The minor cannabinoid cannabigerol (CBG) is a highly specific blood biomarker of recent cannabis smoking

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ABSTRACT

Introduction: The determination of recent cannabis use is of forensic interest in the investigation of automotive crashes, workplace incidents and other mishaps. Because $\Delta 9$-tetrahydrocannabinol may persist in blood after psychoactive effects of intoxication resolve, particularly in regular users, short-lived minor cannabinoids such as cannabigerol have merited examination as adjunct indicators of recent cannabis inhalation.

Methods: As part of an observational cohort study, whole blood cannabinoids including cannabigerol were measured in whole blood by liquid chromatography with tandem mass spectrometry at baseline, and 30 minutes after initiation of a 15-minute supervised interval of *ad libitum* cannabis smoking in occasional (1–2 days/week over the past 30 days) ($n = 24$) and daily cannabis smokers ($n = 32$). Per protocol, subjects self-reported abstention from inhaling cannabis (>8 h) or ingesting cannabis (>12 h) prior to baseline measurement.

Results: At baseline, none of the occasional users had detectable cannabigerol (limit of detection = $0.2 \mu g/L$), whereas cannabigerol was detectable post-smoking in 7 of 24 (29%). Among daily cannabis users, 2 of 32 (6%) had detectable cannabigerol at baseline, increasing to 21 of 32 (66%) post-smoking. The odds ratio for recent cannabis smoking associated with a detectable cannabigerol was 27 (95% confidence interval: 6.6, 110.3). In this mixed cohort of occasional and daily cannabis users, receiver operator characteristic curve analysis indicated that whole blood cannabigerol concentration of $\geq 0.2 \mu g/L$ had 96% specificity, 50% sensitivity, and 73% accuracy for identifying a 15-minute interval of *ad libitum* cannabis smoking initiated 30 minutes earlier. Post smoking blood $\Delta 9$-tetrahydrocannabinol (median = $5.6 \mu g/L$ in occasional users, $21.3 \mu g/L$ in daily users) was significantly correlated with post-smoking cannabigerol ($P < 0.0001$).

Conclusion: Whole blood cannabigerol may have forensic utility as a highly specific albeit insensitive biomarker of recent cannabis smoking.

Introduction

Cannabigerolic acid is a phytocannabinoid that occurs naturally in the cannabis plant [1–3]. As shown in Figure 1, cannabigerolic acid undergoes enzymatic conversion in the plant to tetrahydrocannabinolic acid and cannabidiolic acid, which decarboxylate after exposure to heat (e.g., by smoking, vaping or baking plant material) to form two cannabinoids of particular pharmacological interest, $\Delta 9$-tetrahydrocannabinol (THC) and cannabidiol. In contemporary commercial sources of cannabis flower (buds) cannabigerolic acid is commonly present on the order of one percent by dry weight, although specially bred cultivars may intentionally have cannabigerolic acid concentrations approximately 10-fold higher [4–6]. Heating or smoking of cannabis flower decarboxylates cannabigerolic acid to cannabigerol, a nonpsychoactive cannabinoid that has been detected in the blood of people who use it. In a study in which 11 frequent and nine occasional cannabis users smoked a relatively low THC concentration joint (6.9% total THC), CBG was detected in the whole blood of all those with frequent use and seven of those with occasional use [7]. The duration of detection was notably brief, no more than 30 minutes (min) after the inception of smoking in the frequent smokers and no more than 20 min in those with occasional use, resulting in the authors' suggestion that detection of cannabigerol in blood may be an indication of recent cannabis inhalation [7].

If detectable blood cannabigerol is a specific biomarker of very recent cannabis use in individuals with frequent as well
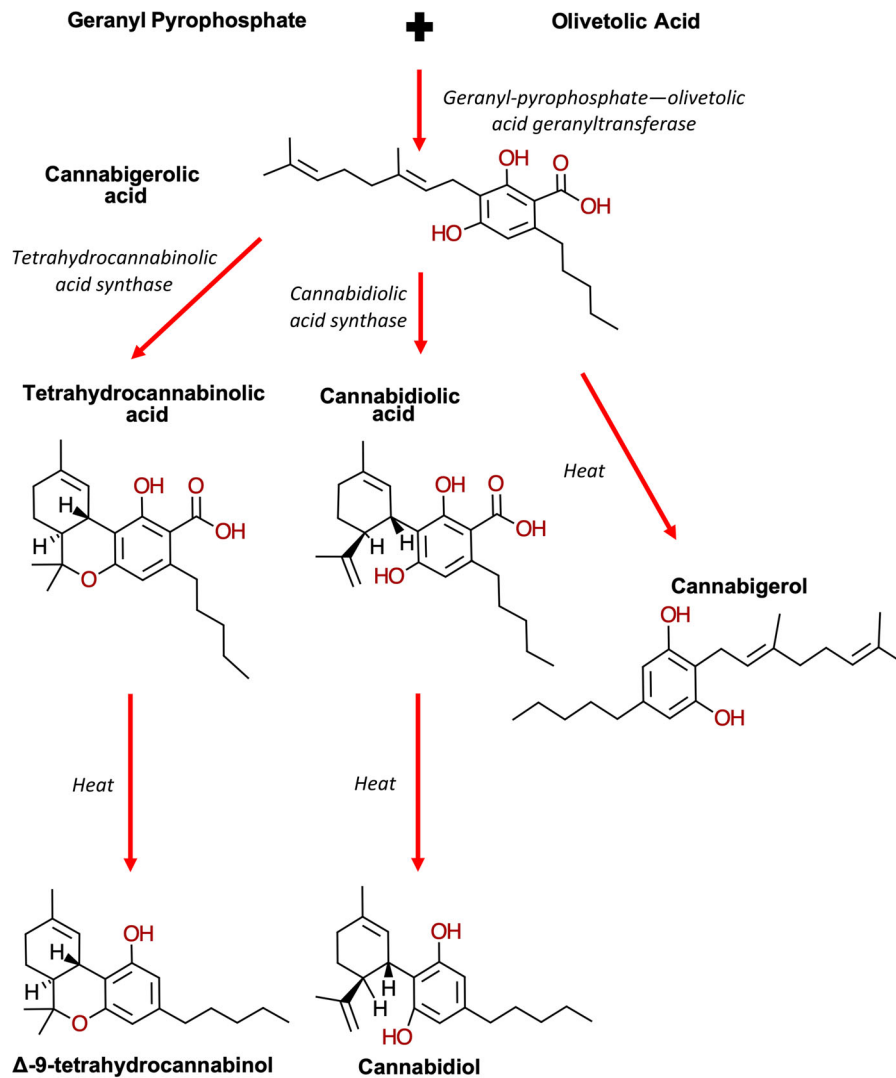
Figure 1. Synthesis pathway for the cannabinoids cannabigerol, tetrahydrocannabinol and cannabidiol. Tetrahydrocannabinolic acid and cannabidiolic acid are formed enzymatically in the cannabis plant. Although minor amounts of cannabigerol, tetrahydrocannabinol and cannabidiol may occur in native plant material, most are formed after heat-induced decarboxylation (e.g., by smoking, vaping, or baking). (Adapted from Pattnaik et al, [1]).

as occasional use, it may have utility as an adjunct to blood THC in some investigations. Forensic investigations of the potential contribution of recent cannabis use to individuals' involvement in transportation crashes or workplace mishaps have typically focused on the blood concentration of THC, the principal psychoactive component of the plant. However, THC may be detectable in the blood considerably longer than the four to eight hours usually associated with psychoactive effects following acute cannabis inhalation or ingestion [8]. This is particularly true in people with a pattern of daily or near daily cannabis use, for whom equilibration of highly lipophilic THC between adipose tissue and the blood results in detectable blood THC concentrations for days to several weeks following cessation of use [9].

The objective of the present study was to examine whether the blood concentration of cannabigerol can discriminate recent cannabis smoking (within the past 30 min) from baseline status (i.e., following 8 or more hours of cannabis abstinence) in a cohort of subjects with a pattern of either daily or occasional cannabis use.

Methods

Study design and subjects

This study was part of a larger investigation that prospectively examined the within-subject change in performance on driving simulator measures and on tablet-based psychomotor tests assessed at a pre-smoking baseline and again 30 min after the start of a 15-minute interval of acute cannabis smoking or rest [10]. For this report, we present the analysis of blood THC and cannabigerol concentration collected as a part of that project. Healthy adults (age 25–45) were recruited in the Denver, Colorado area between October 2018 and February 2020. Since a key objective of our larger study was to investigate the role of cannabis use history on acute changes in performance, subjects were recruited (within age and gender quotas) whose cannabis use pattern consisted of either (1) daily cannabis use defined as smoking or vaping cannabis flower product at least one time per day, every day of the week for 30 days prior to enrollment; or (2) occasional cannabis use defined as smoking or vaping

cannabis flower product on at least one day but no more than two days per week in the 30 days prior to enrollment. Use was inclusive of any other cannabis product (e.g., edibles), as long as their typical usage pattern included smoking or vaping. Enrollment criteria pertinent to the present report included the exclusion of individuals with a past or current history of significant medical illness, those who would not agree to refrain from use of nonprescription psychotropic drugs, opioids, or sedative hypnotics during the study, individuals with a body mass index $>35 \, kg/m^2$, and those who were pregnant or nursing an infant. No included subjects had consumed medications that exhibited moderate or strong inhibition of the cytochrome P-450 enzymes involved in THC metabolism.

Participants who met full study enrollment criteria based on a web-based questionnaire attended an in-person screening visit to review and confirm the criteria. Cannabis use history was assessed by completion of a 30-day timeline follow-back calendar reporting all cannabis use. Participants completed an alcohol breath test (Lifeloc FC10[TM]) to screen for acute alcohol use and provided a urine sample to test for illicit drug use or use of prescription drugs not prescribed (30 mL Alere brand 13-panel iCup®). A positive urine 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH, TCH-carboxylate) was not exclusionary for occasional users and was requisite for daily users. A data collection visit was then scheduled within 10 days, and usually less than a week from the screening visit. For the data collection visit, participants were instructed not to use inhaled cannabis for at least 8 h and not to consume edible cannabis for at least 12 h before the appointment. Their cannabis use pattern between the screening visit and data collection visit was also verified by review of a diary detailing the time and amount of all cannabis use, other medication and drug use, and sleep duration.

Measurements: cannabis consumption and blood cannabinoids

Cannabis use occurred within an observational, naturalistic design in which subjects obtained their own cannabis flower (bud) from a state-licensed Colorado dispensary that was brought to the study site in its original labeled packaging. The labeling listed the total percent THC (tetrahydrocannabinolic acid + THC), which for this study was required to be between 15% and 30% by weight and less than 2% cannabidiol by weight. The cannabigerolic acid and cannabigerol content of the product were not listed. During a 15-minute interval, participants in the user groups were instructed to smoke *ad libitum* "the amount you most commonly use for the effect you most commonly desire." Smoking occurred *via* a pipe, joint (rolled cigarette), bong or vaporizer according to the participant's choice. Only one subject, with a pattern of occasional use, used a vaporizer. The smoking occurred in a ventilated room with the subjects seated in a recliner.

Prior to use, and 30 min after the start of smoking (15-minutes after the end of the smoking period), a certified phlebotomist collected approximately 10 mL of whole venous blood into grey-top tubes (BD brand vacutainer tubes containing 100 mg sodium fluoride and 20 mg potassium oxalate additive). Blood was stored at approximately 4 °C (39.2 °F) for analysis within 30 days. Whole blood samples were shipped on cold packs to the Colorado State University Analytical Toxicology Laboratory for analysis.

Whole blood samples were prepared for liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis by using solid phase extraction following a published methodology by Schwope et al. [11]. Prepared calibrators, controls, and samples were analyzed with an Agilent 1290 Ultra High Performance Liquid chromotography system coupled to an Agilent 6460 triple quadruple mass spectrometer equipped with an Agilent Jet Stream electrospray ionization source (Agilent, Santa Clara, CA). Cannabinoids were first chromagraphically separated on a Restek Raptor Biphenyl column (2.1 × 100 mm, 5 μm) held at 40 °C. A sample volume of 10 μL was injected in a mixture of water with 5 mM ammonium acetate/0.1% acetic acid (A) and 15% methanol in acetonitrile (B) at a flow rate of 0.4 mL/min. The gradient elution used was 30% B for 1 min, increasing to 100% B at 7 min, and held at 100% B for 3 min. The ionization source conditions used were as follows: nebulizer 45 psi; gas flow of

Table 1. Participant demographic characteristics by cannabis use history.

Demographic	Daily use $n = 32$	Occasional use $n = 24$
Gender	n (%)	n (%)
Male	18 (56)	14 (58)
Female	14 (44)	10 (42)
Age (y)		
Mean (SD)	33.6 (5.7)	31.5 (4.9)
Median	32.7	30.1
Range	(25.4, 45.3)	(25.1, 41.3)
Interquartile Range (IQR)	(28.7, 37.4)	(28.0, 34.7)
Cannabis use Mean (standard deviation)		
Age at first use, years	17.2 (5.7)	17.6 (4.7)
Number of days used, past 30	29.7 (1.2)	5.7 (2.6)
Number of days use per week, past 30	7.0 (0.0)	1.5 (0.5)
Times used per day on average, past 30	5.1 (4.6)	1.4 (0.9)
Time in hours of abstinence prior to baseline blood collection[a]	13.0 (2.6)	39.1 (30.6)

[a]Due to missing values, the mean and standard deviation (SD) were calculated based on 29 daily users and 22 occasional users.
Occasional cannabis use defined as smoking or vaping cannabis flower product on at least one day but no more than two days per week in the 30 days prior to enrollment.

Table 2. Whole blood cannabigerol and Δ9-tetrahydrocannabinol concentrations in participants with daily or occasional use at baseline and 30 min post-inception of a 15 min interval of *ad libitum* cannabis smoking.

| | Daily use (n = 32) | | | | | | Occasional use (n = 24) | | | | | |
| | Baseline | | | Post-smoking (30 min) | | | Baseline | | | Post-smoking (30 min) | | |
	% ≥ LOD	Median (μg/L)	Range (μg/L)	% ≥ LOD	Median (μg/L)	Range (μg/L)	% ≥ LOD	Median (μg/L)	Range (μg/L)	% ≥ LOD	Median (μg/L)	Range (μg/L)
CBG	6.3	0	0–1.4	65.6	0.5	0–2.9	0	0	0-0	29.2	0	0–1.0
THC	87.5	2.7	0–26.0	100	21.3	1.3–146.7	0	0	0-0	100	5.6	1.0–29.6

Limit of detection (LOD) = 0.2 μg/L for cannabigerol and Δ9-tetrahydrocannabinol: min = minutes.

12 L/min at 330 °C; sheath gas flow of 12 L/min at 390 °C. The electrospray ionization polarity was set to positive for THC. Negative ionization was used for THC-carboxylate. Two ion transitions (m/z) were monitored for each analyte and the corresponding deuterium-labeled internal standard. The data collection and processing were performed by using Agilent MassHunter Quantitative software (B.08.01). Quantitation was performed with linear regression using 6-point calibration curves. For both THC and cannabigerol, limits of quantitation (LOQ) were 0.5 μg/L, and limits of detection (LOD) were μg/L. Additional cannabinoids were also measured (data not shown for this report).

## Data analysis

The sample size was based on the parent study examining cannabis-induced impairment in the driving simulator [10]. The final participant count for this examination of blood cannabinoids was 56, consisting of 24 subjects with a pattern of occasional use and 32 with a pattern of daily use. The median, mean and standard deviation of THC and cannabigerol were calculated from whole blood obtained at pre-smoking baseline and at 30 min after the inception of the 15-minute *ad libitum* cannabis smoking interval. The final datasets for whole blood THC and cannabigerol each contained 112 values, corresponding to a baseline measurement and a post-smoking measurement for each of the 56 participants. Logistic regression models were built to examine the association between a detectable (≥ LOD) whole blood cannabigerol and recent cannabis smoking (i.e., 30 min post inception of smoking). A receiver operating characteristic (ROC) curve was created to examine the optimal cut-point of whole blood CBG that discriminated the dichotomous outcome of whether or not the value was obtained from the baseline or post-smoking blood collection based on an optimal combination of accuracy, specificity, Youden's J statistic ((J = sensitivity + specificity − 1), and the distance to the upper left-hand corner of the ROC curve (coordinate 0,1). To account for the high number of values less than the LOQ (i.e., left-censored data), the relationship between post-smoking whole blood cannabigerol and THC concentration (n = 56 observations) were assessed by Tobit linear regression. All the data analysis was performed using SAS 9.4 (SAS Institute, Cary NC).

Results

The demographic features of the 56 subjects included in this analysis are presented in Table 1.

Baseline and post-smoking laboratory data on the detectability, median, and range of cannabigerol and THC in blood are shown in Table 2. At baseline, cannabigerol was not detectable (i.e., was less than the LOD) in all 24 of those with occasional use and in 30 of 32 of those with daily use. At 30 min following the inception of the 15-minute *ad libitum* cannabis smoking interval, cannabigerol was detectable (≥ LOD of 0.2 ng/mL) in 28 of 56 participants (48%). This included seven of 24 (29%) of the occasional use participants and 21 of 32 (66%) of the daily use participants. The group
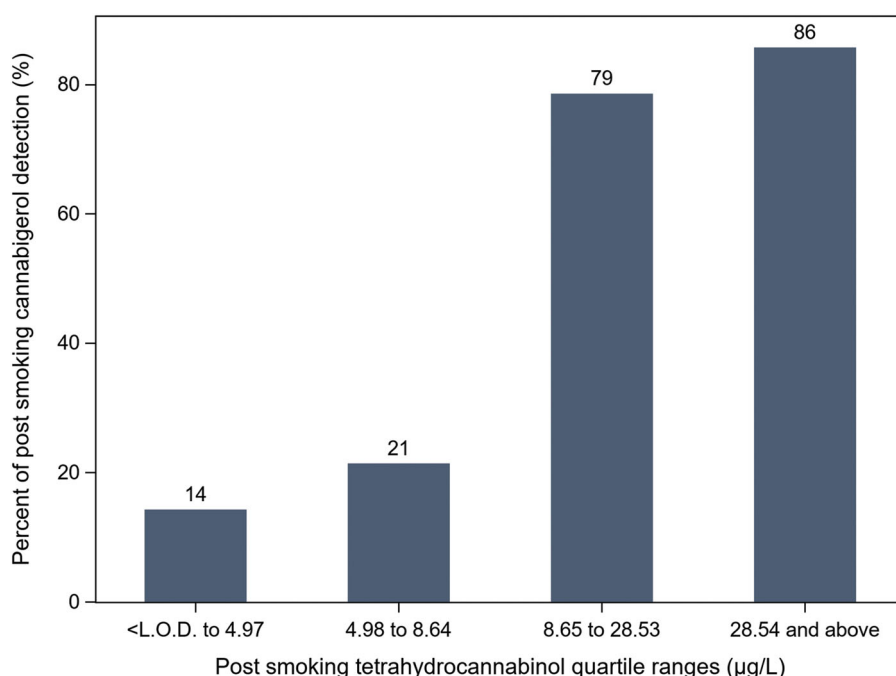
Figure 2. Percentage of post-smoking whole blood samples with a detectable cannabigerol value ($\geq 0.2\,\mu g/L$) by quartiles of $\Delta 9$-tetrahydrocannabinol ($n = 56$). LOD: limit of detection ($0.2\,\mu g/L$).
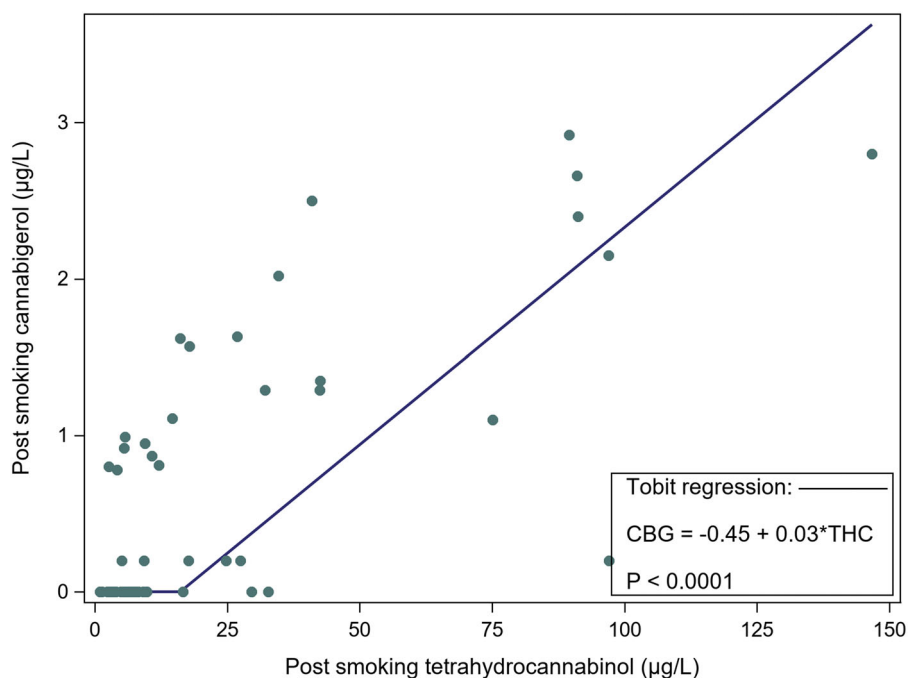

Figure 3. Tobit linear regression of post-smoking whole blood cannabigerol (CBG) by $\Delta 9$-tetrahydrocannabinol (THC). LOD $= 0.2\,\mu g/L$, LOQ $= 0.5\,\mu g/L$ for cannabigerol and tetrahydrocannabinol. n $= 56$.

differences in the percentage of detectable cannabigerol was not statistically significant at baseline (Fisher's $P = 0.50$) and was statistically significant at post-smoking ($P = 0.01$).

At baseline, whole blood THC was nondetectable in all the participants with a pattern of occasional use and had a median value of $2.7\,\mu g/L$ in those with daily use. Post-smoking, the median THC concentration in daily users ($21.3\,\mu g/L$) was almost four-fold higher than the median in those with occasional use ($5.6\,\mu g/L$). Figure 2 displays the percentage of subjects with a detectable post-smoking cannabigerol value

by quartiles of post-smoking THC. Tobit linear regression of the data shown in Figure 3 revealed a significant correlation between post-smoking cannabigerol and THC ($P < 0.0001$). Of the 28 subjects with a detectable post-smoking cannabigerol, all but two had a post-smoking THC $\geq 5\,ng/mL$.

The only subjects who had detectable whole blood cannabigerol at baseline were two participants with a pattern of daily use whose baseline cannabigerol THC and THC-carboxylate were 1.21 and $1.36\,\mu g/L$, 14.95 and $15.66\,\mu g/L$, and 117 and $108\,\mu g/L$ respectively.
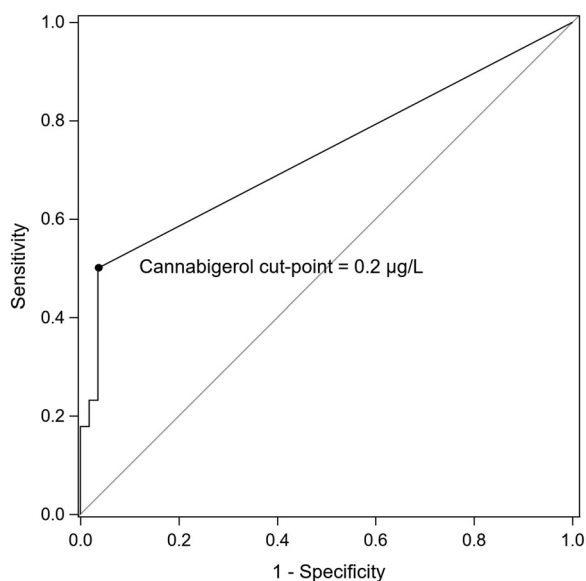
Figure 4. Receiver operator characteristic curve of whole blood cannabigerol concentration as an indicator of whether a subject had recently smoked cannabis ($n = 56$). For cutpoint of whole blood cannabigerol $= 0.20\,\mu g/L$: Area under the curve $= 0.7305$.

Table 3. Cannabigerol in whole blood. Predictive characteristics of a cut-point of 0.20 ng/mL for recent cannabis smoking in the entire subject cohort ($n = 56$).

	Actual cannabis consumption status	
	Baseline	Post Smoking
Cannabigerol < 0.20 +μg/L	54 (true negative)	28 (false negative)
Cannabigerol ≥ 0.20 +μg/L	2 (false positive)	28 (true positive)

Sensitivity: 50%; Specificity: 96%; Accuracy: 73%.

Figure 4, based on all pre and post-smoking blood results ($n = 112$) from all 56 subjects, presents a receiver operator characteristic curve of sensitivity versus (1 – specificity) for whole blood cannabigerol as an indicator of whether a subject had recently smoked cannabis. A cut-point for whole blood cannabigerol of $0.20\,\mu g/L$ yielded highest accuracy (0.73) and the largest Youden J statistic (sensitivity + specificity − 1; $J = 0.46$), with a specificity of 0.96 and a sensitivity of 0.50 for prediction of recent cannabis smoking. Table 3 presents the 2×2 confusion matrix for the cannabigerol cut-point of $0.20 + \mu g/L$. The odds ratio for recent cannabis smoking was 27 (95% CI: 6.6, 110.3) for those who had a detectable cannabigerol compared to those who did not have a detectable cannabigerol.

Discussion

We found that any detectable concentration of cannabigerol in whole blood (i.e., a value $>0.2\,\mu g/L$) is a highly specific indicator of smoking of cannabis initiated 30 min earlier, with a specificity of 96 percent. Sparse prior data that has suggested that cannabigerol may be a useful inclusionary marker of very recent cannabis smoking. Newmeyer et al. [7] found that whole blood cannabigerol was nondetectable at baseline in all of their subjects ($n = 11$ frequent smokers, $n = 9$ occasional smokers) after 19 h of supervised abstinence.

Cannabigerol was briefly detectable after the inception of a ten-minute interval of *ad libitum* smoking (median time of last detection of 15 min and 10 min respectively in the 10 frequent smokers and five occasional smokers with measurable post-smoking values). Sensitivity and specificity of cannabigerol detection at any time point were not reported in that study. In a cross-sectional analysis of blood cannabinoids in cannabis users ($n = 22$), Kraemer et al. [12] observed a serum cannabigerol concentration $>0.5\,\mu g/L$ (the LOQ) in three subjects with a self-reported interval since last cannabis inhalation of approximately 14, 17, and 23 h respectively (data read from their Figure 5). Assuming the ratio of serum to whole blood cannabigerol, like that of serum to whole blood THC, is approximately 2:1, their results would be consistent with our observation that smokers with a pattern of daily use may rarely have a detectable whole blood cannabigerol ($\geq 0.2\,\mu g/L$) more than 8 h since last cannabis inhalation. We observed that the likelihood of cannabigerol detection increases as blood THC concentration increases. This may be a consequence of a correlation between total cannabigerol (cannabigerolic acid + cannabigerol) and total THC (tetrahydrocannabinolic acid + THC) in most cannabis cultivars.

A limitation of the present study included the lack of information on the total cannabigerol content of the cannabis flower that was smoked. The total cannabigerol (cannabigerolic acid + cannabigerol) concentration is generally low in the cannabis plant, ranging from 1-3% of the plant mass [6]. Variability in the total content of cannabigerol in this investigation is likely to exist secondary to different cannabis strains with varied activity of the three major synthesis enzymes in the cannabinoid pathway [17], unknown age of the cannabis product, and unknown storage methods of the cannabis product [18], all of which impact the content of cannabigerol. State laboratories within Colorado analyze the content of cannabigerol in cannabis products, however, the cannabigerol concentration is not publicly reported and not required on product labels. Logistical constraints prevented supervised overnight abstinence of subjects prior to baseline data collection. Without overnight in-patient supervision, this investigation cannot exclude the possibility that some subjects, contrary to their report, were not abstinent for the requested interval prior to baseline blood collection, or that they used medications or other agents that may interfere with cannabinoid metabolism. The post-smoking blood collection occurred at only one time point which limited the ability to fully characterize the pharmacokinetic profile of the inhaled cannabinoids. Our collection of blood samples at 30 min after cannabis smoking may not reflect more common forensic scenarios where blood samples are obtained one or more hours after cannabis use. The sensitivity of cannabigerol as an indicator of recent cannabis smoking could have been enhanced by utilizing lower detection limits for cannabigerol in whole blood. However, the LC-MS/MS method used analyzed for several other cannabinoids and sensitivity for these other analytes would have been compromised by specifically targeting a lower cannabigerol detection limit. Future studies could enhance the sensitivity by

including a LC-MS/MS method optimized for cannabigerol only.

We are conducting pharmacokinetic studies of cannabinoids following cannabis product inhalation that will investigate the temporal pattern of cannabigerol at multiple additional time points. Based on the undetectability of cannabigerol in the urine of cannabis users [13], and the finding that cannabigerol was detectable in urine only after hydrolysis with β-glucuronidase [14], it appears that cannabigerol undergoes *in vivo* glucuronidation. The chemical structure of this glucuronidated metabolite and the temporal pattern of its appearance in blood after inhaled or ingested cannabis remain to be determined. It is currently unknown if cannabigerol-glucuronide or cannabigerol is a better biomarker of recent cannabis use. Deconjugation of cannabigerol and the subsequent determination of total cannabigerol may be an enhancement or detriment to the biomarker utility. Future laboratory methods would benefit from separate analysis of both intact cannabigerol-glucuronide and cannabigerol to determine their individual biomarker utility.

In conclusion, our findings indicate that the presence of detectable cannabigerol in blood is a highly specific but insensitive marker of recent cannabis smoking. Because acute subjective, psychomotor and neurocognitive effects of cannabis smoking are typically greatest within 30 or 60 min of smoking inception in subjects for whom such effects occur [8,15,16] cannabigerol may have utility as an adjunct to measurement of other blood cannabinoids for forensic and other related investigations. Cannabigerol detection may also aid assessment of recent cannabis use in chronic daily cannabis users for whom detection of THC in the blood extends several hours to days beyond time of last intake [19].

Disclosure statement

Funding

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