Oral lipid-based formulations alter delivery of cannabidiol to different anatomical regions in the brain

Alice Brookes[a], Adelaide Jewell[a], Wanshan Feng[a], Tracey D. Bradshaw[a], James Butler[b], Pavel Gershkovich[a,*]

[a] *School of Pharmacy, University of Nottingham, Nottingham, NG7 2RD, UK*

[b] *GlaxoSmithKline Research and Development, Park Road, Ware, Hertfordshire, SG12 0DP, UK*

***Corresponding author**: Pavel Gershkovich, PhD
School of Pharmacy, Biodiscovery Institute (BDI)
University of Nottingham, University Park
Nottingham, UK
NG7 2RD
Tel: +44 (0) 115 846 8014
Fax: +44 (0) 115 951 3412
Email: pavel.gershkovich@nottingham.ac.uk

Abstract

Delivery to the brain is a challenging task due to its protection by the blood-brain barrier (BBB). Lipids and fatty acids are reported to affect the permeability of the BBB, although this has not been reported following oral administration. Cannabidiol (CBD) has high therapeutic potential in the brain, therefore, tis work investigated CBD delivery to anatomical brain regions following oral administration in lipid-based and lipid-free vehicles. All formulations resulted in a short brain T_{max} (1 h) and brain-plasma ratios ≥3.5, with retention up to 18 h post administration. The highest CBD delivery was observed in the olfactory bulb and striatum, and the medulla pons and cerebellum the lowest. The lipid-free vehicle led to the highest levels of CBD in the whole brain. However, when each anatomical region was assessed individually, the long chain triglyceride-rich rapeseed oil formulation commonly showed optimal performance. The medium chain triglyceride-rich coconut oil formulation did not result in the highest CBD concentration in any brain region. Overall, differences in CBD delivery to the whole brain and various brain regions were observed following administration in different formulations, indicating that the oral formulation selection may be important for optimal delivery to specific regions of the brain.

Keywords:

Lipid-based drug delivery; Oral; Brain regions; Blood-brain barrier; Cannabidiol

Abbreviations

ABC	ATP-binding cassette
ACN	Acetonitrile
AD	Alzheimer's disease
ANOVA	Analysis of variance
AUC	Area under the curve
BBB	Blood-brain barrier
BCECs	Brain capillary endothelial cells
BSU	Bio Support Unit
CBD	Cannabidiol
CBDA	Cannabidiolic acid
C_{max}	Maximum concentration
CNS	Central nervous system
DDT	4,4-Dichlorodiphenyultrichloroethane
DS	Dravet syndrome
FDA	Food and Drug Administration
GBM	Glioblastoma multiforme
i.p.	Intraperitoneal
i.v.	Intravenous
LGS	Lennox Gastaut syndrome
LLOQ	Lower limit of quantification
MCT	Medium chain triglyceride
MS	Multiple sclerosis
P-gp	P-glycoprotein
PK	Pharmacokinetic
SD	Standard deviation
THC	Δ^9-tetrahydrocannabinol
T_{max}	Time of maximum concentration
TMZ	Temozolomide

1. Introduction

1.1. Fatty acids and the blood-brain barrier

Delivery of drugs to the brain is very important when treating diseases associated with the central nervous system (CNS), such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease and brain cancers. However, the blood-brain barrier (BBB) presents an obdurate challenge for drug delivery when targeting the brain. The BBB is a physical barrier between the blood and the central nervous system, restricting the movement of compounds into the CNS. The protective BBB is formed of tightly packed brain capillary endothelial cells (BCECs) that surround blood capillaries and are supported by astrocytes, creating tight junctions between cells (N. J. Abbott et al., 2010). BCECs exhibit specific ATP-binding cassette (ABC) transporters such as P-glycoprotein (P-gp; ABCB1; multidrug resistance protein-1) efflux pump, which is responsible for multi-drug resistance (T. M. Grogan et al., 1993). This, combined with other structures specific to the BBB limit the passage of drugs across the barrier (N. J. Abbott et al., 2010).

Most brain delivery studies to date investigate the delivery of molecules to the whole brain (A. V. Vergoni MD et al., 2009; F. E. Abdelrahman et al., 2015; J. Frigell et al., 2014; X. Y. Ke et al., 2010). However, it is known that various anatomical regions of the brain have different structures and chemistries, and are responsible for diverse physiological activity (A. Martin and Chao, 2001; Ackerman, 1992). Studies that investigate delivery to different anatomical brain regions usually do so by *in vivo* imaging. This is usually a qualitative technique (A. S. Yu et al., 2013; F. Sousa et al., 2010; J. Shen et al., 2013; L. Sztriha and Betz, 1991; T. Sprenger et al., 2005), whereas quantitative methods improve understanding of the detailed distribution. When developing new treatments for brain-located diseases, quantitatively investigating the delivery of drug molecules to the desired anatomical region of the brain is sometimes more important than studying the whole brain. For example, the aggressive brain cancer glioblastoma multiforme (GBM) is most commonly located in the frontal, temporal and parietal lobes of the brain, requiring delivery of chemotherapeutic agents to these locations (B. Jeremic et al., 1994). In contrast, AD usually begins destroying neurons within the hippocampus (M. M. A. Engels et al., 2016).

Oral administration of drugs is generally preferred due to the ease of administration and better patient experience and compliance. Oral lipid-based formulations are a common choice to improve the systemic bioavailability of lipophilic drugs *via* increased solubility, permeability and, if intestinal lymphatic transport is involved, avoiding hepatic first-pass metabolism (O. M. Feeney et al., 2016). Certain lipids have also been reported to affect the permeability of the BBB (A. Brookes et al., 2022). The effect is thought to be dependent on the fatty acid composition, including chain length and degree of saturation.

Triglycerides are the most common lipids used in lipid-based formulations (Hauss, 2007), as their structure is simple and are also a main lipid in the human diet (O. M. Feeney et al., 2016; Ros, 2000). After oral administration, triglycerides undergo a digestion process in the intestinal lumen resulting in free fatty acids and monoglycerides (J. A.Yáñez et al., 2011). Following absorption into enterocytes, short and medium chain ($C \leq 12$) fatty acids diffuse to the basolateral side and enter the blood circulation *via* the portal vein. On the other hand, long chain fatty acids are re-acylated and assembled into chylomicrons (large triglyceride-rich lipoproteins) in the enterocytes, and then enter the systemic circulation *via* the mesenteric lymph and thoracic lymph duct. Differences in digestion and in absorption pathways could result in different effects on the BBB, including the time after administration before an effect on the barrier is seen. However, there are still substantial gaps at present in the understanding of the effects of lipids on BBB permeability after oral administration (A. Brookes et al., 2022).

Oleic acid (carbon chain length 18, with 1 double bond, C18:1) is thought to interact with the BCECs membranes of the BBB to increase permeability, which appears to be reversible after 80-90 mins (A. Brookes et al., 2022; L. Sztriha and Betz, 1991). Sztriha et al studied the effects of oleic acid infusion

on BBB permeability by studying the distribution of Evans blue dye in rat brains. The dye was found most prominently in the hippocampus, left parasagittal cortical area and right cortical area, and occasionally in the right cerebellar hemisphere after administration of 10^{-5} M oleic acid. The authors suggested that at low concentrations, oleic acid penetrates into membranes and alters physiological function in a membrane-stabilizing manner (L. Sztriha and Betz, 1991). At higher concentrations, oleic acid monomers can form micelle structures by aggregation, which when incorporated into a membrane physically disrupt the lipid-bilayer (L. Sztriha and Betz, 1991). Alternatively, oleic acid is known to activate protein kinase C, which can lead to changes in BBB permeability in a reversible manner (L. Sztriha and Betz, 1991).

Linoleic acid (C18:2) is also reported to increase permeability of molecules across the BBB, as demonstrated by Ke et al when conjugated to paclitaxel (X. Y. Ke et al., 2010), and has been shown to increase the permeability of tight junctions, a prominent structural feature of the BBB (W. G. Jiang et al., 1998). Another fatty acid, myristic acid (C14:0), is also reported to enhance BBB permeability (A. Brookes et al., 2022; J. Shen et al., 2013). The C14 chain length is suggested to be optimal for affecting BBB permeability after intravenous (i.v.) injection, providing sufficient hydrophobic interaction, but preventing strong binding by longer chains (J. Shen et al., 2013).

1.2. Cannabidiol

Cannabidiol (CBD) is the most abundant non-psychoactive cannabinoid of the *Cannabis Sativa* plant. CBD has been administered orally in a range of lipid-based formulations (A. Zgair et al., 2017; A. Zgair et al., 2016; W. Feng et al., 2021). It has high potential medicinal value, with reports of activity against anxiety, schizophrenia, MS, and cancer. CBD is a highly lipophilic molecule, known to cross the BBB after oral administration (F. C.alapai et al., 2020; J. Aparicio-Blanco et al., 2019; J. Aparicio Blanco et al., 2019; S. Deiana et al., 2012). The biodistribution of other phytocannabinoids to the brain have been studied following alternative administration routes including i.v. and intraperitoneal (i.p.) injection, generally reporting a brain time of maximum concentration (T_{max}) later than plasma T_{max} (F. C.alapai et al., 2020; L. L. Anderson et al., 2019). It has also been reported that higher levels of CBD are delivered to the brain than Δ^9-tetrahydrocannabinol (THC) after i.v. injection (F. C.alapai et al., 2020; Grothenhermen, 2003).

Hložek et al reported that oral administration of CBD in sunflower oil to rats (10 mg/Kg) resulted in higher CBD absorption compared to subcutaneous administration (T. Hložek et al., 2017). Although they only studied administration in sunflower oil, their suggestion that administering CBD in oil results in high bioavailability is in line with other reports in the literature (A. Zgair et al., 2017; W. Feng et al., 2021). When CBD was orally administered in a sesame oil formulation by our group, a 3-fold higher bioavailability was observed, compared to a lipid-free administration (A. Zgair et al., 2016; W. Feng et al., 2021). We later showed that the CBD concentration in the lymph fluid after oral administration in a sesame oil formulation was 250-fold higher than in plasma (A. Zgair et al., 2017).

The aim of this work was to assess the delivery of CBD across the BBB and determine the biodistribution of CBD between various relevant anatomical regions within the brain. Based on previous work and the fatty acids suggested to effect BBB permeability, the lipid-based oils chosen to study in this work were sesame, coconut, and rapeseed oils. Sesame oil is composed mainly of long chain linoleic and oleic acids at 30 and 44%, respectively. The remaining fatty acids present are palmitic acid (C16:0) at 13% and stearic acid (C18:0) at 8%, with traces of other fatty acids of chain length ≥C16 (W. Feng et al., 2022). Coconut oil's largest component is medium chain lauric acid (C12:0) at 29% composition. Coconut oil also contains myristic acid (21%), palmitic acid (18%), oleic acid (14%) and small amounts of octanoic (C8:0), decanoic (C10:0) and linoleic acid (W. Feng et al., 2022). Similar to sesame oil, rapeseed oil is also predominantly composed of long chain oleic acid (63%) and linoleic acid (20%),

with small amounts of palmitic acid (4%), stearic acid (2%) and linolenic acid (C18:3, 10%) (A. Lewinska et al., 2015). Based on the fatty acid composition of these oils, it could be expected that sesame oil and rapeseed oil would result in the highest permeation across the BBB. However, coconut oil contains myristic acid, which has also been reported to increase BBB permeability. A lipid-free formulation of CBD was also assessed for whole brain delivery and for distribution between different anatomical brain regions.

2. Material and Methods

2.1. Materials

Plant derived CBD was purchased from THC Pharm (Frankfurt, Germany). 4,4-Dichlorodiphenyultrichloroethane (DDT), sesame oil, coconut oil and rapeseed oil were purchased from Sigma Aldrich (Dorset, UK). High purity propylene glycol was purchased from VWR (Poole, UK). All other solvents and reagents used were of HPLC grade or higher and purchased from Fisher Scientific (Leicester, UK).

2.2. Animal experiments

The experiments were reviewed and approved by the University of Nottingham Ethical Review Committee in accordance with the Animals [Scientific Procedures] Act 1986. Studies were carried out following the National Research Council's Guide for the Care and Use of Laboratory Animals. Male Sprague Dawley rats (275-325 g, Charles River Laboratories, UK) were used for biodistribution studies. The animals were housed in a temperature and humidity-controlled environment with a 12 h light-dark cycle in University of Nottingham Bio Support Unit (BSU) with free access to food and water.

2.3. Biodistribution studies

Following five days acclimatization, the animals were fasted overnight with free access to water. CBD was solubilised in sesame oil, coconut oil or rapeseed oil, or in a lipid-free vehicle (propylene glycol:ethanol:water, 80:10:10, v/v/v). All formulations (12 mg/mL CBD) were prepared on the day of the experiment and were administered by oral gavage at a dose of 12 mg/Kg. This dose was selected as it is well below the concentration where CBD has previously been demonstrated to effect the lipolysis of oils (80 mg/mL) (Zgair, 2017). Animals were humanely sacrificed at the pre-determined time points of 1, 2, 3, 5, 8, 12, 15 and 18 h post administration (n = 3 animals per time point, per formulation). Brain tissue was collected and dissected based on Spijker (2011) (Spijker, 2011). With the ventral side of the brain facing down, the olfactory bulb was removed before removing the cerebral stem and isolating the cerebellum from the medulla and pons. The cortex was opened from the midline by placing closed forceps between the two cortex halves and gently opening, as depicted in Spijker (2011) (Spijker, 2011). The cortex was moved aside to allow the removal of the hippocampus from both left and right sides. The cortex was folded back into place and the front section of the brain was removed as the frontal lobe. This allowed the striatum to be located and part of it isolated from the frontal lobe. The remaining tissue was separated into the parietal, temporal and occipital lobes. Tissues were kept frozen at -80 °C until analysis.

2.4. Bioanalytical procedures

Collected tissues were homogenised in water (1:2, w/v) at 30,000 rpm using POLYTRON PT 10-35 GT (Kinematica AG, Luzern, Switzerland) before analysis.

The analysis of CBD concentration in homogenates was performed using a previously validated HPLC-UV method for plasma (A. Zgair et al., 2015). The method was first assessed to be suitable for brain tissue by analysing samples of blank tissues and tissues spiked with CBD to ensure that no matrix-related interfering peaks are present. In brief, for sample preparation, 10 µL DDT solution (internal standard, 50 µg/mL in acetonitrile (ACN)) was spiked into 100 µL of sample (tissue homogenate). Cold ACN (450 µL) was added for protein precipitation and the sample was vortex-mixed, followed by the

addition of 450 µL water and further vortex-mixing. Liquid-liquid extraction was performed with 3 mL hexane by vortex-mixing for 5 min. The samples were centrifuged at 3500 rpm, 10 °C for 10 min before the organic phase was evaporated until dry under nitrogen at 37 °C. The dry residual was reconstituted in 100 µL ACN.

An HPLC system comprising of Waters 1525 pump, 717 autosampler, 2996 photodiode array detector, X-ACT (Jour Research) degasser and Kontron Instruments 480 column oven was used for analysis. Separation was achieved using an ACE 3 C18-PFP 150 mm x 4.6 mm, 3 µm column with an ACE C18-PFP 3 µm guard column at 55 °C. The isocratic mobile phase was 62% acetonitrile in water at a flow rate of 1 mL/min. Absorbance was monitored at 220 nm. Data were processed using Empower II software (Waters, Milford, MA, U.S.). The retention times of CBD and internal standard (DDT) were 9 and 24 min, respectively. The lower limit of quantification (LLOQ) of CBD in brain tissue was 20 ng/g.

2.5. Data Analysis

All data are presented as mean ± standard deviation (SD) of the n = 3 animals per time point, per formulation. One-way analysis of variance (ANOVA) was used to assess significance of differences between the dosing groups. With $\alpha = 0.05$, a $p = 0.05$ was considered statistically significantly different. Statistical analysis was performed using GraphPad Prism version 9.2.0 (GraphPad Software, San Diego, CA, USA). Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis using Phoenix WinNonlin 6.3 Professional (Certera, Princeton, NJ, U.S.).

3. Results

3.1. Delivery of CBD to the whole brain

The biodistribution of CBD to the brain following oral administration in lipid-based and lipid-free formulations were assessed up to 18 h post administration. The concentrations of CBD in the whole brain are shown in Figure 1. Parameters derived from brain concentration data and plasma PK concentration-time profile collected in a previously-performed PK study (Feng *et al.* (W. Feng et al., 2022; W. Feng et al., 2021)), including the T_{max}, maximum concentration (C_{max}) and area under the curve (AUC) are represented in Table 1. Since post-mortem changes in concentrations of drugs in blood and plasma have been previously reported (M. C. Yarema and Becker, 2005; T. Hilberg et al., 1999a; T. Hilberg et al., 1999b; T. L. Perry et al., 1981), it was decided to use plasma concentrations from previously obtained PK studies for comparison. Statistically significant differences in CBD concentrations in the whole brain were found at 1 h post administration ($p<0.0001$): where both the lipid-free vehicle and sesame oil formulation led to significantly higher levels than the other two vehicles. Additionally, the lipid-free formulation resulted in higher ($p<0.05$) CBD concentration than the sesame oil formulation at 1 h.

Administration of CBD in the lipid-free vehicle resulted in the highest C_{max} (2712 ± 2365 ng/g) and $AUC_{0-\infty}$ (3270 ± 1890 h*ng/g) when the brain was analysed as a whole (Figure 1). This was then followed by the sesame oil, and then coconut oil and rapeseed oil formulations (the latter two being not significantly different from each other). The T_{max} always occurred at 1 h post administration, despite the varied previously obtained plasma T_{max} (Table 1). Exposure (AUC) of the brain tissue to CBD was consistently higher than plasma exposure, with drug still detectable as late as 18 h after administration.

Table 1. Pharmacokinetics parameters of CBD in plasma and whole brain after oral administration to rats. Whole brain data are shown in Figure 1, plasma data was collected and reported in previously performed PK study and shown here for comparison (Feng *et al.* (W. Feng et al., 2022; W. Feng et al., 2021)). All data are presented as mean ± SD, brain regions n = 3, plasma n = 6. One-way ANOVA with Dunnett's multiple comparisons was performed, lipid-based groups were compared to the lipid-free group, $\alpha = 0.05$, * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, **** = $p<0.0001$.

		T_{max} (h)	**C_{max} (ng/mL or ng/g)**	**$t_{1/2}$ (h)**	**AUC_{0-t} (h*ng/mL or h*ng/g)**	**$AUC_{0-\infty}$ (h*ng/mL or h*ng/g)**	**Brain-plasma ratio[b]**
Lipid-free	Plasma[a]	5	55 ± 39	2.3	-	356 ± 83	9.2
	Whole brain	1	2712 ± 2365	9.6	2989 ± 1863	3270 ± 1890	
Sesame oil	Plasma[a]	3	164 ± 142	1.5	-	865 ± 342	3.5
	Whole brain	1	1836 ± 473*	4.6	2949 ± 242	3061 ± 242*	
Coconut oil	Plasma[a]	5	84 ± 72	1.5	-	413 ± 164	4.3
	Whole brain	1	876 ± 338****	3.9	1525 ± 486*	1794 ± 373**	
Rapeseed oil	Plasma[a]	5	118 ± 54	1.7	-	587 ± 287	4.6
	Whole brain	1	539 ± 340****	10.1	1803 ± 365*	2726 ± 1635*	

[a] Plasma data used were collected in a previously performed PK study (Feng *et al.* (W. Feng et al., 2022; W. Feng et al., 2021)) due to reported post-mortem changes in blood and plasma concentrations (M. C. Yarema and Becker, 2005; T. Hilberg et al., 1999a; T. Hilberg et al., 1999b; T. L. Perry et al., 1981).

[b] Brain-plasma ratio calculated by dividing the whole brain $AUC_{0-\infty}$ by the plasma $AUC_{0-\infty}$.

3.2. Distribution of CBD between various relevant anatomical brain regions

The biodistribution of CBD to specific anatomical regions of the brain was assessed following oral administration in a lipid-free vehicle, sesame oil, coconut oil and rapeseed oil formulations. The animals were sacrificed, and brain tissue was collected and dissected at time points up to 18 h post administration. Figure 2 shows the comparison of CBD concentrations in relevant anatomical brain regions to the previously obtained plasma PK profile for each formulation studied. Figure 3 shows the same data, re-formatted to compare the delivery of CBD to each brain region after administration in the different formulations. The pharmacokinetic parameters of the delivery of CBD to the anatomical brain regions is shown in Table 2.

Figure 2 allows comparison of the previously obtained plasma PK profile (W. Feng et al., 2022; W. Feng et al., 2021) with the anatomical brain regions, including the whole brain. Statistically significant differences in brain regions CBD concentrations compared to the plasma concentration were seen at 1, 8 and 12 h post administration. Plasma PK profile data were obtained in a previous study (W. Feng et al., 2022; W. Feng et al., 2021) and therefore stops at 12 h, since the concentration is reaching the LLOQ of the bioanalytical method (10 ng/mL) (A. Zgair et al., 2015). However, CBD concentrations in certain anatomical regions of the brain remain substantially higher, >100 ng/g even 18 h after administration.

Table 2. Pharmacokinetic parameters of CBD in anatomical brain regions after oral administration to rats (12 mg/Kg). All data are presented as mean ± SD, n = 3. Data also presented in Figures 2 and 3.

		T_{max} (h)	C_{max} (ng/g)	$t_{1/2}$ (h)	AUC_{0-t} (h*ng/g)	$AUC_{0-\infty}$ (h*ng/g)
Lipid-free	Olfactory bulb	1	27542 ± 47390	2.2	53785 ± 85988	-
	Frontal lobe	1	1206 ± 1858	6.2	2066 ± 1279	2747 ± 1003
	Striatum	1	4373 ± 5637	5.7	14291 ± 6280	23480 ± 2210
	Hippocampus	1	1674 ± 2467	6.0	2270 ± 1589	3062 ± 1683
	Temporal lobe	1	874 ± 1388	12.0	1473 ± 1041	2184 ± 1045
	Parietal lobe	1	662 ± 1098	4.8	1644 ± 1411	2120 ± 1188
	Occipital lobe	1	10792 ± 17103	10.8	8157 ± 11677	8593 ± 11560
	Medulla pons	1	1525 ± 2421	14.0	2109 ± 1819	2633 ± 2383
	Cerebellum	1	1742 ± 2895	7.7	2296 ± 2373	3597 ± 3875
Sesame oil	Olfactory bulb	1	19126 ± 8473	2.7	31368 ± 18452	32556 ± 17785
	Frontal lobe	1	2413 ± 234	6.1	3759 ± 1498	4505 ± 1527
	Striatum	1	34751 ± 26284	7.2	27831 ± 16151	33792 ± 15254
	Hippocampus	1	2873 ± 1434	5.3	4599 ± 636	5574 ± 876
	Temporal lobe	1	1979 ± 378	2.6	4005 ± 1155	4256 ± 1025
	Parietal lobe	1	1891 ± 383	5.1	2660 ± 188	2963 ± 265
	Occipital lobe	1	1163 ± 1966	4.6	2532 ± 1989	2839 ± 1914
	Medulla pons	1	1371 ± 474	6.6	2429 ± 301	5929 ± 3133
	Cerebellum	1	1669 ± 495	6.8	2699 ± 892	3110 ± 875
Coconut oil	Olfactory bulb	1	6213 ± 3494	17.1	9214 ± 4330	28113 ± 6108
	Frontal lobe	1	1355 ± 1008	5.2	2565	3112
	Striatum	1	36810 ± 60180	2.8	40475 ± 4715	44372 ± 1205
	Hippocampus	1	737 ± 267	2.9	1326 ± 633	1482 ± 577
	Temporal lobe	1	455 ± 282	7.2	1270 ± 105	10327 ± 15426
	Parietal lobe	1	918 ± 383	15.2	1719 ± 1023	2215 ± 1264
	Occipital lobe	1	837 ± 646	6.4	1556 ± 916	1953 ± 913
	Medulla pons	1	720 ± 383	5.9	1308 ± 192	1662 ± 263
	Cerebellum	1	806 ± 459	17.3	1165 ± 319	1919 ± 277
Rapeseed oil	Olfactory bulb	1	2013 ± 1422	-	1785 ± 1212	-
	Frontal lobe	1	893 ± 724	7.8	1746 ± 606	2163 ± 519
	Striatum	1	20176 ± 30471	-	60381 ± 74716	-
	Hippocampus	1	1215 ± 998	3.4	3287 ± 859	4271 ± 1063

	Temporal lobe	1	611 ± 433	1.7	1883 ± 242	1965 ± 241
	Parietal lobe	1	293 ± 263	15.7	1749 ± 737	3180 ± 1445
	Occipital lobe	3	461 ± 571	8.5	3589 ± 2544	4636 ± 4173
	Medulla pons	1	319 ± 87	7.6	1167 ± 164	1393 ± 1897
	Cerebellum	1	665 ± 636	9.4	1717 ± 592	2738 ± 1475

The lipid-free vehicle led to statistically significant highest C_{max} compared to the lipid-based vehicles in the occipital lobe (10792 ± 17103 ng/g) and cerebellum (1742 ± 2895 ng/g). There were also statistically significant differences seen in the frontal lobe, hippocampus, temporal lobe, and parietal lobe, where the sesame oil formulation resulted in the highest C_{max}. In the striatum, both the sesame oil and coconut oil formulations resulted in significantly higher ($p<0.01$) C_{max} than the lipid-free vehicle. The lipid-free vehicle exhibited the fastest fall in CBD concentration. By 2 h post administration, the lipid-based vehicles all gave higher concentrations than following administration of CBD in the lipid-free vehicle.

CBD was found at the highest concentrations in the olfactory bulb (27542 ± 47390 ng/g) and striatum (36810 ± 60180 ng/g), followed by the occipital lobe (10792 ± 17103 ng/g). The lowest C_{max} were found in the parietal lobe (293 ± 263 ng/g), occipital lobe (461 ± 571 ng/g) and medulla pons (319 ± 87 ng/g), all after administration in the rapeseed oil formulation (Table 2).

In some brain regions, profiles with second concentration peaks were observed, demonstrated in Figure 3. This was seen after administration in the lipid-free vehicle in the frontal lobe, parietal lobe, and cerebellum. After administration in the sesame oil formulation this was observed in the olfactory bulb, frontal lobe, striatum, temporal lobe, and medulla pons. After administration in the coconut oil formulation second concentration peaks were observed in the olfactory bulb and striatum at 5 and 12 h. This phenomenon was also seen after administration in the rapeseed oil formulation in the striatum, hippocampus, occipital lobe, and medulla pons.

4. Discussion

Previous literature (L. L. Anderson et al., 2019; S. Deiana et al., 2012) generally suggests that CBD delivery to the brain is slow, exhibiting a T_{max} substantially later than that seen in plasma. However, a study by Hložek et al demonstrated a brain T_{max} at the same time as the plasma T_{max} after administration in sunflower oil (T. Hložek et al., 2017). The plasma T_{max} following administration of formulations used in this work, lipid-free, sesame oil, coconut oil and rapeseed oil solutions, are 5 h, 3 h, 5 h and 5 h, respectively (Table 1, obtained and calculated in our previous report (W. Feng et al., 2022; W. Feng et al., 2021) from studies using the same dose and administration route as this study). Therefore, the delivery of CBD to the brain in this study was expected to be between 5-8 h based on available literature. Interestingly, in our hands the observed T_{max} for all studied vehicles was as early as 1 h post administration (Table 1), earlier than that expected based on reports in the literature. However, to the best of our knowledge this is the first reporting of oral administration of CBD in formulations with the oils used in this work, therefore some difference from the formulations reported in the literature is to be expected. This rapid delivery to the brain suggests that high levels in the plasma might not be required for efficient delivery to the brain, as the plasma T_{max} reported by Feng *et al.* (W. Feng et al., 2022; W. Feng et al., 2021) (demonstrated in Figure 1 and 2) is later than the brain T_{max}.

Hložek et al reported a C_{max} of ~250 ng/g at 2 h after oral administration of CBD in sunflower oil at a dose of 10 mg/Kg (T. Hložek et al., 2017). Studying the fatty acid compositions of the oils, sesame oil is similar to sunflower oil, with slightly more oleic acid and less linoleic acid (W. Feng et al., 2022). The dose used in the current study is slightly higher than Hložek et al's work (12 mg/Kg). Using allometric scaling, the human equivalent dose would be ~2 mg/Kg, this is still a low dose compared to human clinical trials of CBD (CBD has reportedly been safely administered to humans at doses of 1500 mg/Kg in clinical trials) (A. B. Nair and Jacob, 2016; M. M. Bergamaschi et al., 2011; U.S. et al., 2005). Therefore, a C_{max} around 300 ng/g would demonstrate similar brain delivery by sesame and sunflower oil-based formulations. However, in our current work the C_{max} after administration in a sesame oil formulation was earlier than Hložek et al observed (T_{max} = 1 h), and as high as 1836 ± 473 ng/g (Table 1), 6-times higher than expected. The higher oleic acid content in sesame oil may be behind the difference in brain delivery, as mentioned, oleic acid is reported to increase the permeability of the BBB (A. Brookes et al., 2022; L. Sztriha and Betz, 1991; W. Feng et al., 2022).

The calculated brain-plasma ratios are all ≥3.5 (Table 1), whereas previously in the literature these are reported <1 for cannabinoids, apart from cannabidiolic acid (CBDA), which had a ratio of 1.9 after i.p. injection (L. L. Anderson et al., 2019), demonstrating the improved delivery of CBD to the brain after oral administration in the formulations used herein. A ratio greater than 1 demonstrates increased accumulation of CBD in brain tissue compared to the plasma. The highest ratio is observed for the lipid-free formulation (9.2), predominantly due to the lower plasma exposure ($AUC_{0-\infty}$ = 356 ± 83 h*ng/mL), however both the $AUC_{0-\infty}$ and C_{max} in brain are highest for the lipid-free vehicle (3270 ± 1890 h*ng/g and 2712 ± 2365 ng/g, respectively). Comparing this to the other vehicles, the sesame oil formulation produced the closest $AUC_{0-\infty}$ and C_{max} (3061 ± 242 h*ng/g and 1836 ± 473 ng/g, respectively) to the lipid-free formulation. However, the brain-plasma ratio is the lowest for the sesame oil formulation (3.5), potentially due to the high plasma exposure observed ($AUC_{0-\infty}$ = 865 ± 342 h*ng/mL). The coconut and rapeseed oil formulations produced similar, slightly higher ratios than the sesame oil formulation (4.3 and 4.6, respectively).

When comparing the lipid-based formulations, the C_{max} and AUC would suggest that the sesame oil formulation results in the highest BBB permeability of the lipid-based formulations (Table 1). However, the brain-plasma ratio suggests this is not the case, as both coconut and rapeseed oil formulations have higher ratios, with the rapeseed oil formulation exhibiting the highest ratio. This is consistent with reports in the literature as rapeseed oil contains relatively high oleic acid content of 62% (compared to

44% in sesame oil and 14% in coconut oil), reported to increase BBB permeability (L. Sztriha and Betz, 1991).

Studying the whole brain, the delivery profiles of each formulation are similar, showing no significant differences in CBD concentrations after 1 h (Figure 1). However, when the brain is studied in more detail by anatomical regions, different delivery profiles can be observed (Figures 2 and 3).

The highest CBD concentrations were found in the olfactory bulb and the striatum (Figure 2). After the T_{max} at 1 h in the olfactory bulb, the concentrations drop significantly at 2 h. Second concentration peaks are seen after administration in the sesame oil formulation (5 h), and at 12 h for the coconut oil and lipid-free formulations. The highest C_{max} and AUC_{0-t} were observed after administration in the lipid-free vehicle at 27542 ± 47390 ng/g and 53785 ± 85988 h*ng/g, respectively. Whereas the lowest exposure was observed after administration in the rapeseed oil formulation at 1785 ± 1212 h*ng/g, as CBD was not detected after 2 h. The large difference between the lipid-free and rapeseed oil formulations suggests that the composition of the orally administered oil affects the distribution of the co-administered lipophilic drug. Delivery to the olfactory bulb is important to understand in general, as it is involved in neurodegenerative diseases, where olfactory-dysfunction is an early symptom of both AD and Parkinson's disease (J. Attems et al., 2014; T. G. Ohm and Braak, 1987). CBD is reported to exhibit activity against AD and is even in clinical trials to reduce symptoms such as agitation (G. Watt and Kart, 2017; Medicine; S. H. Kim et al., 2019). Coconut oil has been reported to be beneficial for neuroprotection against AD, because the medium chain triglyceride (MCT) rich oil induces mild ketosis, which is positively correlated with cognitive performance (H. M. A. Khalil et al., 2020; S. V. Ramesh et al., 2021). Therefore, a coconut oil formulation of CBD would provide additional benefit to AD patients. Whilst the coconut oil formulation did not produce the highest exposure of the olfactory bulb to CBD, it did result in second concentration peaks at later time points, indicating some prolonged delivery (Figure 3).

Comparing the different formulations, delivery of CBD to the frontal lobe is quite consistent over the first 5 h after administration (Figure 2). After this time, the formulations produce different profiles. Both the rapeseed and sesame oil formulations produced second concentration peaks at 12 h, while the coconut oil formulation produced two second peaks (8 and 15 h), and the lipid-free formulation produced one additional peak at 8 h. The second concentration peaks at later time points led to higher exposure. The highest exposure is observed after administration in the sesame oil formulation, 3759 ± 1498 h*ng/g, where the highest second concentration peak is seen. The highest C_{max} is also seen after administration in the sesame oil formulation at 2413 ± 234 ng/g. The rapeseed oil formulation results in the lowest exposure, with an AUC_{0-t} of 1746 ± 606 ng/g. The two oils contain similar fatty acids, although at different ratios with different degrees of saturation (A. Lewinska et al., 2015; W. Feng et al., 2022), possibly affecting the delivery. The frontal lobe is an important region of study, as being the largest region of the brain, it is responsible for a variety of functions including movement, language, and attention (C. Chayer and Freedman, 2001). GBM tumours are commonly located in the frontal lobe (B. Jeremic et al., 1994), and CBD is currently in clinical trials for the treatment of GBM (in combination with THC, chemotherapy with temozolomide (TMZ) and radiotherapy) (U.S. et al.; U.S. et al.). Unpublished work in our group suggests that CBD could enhance the uptake of such imidazotetrazine agents. Higher delivery of CBD to the region could in turn increase the uptake of the imidazotetrazine agent and enhance the response to the treatment. A formulation resulting in higher retention of CBD in the region could have a similar effect, for example Table 2 shows that the rapeseed oil formulation results in the longest $t_{1/2}$ of CBD in the frontal lobe, at 7.8 h. This suggests prolonged exposure to the region, demonstrating the potential of the formulation for use against GBM.

As mentioned above, the striatum exhibits the highest CBD concentrations, along with the olfactory bulb (Figure 2). Similar to all other brain regions, the T_{max} is observed at 1 h for all formulations. Both the coconut oil and sesame oil formulations produce significantly higher C_{max} than the lipid-free vehicle.

They also produce higher exposure (AUC_{0-t} of 40475 ± 4715 and 27831 ± 16151 h*ng/g, respectively) than the lipid-free vehicle. Again, the CBD concentrations increase at later time points after administration in the sesame (15 h), coconut (8 h) and rapeseed (12 h) oil formulations. The increase observed in the rapeseed oil formulation group is quite significant, producing a high AUC_{0-t} of 60381 ± 74716 h*ng/g. There are high levels of cannabinoid receptors located within the striatum (E. M. Jansen et al., 1992; M. Herkenham et al., 1990), possibly explaining the high delivery here. CBD neuroprotective effects are also reportedly linked to activity in the striatum (A. B. Sonego et al., 2016). As mentioned above, coconut oil is reported to exhibit some neuroprotective effects for conditions such as AD (H. M. A. Khalil et al., 2020; N. S. Rahim et al., 2020; S. V. Ramesh et al., 2021). The high CBD C_{max} observed after administration in the coconut oil vehicle indicates a potentially promising formulation to provide neuroprotective effects in the striatum.

The high levels of cannabinoid receptors found in the hippocampus imply that high delivery of CBD occurs to this region (C. A. J. Stern et al., 2017; E. M. Jansen et al., 1992; M. Herkenham et al., 1990). The sesame oil formulation resulted in the highest delivery, C_{max} = 2873 ± 1434 ng/g, and AUC_{0-t} = 4599 ± 636 h*ng/g. The rapeseed oil formulation also resulted in higher exposure of the region to CBD than the lipid-free vehicle, with an AUC_{0-t} of 3287 ± 859 h*ng/g. On the other hand, the coconut oil formulation resulted in the lowest delivery. The hippocampus is a brain region of interest for many reasons. It is where AD usually begins destroying neurons (M. M. A. Engels et al., 2016), and is also associated with a number of brain functions, including memory processing and storage, stimulus response and behaviour (Douglas, 1967; Green, 1964; H. Eichenbaum and Otto, 1992). With the hippocampus involved in so many processes, it is important to understand drug delivery to this region. CBD demonstrates important association with the hippocampus, it is demonstrated to inversely correlate with the grey matter reduction in the hippocampus of cannabis users (in contrast a positive correlation was reported between THC and grey matter reduction). Thus, a neuroprotective effect of CBD in this region is implicated (T. Demirakca et al., 2011). CBD is also demonstrated to activate cannabinoid receptors in the hippocampus to interrupt fear memory consolidation and induce anti-depressant effects (C. A. J. Stern et al., 2017; M. A. Abame et al., 2021).

Studying the temporal lobe, the highest ($p<0.0001$) C_{max} is observed after administration in the sesame oil formulation, at 1979 ± 378 ng/g, where the highest AUC_{0-t} is also seen (4005 ± 1155 h*ng/g). The other three formulations produced similar C_{max} and AUCs. The coconut oil formulation appears to show a fall in concentration at 8 h, but this rises again by 12 h post administration. The sesame oil formulation appears to have two smaller concentration peaks at 3 and 8 h, contributing to the highest exposure by this formulation. This is encouraging as the Epidyolex® formulation (a Food and Drug Administration (FDA) approved CBD treatment for seizures associated with rare forms of epilepsy) contains sesame oil, which we demonstrate as a good excipient for improved delivery to the temporal lobe region (Engel, 1996; European et al.). There are also high levels of cannabinoid receptors present in the temporal lobe, likely contributing to the high CBD delivery to the region (E. M. Jansen et al., 1992; M. Herkenham et al., 1990).

The delivery profiles of CBD to the parietal lobe (Figure 3) appear similar across the formulations studied. All three lipid-based formulations produced higher AUCs than the lipid-free vehicle, and the sesame oil formulation produced a C_{max} significantly higher than all other formulations. The rapeseed oil formulation produced the lowest C_{max}, but had the highest concentrations at later time points, resulting in an AUC_{0-t} larger than the lipid-free vehicle. The lipid-free formulation is the only one to demonstrate a second concentration peak, at 5 h. Overall, the sesame and rapeseed oil formulations produced the highest exposure to CBD in the parietal lobe. As well as the frontal lobe, GBM tumours are also commonly found in the parietal lobe (U.S. et al.). As discussed above, CBD is in clinical trials for GBM combination treatment (U.S. et al.; U.S. et al.), and suggested by unpublished work in our group to increase the uptake of imidazotetrazine agents. Therefore, understanding delivery to this region after administration in different formulations is essential to optimise the effects of CBD.

Delivery to the occipital lobe is particularly interesting as the lipid-free vehicle shows significantly higher initial delivery, although this drops drastically at 2 h. Due to the high initial delivery of CBD, the lipid-free formulation produces the highest AUC_{0-t} (8157 ± 11677 h*ng/g). Of the lipid-based vehicles studied, the rapeseed oil formulation gives the highest exposure, with an AUC_{0-t} of 3589 ± 2544 h*ng/g. The optimal vehicle for delivery to the occipital and temporal lobe regions is different, but both regions are associated with epilepsy and related seizures (Engel, 1996; J. E. Adcock and Panayiotopoulos, 2012; S. Sveinbjornsdottir and Duncan, 1993). Lennox Gastaut syndrome (LGS) and Dravet syndrome (DS) are the two rare forms of epilepsy that Epidyolex is used to treat (European et al.). Whilst LGS is commonly initially located within the temporal lobe, DS can be located in other regions to begin with, and both conditions can spread to affect the whole brain (J. S. Archer et al., 2014; M. Akiyama et al., 2012). Oral delivery in a sesame oil formulation does lead to substantial levels of CBD in all brain regions, however, other vehicles offer superior delivery to certain regions, including the occipital lobe. Possibly the CBD formulation should be considered carefully based on the subtype of condition (i.e. LGS vs. DS) and stage, as early stage conditions can be more localised, meaning that an alternative formulation could offer superior delivery.

High delivery to the medulla pons was also observed initially after administration in the lipid-free vehicle. However, this quickly drops at 2 h. The sesame oil formulation results in higher exposure of this region to CBD (AUC_{0-t} = 2429 ± 301 h*ng/g) than the coconut and rapeseed oil formulations, however, the lipid-free vehicle results in a similar AUC_{0-t} (2109 ± 1819 h*ng/g). This can be explained by the similar C_{max} to the lipid-free vehicle, followed by a peak in delivery in the sesame oil formulation at 18 h. It is evident that CBD delivery variability is lower after administration in the sesame oil formulation, so this would be a good choice for consistent high delivery to the medulla pons. The brainstem is the connection of the brain to the spinal cord, and is therefore the anatomical source of many paralyses, as well as the target for sleep cycle abnormalities (F. Chen et al., 2013; S. Sciacca et al., 2019; Y. Hishikawa and Shimizu, 1995). The therapeutic effects of CBD include delayed paralysis, as well as improving sleep-related behaviours where it would be important to understand delivery to the medulla pons (M. H. N. Chagas et al., 2014; Y. Zhang et al., 2022).

Studying the cerebellum, the lipid-free vehicle initially delivers the highest CBD concentration (C_{max} = 1742 ± 2895), much like other regions at the back of the brain (medulla pons and occipital lobe). This then falls at 2 h. However, in the cerebellum, the lipid-free vehicle demonstrates similar CBD concentrations to the lipid-based formulations after this time point. This results in the highest AUC_{0-t} demonstrated by the lipid-free vehicle, at 2296 ± 2373 h*ng/g. Understanding CBD delivery to the cerebellum is important, as in a resting-state, CBD is reported to normalise connectivity within the cerebellum, which is the brain region that processes motor function (P. L. Strick et al., 2009; R. Nenert et al., 2020; T. Ohyama et al., 2003).

The distribution of CBD in the brain can be correlated with the location of cannabinoid receptors, where locations with high cannabinoid receptors imply CBD reaches those regions at significant concentrations. It is reported that the highest density of cannabinoid receptors in the rat brain is in substantia nigra pars reticulata, followed by the globus pallidus (E. M. Jansen et al., 1992; M. Herkenham et al., 1990). These are structures of the basal ganglia, located within the temporal lobe, where the hippocampus, also exhibiting high levels of cannabinoid receptors, is found (E. M. Jansen et al., 1992; M. Herkenham et al., 1990). This explains the high delivery of CBD to the striatum, hippocampus, and temporal lobe. Prolonged delivery is also demonstrated to the cerebellum, and high levels of cannabinoid receptors are also reported there (E. M. Jansen et al., 1992; M. Herkenham et al., 1990; S. O. Alozie et al., 1980). The medulla pons demonstrates similar delivery profiles to the cerebellum, with prolonged delivery of low concentrations. This is interesting because low levels of cannabinoid receptors are reported in the brainstem (E. M. Jansen et al., 1992; M. Herkenham et al., 1990). Additionally, cannabinoid receptors are not reported to be as high in the olfactory bulb, where high CBD delivery is observed.

Considering the whole brain, the highest C_{max} was observed after administration in the lipid-free vehicle (Table 1). However, when studying the anatomical brain regions (Figure 3), this was only true for the olfactory bulb, occipital lobe, medulla pons and cerebellum. This suggests fast, high delivery to the posterior of the brain and olfactory system after administration of CBD in a lipid-free vehicle. For high exposure at the back of the brain, the rapeseed oil formulation would be the best choice. This is intriguing, as it suggests that delivery of CBD in a lipid-free vehicle does not correlate with the abundance or density of cannabinoid receptors (M. Herkenham et al., 1990).

The rapeseed oil formulation consistently produced prolonged exposure of the brain to CBD, demonstrated by the long half-life ($t_{1/2}$) of 10.1 h (Table 1). The $t_{1/2}$ is similarly long for the lipid-free vehicle (9.6 h), but significantly shorter for the sesame (4.6 h) and coconut (3.9 h) oil formulations. This suggests that the rapeseed oil formulation is allowing for constant movement of CBD into the brain following the initial high concentration at 1 h after administration. Alternatively, it could suggest that CBD is metabolised more slowly when formulated in the rapeseed oil formulation. Further studies would be required to investigate this further.

We can additionally draw from these data that the coconut oil formulation does not lead to the highest C_{max} or AUC in any brain regions. Administration in the coconut oil formulation does result in a higher brain-plasma ratio than the sesame oil formulation (4.3, compared to 3.5). However, as is demonstrated in this work, studying the whole brain is not representative of specific anatomical regions. It has previously been reported that the myristic acid carbon chain length (C14) is short enough to prevent strong binding to BCECs, but long enough to provide hydrophobic interaction with the cell membranes, affecting BBB permeability more efficiently than other fatty acids (J. Shen et al., 2013). This has not been observed in this work, however it may be that there is not enough myristic acid in the coconut oil formulation to see such effects, as only 21% of the fatty acid composition is myristic acid.

5. Conclusions

We demonstrate the importance of studying the delivery of a drug to the specific anatomical regions of interest in the brain. Dissecting and studying the brain by relevant anatomical regions allows visualisation of the differing delivery profiles that cannot be seen when studying the whole brain. This highlights that the vehicle that gives the best delivery to the whole brain will not necessarily result in the highest delivery to every brain region. We also demonstrate the high delivery of CBD to the brain after oral administration at a relatively low dose, with all vehicles resulting in a brain-plasma ratio ≥3.5. Oral administration of CBD in the rapeseed oil formulation results in the highest whole brain-plasma ratio. This is potentially a result of the high oleic acid (62%) content of the oil. Whilst sesame oil also contains oleic acid (44%), the same effects are not seen in the whole brain. However, oral administration in the sesame oil formulation did result in the highest delivery to specific anatomical brain regions, including the hippocampus and temporal lobe, where sesame oil-based formulations, such as Epidyolex®, should be delivering CBD for treatment. Administration in a coconut oil formulation containing myristic acid, which is thought to increase permeability of the BBB, did not yield higher concentrations in the brain. However, the explanations of differing delivery as a result of fatty acid content are currently a hypothesis only. The work herein does demonstrate the different delivery profiles of CBD between the anatomical brain regions following oral administration.

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7. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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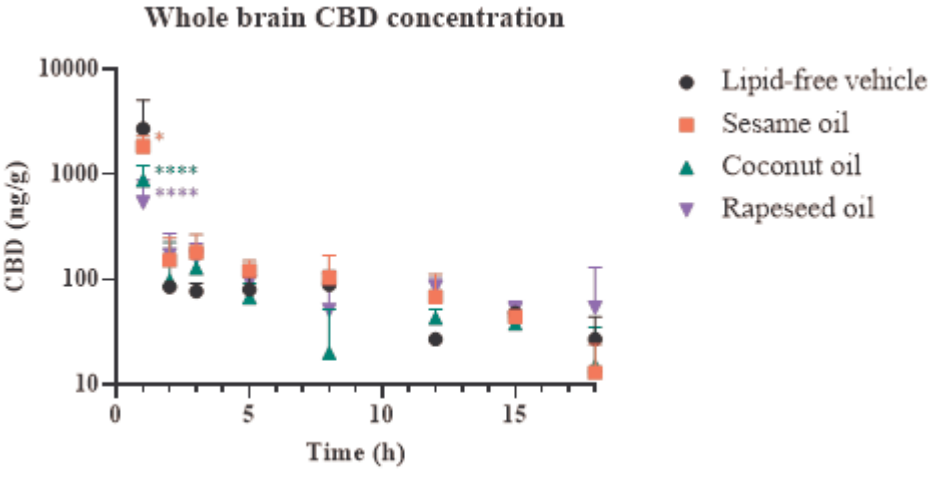
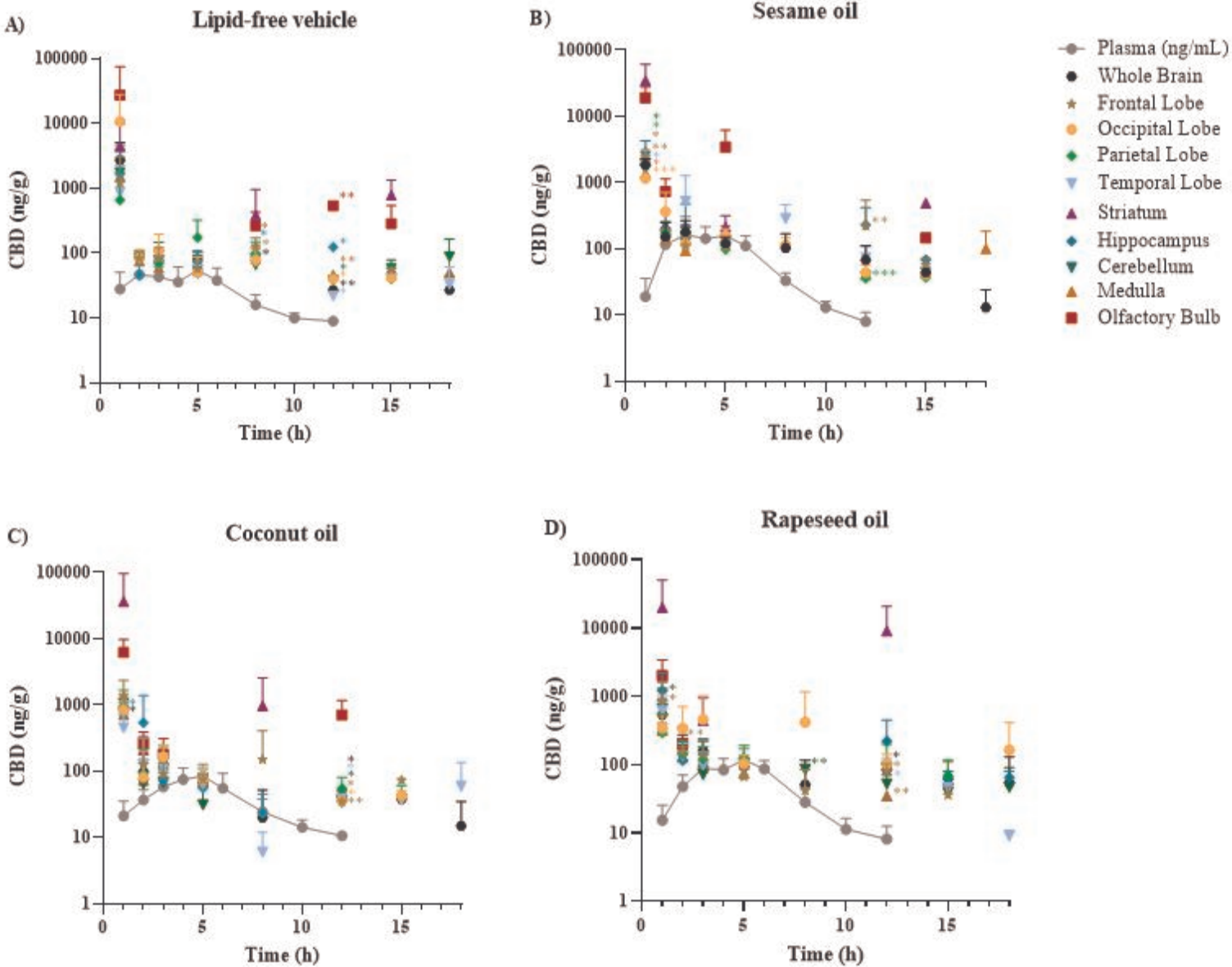
Figure captions

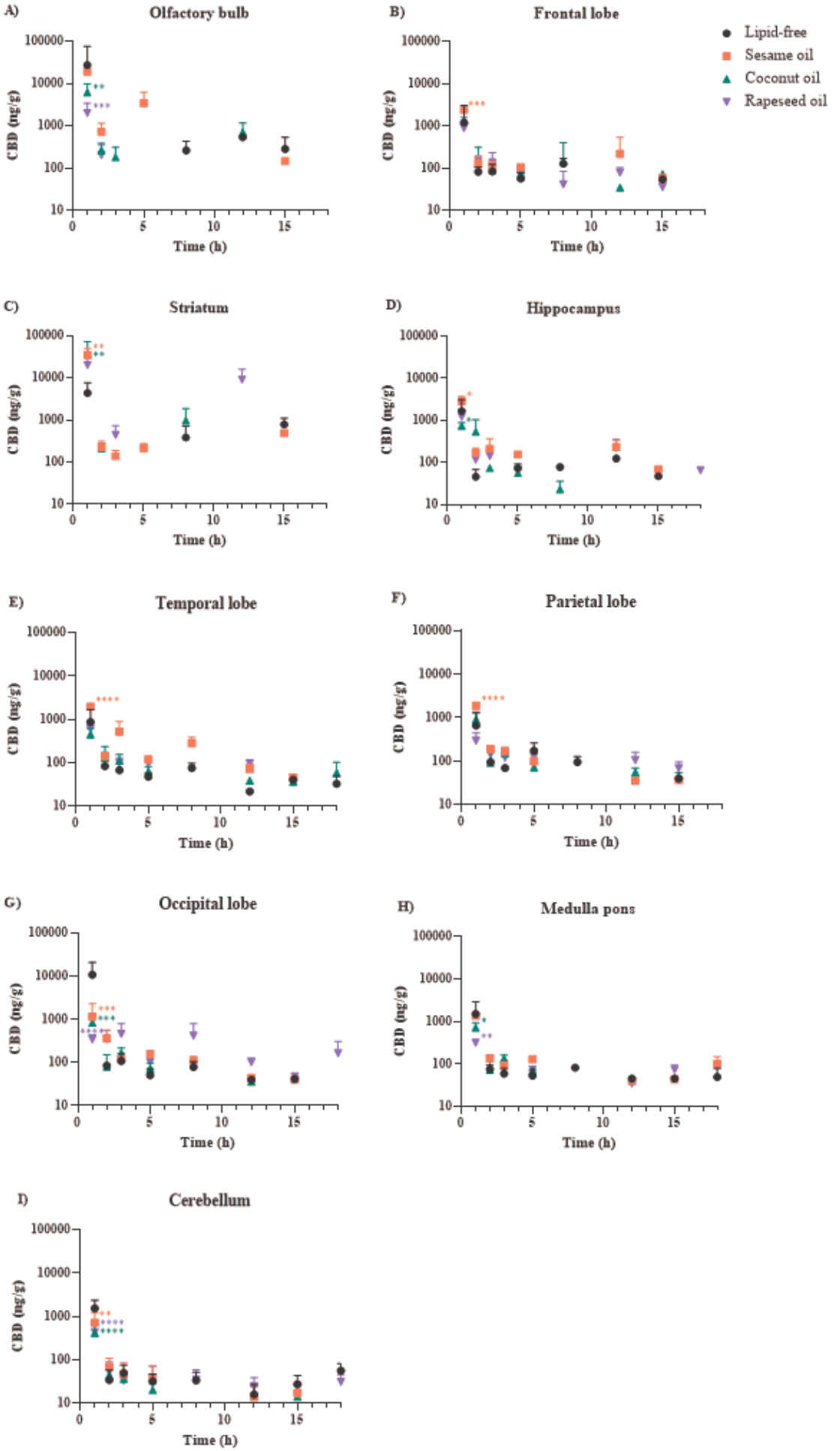
Figure 1. Cannabidiol (CBD) concentrations in whole brain after oral administration (12 mg/Kg) in lipid-free vehicle, sesame oil, coconut oil or rapeseed oil formulations to rats. All data are presented as mean ± SD, n = 3. Pharmacokinetic parameters are presented in Table 1. One-way ANOVA with Dunnett's multiple comparisons performed, lipid-based groups were compared to the lipid-free group, α=0.05, * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, **** = $p<0.0001$.

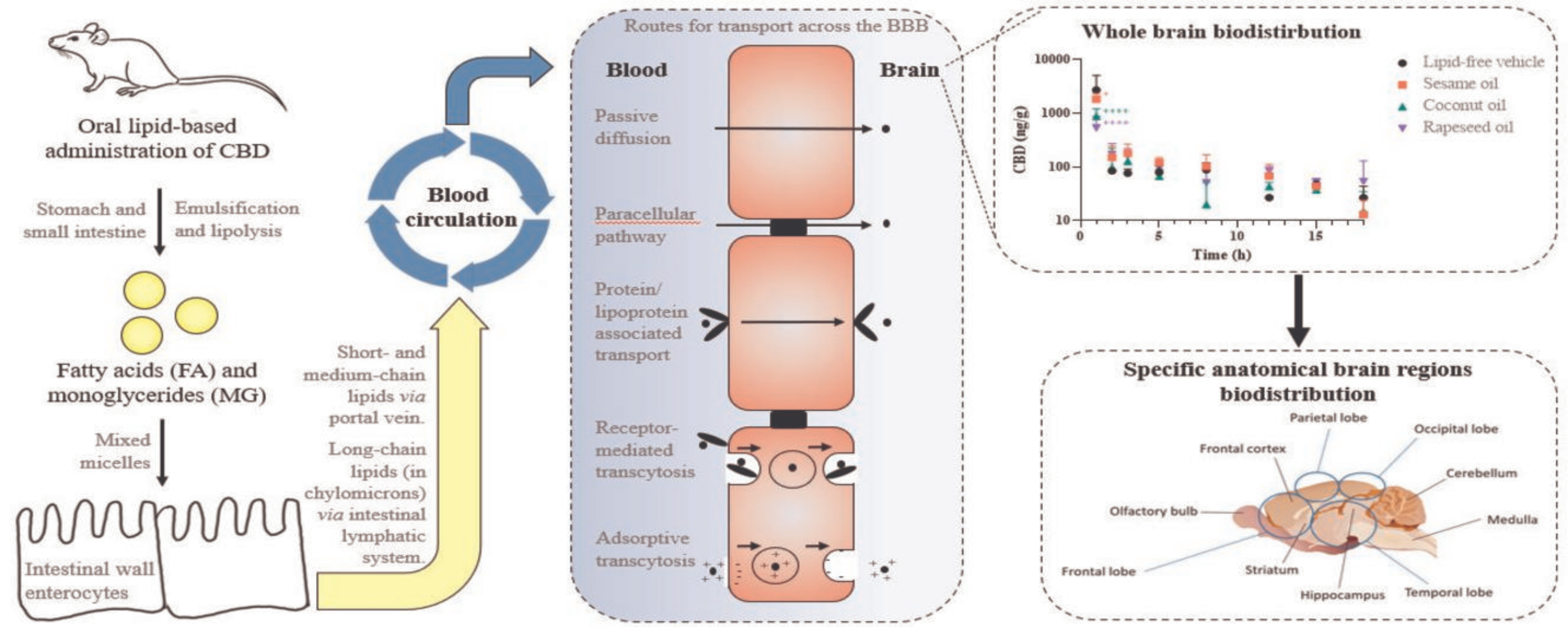
Figure 2. Cannabidiol (CBD) concentration in anatomical brain regions vs. plasma after oral administration (12 mg/Kg) to rats in (A) lipid-free vehicle, (B) sesame oil, (C) coconut oil and (D) rapeseed oil formulations, plasma data collected and reported in previous PK study (W. Feng et al., 2022; W. Feng et al., 2021). All data are presented as mean ± SD, brain regions n = 3, plasma n = 6. Pharmacokinetic parameters of the brain regions are presented in Table 2. One-way ANOVA with Dunnett's multiple comparisons performed, lipid-based groups were compared to the lipid-free group, α = 0.05, * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$.

Figure 3. Cannabidiol (CBD) concentrations in anatomical brain regions (A) olfactory bulb, (B) frontal lobe, (C) striatum, (D) hippocampus, (E) temporal lobe, (F) parietal lobe, (G) occipital lobe, (H) medulla pons and (I) cerebellum after oral administration (12 mg/Kg) to rats in lipid-free vehicle, sesame oil, coconut oil and rapeseed oil formulations. All data are presented as mean ± SD, n = 3. Pharmacokinetic parameters of the data are presented in Table 2. One-way ANOVA with Dunnett's multiple comparisons performed at each time point, lipid-based groups were compared to the lipid-free group, α = 0.05, * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, **** = $p<0.0001$.


Whole brain CBD concentration
10000
1000
100
10
CBD (ng/g)
0
5
10
15
Time (h)
*
****
****
Lipid-free vehicle
Sesame oil
Coconut oil
Rapeseed oil


A)
Lipid-free vehicle
B)
Sesame oil
C)
Coconut oil
D)
Rapeseed oil
CBD (ng/g)
Time (h)
Plasma (ng/mL)
Whole Brain
Frontal Lobe
Occipital Lobe
Parietal Lobe
Temporal Lobe
Striatum
Hippocampus
Cerebellum
Medulla
Olfactory Bulb


A)
Olfactory bulb
B)
Frontal lobe
C)
Striatum
D)
Hippocampus
E)
Temporal lobe
F)
Parietal lobe
G)
Occipital lobe
H)
Medulla pons
I)
Cerebellum
Lipid-free
Sesame oil
Coconut oil
Rapeseed oil
CBD (ng/g)
Time (h)


Oral lipid-based administration of CBD
Stomach and small intestine
Emulsification and lipolysis
Fatty acids (FA) and monoglycerides (MG)
Mixed micelles
Intestinal wall enterocytes
Short- and medium-chain lipids via portal vein.
Long-chain lipids (in chylomicrons) via intestinal lymphatic system.
Blood circulation
Routes for transport across the BBB
Blood
Brain
Passive diffusion
Paracellular pathway
Protein/ lipoprotein associated transport
Receptor-mediated transcytosis
Adsorptive transcytosis
Whole brain biodistirbution
CBD (ng/g)
Time (h)
Lipid-free vehicle
Sesame oil
Coconut oil
Rapeseed oil
Specific anatomical brain regions biodistribution
Parietal lobe
Occipital lobe
Frontal cortex
Cerebellum
Olfactory bulb
Medulla
Frontal lobe
Striatum
Hippocampus
Temporal lobe