Oral administration of sesame seeds-derived oleosomes facilitate systematic bioavailability and intestinal lymphatic targeting of cannabidiol

Yufei Zhu [1], Giovanna Lollo [3,4], Vincenzo Di Bari [2], David Gray [2], Maria Marlow [1], Pavel Gershkovich [1]

[1] School of Pharmacy, University of Nottingham, Nottingham, UK; [2] School of Biosciences, University of Nottingham, Loughborough, UK; [3] University of Lyon 1, CNRS, LAGEPP UMR 5007, Villeurbanne, France; [4] Institut universitaire de France (IUF), Paris, France

Background: Inflammatory bowel disease (IBD) is a condition where the immune system attacks its own intestinal tissue. It is divided into Ulcerative Colitis and Crohn's disease subtypes. Targeting intestinal lymph nodes is a strategy to deliver immunomodulators directly to decrease the expression of inflammatory cytokines, which play an important role in the pathophysiology of IBD. Lipid-based formulations composed of long chain triglycerides facilitate the intestinal lymph nodes targeting and higher systemic bioavailability through chylomicrons (CMs) pathway. Cannabidiol (CBD) is a highly lipophilic non-psychoactive phytocannabinoid derived from Cannabis plant. It activates endocannabinoid system and regulates inflammatory cytokines, such as IL-6 and TNF- α. However, due to the high lipophilicity and first pass metabolism, CBD has limited oral bioavailability of around 8%. Co- administration of CBD with long chain triglyceride facilitates the oral bioavailability and intestinal lymphatic targeting. In our previous work, sesame and olive oil vehicles led to the highest bioavailability of CBD (22%) in comparison to other vegetable oils. On the other hand, rapeseed-derived oleosomes formulation increased the oral bioavailability of CBD to 27%. Oleosomes are natural lipid droplets where the seeds store energy in the form of triglycerides, which are important for germination. The structure of oleosomes is similar to lipoproteins (0.5- 2.5 μm in diameter) with the surface coated by vegetable proteins, while the core contains large amounts of unoxidized oils.

Therefore, the aim of this project is to further improve the oral bioavailability and mesenteric lymph nodes targeting of CBD through development of sesame seeds oleosome drug delivery systems.

Methods: Head-to-head comparison between sesame oleosomes to oleosome-like artificial emulsion formulations were conducted. Pure sesame oil formulation was also included as a comparison group. *In-vitro* studies included protein analysis, peroxide value determination and pH- state lipolysis. *In-vivo* studies included low dose (3.3 mg/kg) and high dose (12 mg/kg) assessments of CBD pharmacokinetics and biodistribution. Lymph nodes were harvested at various time points. In addition, TNF- α levels were measured in mesenteric lymph nodes in the high dose (12 mg/kg CBD) group.

Results: Sesame oleosomes formulation administration resulted in the oral bioavailability of CBD of 55%, which is 2.4- fold and 2.2- fold higher than sesame oil and artificial emulsion group, respectively. To the best of our knowledge, this is the highest oral bioavailability of CBD in rodents reported so far in the literature. The highest concentration and tissue/ plasma concentrations ratio of CBD in mesenteric lymph nodes was found in sesame oleosomes group at plasma Tmax time point. Moreover, lower level of TNF-a was observed at 1-hour time point in mesenteric lymph nodes following administration of sesame oleosomes in comparison to sesame oil vehicle.

Conclusions: Sesame oleosomes formulation leads to the highest CBD oral bioavailability in comparison to other reported lipid-based formulations, suggesting that oleosomes are a promising oral delivery platform of CBD for improved IBD therapy.