Appendix 1

Table A1 Overview of various inflammatory and anti-inflammatory mediators in OA and their mechanisms. *Modified table by Yunus et al.*[13]

Inflammatory mediators	Description of mechanism
Cytokines and chemokines	**IL-1, IL-6, IL-8:** · Inhibit matrix synthesis and promote cellular apoptosis. · Autocrine/paracrine agent; induce chondrocytes to produce proteases, nitric oxide, and eicosanoids such as prostaglandins and leukotrienes. **IL-1:** · Induce the synthesis of matrix metalloproteinases (MMP-1, MMP-3, MMP-13), TNF-α, IL-6 and IL-8 to drive the cartilage matrix breakdown. · Decreases the synthesis of proteoglycans, aggrecan, and type II collagen. **IL-6 and IL-8:** · Secreted by senescent cells, responsible for the loss of the cartilage extracellular matrix (ECM) and the capability to maintain and repair.
Proteases	MMP-1, -3, -13 and ADAMT-4: · Degradation of collagenous framework and ECM **MMP-3:** · Activator of other collagenases (MMP-1, -8, -13) that are implicated in type II collagen degradation. **MMP-13:** · Most important role during OA pathogenesis. · Secreted by hypertrophic chondrocytes in OA cartilage. · Degrades type II collagen as the main articular ECM.
iNOS	· Induce inhibition the synthesis of both proteoglycans and collagen. · Upregulate the synthesis of matrix metalloproteinases. · Induce chondrocyte apoptosis; reduced the survival of cells and inhibited mitochondrial respiratory chain function and ATP synthesis.

COX-2 (PGE2)	· Suppress the production of proteoglycans, enhances the degradations of both aggrecan and type II collagen. · Involves inflammation, apoptosis, angiogenesis. · Enhances the effects of IL-6, MMP-3, and MMP-13.
Anti-inflammatory mediators	**TGF-β:**
	· Act as a signaling molecule for reparatory cells.
Cytokines	**IL-4 and -10:**
	· Inhibition of MMPs, PGE2, COX-2 and iNOS and apoptosis of chondrocytes, **IL-13:**
	· Inhibits the inflammatory processes, protects chondrocytes, reduces the secretion of inflammatory cytokines and metalloproteinases.