UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

Evaluation of novel therapeutic compounds for metabolic dysfunction-associated steatohepatitis using advanced multicellular 3D in vitro models

2)Abstract (max 500 words)

Metabolic dysfunction-associated steatohepatitis (MASH) has become a major health threat across Europe, due to the increasingly widespread unhealthy use of processed foods, alcohol, and the epidemic of obesity. MASH, formerly known as non-alcoholic steatohepatitis (NASH), is a severe liver condition characterized by inflammation, cell damage, and fat accumulation, is closely linked to obesity, type 2 diabetes, and cardiovascular diseases. With limited treatment options currently available, there's an urgent need for new therapeutic approaches for MASH.

This PhD project leverages the potential of natural products, known for their anti-inflammatory, antioxidant, and antifibrotic properties, as a source of new therapeutic compounds. The research will be focused on evaluating the therapeutic potential of natural-derived compounds for MASH using advanced 3D liver models that accurately mimic the complex pathophysiology of MASH. These models will be used to screen and evaluate novel compounds, particularly those derived from natural sources, for their potential in treating MASH.

The research program is structured around four main tasks:

1. Screening of 5-7 compounds, one for each main classes of phytochemicals, in 3D liver model: The initial phase involves the screening of 5-7 classes of phytochemicals using a 3D multicellular spheroid (MCS) model set up with the aim to test the effects on lipid accumulation, stellate cell activation, and macrophage polarization, identifying the most promising candidates for further investigation.
2. Botanical Extract Library: Based on the initial screening results, a library of botanical extracts enriched with the most promising phytochemicals will be created. These extracts will be evaluated using the MCS model to determine their therapeutic potential, with the most effective extract selected for further testing.
3. Advanced 3D MASH Model Development: A more complex *in vitro* organoid system will be developed using human-derived cells, including hepatocytes and immune cells differentiated from PBMCs. This advanced model aims to more accurately replicate MASH features, including steatosis, inflammation, and fibrosis. It will allow for a more comprehensive study of hepatocyte metabolism, stellate cell activation, and immune cell interactions.

4. Botanical Extract Evaluation: The most promising botanical extracts identified in earlier stages will be tested in the advanced organoid system. This evaluation will include assessments of lipid accumulation, stellate cell activation, and immune cell characterization. Additionally, metabolomics and lipidomics analyses will be conducted to understand the biological pathways affected by MASH and to assess the safety of the botanical extracts.

By using advanced 3D models, this research aims to overcome limitations of traditional cell culture methods, providing a more physiologically relevant environment for compound screening.

The goal is to identify promising ingredients for nutraceuticals that could effectively mitigate MASH. This multidisciplinary approach, combining expertise in natural product research and advanced in vitro modelling, has the potential to significantly advance therapeutic strategies for MASH and contribute to broader liver disease management.