The Interplay between Liver First-Pass Effect and Lymphatic Absorption of Cannabidiol and its Implications for Cannabidiol Oral Formulations

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Abstract

For highly lipophilic drugs, passage into the intestinal lymphatic system rather than portal vein following oral administration may represent a major alternative route of delivery into the general circulation. Increasing intestinal lymphatic transport provides an effective strategy to improve oral bioavailability when hepatic first-pass metabolism is a major rate-limiting step hampering access to the systemic circulation after oral dosing. The transfer of orally administered, highly lipid-soluble drugs to the lymphatic system is mediated by their association with chylomicrons, large intestinal lipoproteins which are assembled in the enterocytes in the presence of long-chain triglyceride or long-chain fatty acids. Due to its very high lipophilicity, cannabidiol (CBD) has physicochemical features (e.g. logP=6.3) consistent with an oral absorption mediated at least in part by transport via the intestinal lymphatic system. CBD also undergoes extensive first-pass hepatic metabolism. Formulation changes favoring diversion of orally absorbed CBD from the portal to the lymphatic circulation pathway can result in reduced first-pass liver metabolism, enhanced oral bioavailability and reduced intra- and inter-subject variability in systemic exposure. In this manuscript we discuss: (i) evidence for CBD undergoing hepatic first-pass liver metabolism and lymphatic absorption to a clinically important extent, (ii) the potential interplay between improved oral absorption, diversion of orally absorbed drug to the lymphatic system, and magnitude of pre-systemic elimination in the liver; and (iii) strategies by which innovative chemical and/or pharmaceutical delivery systems of CBD with improved bioavailability could be developed.

Key points

- Cannabidiol (CBD) has low and variable oral bioavailability (approximately 6% on average), due to incomplete gastrointestinal absorption and extensive pre-systemic elimination in the liver.
- Because of its very high lipophilicity, CBD has physicochemical features (e.g. logP=6. 3) consistent with absorption being mediated at least in part by transport via the intestinal lymphatic system.
- Innovative products/formulations that improve CBD solubilization in the gastrointestinal tract and re-route orally absorbed CBD from the portal to the lymphatic circulation can reduced the extent of hepatic first-pass metabolism, enhance oral bioavailability and reduce intra- and inter-subject variability in systemic exposure.
- The potential interplay between improved oral absorption, diversion of orally absorbed drug to the lymphatic system, and magnitude of hepatic-first pass effect should be considered in the design of new chemical and/or pharmaceutical delivery systems of CBD.

Introduction

Absorption from the gastrointestinal tract into the portal vein represents the best characterized pathway by which orally administered drugs enter the systemic circulation. Although the intestine also has a rich network of lymphatic vessels, the flow rate of intestinal lymph fluid is 500- to 100-fold lower than the blood flow through the portal vein, and absorption through the lymphatic system is negligible for the majority of small molecule drugs [1]. However, increasing evidence indicates that, for highly-lipid soluble drugs with low water solubility and a high affinity for lipoproteins, passage into the intestinal lymphatic system may represent a major alternative route of delivery into the general circulation [2]. In contrast to portal blood, mesenteric lymph flows directly from the mesenteric duct to the thoracic duct, and from there to the systemic circulation at the junction of the left subclavian and jugular veins, without passing through the liver at first pass. Therefore, increasing intestinal lymphatic transport may provide an effective strategy to improve oral bioavailability when hepatic first-pass metabolism is a major rate-limiting step hampering access to the systemic circulation.

The transfer of highly-lipid soluble orally administered drugs to the lymphatic system is mediated by their association with chylomicrons, large intestinal lipoproteins which are assembled in the enterocytes in the presence of long-chain triglyceride or long-chain fatty acids [3]. The availability of a source of lipids for lipoprotein formation represents a mechanism by which lipid-based formulations or concurrent intake of a high-fat meal can enhance the oral bioavailability of drugs with low water solubility [4]. Additionally, lipid-rich food and lipid excipients can facilitate solubilization of drug molecules in the intestinal lumen, thereby providing an additional mechanism to improve oral bioavailability [2].

Due to its very low water solubility (12.6 mg/L) and high lipophilicity as indicated by a logP of 6.3, the antiseizure medication cannabidiol (CBD) has physicochemical features consistent with potential absorption via the intestinal lymphatic system. CBD also undergoes extensive hepatic metabolism [5] and shows negligible renal excretion [6], which classifies it as a BCS/BDCCS Class 2 drug (poorly water-soluble, highly

permeable, highly metabolized drug) according to the Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS), respectively [7]. Importantly, CBD shows a high intra- and inter-subject pharmacokinetic variability [8, 9]. This is largely related to its very low oral bioavailability in humans, which is due to incomplete absorption as well as extensive pre-systemic metabolism in the liver [5, 7]. If CBD is at least in part susceptible to uptake by the lymphatic intestinal system, the implications in terms of biopharmaceutical optimization could be important. In fact, formulation changes favoring diversion of orally absorbed CBD from the portal to the lymphatic pathway could result in reduced hepatic first-pass metabolism and enhanced oral bioavailability. Improving CBD's oral bioavailability, in turn, would be expected to reduce intra- and inter-subject variability in systemic exposure[7, 10]. In a study of bioequivalence data for 65 immediate-release drugs, for example, the coefficient of variation (%CV) for intra-subject variability in plasma exposure has been been found to decrease from 30─65% when oral bioavailability is below 5% to less than 20% when bioavailability is above 80% [10]. Therefore, the advantages of a novel formulation of CBD with improved bioavailability in minimizing variability in clinical response could be considerable.

The purpose of this article is to: (i) review the evidence for CBD undergoing extensive first-pass metabolism, and its susceptibility to lymphatic absorption; (ii) assess the potential interplay between improved oral absorption, diversion of orally absorbed drug to the lymphatic system, and magnitude of pre-systemic elimination in the liver; and (iii) discuss strategies by which innovative chemical and/or pharmaceutical delivery systems of CBD with improved bioavailability characteristics could be developed.

CBD as a drug with a high hepatic extraction ratio

The absolute bioavailability (F) of CBD in humans after oral dosing under fasting conditions is generally reported to be about 6% [5, 11-15], as recently confirmed in a formal pharmacokinetic study conducted by the manufacturer of the FDA-approved formulation [Morrison G, personal communication, April 2020]. Its clearance (CL) as

determined in the only published study in humans, in which deuterium-labeled drug (20 mg) was administered intravenously to 5 healthy subjects, has been estimated at 1240 ± 240 mL/min (mean ± SD, range 960-1560 mL/min) [15]. The latter value, however, may represent an overestimate because calculated based on AUC values calculated up to 48 hours (2 subjects) and 72 hours (3 subjects), respectively. Assuming that CBD blood-to-plasma ratio is about 1, as in the case of tetrahydrocannabinol (THC) [13, 16, 17], and that CBD elimination occurs primarily in the liver [12, 13], a CL value of 74 L/h corresponds to a liver extraction ratio (E) in the order of 65-70% [13, 15, 17, 18].

Based on the above measures, CBD behaves pharmacokinetically as a drug with a high liver extraction ratio (E), which implies that its total body (metabolic) clearance is predicted to be affected more by changes in liver blood flow (Q) than by induction or inhibition of drug metabolizing enzymes [18, 19]. According to the well-stirred model of hepatic elimination, in which instantaneous and complete mixing of circulating blood is assumed to occur within the liver, F can be estimated by using equation 1:

$$F = F_f F_{GI}(1-E) = F_f F_{GI} Q/(Q + f_u CL_{int}) \quad (1)$$

where F_f, F_{GI}, CL_{int} and f_u represent the fraction of the CBD dose that is neither lost in the feces nor decomposed in the lumen, the fraction of the dose escaping gastrointestinal first-pass metabolism, the hepatic intrinsic clearance of CBD and the unbound fraction of CBD in blood, respectively [18, 19]. Equation 1 assumes that E is concentration independent (e.g., that saturation of first-pass metabolism does not occur during the absorptive phase), and does not take into consideration potential absorption through intestinal lymphatic vessels, a possibility that will be discussed in the subsequent part of this article.

CBD is negligibly excreted unchanged in urine [20], and its systemic exposure is increased by more than 5-fold in patients with severe hepatic impairment, an observation suggestive of metabolism taking place primarily in the liver [21]. Therefore, it is

reasonable to assume that CBD undergoes minimal intestinal first-pass metabolic loss upon oral administration, i.e., that F_{GI} approaches 1. Thus, based on equation 1, changes in CBD intrinsic clearance (CL_{int}) in the liver due to induction or inhibition of its metabolism would be expected to result in prominent changes in bioavailability after oral administration. On the other hand, changes in CBD CL_{int} would be expected to cause more modest changes in systemic exposure after parenteral administration, as is the case for drugs subject to high, flow-dependent hepatic extraction [18, 19, 22, 23].

Lymphatic absorption of CBD

As discussed in the introduction of this article, orally administered lipophilic drugs may gain access to the systemic circulation via the intestinal lymphatics following incorporation into large lipoproteins such as chylomicrons [24-26]. In fact, chylomicrons are too large for direct passage to the blood capillaries, and are dependent on transfer to the lymphatic system for their absorption together with the incorporated lipophilic drug [27-29]. The passage of drugs to the intestinal lymph seems to be enhanced by their co-administration with long-chain lipids preferentially to short- and medium-chain lipids [30], and is influenced by the physicochemical characteristics of the drug, primarily a distribution coefficient (logD) at pH 7.4 >5 and a solubility in long-chain triglycerides >50 mg/g [31, 32]. Marketed oral formulations of THC (Marinol®) and CBD (Epidiolex®) contain sesame oil, which is mostly composed of long-chain triglycerides. It has been stated that the rationale for adding sesame oil to these formulations is to dissolve the lipid-soluble cannabinoids [29].

In a carefully conducted study in a rat model, Zgair et al [29] found that plasma exposure to orally administered CBD and THC increased by 2.5-fold and 3-fold, respectively, when the compounds were co-administered with lipids compared with intake without lipids [29]. Following *in vitro* lipolysis, more than 30% of THC and CBD were found to be distributed into the micellar fraction, indicating that at least one third of an oral dose could be absorbed if these cannabinoids are co-administered with lipids. Further experiments confirmed the association of CBD with chylomicrons, suggesting that

incorporation of pharmaceutical lipid excipients in the CBD oral dosage form could increase substantially its oral bioavailability by rerouting partly its absorption from the portal vein to the intestinal lymphatic system. The amount of lipids present in a high-fat meal is sufficient to activate CBD intestinal lymphatic transport and to increase its oral bioavailability [29]. The lymphatic transport of CBD was confirmed by the same authors in a subsequent study in which CBD levels were monitored directly in mesenteric lymph [33].

Measurement of drug levels in the intestinal lymph requires complex invasive procedures which have been done in humans only under exceptional circumstances [34]. However, the physicochemical characteristics of CBD, coupled with the evidence from the animal studies discussed above, are fully consistent with the possibility of CBD undergoing intestinal lymphatic transport also in humans. The observation that CBD bioavailability increases four-fold when the drug is taken together with a high fat-meal [8, 9, 35] is also fully compatible with a lipid-driven enhancement of intestinal lymphatic transport, similarly to findings from animal studies [29, 33].

In this regard, a particularly valuable contribution, which is relevant to understanding the determinants of CBD bioavailability in humans and experimental animals, is an elegant study conducted with another cannabinoid drug, the CB_1 and CB_2 receptor agonist CRA13 (SAB-378) [36]. By conducting parallel experiments in humans and in lymph-cannulated dogs, Trevaskis and coworkers demonstrated that enhancement of the oral bioavailability of CRA13 when given with a high-fat meal does not result from increased absorption *per se* but from a significant increase in its transport into the lymphatic system and consequent reduction in its first-pass metabolism in the liver [36]. In fact, the poor absolute bioavailability of CRA13 in fasted dogs (8-20%) was not due to failure to pass through the gastrointestinal epithelium, but to a large hepatic first-pass effect, which could be bypassed partly when CRA13 was administered with food and its absorption was diverted to the lymphatic pathway. The physicochemical properties of CRA13 (logP 6.9, water solubility 19 mg/L, molecular weight 369) are similar to those of CBD (logP 6.3, water solubility 13 mg/L, molecular weight 314)[37], suggesting that these findings could be reasonably extrapolated to CBD.

The interplay between CBD oral absorption, lymphatic transport and liver first-pass metabolism

For a drug like CBD which is highly likely to be taken up at least in part into intestinal lymphatic vessels, the fraction of the dose absorbed from the gastrointestinal tract can be defined as the sum of the fraction absorbed via the lymphatic (f_{lymph}) system and thus not exposed to liver first-pass effect, and the fraction absorbed via the portal system (f_{portal}) [27]. Incorporating f_{lymph} and the portal system f_{portal} into equation 1 yields equation 2:

$$F = F_f F_{GI} [f_{lymph} + f_{portal}(1-E)] = F_f F_{GI} [f_{lymph} + f_{portal} Q/(Q + f_u CL_{int})] \quad (2)$$

Intra- and inter-subject variability in F results from the many factors that influence each of the key elements of equation 2. For example, F_f is dependent not only on the properties of the drug and the formulation used, but also on the presence and composition of any co-administered food, rate of gastrointestinal motility, activity of transporter systems, and drug-drug interactions within the gastrointestinal lumen [38, 39], whereas CL_{int} is influenced by factors that affect the activity of drug transporters and hepatic drug metabolizing enzymes, including age, genetic polymorphisms, endocrine influences, enzyme induction, enzyme inhibition, and disease states [39, 40]. With respect specifically to f_{lymph}, this is influenced primarily by a drug's ability to associate with chylomicrons in the enterocyte, which in turn is dependent on the drug's physico-chemical properties, availability of a source of lipids (especially long-chain lipids) and characteristics of the formulation [25, 32]. By stimulating the production of lymph, dietary or formulation-based lipids can also increase mesenteric lymphatic flow [41], although lymph flow *per se* is likely to affect rate more than extent of lymphatic absorption.

Following oral dosing, most small-molecule drugs are absorbed via the portal vein (i.e. $f_{portal} > f_{lymph}$), which for drugs with a high hepatic extraction (E) results to extensive pre-

systemic elimination. By diverting the absorbed drug from the portal to the lymphatic transport, pre-systemic elimination can be minimized and oral bioavailability can be enhanced [32]. The relative contribution of lymphatic (f_{lymph}) and portal pathways (f_{portal}) to overall absorption can be formulation-dependent, and a successful formulation targeting the lymphatic circulation could mitigate CBD susceptibility to hepatic first-pass metabolism.

In a series of simulations, Brocks and Davis [27] have shown that the impact of lymphatic absorption on systemic drug exposure is influenced by the extent by which a drug is removed from the blood flowing through the liver [27]. Drugs with low E (<30%) are not likely to have any systemic bioavailability advantage from diverting their gastrointestinal absorption from the portal to the lymphatic system. As depicted in equations 1 and 2, for drugs with low E values, even a relatively large percent change in E will have a negligible effect on oral bioavailability, because these drugs are subject to little or no hepatic first-pass effect. A diversion from portal to lymphatic absorption can impact oral bioavailability only for drugs with E>30%, whose systemic exposure is influenced by hepatic first-pass metabolism. The higher is a drug's E value, the greater is the potential to increase its oral bioavailability through a formulation-dependent enhancement of lymphatic absorption.

Because CBD has a high E value (estimated at 65-70%), it is an attractive candidate for the development of innovative formulations enhancing its intestinal lymphatic absorption. An oral formulation that will divert CBD absorption from the portal to the lymphatic pathway (i.e., decrease f_{portal} and increase f_{lymph} in equation 2) could exert a large effect on the oral bioavailability of CBD. As discussed above, the average absolute oral bioavailability of CBD is about 6% after intake under fasting conditions [5, 7], and increases 4-fold when the drug is co-administered with a lipid-rich meal [8, 9, 35], probably due at least in part to facilitation of lymphatic transport [29]. An innovative formulation which is as effective as a high-fat meal in improving CBD dissolution in the intestinal fluids and in diverting CBD absorption from the portal to the lymphatic system would be expected not only to provide a similar bioavailability enhancement, but also to reduce intra- and inter-individual variability in systemic exposure and to minimize the

magnitude of drug interactions affecting presystemic CBD metabolism in the liver, and the adverse effects that might arise from such interactions. Even if such an innovative formulation were still subject to an interaction with food, that interaction could be avoided by administering the product away from meal times. The overall result would be a more consistent bioavailability than that obtained by co-administration with food, whose effects on CBD pharmacokinetics are highly variable in relation to the composition of the meal [8]. A formulation causing a diversion of CBD uptake into the lymphatic vessels to a greater extent than that achieved with a high-fat meal could increase CBD bioavailability further, potentially above the 35% ceiling which based on hepatic clearance estimates applies if entry into the systemic circulation only occurs via the portal system. It should be noted that incorporation of a drug into lipoproteins may affect not only the pathways by which the drug reaches the systemic formulation, but also its tissue distribution and rate of hepatic metabolism [1]. These potential pharmacokinetic changes will require careful exploration, as they may impact on the extent and time course of pharmacological activity.

Potential strategies to facilitate lymphatic absorption

Potential strategies by which innovative lymphatic system-targeted CBD formulations with improved oral bioavailability can be developed include (i) use of chemical drug delivery systems or prodrugs and (ii) use of pharmaceutical drug delivery systems.

The former approach has been utilized to design prodrugs of testosterone that are based on a glyceride template that mimics the digestion, re-esterification and lymphatic transport pathways of dietary triglycerides [42]. In these experiments, testosterone was used as a model drug for substances undergoing extensive hepatic first-pass metabolism. The mean absolute oral bioavailability (± SD) of testosterone (F) and of a commercially-available lipophilic prodrug testosterone undecanoate in humans is only 3.6 ± 2.5% and 6.8 ± 3.3%, respectively [43]. The bioavailability of the undecanoate is further limited by intestinal metabolism, even though some lymphatic absorption does occur, as shown by a study done in 4 patients who had a thoracic duct catheter inserted after neck dissection

surgery [34]. The glyceride-mimetic prodrugs designed to improve testosterone bioavailability were constructed by bridging testosterone and the alkyl-substituted glyceride moiety (e.g. 1,3-diacylglycreol oxidized to its acid-terminated triglyceride) with a five-carbon self-immolative spacer to which a linker was inserted [42]. The entire glyceride-mimetic moiety was conjugated to testosterone via an esteric bond. Following oral administration to rats, the glyceride-mimetic prodrugs were hydrolyzed to testosterone yielding a plasma exposure that was significantly higher than that obtained after oral dosing of testosterone and the undecanoate. The oral bioavailability of testosterone increased with increasing cumulative extent of lymphatic transport, which was 0% for testosterone, 1.9% for testosterone undecanoate and 9.5─28% for the glyceride-mimetic prodrugs [42]. The testosterone undecanoate formulation was a solution in oleic acid encapsulated in a soft gelatin capsule. This shows that a combination of a lipophilic prodrug in oily solution that is mainly absorbed by lymphatic transport is not sufficient to increase testosterone's F value above 6.8%. In order to obtain an F>10% there was a need to design glyceride-mimetic prodrugs with a self-immolative spacer to that includes a linker as described above [42].

Another lymphatic system-targeted approach using lipophilic-activated ester prodrugs was applied by Lee at al. [28] to deliver bexarotene and retinoic acid to the intestinal lymphatic vessels. A range of carboxylic ester prodrugs of bexarotene were designed, and all esters showed improved association with chylomicrons, which indicated an improved potential for delivery to the intestinal lymphatic system. The rate at which the prodrugs were converted to bexarotene in lymph fluid was the primary determinant of their delivery to the intestinal lymphatic system. Activated ester prodrugs were prepared to enhance the conversion rate in comparison to simple alkyl ester prodrugs [28]. Because CBD has lipophilic properties similar to those of testosterone and bexarotene, it could be a suitable candidate for utilization of the prodrug approach.

As mentioned above, an alternative approach to develop a lymphatic-system targeted product involves the use of pharmaceutical delivery systems which incorporate dietary fats and pharmaceutical lipid excipients to mimic the absorptive milieu associated with ingestion of a high-fat meal [27, 29, 33]. By using this approach, Zgair et al. [29]

investigated the effect of orally administered lipids on the exposure of THC and CBD, and concluded that co-administration with dietary lipids or pharmaceutical lipid excipients diverting absorption to the lymphatic vessels has the potential to increase substantially the oral bioavailability of both cannabinoids [29]. In another study, Liao et al. [44] prepared a complex of the flavonoid baicalein with phospholipids and incorporated it into a self-microemulsifying drug delivery system (SMEDDS) with the aim of improving baicalein's oral bioavailability by enhancing its lymphatic absorption. *In vivo* experiments in rats demonstrated that the bioavailability of SMEDDS-incorporated baicalein was increased by 342.5% compared with the bioavailability of baicalein given as such. When the baicalein-phospholipid complex was incorporated into a SMEDDS, the bioavailability of the flavonoid (relative to baicalein administered as such) increased to 448.7%. Lymphatic transport studies revealed that after dosing with baicalein as such, 81.2% of the orally absorbed flavonoid entered the circulation directly through the portal vein, and approximately 18.8% was taken up by the lymphatic system. Incorporation into a SMEDDS increased the proportion taken up by the lymphatic system from 18.8% to 56.2%, and the increase was even greater (to 70.2%) when the SMEDDS-incorporated baicalein-phospholipid complex was administered. Therefore, the self-microemulsion not only improved significantly the oral bioavailability of baicalein, but also increased its extent of absorption via the lymphatic system, the effect being more prominent when the flavonoid was given as phospholipid complex [44]. The potential value of approaches based on use of phosphospholipid complexes combined with a self-emulsifying system is further illustrated by studies with silybin, a water-insoluble flavonolignan which is the main active component of silymarin, an extract of the milk thistle plant (*Silybum marianum*). Tong et al. [45] prepared a silybin–phospholipid complex, which was then encapsulated into a self-nanoemulsifying drug delivery system (SNEDDS). Using a dynamic *in vitro* digestion model, the lipolysis of the silybin–phospholipid complex in the SNEDDS was found to be related mainly to the properties of the lipid excipients. Experiments with an *in situ* perfusion model showed that the intestinal absorption of silybin was highest for the SNEDDS-incorporated silybin–phospholipid complex, intermediate for the silybin–phospholipid complex alone, and

lowest for silybin itself. The extent of lymphatic transport for the silybin–phospholipid complex and for the SNEDDS-incorporated silybin–phospholipid complex was 12.2- and 22.7-fold higher, respectively, than that for silybin [45]. In lymph duct cannulated rats, the relative bioavailability of the silybin–phospholipid complex was 12.7 times as high as that of silybin, while the bioavailability of the SNEDDS-incorporated silybin–phospholipid complex was 18 times as high as that of silybin. Interestingly, an earlier study in humans demonstrated that administration of silybin in the form of a complex with phosphatidylcholine resulted in a 4.6-fold increase in silybin oral bioavailability relative to silybin administered as silymarin [46]. The increase in silybin bioavailability obtained with the phosphatidylcholine complex compared with sylibin administered as silymarin was probably markedly underestimated, because the assay used did not differentiate silybin from isosilybin, another component of silymarin [47]. Whether the improved bioavailability of silybin given as a complex with phosphatidylcholine in humans is related at least in part to enhanced lymphatic absorption and avoidance of hepatic first-pass metabolism is not known, but this possibility would be consistent with the results of animal studies [45]. Importantly, the similar low-water solubility of CBD (12.6 mg/mL) and silybin (9.8 mg/mL) suggests that a pharmaceutical approach based on utilization of a phospholipid complex incorporated into SNEDDS [45] could be applied successfully also to CBD. In fact, the interest in developing novel self-emulsifying delivery systems for CBD, including SNEDDS, is growing, and results of early pharmacokinetic studies appear to be promising [48-50].

Whether any of the strategies described above would succeed in enhancing the oral bioavailability of CBD up to (or above) the level (about 25%) observed with the currently available FDA-approved formulation taken together with a high-fat meal remains to be determined. However, since hepatic first-pass metabolism is the main factor limiting CBD's oral bioavailability (F), even a more modest bioavailability enhancement would be valuable if it is associated with reduced intra- and inter-individual variability, and less susceptibility to food effects. Of note, such an enhancement is unlikely to be achieved by increasing the amount of sesame oil in the current FDA-approved formulation (e.g., using a less concentrated formulation) because the large volume required would adversely

affect palatability and compliance, and entail an excessive caloric intake. Attractive development strategies to consider in pharmaceutical delivery systems may include use of pre-digested lipids, incorporation in the formulation of various surfactants, and use of optimized mixtures of short, medium and long-chain triglyceride or fatty acids. In particular, use of pre-digested lipid formulations, containing fatty acids and monoglycerides instead of triglycerides, could remove intra- and inter-subject variability related to differences in the digestion of lipids in the gastrointestinal tract [51].

In addition to diverting absorption from the portal to the lymphatic system, alternative strategies to improve the oral bioavailability of CBD are being considered. An interesting approach, that can be combined with lymphatic-targeted strategies, involves incorporation in the formulation of compounds which may enhance oral bioavailability by inhibiting CBD drug metabolizing enzymes and thereby reducing the extent of its first-pass effect [52]. Preliminary encouraging results have been obtained by incorporating piperine into a SNEDDS-based delivery system [52, 53], but further studies are required to determine the actual potential of this approach in terms of pharmacokinetic performance and clinical safety.

Final considerations and conclusions

The evidence discussed in this article indicates that CBD shows suboptimal pharmacokinetics due its low solubility in intestinal contents, incomplete oral absorption and prominent fist-pass effect in the liver. These factors result in a large intra- and inter-subject variability in oral bioavailability, which is further compounded by pronounced food effects [8, 9, 35]. Because a large variability in CBD plasma concentrations could adversely affect clinical response, there is scope for developing innovative chemical and/or pharmaceutical delivery systems associated with enhanced and more consistent bioavailability. Potential breakthroughs in addressing this goal may come from evidence that CBD has physicochemical and pharmacokinetic characteristics compatible with absorption taking place partly through the lymphatic system, as confirmed by animal studies. Delivery systems designed to enhance CBD solubilization in the intestine and

divert absorption from the portal to the lymphatic system could improve CBD bioavailability substantially. Irrespective of the enhancement in systemic exposure achieved, such delivery systems could also reduce markedly pharmacokinetic variability, particularly if these systems succeed in attenuating bioavailability changes in relation to food intake [8, 9, 35] and meal composition [8]. When developing innovative CBD delivery systems, consideration should also be given to existing concerns about the burden of allergies associated with sesame oil [54], the main excipient present in the current FDA-approved CBD formulation. This implies that novel CBD delivery systems, in addition to benefits derived from greater and more consistent bioavailability, could also be associated with advantages in terms of improved tolerability and safety.

Compliance with ethical standards

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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