

**Table S1.** Neutrophil-derived Products and their role in osteoarthritis.

Products	Function in OA Pathology	References
Elastase	ECM Degradation, Tissue destruction, pro-MMP-13 activator	[38]
CXCL8 (IL-8)	Neutrophil chemoattractant	[31]
CCL2 (MCP-1) and CCL4 (MIP-1)	Positively associated with joint pain	[30]
CCL19 and CCR7	VEGF secretion and further neoangiogenesis	[190]
TNF- $\alpha$	Increasing reactive oxygen species (ROS); Inhibits chondrogenic progenitor cells (CPCs) migration	[32,33,35]
IL-1 $\beta$	Neutrophil chemoattractant; Enhancement of MMP expression	[30]
IL-22	Enhancement FLS proliferation; Up-regulation MMP1 and S100A8/A9 production	[39]
IL-17	Raising local Fc $\gamma$ R-carrying neutrophils	[41]
IFN- $\gamma$	Up-regulation of Fc $\gamma$ R in macrophages and neutrophils	[41]

**Table S2.** The potential pharmacological function.

Treatment	Function	References
NSAIDs	Inhibiting neutrophil aggregation and degranulation independent of COX and PGE2 release Reducing C5a- and CXCL8-induced neutrophil migration Reducing F-actin polymerization	[97]
Glucocorticoids	Dual function as Inhibitor or inducer of apoptosis in neutrophils anti-inflammatory or pro-inflammatory effects on neutrophils Changing neutrophils' maturation, extravasation, adhesion, metabolism, and activation	[99]
Hyaluronic acid	Decreasing the p-AKT expression level in synovial-fluid neutrophils Decreasing the levels of phosphorylated p38MAPK, NF- $\kappa$ B, p53, Bax, and Caspase-3 in syno-vial fluid neutrophils	[100,103]
TNF- $\alpha$ blockers	Attenuating the generation of pro-inflammatory cytokines, chemokines, and MPO by neutrophils Upregulating of adhesion molecules expression Priming of respiratory burst in adherent neutrophils Reducing neutrophil ROS production [108] Reducing the influx of neutrophils from inflamed joints Inhibiting CD69 expression on arthritic neutrophils Downregulating neutrophil chemoattractant IL-8. modulating miRNA levels in neutrophils	[105]
IL-1Ra (e.g., Chondrogenic progenitor cells and Anakinra)	reducing neutrophil recruitment and degranulation Inhibiting NET formation in neutrophils	[2,122]
Monoclonal anti-IL-1 $\beta$ antibody (e.g., Canakinumab)	Downregulating of MAPK14 and NF- $\kappa$ B Upregulating GRP78	[123,125]
Recombinant IL-37	Reducing CXCL1, MIP1 $\alpha$ /CCL3, IL-1 $\alpha$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and the neutrophil enzyme MPO	[121]
Anti-IL-6 receptors NE inhibitors (e.g., Sivelestat sodium hydrate and Polydatin)	modulating miRNA levels in neutrophils Inhibiting TNF- $\alpha$ , IL-6, and NO secretion Inhibiting PAR2, p44/42 MAPK activity	[126,136] [140,141]

	Inhibiting NF- $\kappa$ B and HMGB1	
APPA (apocynin and paeonol)	Reducing neutrophil degranulation and NET formation	[148]
	Dysregulating TNF- $\alpha$ and IL-8 expression and ROS generation by neutrophils	
G-CSF receptor blockers	Inhibiting cytokine-driven signaling pathways (i.e., NF- $\kappa$ B and Erk1/2 pathways) suppressing chemokines (KC, MCP-1) and pro-inflammatory cytokines (IL-1 $\beta$ , IL-6) production	[61]
	Decreasing CXCR2 and increasing CD62L expression	
MSCs <sup>1</sup>	suppressing NO secretion in neutrophil Decreasing fMLP in neutrophil inducing respiratory burst in neutrophil Reducing the adhesion, infiltration, and recruitment of neutrophils through TNF-stimulated gene 6, CXCL2, and CXCR2 polarizing the pro-inflammatory N1 subset into the immune modulatory N2 Altering the expression of IL-6, PDGF, angiopoietin-1, HGF, and VEGF	[159,163]
Neutrophil-NPs <sup>2</sup>	Neutralizing inflammatory cytokines Inhibiting apoptosis of inflamed chondrocytes	[170,172]
Neutrophil-derived exosomes	Inhibiting pro-inflammatory factors production	[187]
	Inducing Th17/Treg cell balance regulation	
NDMVs <sup>3</sup> enriched in AnxA1	Downregulating TNF $\alpha$ -induced expression of IL-5, IL-6, IL-8, MCP-1, IFN $\gamma$ , and MIP-1 $\beta$ polarizing MQs towards a more anti-inflammatory M2 phenotype	[92,189]

<sup>1</sup> Mesenchymal stem cells

<sup>2</sup> Neutrophil nanoparticles

<sup>3</sup> Neutrophil-derived microvesicles