**Targeting Senescence with Phytocannabinoids: A Novel Approach to Promote Healthy Ageing**

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**Background and aims.** Cellular senescence, characterized by a state of stable and irreversible cell cycle arrest, triggered by various stressors, contributing to ageing and age-relate diseases, leading to the accumulation of senescent cells and senescence-associated secretory phenotype (SASP) factor release. The development of senotherapeutics, compounds that either eliminate senescent cells (senolytics) or modulate their phenotype (senomorphics), has emerged as a promising strategy to mitigate aging-related diseases and promote healthy longevity (Chaib et al., 2022).

Phytocannabinoids, naturally occurring compounds derived from the Cannabis plant, encompass over 100 bioactive molecules with diverse pharmacological properties, including anti-inflammatory, antioxidant, and neuroprotective effects. These attributes suggest their potential as senotherapeutic agents. However, their specific effects on cellular senescence remain unclear.

This project aims to investigate the senotherapeutic potential of phytocannabinoids using well-established cellular senescence models. By assessing their impact on key senescence markers and SASP modulation, this research will provide insights into their therapeutic viability for age-related conditions.

**Methods.** Cellular senescence was induced in IMR-90 human lung fibroblast cells using doxorubicin (DOX, 0.5µM, 48h), followed by a 5-day recovery period in fresh medium to allow the establishment of a stable senescent phenotype. Cells were then treated with selected phytocannabinoids. Senescence-associated markers, including p16^INK4a and SA-β-galactosidase were characterized using immunofluorescence staining. To evaluate compound selectivity, cell viability assays were performed in both senescent and non-senescent cells determine selective cytotoxicity and differentiate between senolytic and senomorphic effects. Navitoclax (ABT-263), a well-known senolytic agent, was included as a positive control.

**Results.** Cell viability analysis confirmed that 1 µM ABT-263, used as a positive control, significantly reduced DOX-induced senescent cells compared to the non-senescent cells. Among the phytocannabinoids, CBC exhibited senolytic activity only at 30 µM, with a significant reduction in senescent cells (*p*<0.0001). CBCV and CBCA showed no significant effects at low concentrations (3 µM and 10 µM), but both induced selective reduction of senescent cells within their respective groups at 30 µM without affecting non-senescent cells, indicating potential senolytic properties.

**Conclusion/Discussion.** This study highlights the therapeutic potential of phytocannabinoids with anti-ageing properties, as demonstrated in human cell models. As interest in cannabis-derived compounds grows within the field of gerotherapeutics, these findings support the potential integration of phytocannabinoids into targeted senotherapeutic strategies for healthy ageing and age-related disease.

**References:**

Chaib, S., Tchkonia, T., & Kirkland, J. L. (2022). Cellular senescence and senolytics: the path to the clinic. Nat Med, 28(8), 1556-1568. <https://doi.org/10.1038/s41591-022-01923-y>