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THE CONTENT OF BASIC CANNABINOIDS AND THEIR MUTUAL RATIOS IN *CANNABIS SATIVA* L. PLANT

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Cannabinoids are typical chemical ingredients of a Cannabis sativa L. plant. The main psychoactive ingredient of this plant is Δ^9-tetrahydrocannabinol, whose content mostly determines the strength or potential of a cannabis product. In addition to this ingredient, the forensic analysis also includes determination of the presence and content of cannabidiol and cannabinol. Over the last couple of decades, there have been changes in chemical composition of cannabis products in many countries, and they manifest through the increase of total psychoactive potential. Monitoring of basic cannabinoids content and their mutual ratios, processed in this paper, has shown that there is a growing number of samples with high tetrahydrocannabinol (THC) content, while the cannabidiol (CBD) content is very low or is not present in samples at all. The THC/CBD ratio also confirms changes in plant chemotype in terms of increasing total psychoactive potential of a cannabis plant.

Keywords: cannabinoids, Δ^9-tetrahydrocannabinol, cannabidiol, cannabinol.

INTRODUCTION

A cannabis plant (lat. *Cannabis sativa* L.) is one of the oldest cultivated plants in the world. Throughout history, it has been grown for various purposes (for example stems are used for fiber and paper production, seeds can be used for animal food or can be used to make seed oil, and there are many other products that are known) (1). A long time ago, cannabis products were used for medical purposes, while such practice was not present in official medicine of the twentieth century although its effectiveness for treating various diseases has been well known (1, 2). An increased level of interest for research in the field of its use in medicine came after the discovery of endocannabinoid system (including CB1 and CB2 cannabinoid receptors) which interacts with cannabis plant ingredients (3).

Flower tops and leaves contain a psychoactive substance, and very often are used for the production of illegal drug products (marijuana, hashish, and cannabis oil). The simplest illegal cannabis product, dried plant material (also known as marijuana), is produced in almost every country, while the production of cannabis resin, better known as hashish, is limited to several countries in North Africa, Middle East, and South-West Asia. Europe has been one of the major consumers of cannabis resin for long, but lately it has been recorded that herbal cannabis has been prevalent in many countries (4).

The cannabis plant is the most common type of illegal drug in the Republic of Srpska, where over 90% of confiscated illegal drugs is marijuana, whereas cannabis resin (hashish) and cannabis oil are rare. Lately, cannabis oil has been present because some patients

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purchase it for medical reasons, even though cannabis products still have not been approved for therapeutic and medical purposes.

Cannabis plant contains more than 500 chemical compounds, 104 of which belong to the group of terpenophenolic compounds, known as cannabinoids (5). For forensic purposes, the content of three basic cannabinoids is determined in a plant and its products: Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN). THC is the main psychoactive ingredient, on whose content the potential of cannabis products is usually assessed. Furthermore, it is known that illegal cannabis samples have low CBD content, which has the ability to reduce psychoactive effects of THC. Over the last couple of years, it has been noted that CBD concentration is still decreasing, resulting in the change of THC/CBD ratio (6). Cannabinol (CBN) is not present in significant quantities in a fresh plant, but it is created as a product of THC degradation when the picked plant material has been stored, so the CBN/THC ratio can be used for age assessment of plant samples (7-9). The content and mutual ratios of basic cannabinoids can be used to determine the chemical phenotype (chemotype) of a plant, in order to distinguish the so-called drug-type or fiber-type plants (10-12). However, the practice has shown that those parameters are insufficient for precise determination a certain cannabis plant type and can cause uncertainties in court proceedings. This issue can be solved by applying of a more detailed ingredient analysis, which would include a greater number of cannabinoids and some other compounds (terpenes, for example) which would improve determination of a chemical profile and plant type characterization (2,13). Consequently, the process of differentiation in forensic practice between drug-type and fiber-type plants does not completely rely on chemical characterization based on mutual ratios of cannabinoids. Content of a psychoactive ingredient is crucial to assess if a plant can be used as a drug. The chemotype index calculated according to mutual ratios of basic cannabinoids is usually used to determine a plant type for growing for industrial purposes, where, aside from chemotype, the content of psychoactive ingredients is also taken into account. For example, most European countries allow growing of a so-called fiber-type cannabis plant, with a chemotype index lower than 1 and THC content up to 0.2% (14).

As an indicator what is currently used in public, the monitoring process for potential of illegal cannabis products is important to raise awareness on negative health effects, especially when more potent products are used (6). The use of cannabis products for recreational purposes has negative consequences on a person`s health, particularly in early adolescence, and these consequences are generally manifested by affecting the brain, lungs and vascular system. Increase in the treatment of cannabis use disorders correlates with the fact that high-potency cannabis products pose a greater health risk for the users (15, 16). An increase in visits to medical institutions has been recorded for adolescents (aged 15-17), related to marijuana use, in almost 50% of cases from 2005 to 2010 (17), which matches with an increase in cannabis potential over that period of time (16).

The aim of this paper is to provide an insight and assessment of the trends in the Republic of Srpska, from the total psychoactive potential of cannabis samples point of view and the change of cannabis plant chemotype through time, and as well as to provide a comparison with state and trends in other countries.

EXPERIMENTAL

Plant material

The samples confiscated in the Republic of Srpska from 1999 to 2008 and from 2011 to 2016 were analyzed at the chemical laboratory of the Forensic Unit at the Republic of Srpska Ministry of the Interior. Quantitative analysis of a sufficient number of samples was not carried out in 2009 and 2010, so those years were not included in this study.

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In total, 3718 samples of plant material of different forms were analyzed: dried plant tops, dried and fragmented plant material (marijuana), content of improvised cigarettes ("joint") and fresh plant. The samples were kept at room temperature, in dark spaces.

The samples of plant material were not classified according to their origin (local or imported), way of growing (indoor or outdoor), type (sinsemilla, industrial hemp, etc.), because these data for seized illegal samples are not always available, and it is not easy to assess them according to their appearance, especially when a sample is in a form of a fragmented plant material prepared either for market distribution or for usage.

It is known that the content of cannabinoids varies in plant samples, depending on the plant maturity degree, age of samples (how long it was stored after the picking process or when it was delivered to a laboratory compared to the time of confiscation), also composition of a sample (share of certain plant parts: stem bits, leaves or flower tops). Because of that, the samples were prepared depending on their form. Where possible, the plant tops, as a representative, were selected. Before the sample was taken for further analysis, the dried plant material from which seeds and stem parts were previously removed, was fragmented and homogenized. When taking samples for the analysis from improvised cigarettes, the tobacco was removed, if it was present. The fresh plants were dried at room temperature for 2 to 3 days until the leaves became brittle (14). Chloroform (99-99.4% purity) was used for the extraction of the plant samples.

Determination of chemical compositions

The analysis of basic cannabinoids was conducted using gas chromatograph with a flame ionization detector (GC-FID). The instrument used from 1999 to 2008 was the GC-17A (Shimadzu), and from 2011 to 2016 it was the GC Trace (Thermo Scientific). The reference standards of Altech® and Lipomed® were used for the process of identification and quantification of basic cannabinoids.

The operating conditions for the instruments were: injector temperature: 280 °C, carrier gas flow (N_2): 2 ml min^{-1}, temperature of the chromatographic oven: 260 °C (isothermally). The capillary column with a stationary phase of 5% diphenyl and 95% dimethylpolysiloxane is used for the process of separation of components, with the elution order of basic cannabinoids: cannabidiol, tetrahydrocannabinol, and cannabinol.

Identification of cannabinoids in the samples was done based on the retention time (Rt) of an individual cannabinoid in previously analyzed referent standard solutions of basic cannabinoids, whereas the quantitative analysis of basic cannabinoids was conducted based on the external standard method.

The data obtained from this analysis (percentage content of THC, CBD, and CBN) and by calculation (mutual ratios of basic cannabinoids) were processed with Microsoft Excel 2016.

RESULTS AND DISCUSSION

Content of cannabinoids

The total content of cannabinoids in plant samples was determined with the gas chromatographic analysis, which includes neutral cannabinoids and cannabinoid acids. In fact, the process of decarboxylation of cannabinoid acids into neutral cannabinoids occurs in the injector under the influence of high temperature (13). Content of cannabinoids is presented in a form of percentage of an individual cannabinoid in a dry weight plant material, as is common in forensic practice.

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Apart from occasional variations, the average concentration of the psychoactive ingredient THC (so-called average annual potential), has an increasing trend over time (Figure 1).

In total, the potential of illegal cannabis plant material is increasing, from 1.95% THC in 1999 to 4.95% in 2016, with reaching the maximum in the year 2013 (5.91% THC). It has been shown, by monitoring the prevalence of high-potency cannabis samples through time, that the share of high-potency samples (THC > 10%) increases over time, while the number of low-potency samples (THC < 2%) decreases, resulting in total increase of the average annual potential of the seized cannabis plant material samples over the years. The samples with 2 - 5% THC are still the most numerous ones and their share is relatively stable in time (18).

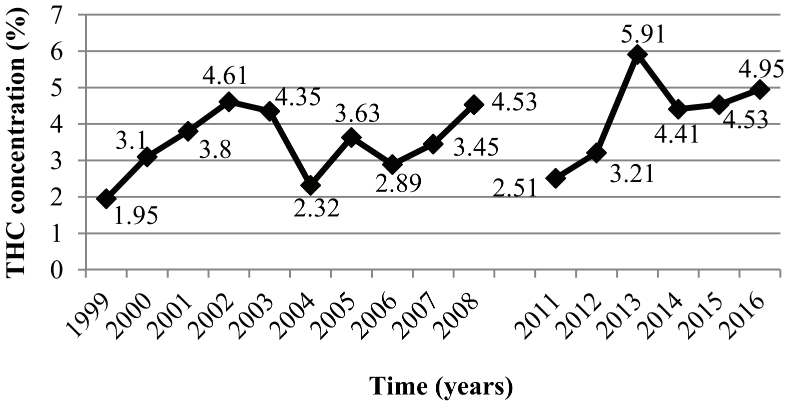

Figure 1. Diagram of average THC concentration, specified for every year

While monitoring the CBD content in the samples, it is clear that its concentration is decreasing in the last couple of years (Figure 2), from approximately 0.5%, what the average was until the year 2012, to approximately 0.26% from 2013 to 2016.

At the same time, a greater number of samples with no CBD at all has been detected, which was not the case previously. CBD was regularly present in samples up to 2006; in 2007 it was determined that 3.6% samples did not contain CBD; in 2013, 6.7% samples did not contain CBD, while the number of samples without CBD increased up to 17.4% in 2014 and stayed like this to 2016.

As CBD has antipsychotic effects, in other words, it reduces the psychoactive potential of THC, which further decreases the recreational value of cannabis, so this means that the consumers who take cannabis without CBD can be exposed to greater risk because high-potency cannabis products without CBD have potential to be more damaging. Therefore, The United Nations Office on Drugs and Crime has recommended monitoring, not only the level of THC but also the level of CBD in the evaluations of cannabis potential (19).

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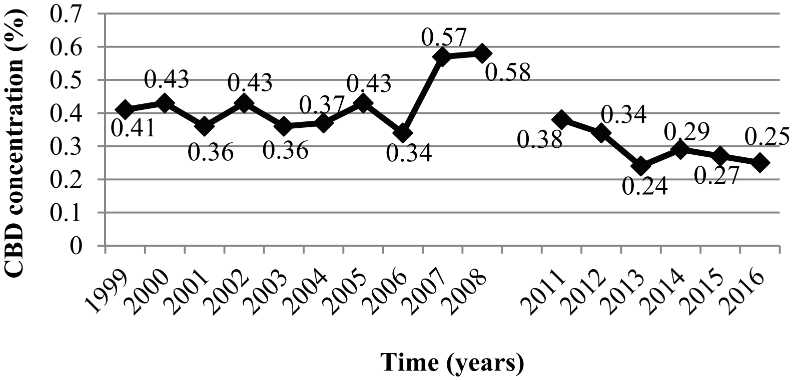

Figure 2. Diagram of average CBD concentration, specified for every year

Cannabinol (CBN) is not present in a fresh plant and is considered the primary product of THC degradation during the storing process of plant material, and it can also be used as an indicator for sample's age. Some studies have shown that the THC content reduces by half during one year of storage time of plant material at room temperature. However, the process of degradation has been greatly affected by the storage conditions, such as humidity and temperature, which should be taken into consideration during the assessment of sample's age based on CBN/THC ratio (7, 9). Nevertheless, it can be said that the general rule is: the higher the CBN/THC ratio, the samples are older.

Specified in the diagram of CBN concentration (Figure 3), it is evident that until the year 2007, the samples had lower CBN (from 0.07 to 0.2%), as opposed to the samples from a later date, when the CBN content spanned from 0.28 to 0.65%.

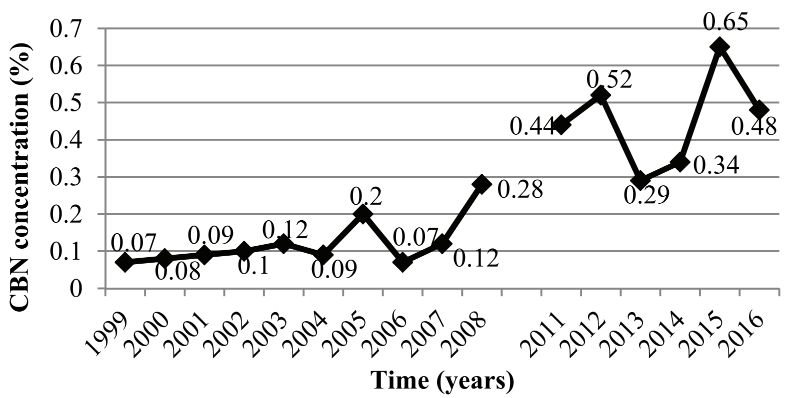

Figure 3. Diagram of average CBN concentration, specified for every year

A higher level of CBN concentration in samples delivered for analysis in recent years can be related to the dynamic of their delivery to laboratory. Previously, the samples were delivered to the laboratory straight away after the confiscation, so the analyzed cannabinoids content was truly representing the parameters at the time of seizure by the authorities. Later, with some changes made for certain low procedures, it has been noted that samples are delivered to laboratory months after the confiscation, and in the meantime,

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they are being kept in deposits, under different conditions. During that storage time, the THC degradation process occurs, so when the analysis takes place, THC is lower and the CBN content is higher than at the time of confiscation. Therefore, by analyzing the older cannabis samples we do not get a true representation of the cannabinoids content in samples at the time of confiscation. Hence, it is highly recommended to deliver the samples of cannabis products to the laboratory immediately after the confiscation, so the analysis result would represent a real state of the cannabinoids content at the time of confiscation, and it would be credible evidence for the purpose of court procedures.

Mutual ratios of basic cannabinoids

The characterization process of a plant for the purpose of distinguishing chemical phenotype (chemotype) is done based on the determination of basic cannabinoids mutual ratios, defined as the chemotype indexes. Waller, Fetterman and their colleagues (10, 12) suggested a characterization method based on a mutual ratio of basic cannabinoids:

$$Chemotype\ index = \frac{THC[\%] + CBN[\%]}{CBD[\%]} \quad [1]$$

The samples with this ratio greater than 1 were classified as "drug-type", and samples with ratios below 1 as "fiber-type" cannabis. Fetterman and colleagues also recognized two chemotypes based on the THC/CBD ratio, where the "drug-type" plant characterizes the ratio THC/CBD > 1, and the "fiber-type" plant characterizes the ratio THC/CBD < 1. Small and Beckstead recognized the intermediate chemotype. According to their system of classification, plants with higher THC/CBD ratio (considerably higher than 1) belong to chemotype I (drug-type), plants with THC/CBD ratio close to 1 belong to chemotype II (intermediate type), while plants with low THC/CBD ratio (considerably lower than 1) belong to chemotype III (fiber-type) (11).

In accordance with the system of classification by Hillig and Mahlberg, who used the THC/CBD logarithm ratio, three cannabis plant chemotypes can be determined: chemotype I - drug-type plants that have high $\log_{10}$(THC/CBD) > 1 (corresponding to the ratio THC/CBD > 10), chemotype II - intermediate-type plants have intermediate $\log_{10}$(THC/CBD) ratios between -0.6 and 1 (corresponding to the ratio of THC/CBD from 0.25 to 10). Chemotype III – fiber-type plants that have the $\log_{10}$(THC/CBD) < -0.7 (corresponding to the ratio of THC/CBD < 0.2) (11, 20).

Based on the content analysis of three basic cannabinoids in samples of plant materials, which are the main object of this study, the final calculation of their mutual ratios was carried out in all three previously specified ways, and the results are, along with the matching chemotype, presented in Table 1.

Based on the data from Table 1, it can be concluded that chemotype indexes, done according to Waller and Fetterman, correspond to the drug-type sample (chemotype I), while chemotype indexes have done according to the logarithmic value of the THC/CBD ratio place some samples into the intermediate-type cannabis (chemotype II).

Generally, it can be said that the use of chemotype indexes according to the logarithmic value of the THC/CBD ratio is in favor of the intermediate or fiber-type cannabis, while the use chemotype indexes according to Waller and Fetterman classifies most samples into drug-type.

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Table 1. The mutual ratio of basic cannabinoids and chemotype, specified for every year

Year	(THC + CBN)/CBD	THC/CBD	chemotype	$\log_{10}$ (THC/CBD)	chemotype
1999	4.93	4.76	I	0.68	II
2000	7.39	7.21	I	0.86	II
2001	10.80	10.56	I	1.02	I
2002	10.95	10.72	I	1.03	I
2003	12.42	12.08	I	1.08	I
2004	6.51	6.27	I	0.80	II
2005	8.91	8.44	I	0.93	II
2006	8.71	8.50	I	0.93	II
2007	6.26	6.05	I	0.78	II
2008	8.29	7.81	I	0.89	II
2011	7.76	6.61	I	0.82	II
2012	10.97	9.44	I	0.97	II
2013	25.83	24.63	I	1.39	I
2014	16.38	15.21	I	1.18	I
2015	19.18	16.78	I	1.22	I
2016	21.72	19.80	I	1.30	I

Taking into account that the chemotype index is determined in order to separate fiber-type plants grown for industrial purposes, from drug-type plants intended for abuse, further study and comparison of chemotype indexes obtained in different ways can contribute to adjustment and development of criteria for regulations of permitted growing, for which there is an increasing interest (21).

The mutual ratio of basic cannabinoids, especially THC and CBD, is significant because it can provide an insight into risks of psychotic effects, including the risks of developing an addiction. Cannabis products that have a higher content of psychoactive THC and lower content of antipsychotic CBD are more potent and pose a higher risk (22). Therefore, the THC/CBD ratio, in a certain way, represents the total psychoactive potential of a plant.

When the average annual concentrations of THC and CBD are studied, it can be noted the increasing THC and decreasing CBD trend (Figure 1 and 2), which further results in THC/CBD ratio change from approx. 5, as it was recorded in 1999, to approx. 25 in 2013 (Table 1 and Figure 4), and thus with that the increase of total cannabis potential.

This increasing trend of cannabis potential in the Republic of Srpska corresponds to those of international trends. Over the years, these trends have recorded a dramatic increase in the potential of cannabis products, resulting in a negative impact on a user's health (15, 23, 24).

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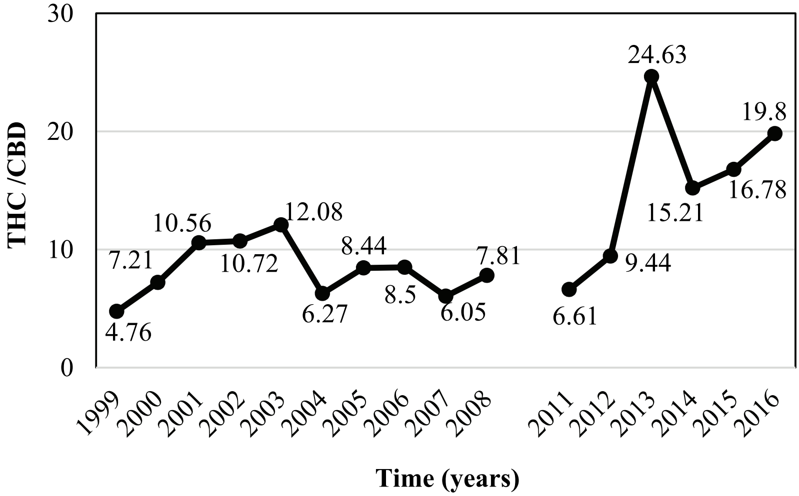

Figure 4. THC/CBD ratio, specified for every year

CONCLUSIONS

The content of basic cannabinoids in the cannabis plant material, confiscated in the Republic of Srpska, varies, but the trends were nonetheless recorded. The increase of the psychoactive ingredient tetrahydrocannabinol (THC) content in samples is evident. The average concentration of THC culminates with 5.91% THC in 2013, while it was only 1.95% THC in 1999.

On the other hand, the decrease of cannabidiol (CBD) content has been revealed in samples, from approx. 0.5% on average in 2012, to approx. 0.26% from 2013 to 2016. In addition, there has been a record of a growing number of samples without CBD, which was not the case previously.

The THC increase and CBD decrease have resulted in the change of THC/CBD ratio, from approx. 5 in 1999 to approx. 25 in 2013, what is reflected in the increase of total cannabis potential.

By comparing the chemotype index used to distinguish industrial plants from drug-type plants, it was revealed that the chemotype index defined by the $\log_{10}$(THC/CBD) ratio goes in favor of the intermediate-type and industrial-type plant, as opposed to the chemotype index defined according to (THC + CBN)/CBD or THC/CBD ratio. The studies that specialize in comparing the chemotype indexes obtained in different ways can contribute to improving criteria for regulations of cannabis plant permitted growing.

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