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	[195]
TNF-α	Increasing ROS; Inhibits chondrogenic progenitor cells (CPCs) migration	[32,33,35]
IL-1β	Neutrophil chemoattractant; Enhancement of MMP expression	[30]
IL-22	Enhancement FLS proliferation; Up-regulation MMP1 and S100A8/A9 production	[39]
IL-17	Raising local FcgammaR-carrying neutrophils	[41]
IFN-γ	Up-regulation of FcgammaR 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	[99]
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	[101]
Hyaluronic acid	Decreasing the p-AKT expression level in synovial-fluid neutrophils Decreasing the levels of phosphorylated p38MAPK, NF-κB, p53, Bax, and Caspase-3 in syno-vial fluid neutrophils	[102,105]
TNF-α 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 [112] Reducing the influx of neutrophils from inflamed joints Inhibiting CD69 expression on arthritic neutrophils Downregulating neutrophil chemoattractant IL-8. modulating miRNA levels in neutrophils	[109]
IL-1Ra (e.g. Chondrogenic progenitor cells and Anakinra)	reduing neutrophil recruitment and degranulation Inhibiting NET formation in neutrophils	[5,126]
Monoclonal anti-IL-1β antibody (e.g. Canakinumab)	Downregulating of MAPK14 and NF-κB Upregulating GRP78	[127,129]
Recombinant IL-37	Reducing CXCL1, MIP1α/CCL3, IL-1α, TNF-α, IL-1β, IL-6, and the neutrophil enzyme MPO	[125]
Anti-IL-6 receptors	modulating miRNA levels in neutrophils	[130,138]
NE inhibitors (e.g. Sivelestat sodium hydrate and Polydatin)	Inhibiting TNF-α, IL-6, and NO secretion Inhibiting PAR2, p44/42 MAPK activity	[142,143]

APPA (apocynin and paeonol)	Inhibiting NF-κB and HMGB1 Reducing neutrophil degranulation and NET formation Dysregulating TNF-α and IL-8 expression and ROS generation by neutrophils	[155]
G-CSF receptor blockers	Inhibiting cytokine-driven signaling pathways (i.e., NF-κB and Erk1/2 pathways) suppressing chemokines (KC, MCP-1) and pro-inflammatory cytokines (IL-1β, IL-6) production Decreasing CXCR2 and increasing CD62L expression	[63]
MSCs[1]	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	[163,167]
Neutrophil-NPs[2]	Neutralizing inflammatory cytokines Inhibiting apoptosis of inflamed chondrocytes	[174,176]
Neutrophil-derived exosomes	Inhibiting pro-inflammatory factors production Inducing Th17/Treg cell balance regulation	[191]
NDMVs[3] enriched in AnxA1	Downregulating TNFα-induced expression of IL-5, IL-6, IL-8, MCP-1, IFNγ, and MIP-1β polarizing MQs towards a more anti-inflammatory M2 phenotype	[94,193]

[1] Mesenchymal stem cells; [2] Neutrophil nanoparticles; [3] Neutrophil-derived microvesicles.