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Article

Inorganic element profile of medicinal *Cannabis* extracts consumed by pediatric patients

Lisia Maria Gobbo dos Santos[1]*, Santos Alves Vicentini Neto[1], Cristiane Barata-Silva[1], Mayssa de Andrade Fonseca[1], Carolina Duque Magalhães[1], Virgínia Martins Carvalho[2], Ernesto Díaz Rocha[2], Silvana do Couto Jacob[1]

[1]Departamento Química, Instituto Nacional de Controle de Qualidade em Saúde –INCQS/ Fiocruz, Rio de Janeiro, RJ, Brasil, [2]Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil

The increasing number of reports of web-based experiences on the success of *Cannabis*-based therapies in controlling seizures in children suffering from refractory epilepsy have led to efforts by governments and associations to a recent change in legislation. The Brazilian Health Regulatory Agency (ANVISA) allowed the import of *Cannabis* extracts in 2015 and the registration of the first industrialized drug in 2017. In 2019, ANVISA approved procedures for the granting of a Sanitary Authorization for manufacturing and imports, establishing marketing requirements, prescribing, dispensing, monitoring and surveillance of cannabis products for medicinal purposes. Similar to other consumer products of health concern, is necessary to ensure the quality and health safety of these products worldwide. The aim of the present study to evaluate the presence of As, Cd, Pb, Ni, Cu, Co, Cr and Mn present in *Cannabis* extracts and resins used in the treatment of pediatric patients with neurological diseases. Samples (48 national and 24 imported) were analyzed by Inductively Coupled Plasma Mass Spectrometry - ICP-MS. The imported extracts presented more homogeneous inorganic element values, while national extracts showed varied levels, thus indicating the highest health risk.

Keywords: Elements. Mass spectrometry. *Cannabis*. Public Health.

INTRODUCTION

A growing number of internet reports on successful *Cannabis*-based therapy experiences in the control of seizures in children with refractory epilepsy has influenced changes in both legislation and health regulations related to the cultivation and production of *Cannabis* derivatives (Suraev *et al*., 2017; Stone, 2014; Carvalho, 2017).

In the United States, legalization efforts have focused on the state level, with nine states allowing the use of *Cannabis* for medicinal and recreational purposes and another 29, for medicinal use only. In addition to the United States, other countries offer various levels of legality, including full legality (as in Uruguay), partial legality (in the Netherlands) or decriminalization statutes that nullify criminal penalties for possession and use of *Cannabis* for medical purposes (Fornadel *et al*., 2018).

In Brazil, after the Federal Council of Medicine regulated the prescription of cannabidiol (CBD), an active ingredient present in hemp-type *Cannabis* plants, in May 2015, the Brazilian National Health Surveillance Agency (ANVISA) authorized the personal importation of extracts of CBD-rich cannabis (ANVISA, 2015) and the national registration of the first industrialized drug containing phytocannabinoids under the trade name Mevatyl were observed in 2017, marketed in the United Kingdom as Sativex® (ANVISA, 2017). On December 9, 2019, Anvisa approved RDC No. 327, which provides procedures for granting health authorization for the manufacture and import of *Cannabis* products for medicinal purposes,

***Correspondence:** L. M. G. dos Santos. Setor de Elementos Inorgânicos. Departamento de Química, INCQS/Fiocruz. Av Brasil, 4365. CEP: 21040-900, Rio de Janeiro, RJ, Brasil. Phone: (0xx21) 38655258. E-mail: lisia.gobbo@incqs.fiocruz.br. ORCID: https://orcid.org/0000-0002-0652-7538. Carolina Duque Magalhães - ORCID: https://orcid.org/0000-0003-1636-5285

while also establishing requirements for its marketing, prescription, dispensing, monitoring and inspection, as well as other arrangements (ANVISA, 2019). According to the new RDC, the quality control of CBD-based products must obey the resolution set for herbal medicines, which includes the analysis of elemental impurities (ANVISA, 2014), such as inorganic contaminants (arsenic, cadmium and lead), since these elements accumulate in plant material through normal metabolic processes (Machado, 2001; Saidelles *et al.*, 2010).

Studies have reported that *Cannabis* is used to decontaminate soils rich in metallic elements, being an excellent soil phytoremediation agent, and that inorganic elements can be distributed throughout all parts of the plant, at concentrations well above those present in surrounding soil and waters (Rehman *et al.*, 2013; Santos *et al.*, 2017).

Some inorganic elements are considered toxic, such as As, Cd and Pb and are currently classified as carcinogens, with no safe exposure limit (Machado, 2001; Saidelles *et al.*, 2010). In addition, exposure control should be stricter for pediatric populations who use *Cannabis*, as they are more vulnerable and display enzymatic deficiencies, leading to quicker xenobiotic accumulation and intoxication processes at lower exposure doses (Suraev *et al.*, 2017; Stone, 2014).

However, not all inorganic elements are toxic, and some are beneficial or nutritional in nature, such as copper, whose recommended daily intake (RDI) varies from 340 to 890 µg/day for children aged 1-13 years old (ATSDR, 2004a), nickel, at an RDI of 200 to 300 µg/ day (WHO, 2000), manganese, one of the most abundant elements found in nature and that participates in many physiological and biochemical functions (Schafranskia *et al.*, 2019), at an RDI of 1.2-1.9 mg/day for children aged 1-13 years old (ATSDR, 2012), and cobalt, which is part of vitamin B12, essential for maintaining human health (0.16-1.0 mg/ kg body weight) (ATSDR, 2004b).

Inorganic elements present in *Cannabis* can be present in its medicinal extracts, and contaminant levels in medicinal extracts used in Brazil are still unknown. Therefore, the aim of the present study was to evaluate the inorganic element profiles (As, Cd, Pb, Ni, Cu, Co, Cr and Mn) of medicinal *Cannabis* extracts used in the treatment of pediatric patients with neurological diseases monitored in a safety assessment project at the Pharmacy Faculty, a part of the Federal University of Rio de Janeiro.

MATERIAL AND METHODS

Reagents and solutions

All reagents were of analytical grade. Deionized water produced with a Milli-Q® system (Bedford, MA, USA) was used to prepare all solutions. An ICP-3 multielementary stock standard (Perkin Elmer) at 10 mg L^{-1} was used to prepare an intermediate solution at 0.5 mg L^{-1}. Calibration curves were prepared by means of successive dilutions of this solution, in a linear range from 0.5 µg L^{-1} to 50 µg L^{-1}. A 1000 mg L^{-1} rhodium solution (Merck, Germany) was used as the internal standard. Supra pure nitric acid 65% (w/v) (Merck, Germany) and hydrogen peroxide 30% (v/v) (Merck, Germany) were used for the sample digestion process.

Sample preparation

Imported (n = 24) and national (n = 48) *Cannabis* extracts administered to pediatric patients were obtained between June 2017 and December 2018, in a study approved by the Ethics Committee of Hospital Clementino Fraga Filho, nº 2021817.0.00005257, and sent to the National Institute for Quality Control in Health at the Oswaldo Cruz Foundation - INCQS/Fiocruz, for identification and quantification of essential and trace elements. The analyses were carried out at the Inorganic Elements Sector, Chemistry Department, Fiocruz. Cannabidiol and tetrahydrocannabinol levels in the samples were previously quantified by HPLC-DAD at Department of Clinical and Toxicological Analysis, Federal University of Rio de Janeiro.

To evaluate potential matrix effects, different substances used as vehicles during extract preparation (soybean oil, olive oil, coconut oil and glycerin) were analyzed as blanks.

From 0.1 to 0.5 g of each sample were weighed, depending on the amount of material donated by the tutors responsible for the patients. The samples were

then transferred to teflon tubes and 3 mL of nitric acid and 2 mL of hydrogen peroxide were added. The samples were then digested in a high pressure closed system (Ryan, Farrell, 2018) Speed Wave microwave (Berghof, Germany). After cooling, they were transferred to 15 mL Falcon flasks and diluted, and an internal standard was added.

Method validation

The experiments were performed on an inductively coupled plasma mass spectrometer (ICP-MS), model NexION 300D (Perkin Elmer, USA). Argon gas with a minimum purity of 99.996% was supplied by White Martins (São Paulo, Brazil) and used as carrier gas, nebulizer gas and plasma generator. Table I describes the operational ICP-MS conditions. Daily instrument performance evaluations were performed using a standard solution containing 1 μg L^{-1} of Be, Ce, Fe, Na, Li, Mg, Pb, and the results were compared with manufacturer parameters.

TABLE I - ICP-MS analysis conditions

Radio frequency power	1400 W
Cone/Skimmer/ hyper-skimmer	Platinum
Mediated signal	Peak Hopping
Scan per reading	50
Dwell time	15 ms
Replicate reading	1
Replicates	3
Nebulizer gas flow	1 L min^{-1}
Internal Standard	10 μg L^{-1} Rh

The analytical method was validated according to the parameters described in the guidance document on Analytical Method Validation by INMETRO (DOQ-CGCRE-008) and the ISO 17025 standard (INMETRO, 2018; ISO, 2017; USP, 2016b). The work range for the analyzed elements followed ordinance RDC No. 26, May 13th, 2014, which provides for the registration of herbal medicines and the registration and notification of traditional herbal products, and highlights the importance of heavy metals analyses and sets some important definitions for herbal products (ANVISA, 2014), and ordinance RDC No. 42, August 29th, 2013, which provides for MERCOSUL technical regulations on the maximum limit of inorganic contaminants in food (ANVISA, 2013). The LOD (limit of detection) was obtained from a 3:1 signal-to-noise ratio, while the LOQ (limit of quantification) was obtained experimentally, defined as the first point of the calibration curve (Ribani *et al.*, 2004). Accuracy and precision were assessed according to INMETRO, USP and other literature assessments, with recovery acceptance criteria ranging from 80-120% and a percentage of variation coefficient (% CV) not exceeding 20% for each studied element (Table II) (INMETRO, 2018; USP, 2016b; Nelson, Jones, Drvodelic, 2018; Hineman, Astill, 2019). The matrix effect was evaluated through blank assessments, as well as evaluations of the vehicles used in resins and extract *Cannabis* preparation and administration, where the detected values of the analyzed inorganic elements were below the limit of quantification (As, Cd, Pb, Cr, Cu, Ni, Co and Mn).

Statistical analyses

A descriptive statistical analysis was performed using the Microsoft Excel 2010 software, comprising the arithmetic means, range and standard deviation. In addition, a student's t-test, and an analysis of variance (Anova) statistical test was were applied for comparison of the means.

TABLE II - ICP-MS results of the validation tests of the analyzed elements

Element	Isotope mass (AMU)	LD (µg L^{-1})	LD* (mg kg^{-1})	Recovery (%)	%CV (n=5)	Working range (µg L^{-1})
As	75	0.005	0.0008	104	14	0.1-10
Cd	111	0.005	0.0008	109	11	0.1-10
Pb	208	0.043	0.0065	114	14	0.1-10
Ni	60	0.023	0.0035	81	13	0.1-10
Cu	63	0.005	0.0007	110	14	0.1-10
Co	59	0.014	0.0021	105	16	0.1-10
Cr	52	0.022	0.0033	88	16	0.1-10
Mn	55	0.025	0.0038	120	14	0.1-20

LD: limit of detection, CV: coefficient of variation, AMU: atomic mass unit, LD* detection limit of the methodology

RESULTS AND DISCUSSION

National *Cannabis* extracts (n = 48) were obtained either in the unregulated market from clandestine producers or non-governmental organization-NGOs, or were artisanally produced at, while those obtained in the regulated market are imported (n = 24), mainly from the USA. Most of the extracts contained fixed vehicle oil and glycerin (n = 63), and few products were marketed as resins (n = 9), i.e. raw material with cannabinoids concentrates, consumed either pure and administered directly into the child's mouth or diluted in oil, preferably by the caregiver.

Among the assessed elements, the most important for patient safety comprise the toxic metals As, Cd and Pb, classified as carcinogenic by the International Agency for Research on Cancer (IARC/WHO) (WHO, 2010a; ATSDR, 2012; WHO, 2010b), with Pb directly affecting the central nervous system and absorbed 4- to 5-fold times more by children compared to adults (WHO, 2019). Chromium is an essential element in its trivalent form and toxic in its hexavalent form, but prolonged exposure to chromium (III) can also cause certain problems in humans, such as skin allergies and cancer. As recommended intake values for children between 1 and 8 years old are given as total chromium, ranging from 11-15 µg/day/, only total chromium concentrations were evaluated (WHO, 2010c; Franco *et al.*, 2011).

Inorganic element concentrations in *Cannabis* extracts are expressed as mg kg^{-1} and presented in Table III. The mean As concentrations for national and imported extracts were statistically similar ($p > 0.05$), and all values were below the maximum limits set by the Brazilian Pharmacopeia, 5th edition, and the American Pharmacopeia USP <232> (1.5 mg kg^{-1}) (ANVISA, 2010; USP, 2016a). Cd concentrations were below the 0.5 mg kg^{-1} limit for both Brazilian Pharmacopeia and USP, thus not representing health risks (ANVISA, 2010; USP, 2016a).

TABLE III – Concentration, median and range of inorganic elements and cannabinoids in medicinal *Cannabis* extracts consumed by pediatric patients in Brazil

			As	Cd	Pb	Cr	Cu	Ni	Co	Mn	CBDt*	THCt*
			mg kg^{-1}								mg mL^{-1}	
Imported (Commercial products)	USA (n=18)	Means	0.05	0.02	0.3	6.2	2.0	2.4	0.05	1.1	82.0	1.6
		Median	0.03	0.01	0.24	5.3	0.7	0.6	0.02	0.9	52.4	1.4
		Range	0.01 - 0.13	0.004 - 0.05	0.03-0.7	0.3-29.0	0.2- 16.7	0.1-17.6	0.004-0.31	0.1-4.0	13.- 284	0 – 4.3
	Canada (n=1)	Means	0.008	0.02	0.15	0.6	0.2	0.08	0.006	0.04	22.2	2.9
	Germany (n=1)	Means	0.2	0.004	0.2	5.8	26.9	1.2	0.004	7.6	146.4	9.5
National (Artisanal extracts)	Rio de Janeiro (n=21)	Means	0.08	0.03	0.3	5.3	1.2	0.7	0.5	10.7	4.1	3.1
		Median	0.16	0.01	0.1	2.1	0.3	0.2	0.02	1.1	3.1	2.1
		Range	0.01-0.4	0.- 0.2	0.03-4.0	0.50-30.7	0.07-14.9	0.02-5.3.2	<0.002-7.6	0.4-49.5.1	0-21.1	0-13.7
	Santa Catarina (n=7)	Means	0.06	0.02	0.1	4.7	1.1	1.7	0.08	2.3	2.0	26.8
		Median	0.06	0.02	0.07	0.8	0.2	4.2	0.002	0.4	1.8	30.1
		Range	0.007-0.1	0.008-0.02	0.02-0.3	0.6-24.2	0.02-4.4	0.02-10.1	<0.002-0.3	0.16-12.4	0.69-4.7	9.82-43.6
	Minas Gerais (n=3)	Means	0.04	0.02	0.6	2.8	2.2	2.6	0.06	1.9	0.06	0
		Median	0.03	0.01	0.2	1.8	0.7	0.7	0.04	1.2	0.01	0
		Range	0.03-0.07	0.008-0.05	0.02-1.2	1.7-5.7	0.6-4.4	0.4-7.9	0.03-0.10	0.8-4.6	0-0.18	0
	Paraiba (n=9)	Means	0.02	0.03	0.10	1.7	0.7	0.3	0.007	0.4	0.1	0.2
		Median	0.01	0.01	0.11	0.24	0.3	0.1	0.007	0.4	0.1	0.2
		Range	0.006-0.06	0.01-0.02	0.05-0.13	0.2-4.0	0.1-4.5	0.08-1.3	0.005-0.01	0.2-0.8	0-0.35	0-1.5
	Piaui (n=3)	Means	0.10	0.02	0.04	0.5	0.1	0.07	< 0.002	0.3	1.2	0.2
		Median	0.12	0.02	0.03	0.5	0.1	0.07	----------	0.2	1.2	0.2
		Range	0.04-0.1	0.15-0.16	0.03-0.05	0.30-0.6	0.06-0.2	0.05-0.7		0.2-0.5	0-2.3	0-0.6

* CBDt – total canabidiol/THCt – total Δ9-Tetraidrocanabinol

However, 33% of the samples from Minas Gerais contained Pb levels above the maximum value allowed by USP (0.5 mg kg^{-1}) and by the Brazilian Pharmacopeia (1 mg kg^{-1}), while 14% of Rio de Janeiro samples were above the Brazilian Pharmacopeia limit, and 5%, above the USP limit. Paraiba (PB) and Piaui (PI) samples contained concentrations below the maximum limits set by both standards. When compared to RDC No. 42 of 2013 (Pb - 0.6 mg kg^{-1}), resolution for tea, yerba mate, and other vegetables consumed as infusions, 10% of the samples were deemed unsatisfactory, 14% from Rio de Janeiro and 33% from Minas Gerais.

The high Pb values detected in the extracts can be related to the type of preparation and sample exposure to environmental contamination, due to homemade preparation, without any type of quality control. In addition, high mining activities records are noted for Minas Gerais, which can lead to greater soil contamination by inorganic elements and, consequently, higher concentrations in *Cannabis* resin or oil extract samples (DNPM, 2017; IBRAM, 2014). Among the imported extracts, only one sample from the United States contained Pb values above maximum limits the USP and RDC No. 42. The lower values of imported samples are due to the fact that these products are commercial and regulated in their countries of origin, acquired in international markets and sold freely in a lawful manner.

Taking into account the average concentrations of Ni, Cu, Co, Cr and Mn and the Mevatly posology (Consulta Remédios, 2019) the intake of these elements is

lower than 5% of the recommended daily intake/IDR set by international agencies (WHO, 2000; ATSDR, 2004a; WHO, 2010c; Schafranskia *et al.*, 2019; ATSDR, 2004b; ATSDR, 2012).

The first medicine with CBD was registered in 2018 by the U.S. health agency (Food and Drug Administration) under the commercial name of Epidiolex®. This medicine has a concentration of 100 mg mL^{-1} of CBD and is indicated for the treatment of convulsions. Through the results observed the concentrations of CBD in the imported (Commercial products) are in the medicine range, while the national (artisanal extracts) the THC concentration is higher used for a recreational purpose, which can aggravate the pathological conditions due to the lack of adequate medication (Carvalho et al., 2020).

Table IV displays the means and standard deviations (SD) of national and international extracts and resins. National resin samples contained Pb values above the maximum limits set by the Brazilian Pharmacopeia, USP and RDC No. 42 of 2013, while the opposite was observed for international samples. As and Cd concentrations in both national and international samples, were below the maximum limits set by the current legislation (USP, 2016b; ANVISA, 2014; ANVISA, 2013). No statistically significant difference between the concentrations of inorganic elements in national and international oil samples was detected, except for manganese.

Quantified cannabinoid contents were higher in resin, due to the extraction process (Spinelli, 2008), which concentrates these substances, as displayed in Table IV.

TABLE IV - Concentration of inorganic elements ± standard deviation (SD) and cannabinoids in medicinal *Cannabis* resins consumed by pediatric patients in Brazil

		As	Cd	Pb	Cr	Cu	Ni	Co	Mn	CBDt*	THCt*
		mg kg^{-1}								mg mL^{-1}	
Imported											
Oil	Means±SD	0.04±0.08	0.02±0.01	0.2±0.2	6.1±7.3	1.37±2.0	2.10±4.7	0.04±0.07	1.1±0.9	78.8±66.0	1.68±1.4
	Range	0.1-0.1	0.01-0.05	0.03-0.6	0.2-29.0	0.1-8.3	0.05-17.6	0-0.3	0.4-4.0	41-210	0-4.2
Resin	Means	0.08±0.06	0.01±0.004	0.3±0.2	5.4±1.2	9.3±12.0	2.9±4.5	0.07±0.02	2.2±2.7	152±30	4.9±3
	Range	0.04-0.2	0.01-040	0.1-0.8	3.7-6.1	0.5-27	1.1-11.0	0.04-0.09	0.9-7.0	104-189.4	2.6-9.5
National											
Oil	Means	0.06±0.08	0.02±0.03	0.2±0.6	3.9±6.7	0.9±2.3	0.9±7.4	0.1±1.3	3.1±16.1	2.0±4.1	5.8±11.0
	Range	0.01-0.4	<0.002-0.2	0.3-4.1	0.3-24.2	0.1-4.5	0.02-10.1	<0.002-7.6	0.05-79.3	0-12.14	0-43.6
Resin	Means	0.1±0.05	0.01±0.02	1.2±1.3	8.5±4.2	3.7±1.1	3.8±2.9	0.1±0.1	17.4±21.7	12 ±8	250±143
	Range	0.05-0.2	0.01-0.02	0.3-3.1	5.6-14.5	2.7-4.9	1.2-7.9	0.05-0.3	5.6-49.5	0.3-16.8	37-349

* CBDt – total canabidiol/THCt – total Δ9-Tetraidrocanabinol

In addition, inorganic element concentrations in imported oil and resin samples were statistically similar, as observed for the analyzed cannabinoids, whose concentration was increased by about 3-fold. In national samples, inorganic element concentrations increased 2-6-fold, following cannabinoid behavior, with the exception of Cd and Co, which were not significantly altered.

CONCLUSIONS

The proposed method displays adequate sensitivity, precision and accuracy for the assessment of inorganic elements in the studied *Cannabis* samples. In addition, ICP-MS is a robust and flexible technique able to analyze a wide variety of *Cannabis* forms and products in order to meet the growing needs of this industry, as demands

for *Cannabis* testing increases and new inorganic element limits are added to regulations.

The results reported herein allowed for collaboration concerning quality assessments for different types of *Cannabis* extracts consumed by pediatric patients with neurological diseases. This scientific information can be used to support discussions regarding the standardization/regulation of *Cannabis* production and its derivatives in Brazil and their quality control, in order to minimize exposure to the chronically consumed inorganic elements present in these products.

The detected variations in inorganic element concentrations, alongside higher toxic element concentrations, mainly Pb, in national extract samples is due to the fact that most were artisanally prepared, without any quality control. The opposite was noted for imported products, which were more homogeneous, thus evidencing the need for production and control regulations, as well as inspections, in order to guarantee the quality of extracts consumed by pediatric patients, aiming to reduce health risks to this vulnerable population and, thus, avoiding unfavorable public health outcomes.

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