cannabis through genetic and chemical analyses could be undertaken to describe and explain the natural and/or artificial mechanisms behind the potency increase with the aim of controlling the drug market more effectively.

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CONFLICT OF INTEREST

This paper does not have duplicate publication problems, financial or other relationships that could give rise to conflicts of interest; further, the manuscript does not reproduce published material, illustrations or report sensitive personal information about identifiable persons.

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