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Introduction

The cannabis plant has had a long history of medicinal use dating thousands of years [1]. The active components of the plant are named **cannabinoids** with the major ones being **delta-9-tetrahydrocannabinol** and **cannabidiol**.

In recent years there has been a social stigma associated with smoking cannabis, and therefore there is a tendency to administer medicinal cannabinoids orally. Two such examples are **dronabinol** (synthetic delta-9-tetrahydrocannabinol) and **nabilone**, which are used in the treatment of anorexia associated with AIDS and chemotherapy-induced nausea in cancer respectively. The two cannabinoids have varying bioavailabilities and their **mechanism of absorption is currently unknown**.

Many cannabinoids are **lipophilic** in nature, a factor which gives them the potential to be absorbed via the **intestinal lymphatic system** [2,3]. This research project explores this potential.

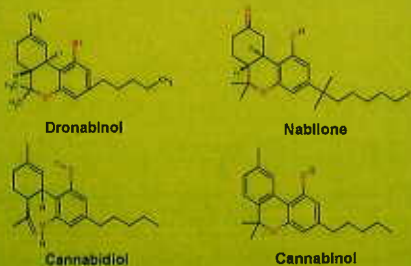


Figure 1: Cannabinoids studied in this project.

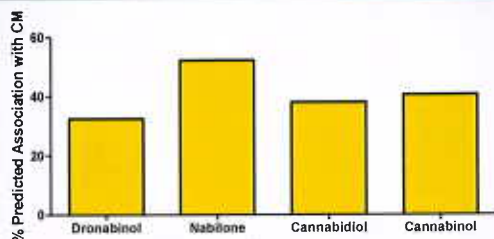


Figure 2: Bar chart showing the predicted association of cannabinoids with CM

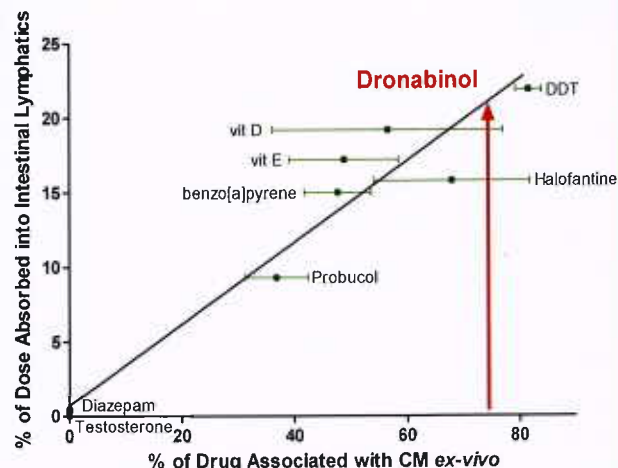


Figure 3 (Left): Lymphatic availability of drugs vs. degree of association of drugs with isolated CM in ex vivo model, with dronabinol added in red. Figure adapted from Gershkovich et al [3].

Methods

- In-silico modeling:** ACD/Labs software was used to predict physicochemical properties of compounds based on their molecular structure. Their association was then calculated based on a previously published model [4].
- Uptake of molecules by plasma-derived isolated CM:** The tested drug was incubated with a CM emulsion and then separated by density gradient ultracentrifugation.
- HPLC-UV Analysis:** A mobile phase consisting of methanol:water (90:10, v/v) at a flow rate of 0.5 ml/min. A Waters Xterra RP 18 (4.6 x 100 mm, 3.5 µm) column was used, and probucool was used as internal standard. This method and the uptake by plasma-derived isolated CM method was based on a previously published method [3].

Results

The physicochemical properties and their predicted association with CM for the four cannabinoids are summarised in Table 1 and Figure 2 respectively.

- The most important physicochemical parameters in predicting CM association is **Log P** and **Log D_{7.4}**.
 - Nabilone** had the highest predicted association with CM (**52.29 %**) out of the four cannabinoids, possibly because of differences in polar surface area and molar volume.
- The *ex vivo* results are shown in Figure 3.
- Dronabinol has **very high affinity** to plasma-derived isolated CM (**74.5 ± 7.9 %**, n=6)
 - Other cannabinoids have yet to be analysed.

Conclusions and Further Work

- In-silico* model had **underestimated** the association of dronabinol with CM (predicted 32.55% and the experimental value of 74.5%) but whether this underestimation is constant has to be confirmed with further experiments.
- High experimental affinity of dronabinol to CM** strongly suggests that intestinal lymphatic transport is likely to be a primary mechanism of its absorption
- In the future, we are looking to further assess the absorption of cannabinoids by *in vivo* pharmacokinetic analysis and extent of intestinal lymphatic transport.

Table 1: Summary table of physicochemical properties for four cannabinoids.

| Property | Dronabinol | Nabilone | Cannabidiol | Cannabinol |
|------------------------|------------|----------|-------------|------------|
| Log D 7.4 | 7.07 | 7.05 | 6.53 | 6.92 |
| Log P | 7.68 | 7.051 | 6.60 | 6.93 |
| Log P - Log D | 0.61 | 0.001 | 0.07 | 0.009 |
| PSA | 29.46 | 46.53 | 40.46 | 29.46 |
| H-Acceptors | 2 | 3 | 2 | 2 |
| Freely Rotatable Bonds | 4 | 7 | 6 | 5 |
| Density | 1.02 | 1.03 | 1.02 | 1.06 |
| Molar Volume | 309.7 | 361.8 | 306.6 | 292.6 |
| H-Donors | 1 | 1 | 2 | 1 |

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