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CURCUMA LONGA AND *BOSWELLIA SERRATA* EXTRACTS MODULATE DIFFERENT AND COMPLEMENTARY PATHWAYS TO EXERT **ANTI-INFLAMMATORY, ANTI-OXIDATIVE AND ANTI-CATABOLIC ACTIVITIES ON CHONDROCYTES:** DECIPHERING OF A TRANSCRIPTOMIC STUDY

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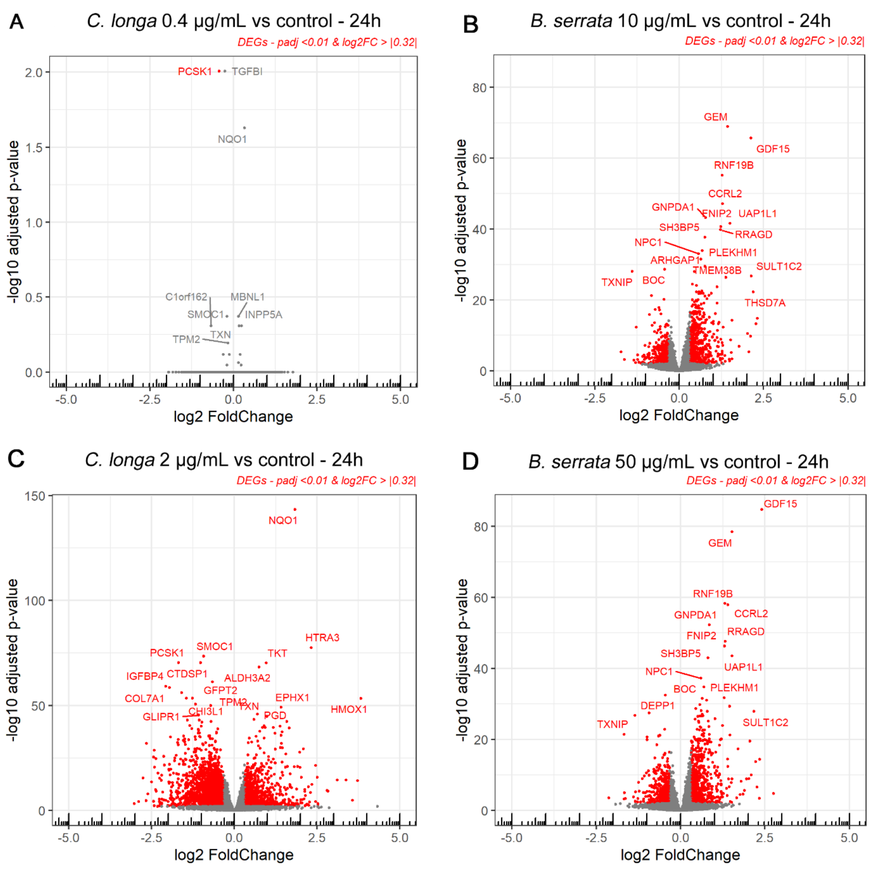
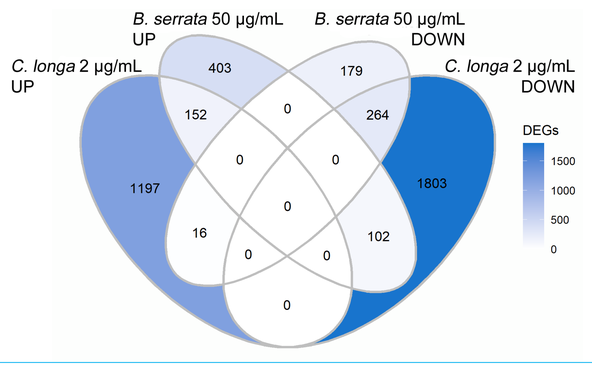
PURPOSE. *Curcuma longa* (CL) and *Boswellia serrata* (BS) extracts are used to relieve osteoarthritis symptoms. The aim of this *in vitro* study was to investigate their mechanisms of action at therapeutic plasmatic concentrations on primary human osteoarthritic (OA) chondrocytes.

METHODS. BS (10-50 µg/ml) and CL (0,4-2 µg/ml corresponding to 1-5 µM of curcumin were evaluated separately or in combination on primary chondrocytes isolated from knee cartilage of 13 patients undergoing total knee replacement. Chondrocytes from each patient were then cultured independently in alginate beads. 24h-treated mRNA from 10 patients was used for RNA-sequencing analysis. Nitrite (NO2), interleukin (IL)-6, CCL2 and Growth Differentiation Factor (GDF)15 were quantified in the culture supernatant after 72h of treatment with BS or CL or a combination of both products (n = 12).

RESULTS

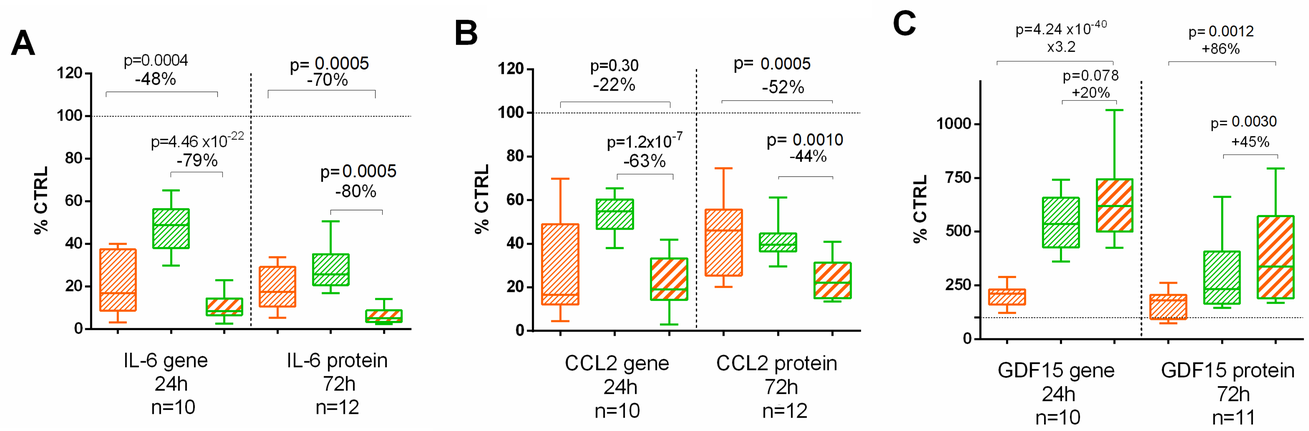
Transcriptomic (RNA-seq)





With CL, the most over-expressed genes were anti-oxidative, detoxifying and cytoprotective genes involved in *Nrf2* pathways (more than 87 genes including HMOX1). Down-regulated genes were principally pro-inflammatory genes (more than 110 genes including IL-1β, TNFα, IL-6 and many chemokines), FGF-1 and catabolic enzymes involved in cartilage degradation (MMP-1,-2,-3,-13, HTRA1 and ADAMTS5). BS anti-oxidant/detoxifying activity was related to the activation of *Nrf1* and *PPARα* pathways. BS anti-inflammatory effects were associated to the over-expression of GDF15 (5.3 fold), to a decrease of cholesterol cell intake and fatty acid metabolism and to a down-regulation of Toll-like receptors (TLR1, TLR4, TLR6, MYD88 and TOLLIP). Finally, BS down-regulated ADAMTS-1, 5 and MMP-3, -13 genes expression.

Proteomic confirmation (ELISA)



ANTI-OXIDATVE/DETOX /SENESCENCE
LDLR **-39%**
HMGCR **-14%**
MT1X x2
UCP2 +20%
HMBG2 +31%

ANTI-DEGRADATION CARTILAGE
ADAMTS-1 **-36%**
ADAMTS-5 **-28%**

ANTI-INFLAMMATORY
IL-6 **-70%**
CCL2 **-52%**
TNFSF10 **-40%**
IL-17RB **-23%**
GDF15 **x2,4**
Voie TLR -20%
(FSTL1/**TLR1-4-6**/TOLLIP/MYD88)

Beneficial effects of B. serrata on C. longa-treated chondrocytes

CONCLUSION

BS and CL have **anti-oxidative**, **anti-inflammatory**, and **anti-catabolic** activities suggesting a protective effect of these extracts on cartilage. Even if they share some mechanism of action, the two extracts act mainly on **distinct pathways**, justifying their association to treat osteoarthritis.

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