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FRI0508 OLIVE OIL POLYPHENOLS AS NOVEL NUTRACEUTICALS IN TREATMENT OF OSTEOARTHRITIS

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Background: Osteoarthritis (OA) is a degenerative disease of the joints characterised by the imbalance of anabolic and catabolic processes in articular cartilage. It is one of the most significant causes of disability in the world affecting over 60% of people over the age of 60, causing joint stiffness, pain and a decrease in the quality of life. Currently no successful disease-modifying agent has been found to prevent or treat the condition. To address this unmet need, alternative approaches, including the use of nutraceuticals as a novel therapeutic intervention are under examination.

Objectives: To analyse if nutraceutical are able to reverse the catabolic activity that contribute to cartilage destruction in OA. Here two polyphenols from extra virgin olive oil (EVOO), oleocanthal (OLC) and ligstroside aglycone (LA), plus a chemically modified acetylated ligstroside aglycone (A-LA), and two marine polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were examined as potential anti-inflammatory agents for OA.

Methods: Human chondrocytes and cartilage explants were extracted from OA femoral heads, cultured and incubated with increasing concentrations of select compounds in combination with the pro-inflammatory cytokines IL-1 β and oncostatin M (OSM). Gene expression levels were analysed by qPCR; nitric oxide (NO), GAG release and cytokines were measured in supernatants by colorimetric assays and Luminex technology respectively. Safranin-O and Alcian blue/Sirius red staining were done to quantify extracellular matrix components from cartilage.

Results: Acetylated ligstroside showed the most promising results for implementation in treating OA as it reduced the expression of pro-inflammatory genes such as inducible nitric oxide (*iNOS*), matrix metalloproteinase-13 (*MMP13*) and interleukin-1 β (*IL1B*) at both RNA and protein levels; decreased nitric oxide (NO) levels from cartilage explants and also reduced proteoglycan (PG) losses in human osteoarthritic cartilage explants and chondrocytes (Figure 1).

Conclusion: These results substantiate the role of nutraceuticals in OA with implications for therapeutic intervention and our understanding of OA pathophysiology.

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Figure 1. Stimulation with A-LA recovered proteoglycan (PG) losses. OA cartilage punches were cultured for 14 days in different conditions then sectioned to show the top superficial layer down to the deep zone at the bottom. Safranin-O staining visualised PG showing how exposure to the inflammatory environment of IL-18/OSM caused losses to PG that were recovered with A-LA 10 μ M but worsened with higher concentrations. Same results were observed with Alcian blue for PG and Sirius Red for collagen in matrix. All scale bars represent 200 μ m.

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FRI0509 3D MICROSTRUCTURE OF INTACT AND OSTEOARTHRITIC HUMAN MENISCUS USING MICRO-COMPUTED TOMOGRAPHY

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Background: Degenerative meniscal lesions are highly prevalent in the general population and are associated with increased risk of knee osteoarthritis (OA). Development of novel methods for visualization of the early degenerative changes in the meniscus could help us better understand meniscal degradation and the onset of OA.

Objectives: To develop and perform *ex vivo* 3D imaging of meniscus posterior horn microstructure with micro-computed tomography (μ CT), and to compare specimens from healthy references with end-stage OA using histology and qualitative μ CT.

Methods: Medial and ipsilateral lateral menisci were retrieved from 10 patients undergoing total knee arthroplasty for medial compartment knee OA (age range 50 to 75 years, 5 women). Additionally, medial menisci were obtained from 10 cadaveric donors without known OA, to serve as reference (age range 18 to 77 years, 5 women). The samples were freshly frozen in -80°C. After thawing, the posterior horns were dissected and fixed, followed by excision of a piece for μ CT imaging (Fig. 1A). The μ CT samples were dehydrated in ascending ethanol concentrations, treated with hexamethyldisilazane (HMDS), and dried in room temperature. They were then imaged with a desktop μ CT (scanning parameters: 40 kV, 250 μ A, 2.0 μ m pixel size, 1815 ms, no additional filtering). For histological analysis, Pauli's histopathological scoring¹ was performed independently by two graders on sections from three regions (Fig. 1A). The graders' consensus was given for each sub-score, from which the final overall consensus scores were calculated for each region. The mean difference in consensus scores (95% CI), adjusted for age and sex, were estimated between the menisci from OA knees and the reference menisci (medial OA menisci vs reference menisci, and lateral menisci from OA patients vs reference menisci) using a mixed linear regression model. The mean difference in consensus scores between the medial and lateral menisci from the same OA patient was calculated using a linear fixed effects model. The models were fitted on all three histological regions, but here we report histology results from region 2, because this region is adjacent to the piece analyzed by μ CT (Fig. 1A).

Figure 1. A: Wedge-shaped sections were cut from the meniscus posterior horn for μ CT analysis and histological scoring (regions 1, 2 and 3). B: The histological consensus scores from region 2 are plotted against the subject's age in the three sample groups (lateral, medial OA, reference). The mean (SD) consensus scores of each group: lateral menisci from OA patients: 9.5 (2.5); medial OA: 14.1 (1.7); reference: 8.5 (3.5). C: Volumetric visualizations of meniscus representing Pauli's histopathological grades 1-4 imaged using HMDS-based μ CT (top row), and their adjacent Safranin-O-Fast Green-stained histological sections (bottom row). It can be seen that the same structural features, such as surface morphology, collagen organization, and tissue calcification, can all be visualized in 3D with μ CT. Grade 1 (scores 0-4): normal tissue. Grade 2 (scores 5-9): mild degeneration. Grade 3 (scores 10-14): moderate degeneration. Grade 4 (scores 15-18): severe degeneration.

Results: 3D visualization of the meniscus with μ CT revealed similar structural changes as histological analysis (Fig. 1C). The histopathological consensus scores were generally higher in medial OA samples as compared to both lateral menisci from OA patients and the reference menisci (Fig. 1B). The mean difference in histological scores (95% CI) was 4.3 (2.5, 6.1) for medial OA menisci vs reference menisci, -0.3 (-2.2, 1.5) for lateral menisci from OA patients vs reference menisci, and 4.6 (3.0, 6.2) for medial OA menisci vs lateral menisci from OA patients.

Conclusion: An HMDS-based 3D μ CT protocol allows unique 3D visualization of meniscus microstructures. The method enables the visualization of considerably large volumes and evaluation of the tissue's 3D