Ginger-derived Extracellular Vesicles Inhibit The Progression Of Osteoarthritis

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INTRODUCTION: Few effective pharmacological treatments exist for osteoarthritis (OA), and new therapeutic strategies are needed. Plant-derived extracellular vesicles (EVs) contain nucleic acids such as microRNAs and growth factors and can modulate gene expression in animals [1]. This study investigated the inhibitory effects of ginger-derived EVs (GDEVs) on OA.

METHODS: In vitro, GDEVs were added to human OA synovial fibroblasts (OASF) and chondrocytes stimulated with IL-1β to evaluate cell proliferation, migration, anti-inflammatory effects, and chondroprotective effects. In vivo, OA was induced in male C57BL/6 mice by destabilization of the medial meniscus (DMM). Mice received weekly intra-articular injections of GDEVs (EV group), hyaluronic acid (HA group), or PBS (control group) and were sacrificed at 8 weeks (n=8 per group). At 7 weeks, Fluorogold (FG), a retrograde nerve tracer, was injected intraarticularly. In a separate cohort, DMM mice received oral GDEVs (EV group) or PBS (control group) twice a week and were sacrificed at 8 weeks (n=7 per group). Behavioral assessment was performed by open-field testing. Histological evaluation and micro-CT were conducted. GDEV cargo expression was also analyzed.

RESULTS: In vitro, GDEVs significantly suppressed the proliferation and migration of OASF. GDEVs reduced IL-6, MMP-3, and COX-2 expression in OASF and MMP-13 and ADAMTS-5 expression in chondrocytes. With the intra-articular injection, total distance traveled was significantly greater in the EV group than in the PBS group, and standing counts were significantly higher in the EV group than in the other two groups. Histologically, the EV group showed significantly lower OARSI scores, synovitis scores, MMP-13 and ADAMTS-5 expressions, and dorsal root ganglia (DRG)'s CGRP expressions than the other two groups. Micro-CT showed a significantly smaller bone volume/ tissue volume of the tibial subchondral bone in the EV group than in the control group. In the oral administration model, the synovitis score was significantly lower in the EV group than in the control group, whereas other outcomes showed no significant differences. Molecular analysis showed that GDEVs were enriched in 6-gingerol and microRNA-149, both of which exhibited anti-inflammatory and anti-proliferative effects in vitro.

DISCUSSION: GDEVs inhibited knee OA through suppression of cell proliferation and migration, anti-inflammatory, chondroprotective, and analgesic effects. GDEVs contain bioactive compounds such as microRNA-149 and 6-gingerol, which have anti-inflammatory effects, and these compounds may contribute to the suppression of OA.

SIGNIFICANCE/CLINICAL RELEVANCE: Natural product-derived GDEVs may represent a promising novel therapeutic option for OA

REFERENCES:
1. Zhao B et al. Exosome-like nanoparticles derived from fruits, vegetables, and herbs: innovative strategies of therapeutic and drug delivery. Theranostics 2024;14(12):4598–4621.

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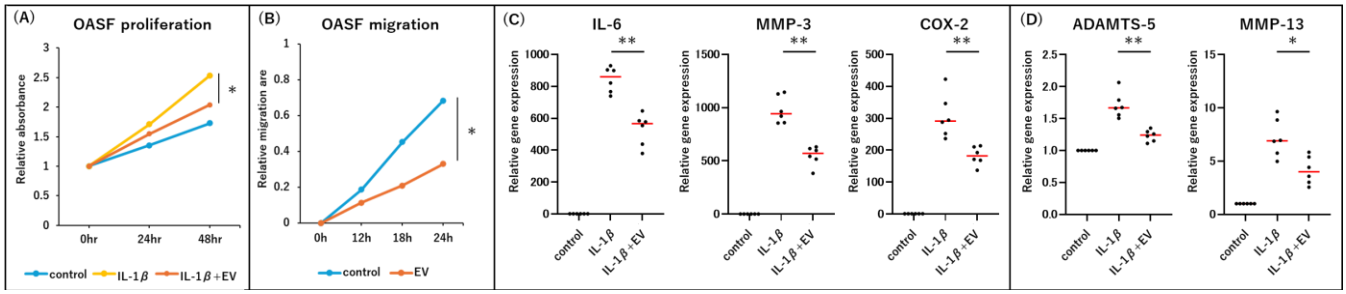

Fig 1. In vitro findings. (A) MTT assay (B) Scratch assay (C) PCR in synovial fibroblasts (D) PCR in chondrocytes * p<0.05, ** p<0.01

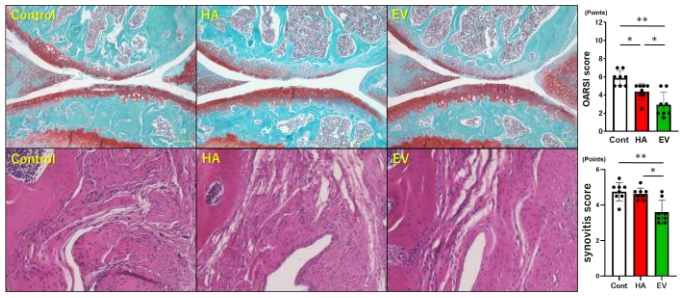

Fig 2. Histological findings after injection between EV, HA, and control group. Intra-articular injection of GDEV could inhibit OA progression and synovitis.

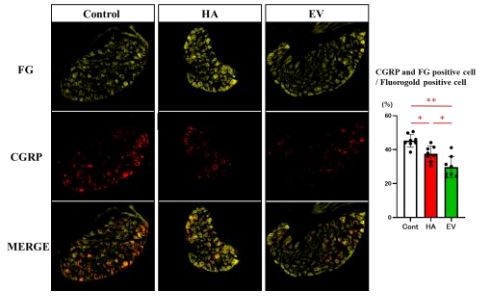

Fig 3. Immunofluorescence staining of DRG (L3-5). Expression of CGRP was significantly inhibited in the EV group.