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Cannabinoid levels description in a cohort of patients with chronic and neuropathic pain treated with *Cannabis* decoction: A possible role of TDM

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ABSTRACT

The phytocomplex of *Cannabis* is made up of approximately 500 substances: terpeno-phenols metabolites, including Δ-9-tetrahydrocannabinol and cannabidiol, exhibit pharmacological activity.

Medical *Cannabis* has several pharmacological potential applications, in particular in the management of chronic and neuropathic pain. In the literature, a few data are available concerning *cannabis* pharmacokinetics, efficacy and safety.

Thus, aim of the present study was the evaluation of cannabinoid pharmacokinetics in a cohort of patients, with chronic and neuropathic pain, treated with inhaled medical *cannabis* and decoction, as a galenic preparation.

In this study, 67 patients were enrolled. Dried flower tops with different THC and CBD concentrations were used: Bedrocan® medical *cannabis* with THC level standardized at 19% and with a CBD level below 1%, Bediol® medical *cannabis* with THC and CBD level standardized at similar concentration of 6.5% and 8%, respectively.

Cannabis was administered as a decoction in 47 patients and inhaled in 11 patients. The blood withdrawn was obtained before the new dose administration at the steady state and metabolites plasma concentrations were measured with an UHPLC-MS/MS method.

Statistically significant differences were found in cannabinoids plasma exposure between inhaled and oral administration of medical *cannabis*, between male and female and cigarette smokers.

For the first time, differences in cannabinoid metabolites exposures between different galenic formulations were suggested in patients. Therapeutic drug monitoring could be useful to allow for dose adjustment, but further studies in larger cohorts of patients are required in order to confirm these data.

Abbreviations: Δ9-THC, Δ9-tetrahydrocannabinol; CBD, cannabidiol; PD, pharmacodynamic; GPCRs, G-protein-coupled receptors; CNS, Central Nervous System; PNS, peripheral nervous system; CBRs, cannabinoid receptors; UHPLC-MS/MS, ultra-high performance liquid chromatography coupled with tandem mass spectrometry; PK, pharmacokinetics; Δ8-THC, Δ8–tetrahydrocannabinol; TDM, therapeutic drug monitoring; CBN, Cannabinol; THCA, Tetrahydrocannabinolic acid; CBDA, Cannabidiolic acid; 11-OH-THC, 11–Hydroxy–Δ9–tetrahydrocannabinol; THC -COOH-, 11–Nor–9carboxy–Δ9–tetrahydrocannabinol; CB_1:, Cannabinoid-receptor type 1; CB_2, Cannabinoid-receptor type 2; CYP, cytochrome.

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1. Introduction

Cannabis (Indian hemp) use has been reported for thousands of years. About 147 million people, 2.5% of the world population, consume *cannabis* (annual prevalence) worldwide [1].

Cannabis is one of the most ancient cultivated plants, due to its adaptability in a wide range of habitats and to its several uses: food, fiber and drug plant [2].

This plant can be classified into three species: *Cannabis sativa*, *cannabis indica* and *cannabis ruderalis* [3]. *Cannabis sativa* is the most used in the western society, with several chemical phenotypes expressing different cannabinoid compositions [4]. In the literature, studies attested the presence of this plant already about 11700 years ago, in the territories of Central Asia and East Asia [5]. Afterwards, it has spread all over the world, thanks to human domestication.

In general, *cannabis* plant contains approximately 540 natural compounds [4], including about 120 phytocannabinoids, with a chemical structure of a skeleton of oxygenated 21 carbon atoms, with a common fragment showing the hydrophobic alkyl chain and a dibenzopyran ring [6].

Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the major constituents in *cannabis*.

Regarding cannabinoid pharmacokinetics (PK), following inhalation, the principal route of *cannabis* administration, THC quickly passes into circulation from the lungs and it is therefore rapidly absorbed by the tissues. In the liver it is first metabolized by cytochrome P450 (CYP), converted into 11–Hydroxy–Δ9–tetrahydrocannabinol (11-hydroxy-THC), a psychoactive compound, further oxidized in 11–Nor–9–carboxy–Δ9–tetrahydrocannabinol (THC-COOH), which may be glucuronidated to 11-nor-9-carboxy-THC glucuronide.

CBD is hydroxylated to 7-hydroxy cannabidiol (7-OH-CBD).

Inhaled cannabinoids show similar PK to those administered intravenously [7], exhibiting higher maximum concentrations compared to oral ingestion [7–13]. After smoking, THC and CBD peak plasma exposures are reached rapidly, in 3 and 10 minutes, respectively [7,12].

The inhaled THC bioavailability ranges from 10% to 35% [7], due to intra- and inter- subject variability, the inhalation characteristics and the used inhalation device [9–11,13,14]. Inhaled CBD has a bioavailability of 31%, and a plasma concentration–time profile similar to THC [7,12].

In the context of medical *cannabis*, the use of a vaporizer for cannabinoid administration is recommended: the PK of vaporized and smoked cannabinoids are comparable, vaporization avoids toxic pyrolytic compounds exposure and the smoked *cannabis* respiratory risks [15].

In addition, inhalation avoids or reduces the extensive first-pass metabolism, characteristic of the oral administration. In this context, THC and CBD absorption is variable: as suggested above, due to extensive hepatic first-pass metabolism [16], oral administration shows lower peak plasma concentration than inhaled administration [17], reaching peak concentration after about 120 minutes [7,18].

Cannabinoids rapidly distribute into lung, heart, brain and liver [17, 19,20], and subsequently into the less vascularized tissues [20]. Particularly, they accumulate in adipose tissues in patients under chronic treatment [13,21].

CBD and THC volumes of distribution (Vd) are high: ~32 l kg^{-1} [12] and 3.4 l kg^{-1} [13], respectively.

It is important to highlight the composition and size of the body and disease influencing blood–tissue barriers permeability could affect the distribution of these molecules [22]. As reported above, THC metabolism is mainly hepatic, via CYP 450 isozymes CYP2C19, CYP2C9 and CYP3A4. Moreover, extra-hepatic tissues expressing CYP450, such as small intestine and brain, have a role in cannabinoid metabolism [13].

CBD is metabolized by CYP2C19, CYP3A4, CYP1A1, CYP1A2, CYP2C9 and CYP2D6 [23]. A few data are available in the literature about the pharmacological activity of CBD metabolites [24].

Regarding pharmacodynamic (PD), in 1988, Allyn Howlett and W.A. Devane discovered the "endocannabinoid system": a complex biological and molecular system playing a central role in several physiological processes such as neurogenesis, neuroprotection, nervous functions, depression, eating and emotional behaviour, recompense, cognition, memory, learning, painful sensation and also in fertility and pregnancy [25–27].

Considering the endocannabinoid system structure, the components include receptors, their ligands, and enzymes involved in their biosynthesis and degradation [28]. In particular, cannabinoid-receptor type 1 and 2, CB_1 and CB2, are the principal receptors [29]. CB_1 is the most abundant GPCR in the central nervous system (CNS) and it is expressed in pre-synaptic neurons of the neocortex, cerebellum and limbic system (amygdala, hippocampus). It is also present in the peripheral nervous system (PNS), where it activates K^+ channels and causes inhibition of neurotransmitter release.

CB_2 has been identified in the immune system, such as in lymphocytes, mast cells and macrophages, and in the CNS on microglia cells and astrocytes [30], where it appears to mediate the anti-inflammatory and immune-regulating properties of these compounds.

The endocannabinoid system has an important role in pain management. As reported in the study of Anand *et al.*, CB_2 receptor antagonists showed antinociceptive activity in inflammatory and nociceptive pain [31]. Several studies highlight that CBD could have therapeutic advantages in treating fibromyalgia, rheumatoid arthritis, arthritis, chronic pain, headache and facial pain [27,32].

Cannabinoids also showed activity against thermal and noxious pain, cancer pain, postoperative pain, pain related to spinal cord injury and traumatic nerve injury and toxic insults [33,34].

These molecules show potent anti-inflammatory activity: inflammation occurs in many pathologies, such as cancer, asthma, rheumatoid arthritis, multiple sclerosis, hepatitis, colitis and dermatologic diseases [27].

In Italy, the Ministerial Decree of 9 November 2015 regulates the authorization, cultivation, import, export and distribution of cannabis [35].

The therapeutic indications for *cannabis* medical use reported in the Ministerial Decree concern: analgesia in pathologies involving spasticity; analgesia in chronic pain; anti-kinetic and anti-emetic activity in nausea and vomiting, caused by chemotherapy, radiotherapy, HIV therapies; the appetite stimulating effect in cachexia, anorexia, loss of appetite in cancer patients or in people living with HIV and in anorexia nervosa; the hypotensive effect in glaucoma and the involuntary body and facial movements reduction in Gilles de la Tourette syndrome.

Regarding the neuropathic (NP) and chronic pain management (CP), the overall prevalence of NP in the population is between 7% and 10% [36] reaching 20–25% in patients subjects with CP [37].

Allodynia and hyperalgesia represent the most important symptoms limiting the quality of life of patients suffering from CP and, in particular, NP.

In addition to these painful symptoms, co-morbidities, such as anxiety, depression, cognitive dysfunction and memory loss have to be considered. These make NP a neuropsychiatric pathology, whose pharmacological treatment is still a challenge today.

Recommended therapeutic options are: anti-epileptic drugs (pregabalin, gabapentin), serotonin and norepinephrine reuptake inhibitors (duloxetine) and tricyclic antidepressants.

Despite these neuropathic options, NP management remains a critical clinical point: pain relief with classic medications is reported by less than 50% of patients and several adverse effects occur [38]. In addition, the current alarming addiction rates and deaths from opioid abuse showed a need to explore other safer treatment options [39].

Some CP and NP patients are evaluating alternative medications for pain management and *cannabis* seems to be a safer alternative to opioids, non-steroidal anti-inflammatory drugs and other treatments.

A review by Vučković et al. [40] analysed scientific studies

performed between 1975 and 2018 on CBD use for the treatment of pain associated with cancer, NP and fibromyalgia, suggesting the efficacy of medical *cannabis* use in pain management [40].

Cannabinoid effectiveness on multiple sclerosis related pain compared with placebo was observed in the CAMS study [41] and in the MUSEC trial, focused on stiffness management [42].

In addition, greater pain reduction was observed in patients treated with nabilone in a trial studied, considering this drug as an additional treatment to gabapentin for NP in multiple sclerosis [43].

In light of all these evidences, *cannabis* has demonstrated its efficacy in pain treatment and in reducing opioid consumption. Consequently, other studies to ensure its effectiveness and safety in pain management are urgently needed.

In addition, all the medical staff involved in the management of NC and NP patients treated with *cannabis* should monitor them, establishing treatment decisions on scientific evidence in order to provide safety and efficacy.

Cannabinoid PK profile, particularly the absorption step, varies significantly depending on the route of administration [44]. Smoking remains the most common administration route among medical *cannabis* users. Inhalation of combusted-dried flowers allows a faster onset of action combined with a higher serum concentration peak compared to the most of other administration routes. However, the combustion process implies the production of toxic molecules, such as polycyclic aromatic hydrocarbons, carbon monoxide and ammonia, commonly associated with respiratory symptoms (bronchitis, cough, phlegm) [45].

The oral route of administration overcomes many of the drawbacks of inhalation with relatively stable serum concentrations [46].

A few data are available in the literature regarding both the PK properties and toxicity of the medical *cannabis* preparations. In addition, optimal dosing in different populations are scarce.

In light of this, therapeutic drug monitoring (TDM) in patients treated with this plant has an important role for personalizing therapy and pharmacovigilance in the development of medical *cannabis* products.

TDM is the clinical practice which measures drugs concentration in patient bloodstream, optimizing the individual dosage regimens. It is used primarily for drugs with narrow therapeutic ranges, drugs with high PK variability, drugs with significant adverse effects and substances with a difficult to monitor target concentration. It allows to use difficult-to-manage medications, optimizing the clinical outcome in patients [47].

In the context of medical *cannabis*, TDM may be used to fix dosing schedules, currently lacking, and optimizing individual therapy [48]. To date, since a few data are available in the literature concerning cannabis PK, this study could be helpful in evaluating the efficacy and safety of medical *cannabis* in treated patients, laying the foundations for the therapeutic range definition.

2. Materials and methods

2.1. Characteristics of enrolled patients

In this study, 67 patients with a diagnosis of NP and CP were enrolled at the "SC Terapia del Dolore – ASL Città di Torino" at the "Oftalmico" hospitals (Turin, Italy).

Inclusion criteria were medical *Cannabis* administration, age of consent and diagnosis of NP and CP.

The study was performed in compliance with the Declaration of Helsinki and local review board regulations. All patients gave written informed consent, according to the local ethics committee standards ("*Cannabis* terapeutica nei pazienti affetti da dolore neuropatico: studio osservazionale", approved by Ethical Committee "A.O.U. CITTA' DELLA SALUTE E DELLA SCIENZA DI TORINO - A.O. ORDINE MAURIZIANO DI TORINO – A.S.L. CITTÀ DI TORINO", n° 0131170 del 25/11/2022).

2.2. Study design and magistral preparations of cannabis plant derivatives

Cannabis was administered as a decoction in 47 patients and inhaled in 11 patients. Patients treated with smoked *cannabis* chose this route of administration, in agreement with the physician.

The used drug was the dried flower tops of the cannabis plant for decoction preparation or for vaporization and it was prepared by the chemist.

Cannabis was provided at the institution by the hospital pharmacy. Different varieties of medical *Cannabis* were used as prescribed by national and regional laws: the main ones are Bediol® and Bedrocan® (Bedrocan International BV, Veendam, the Netherlands); when these specialities were not available, FM2 (Military Chemical and Pharmaceutical Institution of Florence, Italy) and Pedanios (AURORA Cannabis Enterprises Inc., Canada) were used.

Dried flower tops with different concentrations of THC and CBD were used:

- Bedrocan® medical *cannabis* with THC level standardized at 19% and with a CBD level below 1%.
- Bediol® medical *cannabis* with THC and CBD level standardized at the similar concentration of 6.5% and 8%, respectively.
- FM2® medical *cannabis* with THC and CBD level standardized at the similar concentration of 5–8% and 7.5–12%, respectively.
- Pedanios® 22/1 medical *cannabis* with THC and CBD level standardized at the similar concentration of 22% and below 1%, respectively.

The *cannabis* dose for each patient was determined according to the kind of pathology and the pain level evaluated by the physician.

All the patients were naïve for cannabis treatment and all the samples (one for each patient) were obtained at least 15 days after starting the administered dosage.

2.3. Pharmacokinetic analyses

PK analysis was performed before the new dose administration (C_{trough}) at the steady state. Plasma samples were isolated after whole blood centrifugation at 1400 x g for 10 min at 4°C and stored at −80°C until the analysis.

Cannabis plasma concentrations in patients were obtained using a previously published fully validated method [49].

Samples with THC-COOH glucuronide higher than 60 ng/mL and THC higher than 5 ng/mL were considered as effective cannabinoid plasma levels.

The value of 5 ng/mL is

2.4. Statistical analyses

IBM SPSS Statistics software 27.0 for Windows (Chicago, Illinois, USA) was used for statistical analysis.

All of the continuous variables were tested for normality with the Shapiro–Wilk test. The correspondence of each factor was analyzed according to a non-normal or normal distribution with the Kolmogorov–Smirnov test. Non-normal variables were described as median values and interquartile range (IQR); categorical variables as numbers and percentages. Kruskal-Wallis and Mann-Whitney tests suggested differences for continuous variables, with a statistical significance of two-sided p-value < 0.05.

3. Results

3.1. Characteristics of enrolled patients

In this study, 67 patients were enrolled: 9 patients were excluded from the statistical analysis since *cannabis* decoction was incorrectly

Table 1
Characteristics of enrolled patients. IQR= Interquartile range.

Characteristics	
No. of patients	58
Cigarettes smoke, n (%)	19 (32.8%)
Gender (Male), n (%)	20 (34.5%)
Caucasian, n (%)	100%
BMI (Kg/m2), median (IQR)	20.6 (17.9; 23.4)
Age, (years), median (IQR)	61 (52;67)
Fibromyalgia, n (%)	27 (46.6%)
Headache, n (%)	5 (8.6%)
Cancer, n (%)	4 (6.9%)
Other pathologies, n (%)	38 (65.5%)

Table 2
Concomitant class of drugs in enrolled patients.

Drugs	Number of patients (%)
Antidepressant, n (%)	20 (39.2%)
Anti-inflammatory drugs, n (%)	16 (31.4%)
Opioids, n (%)	21 (41.2%)
Analgesics for neuropathic pain, n (%)	16 (31.4%)
Cardiovascular system drugs, n (%)	15 (29.4%)
Vitamin D supplementation, n (%)	9 (17.6%)
Anti-anxiety medications, n (%)	17 (33.3%)
Other, n (%)	26 (89.7%)

Table 3
Characteristics of enrolled patients.

Treatment characteristics	Number of patients
cannabis with THC level standardized at 19% and with a CBD level below 1% (e.g. Bedrocan®), n (%)	30 (51.7%)
cannabis with THC and CBD level standardized at the similar concentration of 6.5% and 8% (e.g. Bediol®), n (%)	28 (48.3%)
Inhaled cannabis, n (%)	11 (19%)

Table 4
Cannabis dosages (mg).

***Cannabis* mg**	**Number of patients**
50	1(1.7%)
100	8 (13.8%)
150	2 (3.4%)
200	12 (20.7%)
250	2 (3.4%)
300	13 (22.4%)
400	8 (13.8%)
450	1 (1.7%)
500	1 (1.7%)
600	2 (3.4%)
900	2 (3.4%)
1100	1 (1.7%)
1200	2 (3.4%)
1400	1 (1.7%)
1500	2 (3.4%)

administered (e.g. scarce compliance and missing dose). Characteristics of enrolled patients were reported in Table1.

Participants had a median age of 61 years (interquartile range 52 – 67 years), 20 (34.5%) were male and the median body mass index was 20.6 (interquartile range 17.9; 23.4) Kg/m2. Participants were all Caucasian.

Considering their diagnosis, most of patients had polypharmacy: 41.2% of patients (n=21) were treated with opioids and 39.2% (n=21) with antidepressants.

All the concomitant classes of drugs were reported in Table 2.

Concerning the variety of administered medical *cannabis*, 51.7% (n=30) of patients were treated with *cannabis* with THC level standardized at 19% and with a CBD level below 1%, while 48.3% (n=28) with medical *cannabis* with THC and CBD level standardized at similar concentration of 6.5% and 8%, as reported in Table 3.

Patients were treated with different *cannabis* dosages: the majority with 300 and 200 mg of *cannabis*/die, 22.4% (n=13) and 20.7% (n=12), respectively.

All the dosages were reported in Table 4 and in Figs. 1 and 2.

3.2. Cannabis metabolites measurements

Concerning cannabinoid PK analysis, all the samples were successfully quantified for each drug. Cannabinoid plasma exposures (expressed as ng/mL) in patients treated with medical *cannabis* with THC level standardized at 19% and with a CBD level below 1% and medical *cannabis* with THC and CBD level standardized at similar concentration of 6.5% and 8% were reported in Tables 5 and 6, respectively.

Statistically significant differences were found in cannabinoid plasma exposure between inhaled and oral administration (decoction) of medical *cannabis* with THC level standardized at 19% and with a CBD level below 1%, except for CBD, THCA and CBD.

Regarding medical *cannabis* with THC and CBD level standardized at similar concentration of 6.5% and 8%, no statistically significant differences between inhaled or oral cannabis were observed.

Cannabinoid plasma concentrations as median and IQR and *p*-values were reported in Tables 5 and 6.

3.3. Factors impacting on cannabis metabolites pharmacokinetics

Regarding the role of gender in influencing cannabinoids plasma concentrations, statistically significant differences were observed between male and female considering COOH-THC, COOH-THC-glucuronide, THCA and CBDA plasma exposure, as shown in Table 7 and in Fig. 3.

Concerning the influence of cigarette smoke on cannabinoids plasma exposure, statistically significant differences were observed between smokers and no smokers, regarding all the cannabis metabolites, except for 11-OH-THC, CBD, THCA and CBDA, as reported in Table 8 and in Fig. 4.

A correlation between BMI (Kg/m2) and Δ9-THC plasma levels (ng/mL) was observed (p= 0.032, S = −0.300), as illustrated in Fig. 5.

Regarding patients treated with *cannabis* decoction, a correlation between *cannabis* dose (mg) and metabolites plasma exposure was suggested: COOH-THC (p=0.005; S=0.411), COOH-THC glucuronide (p=0.005; S=0.403) and CBD (p=0.030; S=0.316).

Considering inhaled *cannabis*, a correlation between *cannabis* dose (mg) and 7–0 H-CBD (p=0.027; S=0.661) and THCA was observed (p=0.024; S= −0.672).

3.4. Regression analysis

Demographic and pharmacological factors able to predict effective cannabinoids concentration were analysed in the logistic regression analysis: gender, inhaled *cannabis*, cardiovascular system drugs and cigarettes smoke remained in the final multivariate model.

4. Discussion

The present work aims at investigating cannabinoids plasma levels in a cohort of patients with NP and CP, treated with medical *cannabis* as a galenic preparation.

Im this study, 58 patients were enrolled: samples were obtained from 11 patients using inhaled Marijuana and 47 using *cannabis* decoction. Blood sampling in patients and volunteers was performed at the C_{trough}.

THC-COOH and THC-COOH-glucuronide were the most abundant observed metabolites, while CBD and Δ9-THC are present at low

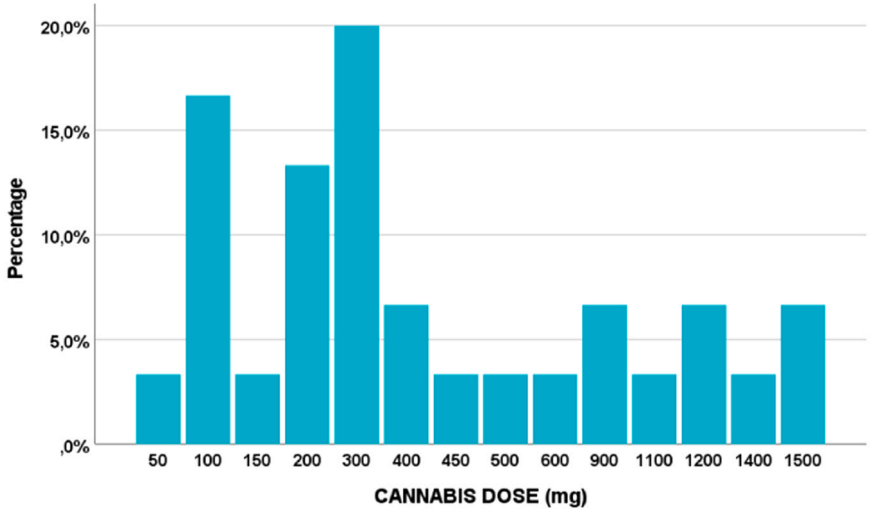

Fig. 1. Dosage distribution of patients treated with *cannabis* with THC level standardized at 19% and with a CBD level below 1%.

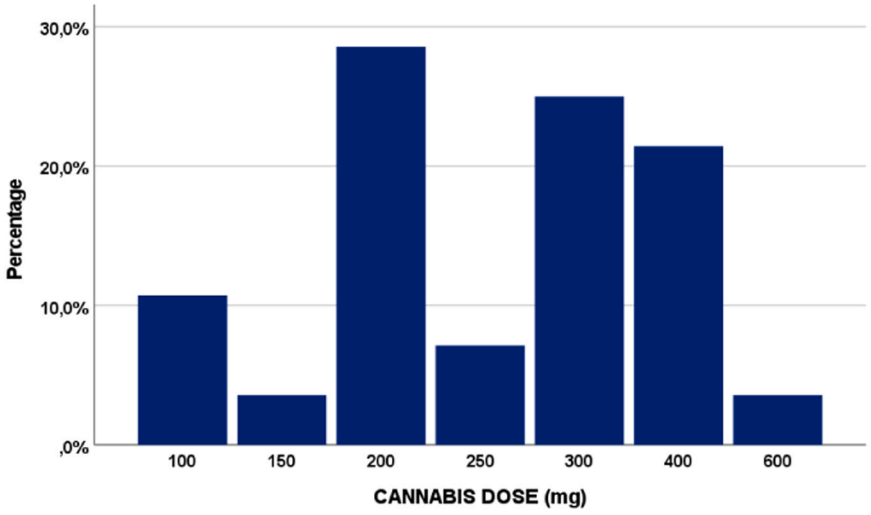

Fig. 2. Dosage distribution of patients treated with medical *cannabis* with THC and CBD level standardized at the similar concentration of 6.5% and 8%.

Table 5
Median and IQR of plasma cannabinoids in patients treated with medical *cannabis* with THC level standardized at 19% and with a CBD level below 1%: differences between inhaled cannabis and oral (decoction) assumption. IQR= interquartile range.

Medical *cannabis* with THC level standardized at 19% and with a CBD level below 1%			
Metabolite	**ng/mL Median (IQR) inhaled cannabis**	**ng/mL Median (IQR) decoction**	***p*-value**
Δ9-THC	14.26 (5.70; 23.99)	5.08 (4.53; 11.04)	**0.011**
OH-THC	0 (0; 11.34)	0 (0; 0)	**0.017**
COOH-THC	62.99 (27.85; 248.33)	10.53 (6.62; 23.59)	**0.004**
COOH-THC-glucuronide	511.35 (103.44; 1076.27)	47.92 (7.32; 80.01)	**0.003**
CBD	5.26 (1.45; 11.45)	2.94 (0.56; 5.73)	0.364
7-OH-CBD	2.26 (0.79;9.82)	0 (0; 0)	**<0.001**
THCA	0 (0;2.11)	3.35 (0; 11.75)	0.127
CBDA	0 (0;0.41)	0 (0; 0.95)	0.546

Table 6
Median and IQR of plasma cannabinoids in patients treated with medical *cannabis* with THC and CBD level standardized at the similar concentration of 6.5% and 8%: differences between inhaled cannabis and oral (decoction) assumption. IQR= interquartile range.

Medical *cannabis* with THC and CBD level standardized at the similar concentration of 6.5% and 8%			
Metabolite	**ng/mL Median (IQR) inhaled cannabis**	**ng/mL Median (IQR) decotion**	***p*-value**
Δ9-THC	5.85 (4.60;/)	4.52 (4.18;5.48)	0.326
OH-THC	0 (0;0)	0 (0;1.39)	0.412
COOH-THC	43.76 (5.21;/)	11.43 (4.91; 21.70)	0.517
COOH-THC-glucuronide	197.70 (17.81;/)	35.07 (10.35; 63.88)	0.404
CBD	7.83 (3.44;/)	2.12 (0;3.72)	0.104
7-OH-CBD	0.96 (0;/)	0 (0;1.67)	0.667
THCA	0 (0;0)	4.89 (0;9.04)	0.100
CBDA	0 (0;0)	1.05 (0;5.76)	0.118

concentrations in blood collected samples, both in patients who smoked and in those who took *cannabis* decoction.

Δ9 -THC plasma concentrations could be useful for the recent *cannabis* use verification, but this becomes problematic in cases of chronic use. Indeed, after frequent *cannabis* exposure, Δ9 -THC accumulates in adipose tissue, from which it is subsequently released [13]: similar plasma exposures in a chronic *cannabis* user (who has been abstinent for a period) and for an unusual user recently exposed to

Table 7
Gender influence on cannabis metabolites plasma exposure.

Analyte (ng/mL)	p-value
Δ9-THC	0.259
OH-THC	0.929
COOH-THC	**0.033**
COOH-THC-glucuronide	**0.008**
CBD	0.078
7-OH-CBD	0.444
THCA	**0.002**
CBDA	**0.027**

cannabis were observed [10].

Regarding CBD, a missing detection of this analyte does not exclude recent intake [50]. In their work, Schwope *et al.* suggested a maximum plasma CBD concentration of 3.4 ng/mL after a *cannabis* cigarette (2 mg CBD) *ad libitum* by an experienced user [50]. In our study, we observed concentrations between 5.26 and 7.83 ng/mL of CBD in smoker patients and about 2 ng/mL in subjects treated with decoction.

Δ8-THC was undetectable in all samples, while 11-OH-THC was undetectable in most of analysed samples. As reported in literature, the active Δ9 -THC metabolite 11-OH-THC could be an indicator of recent *cannabis* use: indeed, it could be detected at < 1 ng/mL concentrations in blood 8 hours after smoked marijuana by occasional *cannabis* users [51]. Confirming our data, also Pellesi *et al.* observed in their work 11-OH-THC lower concentrations than THC and two patients treated with *cannabis* decoction with no detectable 11-OH-THC in blood [52].

CBDA and THCA concentrations < 5 ng/mL were observed only in patients treated with decoction: mean THCA value of 4.89 ng/mL in patients administered medical *cannabis* with THC and CBD level standardized at similar concentration and 3.35 ng/mL with medical *cannabis* with THC level standardized at 19% and with a CBD level below 1%.

Regarding medical *cannabis* with THC level standardized at 19% and with a CBD level below 1%, important statistically significant differences in cannabinoids plasma exposure between inhaled and oral administration were found. THC-COOH showed a mean value of 62.99 ng/mL and 10.53 ng/mL in smokers and in subjects treated with decoction, respectively, while THC-COOH-glucuronide was detected at mean concentration of 511.35 ng/mL in smokers and 47.92 ng/mL in oral administration. This investigation highlights some important differences between the *cannabis* routes of administration: patients taking *cannabis* decoction had a higher CBDA and THCA bioavailability, confirming data published by Pellesi *et al.* [52], but they showed very low cannabinoids plasma concentrations in general. Patients treated with inhaled *cannabis* showed a higher concentration of THC and its metabolites 11-OH-THC and THC-COOH.

Regarding *cannabis* with similar concentrations of THC and CBD (6.5% and 8%) administration, no statistically significant difference was suggested probably due to the limitation in sample size between the two groups (3 inhaled vs. 25 oral administrations). In fact the study is following up, enrolling new patients, in order to clarify this aspect.

It is important to consider that several factors influencing cannabinoid plasma concentrations are present: the used drug form, interindividual differences (such as BMI and gender), life style and pharmacogenetics might have a role in this field. The conversion of the acid precursors to the corresponding cannabinoids, depending on the reaction temperature, could have an impact on plasma concentration variability [51].

An inverse correlation between BMI (Kg/m^2) and Δ9-THC plasma levels (ng/mL) was observed ($p= 0.032$, $S = -0.300$): lower Δ9-THC levels occur in patients with higher BMI. It is probably due to the lipophilic properties of this cannabinoid: as reported above, Δ9 -THC accumulates in adipose tissue and it results less available in plasma.

Regarding the role of gender in influencing cannabinoids plasma concentrations, statistically significant differences were observed between male and female for COOH-THC, COOH-THC-glucuronide, THCA and CBDA plasma levels. Also in this case, we can suppose the role of lipophilic properties of these molecules: sex differences in cannabinoid levels could be related to differences in drug disposition and body fat distribution. Women present a higher body fat percentage than men, suggesting cannabinoids are sequestered in fat cells and less in plasma of women.

In the literature, gender differences in cannabinoid-induced effects related to *cannabis* dependence were suggested [53]: male *cannabis*

Table 8
Cigarette smoke influence on cannabis metabolites plasma exposure.

Analyte (ng/mL)	*p*-value
Δ9-THC	**<0.001**
OH-THC	0.058
COOH-THC	**<0.001**
COOH-THC-glucuronide	**<0.001**
CBD	0.264
7-OH-CBD	**0.021**
THCA	0.979
CBDA	0.163

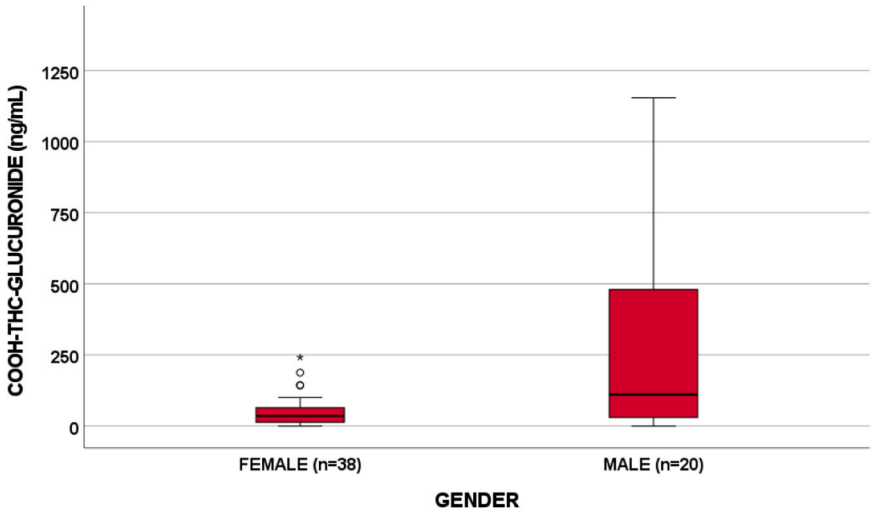

Fig. 3. Influence of gender on COOH-THC-glucuronide exposure ($p = 0.008$). Outliers are represented by little circles, and extreme outliers are represented by little stars.

Table 9
Linear regression analyses: parameters able to predict effective cannabinoid concentrations. Bold represents statistically significant values. BMI: body mass index.

Effective Cannabinoids concentration				
	Univariate regression		Multivariate regression	
Factors	***p*value**	**OR (95% IC)**	***p*value**	OR (95% IC)
Gender	**0.006**	**5.200 (1.616; 16.731)**	**0.028**	16.205 (1.343; 195.581)
Age	0.093	0.960 (0.916; 1.007)		
BMI	0.107	0.889 (0.770; 1.026)		
Mg cannabis	**0.015**	**1.002 (1.000; 1.004)**	0.188	1.003 (0.999; 1.006)
Inhaled cannabis	**0.005**	**10.607 (2.027; 55.497)**	**NC**	
Cannabis preparation	**0.031**	**3.429 (1.123; 10.470)**	0.797	0.752 (0.086; 6.596)
Antidepressant	0.573	1.400 (0.435; 4.508)		
Anti-inflammatory drugs	0.104	0.308 (0.074; 1.276)		
Opioids	0.402	0.600 (0.181; 1.984)		
Analgesics for neuropathic pain	0.303	0.500 (0.134; 1.868)		
Cardiovascular system drugs	**0.047**	**0.192 (0.038; 0.979)**	**NC**	
Vitamin D supplementation	0.374	0.464 (0.086; 2.517)		
Anti-anxiety medications	0.535	0.673 (0.193; 2.353)		
Cigarettes smoke	<0.001	9.333 (2.637; 33.034)	0.022	8.516 (1.358; 53.419)

smokers exhibit higher Δ9-THC circulating levels [54], showing an increased risk of cardiovascular effects than female [55].

Considering the influence of cigarette smoke on cannabinoids plasma exposure, statistically significant differences were observed between smokers and no smokers, considering the principal *cannabis* metabolites. Probably it is due to the high percentage of cigarettes smokers among patients treated with inhaled cannabis, who showed higher cannabinoid levels, but these singular data need to be clarified in further studies. Indeed, in contrast with our results, in the literature several studies reported that smoking increases CYP1A2 and CYP2D6 enzymes activity [56–58].

As an example, fluvoxamine concentrations in smoker patients was significantly lower than non-smokers, after a 50 mg single oral administration in a study of healthy volunteers [59]. In addition, a negative correlation between smoking and clozapine plasma exposure was observed, in accordance with the cigarettes *CYP1A2* induction [60].

Finally, demographic and pharmacological factors predicting effective cannabinoids concentration were observed: gender, inhaled *cannabis*, cardiovascular system drugs and cigarettes smoke resulted predictors.

Samples with THC-COOH glucuronide higher than 60 ng/mL and THC higher than 5 ng/mL were considered as effective cannabinoid plasma levels.

Considering the literature, THC plasma concentrations related to efficacy can vary widely depending on individual variability and the therapeutic context. In addition, our patients were in chronic treatment with cannabis and decoction is characterized by high variability, both in preparation and administration.

In the literature, different studies highlighted the needing for therapeutic drug monitoring of cannabinoids, as reported by Marcella Gherzi *et al.* [61].

In light of these, we set 5 ng/mL as minimum expected concentration in our patients, associated with 60 ng/mL of THC-COOH-glucuronide.

THC-COOH- glucuronide showed the highest plasma concentrations among the cannabis metabolites, despite its lacking of psychoactive activity, as reported by Busardò *et al.* [62].

We set this unified cut-off of 5 and 60 ng/mL according to empirical results obtained from our patients: patients showing concentrations lower than the selected cut-off displayed undetectable concentrations of other metabolites.

As previously mentioned, female gender, inhaled cannabis and cigarettes smoke were predictors of higher cannabinoids concentrations in plasma.

Potential drug interactions may occur between cannabinoids and cardiovascular system drugs.

In the literature, interactions between THC and CBD and anticoagulant and antiplatelet agents were investigated (Greger et al., 2019). Several studies showed cannabis inhibiting warfarin metabolism due to CYP2C9 interactions, resulting in higher plasma exposures. CBD inhibits CYP2C19 that is responsible for the transformation of clopidogrel to its active thiol metabolite.

These studies focused on potential toxic effect of cannabis, describing interactions, risks and side effects of cannabis on anticoagulant or antiplatelet medications use, providing information for clinical decisions about patient care.

No data ara avaiable in the literature about cardiovascular system drugs on cannabinoids plasma exposures.

5. Conclusions

The present study highlighted the variability in cannabinoid metabolites exposures between different galenic formulations. This great variability in cannabinoid formulations results in patient inter-individual difference in concentrations. Consequently, TDM could be useful to allow for dose adjustment and our study could help to identify therapeutic range and to guide this practice.

In addition, since the present study highlights decoction does not allow the achievement of effective cannabinoids plasma concentrations, future perspective could be the treatment with cannabis oil, in order to evaluate the PK and PD parameters.

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CRediT authorship contribution statement

Jacopo Mula: Validation. **Antonio D'Avolio:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Amedeo De Nicolò:** Formal analysis. **Miriam Antonucci:** Formal analysis. **Martina Billi:** Software. **Alice Palermiti:** Validation, Formal analysis. **David De Cori:** Visualization. **Alessandra Manca:** Writing – original draft, Validation, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Flavio Vischia:** Visualization. **Daniele Imperiale:** Visualization. **Nicola Luxardo:** Supervision. **Francesco Chiara:** Methodology. **Jessica Cusato:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Data curation. **Cristina Valz:** Writing – original draft, Project administration, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Alessandra Manca reports a relationship with CoQua Lab srl that includes: equity or stocks. Antonio D'Avolio reports a relationship with CoQua Lab srl that includes: equity or stocks

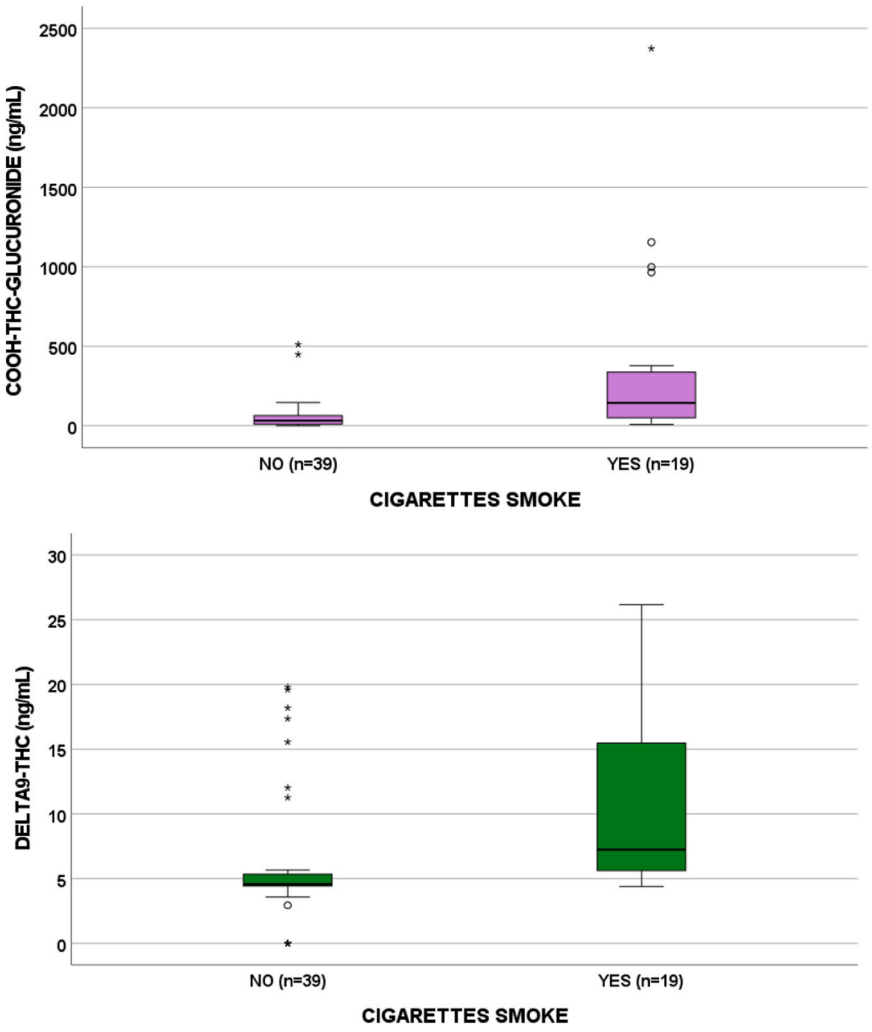

Fig. 4. Influence of cigarette smoke on COOH-THC-glucuronide exposure (p = <0.001) and Δ9-THC (p <0.001). Outliers are represented by little circles, and extreme outliers are represented by little stars.

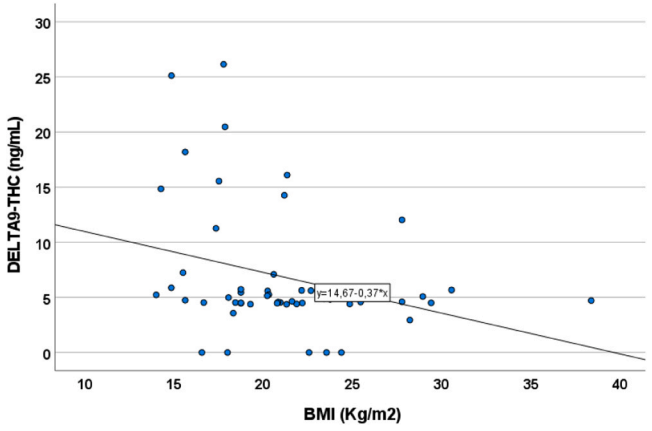

Fig. 5. Correlation between BMI (Kg/m^2) and Δ9-THC plasma levels (ng/mL) (p= 0.032, S = −0.300).

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