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REVIEW

Apremilast in osteoarthritis: exploring its therapeutic mechanisms

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Abstract

Osteoarthritis (OA) is increasingly understood as a complex, inflammatory disease rather than a purely mechanical disorder. Apremilast, a selective phosphodiesterase 4 inhibitor approved for psoriatic arthritis, is amongst several new treatment alternatives that target one of the most important inflammatory pathways involved in OA. Apremilast decreases pro-inflammatory cytokines, such as TNF, IL-1 and IL-6, which are central to cartilage degradation and synovial inflammation. This review explores the mechanistic rationale and available evidence supporting the repurposing of apremilast in OA. We highlight its potential to reduce pain and slow structural progression. Although the data are currently scarce, there remains a strong rationale for its repurposing for the treatment of OA based on its safety profile, oral route of administration and positive treatment adherence. Nevertheless, clinical investigation remains limited. Further research is needed to clarify its therapeutic potential and identify patient populations most likely to benefit.

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Keywords: apremilast, inflammation, osteoarthritis, pain, treatment.

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Introduction

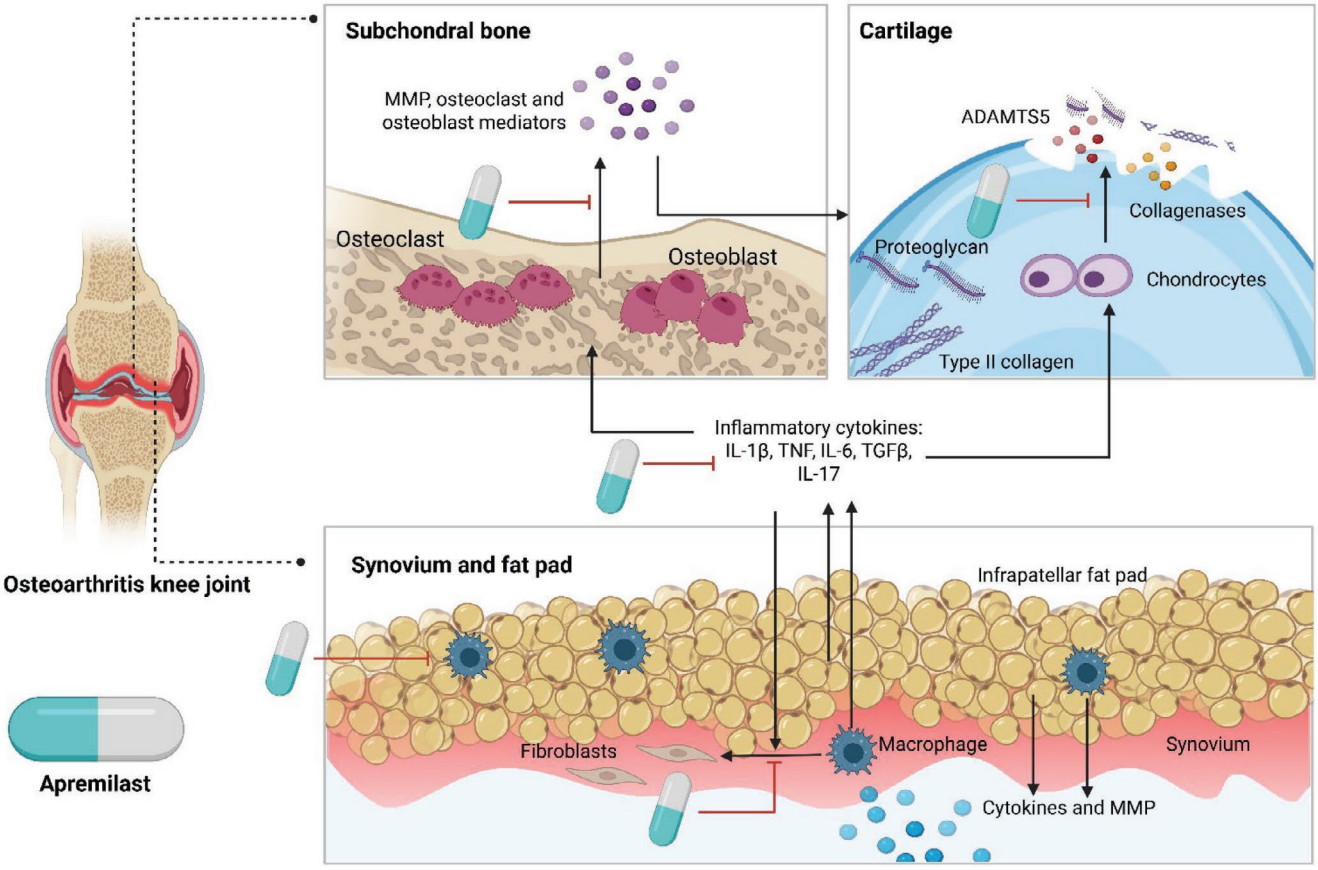
Osteoarthritis (OA), once viewed mainly as a mechanically driven degenerative condition, is now recognized as a complex, multifactorial disease involving chronic inflammation, oxidative stress, metabolic imbalance, and structural damage to cartilage and subchondral bone.[1] The American College of Rheumatology[2] and, more recently, the *European Alliance of Associations for Rheumatology* (EULAR)[3] and National Institute for Health and Care Excellence (NICE)[4] have developed classification and diagnostic criteria for OA of the knee, hip and hand. In a large primary care cohort, the NICE criteria identified the majority of patients with symptomatic or radiographic knee OA, whereas the EULAR and American College of Rheumatology criteria captured only about half.[5] Early-stage diagnostic criteria for knee OA, focusing on symptoms such as stair-related pain, morning stiffness and joint tenderness, allow timely intervention.[6] OA severity is multidimensional, encompassing structural changes, clinical symptoms and emerging biomarkers, and is graded radiographically, commonly via the Kellgren–Lawrence scale (grades 0–4).[7] Clinical severity is assessed using patient-reported outcomes like the *Western Ontario and McMaster Universities Arthritis Index* (WOMAC), which includes domains of pain, stiffness and functional limitations.[8] Notably, in a meta-epidemiological analysis, the Visual Analogue Scale (VAS) for global OA pain showed greater assay sensitivity than the WOMAC pain subscale in detecting treatment effects.[9] These clinical and radiographic measures reflect underlying pathophysiological processes, including inflammatory cytokine activity. Key pro-inflammatory cytokines, such as IL-1β, TNF and IL-17, play essential roles in maintaining

joint degradation, whilst chondrocyte senescence, abnormal angiogenesis and dysregulated bone remodelling further contribute to disease progression (Figure 1).[10]

Apremilast, an oral selective phosphodiesterase 4 (PDE4) inhibitor, has emerged as a promising candidate for the treatment of OA because of its ability to increase intracellular cyclic adenosine monophosphate (cAMP), which activates anti-inflammatory pathways and suppresses pro-inflammatory transcription factors like NF-κB, whilst also modulating the expression of cytokines such as TNF and IL-17.[11,12] It is currently approved for psoriasis, psoriatic arthritis (PsA),[13] and Behçet's disease[14] and has shown potential in preclinical models of fibrotic disorders, such as bleomycin-induced skin fibrosis[15] and Alzheimer's disease,[16] underscoring its broader immunomodulatory and anti-inflammatory effects. In OA models, apremilast appears to reduce cytokine production, decrease oxidative stress and slow cartilage breakdown, whilst also modulating immune responses and protecting chondrocytes from senescence and apoptosis.[17,18]

Although preclinical data suggest that apremilast can reduce pro-inflammatory cytokines, oxidative stress and chondrocyte senescence, clinical validation in OA remains limited and inconclusive. This review explores the therapeutic potential of apremilast in osteoarthritis by examining its effects on the major pathogenic mechanisms underlying the disease. Through a mechanistic lens, it evaluates how apremilast may influence inflammation, oxidative stress, cartilage integrity, subchondral bone remodelling and synovial angiogenesis, offering insight into its possible role as a disease-modifying agent in OA.

Figure 1. Potential effects of apremilast on osteoarthritis (OA) pathogenesis.



Apremilast may modulate key inflammatory and degradative pathways in OA by suppressing pro-inflammatory cytokines and enzymes implicated in disease progression and by downregulating the expression of TNF, IL-1β, IL-6 and IL-17, which are critical drivers of synovitis, cartilage breakdown, and subchondral bone remodelling in OA. Additionally, it may indirectly inhibit matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5), reducing extracellular matrix degradation.
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Methods

This narrative review was conducted to comprehensively evaluate and synthesize current evidence on the therapeutic potential and mechanisms of apremilast in OA. A structured literature search was performed using electronic databases, including PubMed, Scopus, Web of Science and Embase. The search covered articles published from inception to June 2025. Keywords included: "apremilast", "phosphodiesterase 4 inhibitor", "osteoarthritis", "inflammation", "cartilage", "synovium", "cytokines" and "mechanism". Boolean operators such as "AND" and "OR" were used to refine the search strategy.

Only articles published in English and available in peer-reviewed journals were considered. Both preclinical (in vitro, animal) and clinical (human) studies were included. Articles were screened by title and abstract, and relevant full texts were reviewed for inclusion based on their relevance to the pharmacological effects of apremilast in the context of OA pathophysiology. Reviews, meta-analyses, clinical trials, mechanistic studies and case reports were considered.

Review

OA treatment: apremilast insights

Inflammatory cytokines

OA is now understood to involve active inflammatory processes in addition to cartilage degeneration. Pro-inflammatory cytokines play a central role in disease progression. As a PDE4 inhibitor, apremilast may counteract these mechanisms by modulating intracellular signalling pathways. G-protein-coupled receptors (GPCRs), upon stimulation by inflammatory ligands such as prostaglandins, leukotrienes, chemokines and histamine, activate adenylyl cyclase, leading to increased intracellular cAMP levels. cAMP, acting through effectors like protein kinase A (PKA) and exchange proteins activated by cAMP (EPAC), modulates gene transcription by activating transcription factors such as CREB and ATF1, whilst inhibiting pro-inflammatory factors like NF-κB. This results in decreased expression of pro-inflammatory cytokines and increased anti-inflammatory signalling.[19] Intracellular cAMP levels are tightly regulated by their synthesis via adenylyl cyclase and degradation by PDEs, which are a family of 11 enzymes with distinct tissue distributions and substrate specificities. PDE4 is the predominant cAMP-degrading enzyme, playing a key role in controlling inflammatory responses.[20]

Apremilast is an oral small-molecule inhibitor that selectively targets PDE4, leading to sustained elevations in intracellular cAMP. This pharmacological increase in cAMP activates the PKA–CREB signalling axis, which downregulates NF-κB-mediated transcription and, consequently, the expression of key pro-inflammatory cytokines.[19] Apremilast can suppress the expression of IFNγ, TNF, IL-12, IL-17 and IL-23, all of which are major players in the pathogenesis of psoriasis.[21] PsA shares many of these pathogenic pathways, arising from a combination of distinct genetic susceptibilities to environmental triggers. Dysfunctional angiogenesis and early endothelial activation facilitate immune-cell infiltration into the synovium, initiating the inflammatory cascade in PsA. Dendritic cells activate multiple T cell subsets, whilst macrophages, innate lymphoid cells, mucosal-associated invariant T cells, natural killer cells and mast cells amplify inflammation through the production of pro-inflammatory cytokines. The disease is driven by immune-mediated inflammation, particularly through pathogenic $CD8^+$ memory T cells and activation of TNF and IL-23–T helper 17 (T_H17) signalling.[22] Thus, the cytokine profile targeted by apremilast closely aligns with the central inflammatory mechanisms that improve outcomes in patients with PsA.[23]

Evidence suggests that cytokine networks, including IL-1β, TNF, IL-17 and IL-23, contribute to the pathogenesis of OA[24,25] (Table 1). IFNγ has been shown to promote inflammation and degeneration in chondrocytes and osteoblasts via activation of protein kinase R (PKR).[26] In this context, the immunomodulatory effects of apremilast may extend to OA through suppression of these shared inflammatory mediators. In particular, apremilast has been reported to reduce IL-17 expression via activation of the sirtuin 1 (SIRT1) pathway.[27] Collectively, these findings provide a new insight into the use of apremilast in the treatment of OA by targeting inflammatory pathways.

Oxidative stress

Oxidative stress plays a central role in the pathogenesis and progression of OA, a complex, multifactorial joint disease. Excessive production of reactive oxygen species (ROS), including nitric oxide (NO^-), superoxide anion (O_2^-), peroxynitrite ($ONOO^-$) and hydrogen peroxide (H_2O_2), contributes to tissue damage by oxidizing proteins, lipids and DNA in joint structures. Oxidative stress not only damages structural biomolecules but also acts as intracellular signalling molecules that modulate inflammation, chondrocyte apoptosis and extracellular matrix degradation.[28] In OA, synoviocytes and chondrocytes generate ROS that promote synovial inflammation and trigger pathways such as COX2 expression and caspase-mediated apoptosis.[29] Furthermore, ROS impairs mitochondrial function and suppresses autophagy, particularly in meniscal and synovial cells.[30] Additionally, adipose-derived ROS, besides cytokines from

Table 1. Multifaceted actions of apremilast on osteoarthritis pathogenesis.

Pathophysiological parameter in OA	Effect of apremilast	Refs.
Inflammation	Suppression of IL-17, TNF, IFNγ and IL-23	66
Subchondral bone	Prevents osteoclastogenesis	36,72
Chondrocyte	Protects chondrocytes via IL-17 suppression and SOX9 upregulation	27,73
Synovium	Reduces synovial TNF production and synovial hyperplasia. Decreases synovitis and synovial fibroblasts migration	37,74
Oxidative stress	Reduces oxidative stress by inhibiting IL-17 and ameliorates oxidative stress in various tissues through modulation of the SIRT1, cAMP–PKA, and NF-κB signalling pathways	27,33,34
Angiogenesis	Reduces angiogenesis via VEGF suppression	75
Mechanical overloading	BMI and total body fat mass reduction	76,77

BMI, body mass index; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; SIRT1, sirtuin 1; VEGF, vascular endothelial growth factor.

the infrapatellar fat pad, may link metabolic dysfunction with joint degeneration.[31] Collectively, chronic oxidative stress in OA perpetuates a vicious cycle of cellular injury, inflammation and structural joint deterioration.

In chondrocytes, IL-17 is associated with increased oxidative stress and mitochondrial dysfunction. Thus, by inhibiting IL-17 via SIRT1 upregulation, apremilast reduces the generation of ROS and protects against chondrocyte apoptosis.[27] Moreover, apremilast may have an effect beyond IL-17 inhibition, potentially ameliorating oxidative stress. For example, it has been shown to suppress IL-1α-induced oxidative damage and inflammation in endometrial stromal cells by blocking the MyD88–TRAF6–NF-κB signalling axis, a central pathway in oxidative and inflammatory responses.[32] In models of doxorubicin-induced cardiotoxicity, apremilast reversed cardiac injury by reducing oxidative damage. Additionally, in neutrophils, apremilast inhibits ERK and JNK activation through a cAMP–PKA-dependent pathway, thereby suppressing oxidative burst and inflammatory chemotaxis.[33] In preclinical models of acute respiratory distress syndrome, apremilast protected lung tissue by selectively inhibiting PDE4 in neutrophils and reducing ROS generation and inflammatory infiltration.[34]

Effects on chondrocytes

Chondrocytes, the sole cellular component of articular cartilage, are central to cartilage integrity, and their senescence plays a key role in OA pathogenesis. In an in vitro study using IL-17-treated ATDC5 chondrocytes, apremilast significantly reduced the expression of pro-inflammatory mediators such as IL-1β and MCP1, suppressed ROS production and decreased senescence-associated β-galactosidase activity. It also reversed IL-17-induced G0/G1 cell cycle arrest and downregulated senescence-related markers p21 and PAI1. Mechanistically, apremilast restored SIRT1 expression, and knockdown of SIRT1 abolished its protective effects, indicating that SIRT1 mediates the anti-senescence actions of apremilast in chondrocytes.[27] Zhang et al. demonstrated, in primary human chondrocytes, that apremilast dose-dependently reversed IL1α-mediated downregulation of SOX9, COL2A1 and ACAN (all of which are key markers of the chondrogenic phenotype), whilst concurrently attenuating upregulation of the hypertrophic marker COL10A1. These effects were abolished by small interfering RNA-mediated SOX9 knockdown, indicating a SOX9-dependent mechanism.[18]

Effects on subchondral bone

Subchondral bone remodelling is a hallmark of OA progression, marked by increased bone turnover, sclerosis and aberrant angiogenesis, changes that contribute to joint degeneration and pain. Apremilast has demonstrated potential to modulate these pathological processes through both anti-inflammatory and anti-resorptive mechanisms.[35,36] By elevating intracellular cAMP, apremilast downregulates pro-inflammatory cytokines, key drivers of subchondral bone remodelling and synovitis in OA. This attenuation of inflammatory mediators disrupts the cycle of inflammation-induced bone remodelling that underlies OA progression (Table 2).

Beyond its anti-inflammatory effects, apremilast directly inhibits osteoclastogenesis, the process by which osteoclasts are formed. Studies using human peripheral blood mononuclear cells from patients with PsA have shown

Table 2. Stepwise effects of apremilast in osteoarthritis.

Mechanistic step	Effect	Refs.
PDE4 inhibition	Activates PKA–CREB, suppresses NF-kB	39
Cytokine modulation	↓ TNF, IL-17, IL-23; ↑ IL-10	78,79
Osteoclastogenesis inhibition	↓ Osteoclastogenic cytokines, ↓ DC-STAMP	35
Reduced bone resorption	↓ Pit formation by osteoclasts	35,80

CREB, cAMP response element-binding protein; DC-STAMP, dendritic cell-specific transmembrane protein; PDE4, phosphodiesterase 4; PKA, protein kinase A; ↓, decreased or downregulated; ↑, increased or upregulated.

that apremilast dose-dependently suppresses the expression of osteoclastogenic cytokines and reduces the differentiation of osteoclast precursors into mature, bone-resorbing osteoclasts.[35] Importantly, apremilast inhibits the expression of dendritic cell-specific transmembrane protein, a critical fusion protein necessary for osteoclast maturation, thereby limiting bone resorption activity. This direct suppression of osteoclast formation and function contributes to the preservation of subchondral bone integrity in inflammatory arthritis.[35]

Apremilast also modulates the immune environment by reducing the frequency and activity of pathogenic T_H1 and T_H17 cells whilst enhancing regulatory T cells ($CD4^+Foxp3^+$), which collectively help to mitigate inflammation-driven bone damage.[37] In experimental arthritis models, such as collagen-induced arthritis in mice, apremilast treatment delays disease onset, reduces severity and prevents bone erosions, correlating with decreased levels of pro-osteoclastogenic cytokines and reduced osteoclast activity. These findings underscore the dual role of apremilast in controlling both systemic inflammation and local bone remodelling processes.[37]

Clinical studies in PsA and early oligoarticular PsA show that apremilast improves clinical and patient-reported outcomes, with evidence of halting the progression of entheseal bone changes and reducing joint symptoms.[23] However, in OA, robust clinical data remain limited. The pivotal phase II trial in erosive hand OA did not meet its primary and key secondary endpoints, highlighting the need for further research to clarify the therapeutic role of apremilast in OA subchondral bone pathology.[38]

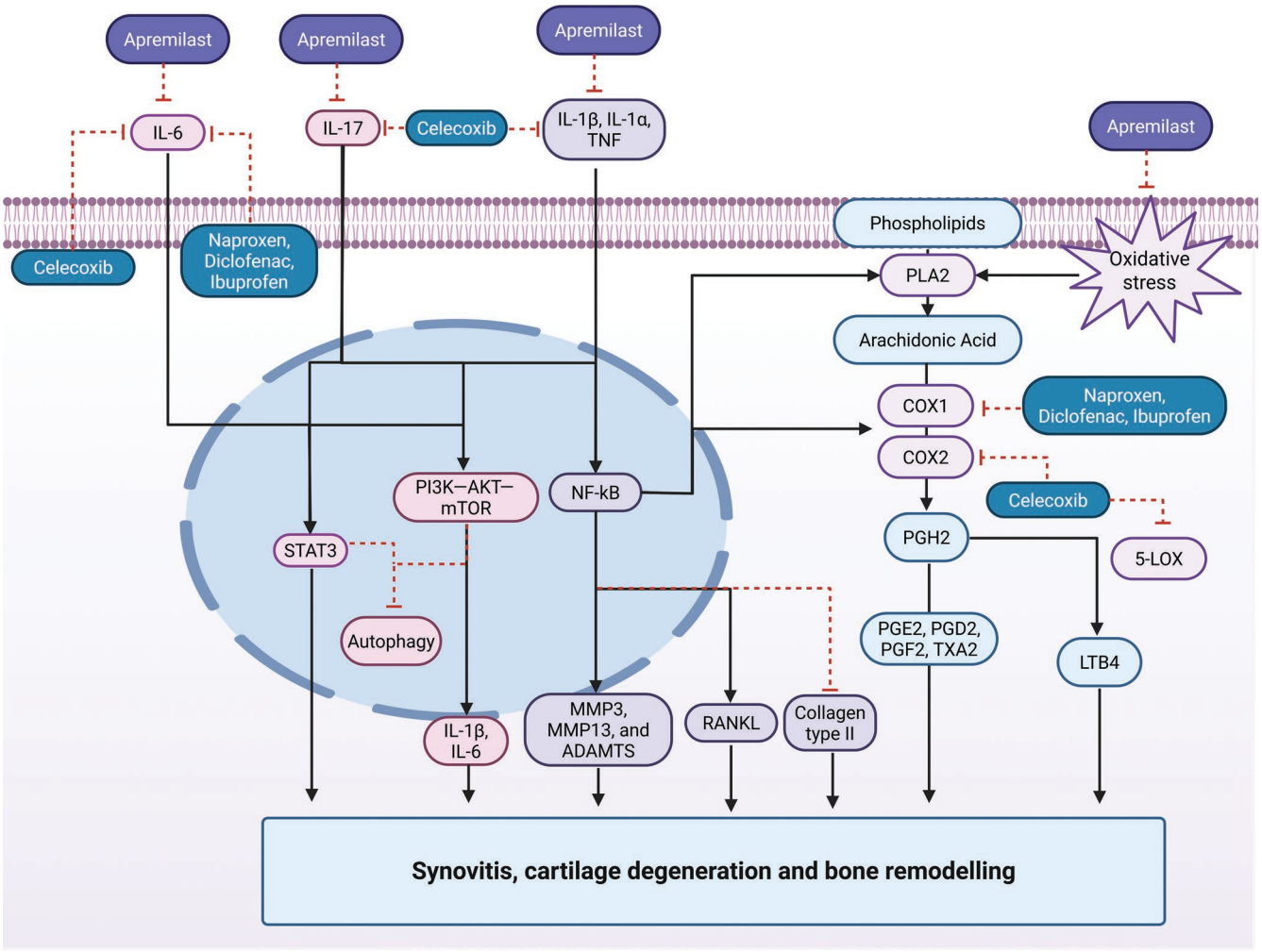
Angiogenesis

PDE4 inhibitors, particularly apremilast, exert indirect anti-angiogenic effects primarily through elevation of intracellular cAMP, which in turn modulates inflammatory signalling. By increasing cAMP levels, apremilast activates PKA and EPAC, leading to suppression of pro-inflammatory transcription factors such as NF-κB and MAPKs.[39] In human endothelial cells, apremilast inhibits TNF-induced expression of VCAM1, E-selectin, matrix metalloproteinase 9 (MMP9) and key inflammatory chemokines. These molecules are closely involved in early vascular activation and tissue remodelling, suggesting that apremilast may indirectly suppress angiogenic processes in inflammatory conditions.[40] Moreover, apremilast suppresses the production of vascular endothelial growth factor (VEGF) in mesenchymal stem cells derived from patients with psoriasis,[41] and inhibits inflammatory cytokines such as TNF, IL-17 and IL-23, which are implicated in the promotion of angiogenesis.[42] Similar anti-angiogenic effects have been observed with other PDE4 inhibitors, such as roflumilast, which attenuated VCAM1 expression and neointimal proliferation in vascular injury models.[43] These findings indicate that PDE4 inhibition interferes with multiple stages of the angiogenic process, including endothelial activation, cytokine-driven vessel sprouting and tissue remodelling.

Intracellular pathways

Apremilast exerts its anti-inflammatory effects by modulating multiple signalling pathways involved in OA pathogenesis, including the inhibition of pro-inflammatory cytokines. IL-1 plays a crucial role in driving chronic inflammation in OA.[44] Upon engagement with its primary receptor, IL-1R1, and co-receptor, IL-1 receptor accessory protein (IL-1RAP), IL-1 activates the mitogen-activated protein kinase (MAPK) pathway, thereby amplifying NF-κB and AP1 signalling (Figure 2). This results in a catabolic cellular environment marked by reduced synthesis of type II collagen and aggrecan and a heightened expression of MMPs and pro-inflammatory cytokines such as IL-6.[45] TNF promotes inflammatory osteolysis by inducing stromal cells to express RANKL, a process critically dependent on IL-1 signalling. Studies show that TNF upregulates both IL-1 and IL-1R1 in stromal cells, and blocking this pathway reduces TNF-driven RANKL production and osteoclast formation by approximately 50%.[46] Beyond its indirect role via RANKL, IL-1 also directly enhances oste-

Figure 2. Proposed mechanistic interactions between apremilast and conventional anti-inflammatory agents in osteoarthritis pathogenesis.



ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AKT, protein kinase B; COX, cyclooxygenase; iNOS, inducible nitric oxide synthase; LTB4, leukotriene B4; MMP, matrix metalloproteinase; NO, nitric oxide; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PGF2, prostaglandin F2; PGH2, prostaglandin H2.
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oclast precursor differentiation, even independently of TNF, by activating p38 MAPK and upregulating key osteoclastogenic genes.[46,47] Additionally, it has been shown that apremilast inhibited IL-1α-induced activation of the MyD88–TRAF6–NF-κB signalling axis in epidermal stem cells[32] and can inhibit osteoclastogenesis by suppressing TNF expression in addition to attenuating the inflammation driven by osteoclastogenesis.[35]

IL-17 contributes to OA progression by disrupting cartilage homeostasis and promoting synovial inflammation. It exacerbates cartilage degeneration by inhibiting autophagy through the PI3K–AKT–mTOR and JAK2–STAT3 pathways. Additionally, IL-17 activates NF-κB and MAPK signalling in chondrocytes, upregulating catabolic factors (IL-6, MMP3, a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS4)) and accelerating matrix degradation. In the synovium, IL-17 amplifies inflammation by inducing pro-inflammatory cytokines (IL-1β, IL-6, IL-23, TGFβ1) and chemokines (CXCL8, CCL20, CXCL3, CXCR4), whilst enhancing MMP9-mediated matrix breakdown. These findings suggest that targeting IL-17 could be a promising therapeutic strategy for OA.[48] Apremilast downregulates IL-17 by activation of SIRT1, thereby protecting chondrocytes.[27]

IL-6 exerts complex and often contradictory effects in OA, influencing cartilage metabolism, synovial inflammation, bone remodelling and muscle function. Upon

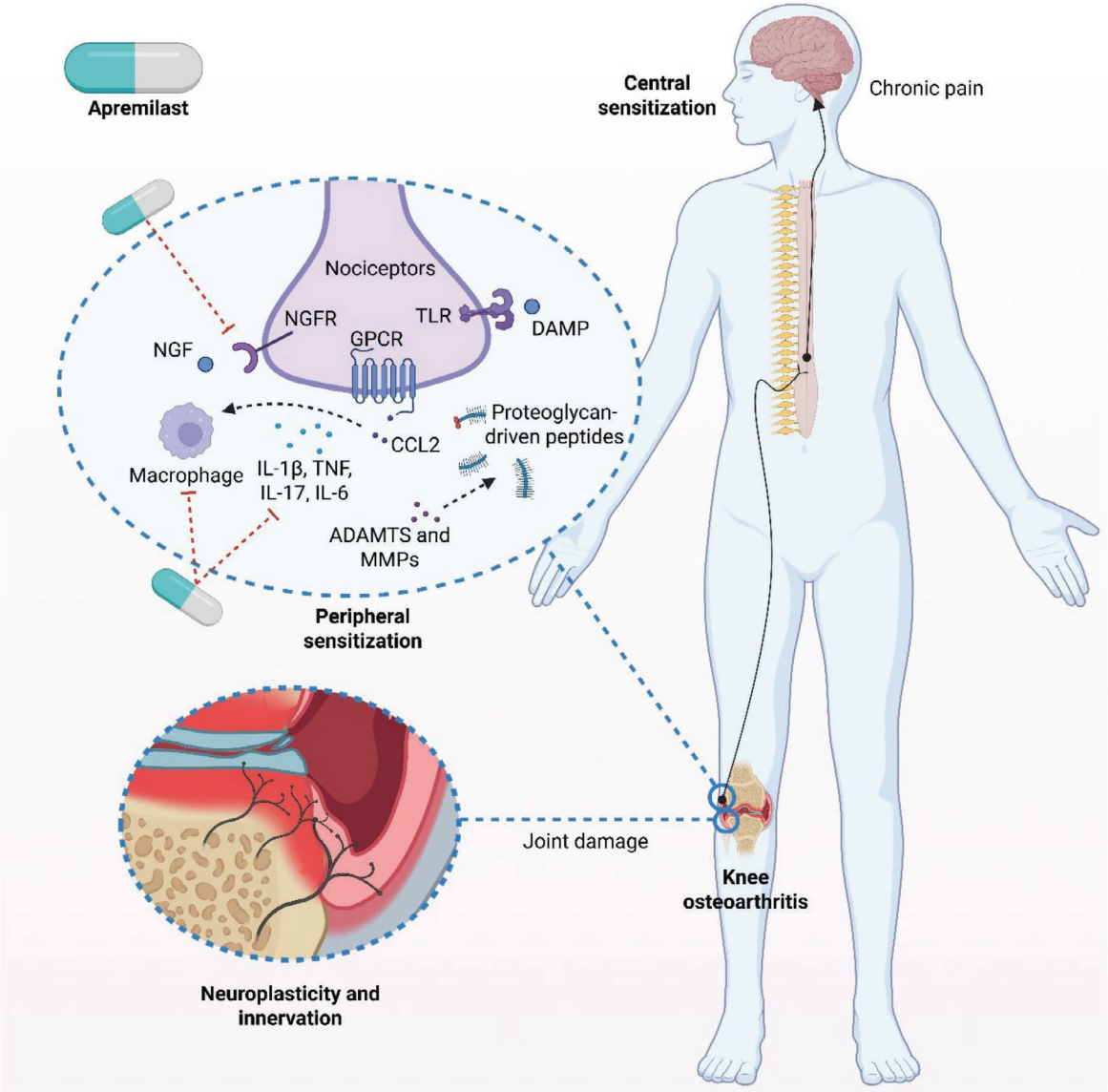
IL-6 binding to its receptor complex, STAT1 and STAT3 are phosphorylated, translocate to the nucleus, and drive transcription of IL-6-responsive genes. This pathway integrates signals from multiple cytokines and contributes to OA progression.[49] In cartilage, IL-6 signalling exhibits both protective and catabolic properties. Classic IL-6 signalling can promote tissue inhibitor of metalloproteinases (TIMPs) and proteoglycan synthesis, suggesting a reparative role. However, it also suppresses collagen type II synthesis, enhances IL-1β-mediated degradation, and induces MMP3, MMP13 and ADAMTS enzymes, contributing to matrix breakdown.[50] Apremilast can suppress IL-6 production by modulating cAMP-dependent pathways, including PKA and CREB, leading to reduced STAT3 activation and downstream inflammatory gene expression. The PALACE trial has demonstrated that apremilast decreases systemic levels of IL-6, TNF and IL-17, whilst enhancing anti-inflammatory mediators like IL-10 and IL-1R antagonist in active PsA, supporting its therapeutic role in joint diseases.[51] Non-steroidal anti-inflammatory drugs (NSAIDs), particularly COX2-selective inhibitors like celecoxib, remain central to symptom management due to their anti-inflammatory properties, though they are not without adverse effects. Whilst extensive data support their clinical efficacy in pain relief and function improvement, the potential disease-modifying properties of NSAIDs, especially celecoxib, remain insufficiently characterized.[52] A recent meta-analysis of 40 clinical trials revealed that COX2 inhibitors are associated with a significantly increased risk of drug-related adverse events, notably, upper gastrointestinal complications such as dyspepsia, gastritis and heartburn.[53] Given the distinct but complementary mechanisms of action of apremilast and NSAIDs, combination therapy may provide a synergistic benefit by targeting both upstream and downstream mediators of inflammation. Celecoxib and other COX inhibitors have been shown to inhibit inflammatory cytokines, including IL-6, IL-17, IL-1β and TNF.[52,54,55] This strategy may allow for dose reduction of individual agents, potentially minimizing adverse effects whilst maintaining therapeutic efficacy. Moreover, apremilast can suppress oxidative stress,[27] which adds another dimension to its anti-inflammatory profile, making it a promising candidate for future combination regimens in OA management.

OA pain and apremilast

Pain in OA is driven by a combination of structural degeneration, inflammation and neurobiological sensitization. Although cartilage breakdown is central to OA, pain correlates more closely with synovitis, subchondral bone marrow lesions.[56] Inflammatory cytokines, such as IL-6, IL-17 and TNF, and activated macrophages play a central role in sensitizing joint nociceptors by reducing their mechanical activation threshold.[57] These mediators promote peripheral sensitization and contribute to pain during both movement and rest.[6] OA involves chronic pain and joint remodelling, with nerve growth factor (NGF) playing dual roles in pain and skeletal repair. Whilst anti-NGF antibodies improve OA pain, they may worsen joint structure by disrupting the role of tropomyosin receptor kinase A (TrkA) in maintaining BMP–SMAD1 signalling and inhibiting NF-κB and RANKL expression. NGFR deficiency enhances bone resorption and reduces subchondral bone integrity.[58] In rabbits with joint instability, anti-NGF improved pain behaviour but led to cartilage loss and abnormal bone growth.[59] These findings highlight a structural trade-off that may explain the risk of rapidly progressive OA with anti-NGF therapy.

Enzymes like ADAMTS4 and ADAMTS5 degrade aggrecan, producing bioactive fragments that directly induce hyperalgesia via Toll-like receptor 2 (TLR2).[60] CCL2–CCR2 signalling within the joint contributes to knee hyperalgesia in experimental osteoarthritis.[61] Neural CCL2–CCR2 signalling contributes to OA pain by recruiting monocytes and macrophages to the joint, dorsal root ganglia and spinal cord, highlighting a novel neuroimmune mechanism involved in the initiation and persistence of chronic OA pain.[62] Macrophages play a central role in the initiation and persistence of OA pain through dynamic communication with sensory neurons. Acting as key mediators of the immune nervous system crosstalk, they respond to inflammatory stimuli by releasing cytokines, growth factors and neuropeptides that sensitize nociceptors and exacerbate chronic pain.[63] Anatomical neuroplasticity, including nociceptor sprouting in synovium, subchondral bone and osteophytes, emerges early in OA and progresses with structural damage. This aberrant innervation correlates with joint damage and may underlie chronic pain in OA.[64] Grey matter volume reduction has also been associated with chronic OA pain, indicating long-term central remodelling.[65] Together, these peripheral and central changes sustain the chronic pain state in OA. In this context, apremilast may serve as a promising therapeutic candidate by downregulating pro-inflammatory cytokines such as TNF, IL-6 and IL-17 (Figure 3).[66] In endothelial and monocytic cells, apremilast downregulates the expression of key pro-inflammatory mediators such as GM-CSF, CXCL10, CCL2 and MMP9.[40] Additionally, apremilast promotes the polarization of macrophages from an M1 to M2 phenotype via NF-κB pathway modulation.[67] This shift may attenuate osteoarthritis pain by reducing inflammation and promoting tissue repair.[68] Apremilast disrupts the PDE4–CD271 (NGF receptor) complex, limiting NGF-driven and TGFβ1-driven fibroblast migration and myofibroblast differentiation.[69] $CD271^+$ synovial cells are increased in rheumatoid arthritis and OA tissues, exhibiting a perivascular distribution and enhanced pro-inflammatory activity, including elevated IL-6 and MMP secretion.[69]

Figure 3. Mechanisms of apremilast in modulating osteoarthritis pain.



ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; DAMP, damage-associated molecular pattern; GPCR, G protein-coupled receptor; MMPs, matrix metalloproteinases; NGF, nerve growth factor; NGFR, nerve growth factor receptor; TLR, Toll-like receptor.
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Limitations

The pivotal phase II trial of apremilast (CC10004) in erosive hand OA demonstrated a lack of efficacy, which failed to meet its primary and key secondary end points. Notably, this trial is available only as an abstract from 2014 and has not been fully published.[70] Since then, no additional clinical trials have been conducted, highlighting a persistent and unresolved gap in the clinical evidence. Further research is needed to evaluate whether apremilast, particularly in combination strategies, could benefit subsets of patients with OA. Long-term safety and efficacy studies will be essential to clarify its role in OA management. Another important limitation is the potential for adverse effects associated with apremilast, most commonly gastrointestinal symptoms such as diarrhoea, nausea and occasional weight loss.[71] Although weight loss could theoretically have a beneficial effect in patients with knee OA and overweight, this is generally an uncommon and incidental finding, and there is currently insufficient evidence to suggest a clinically meaningful impact.[6] Whilst apremilast is generally considered to have a favourable safety profile compared to biologic agents, these side-effects may still limit tolerability and adherence, particularly in older patients with OA and

multiple comorbidities and polypharmacy. Furthermore, the safety and long-term tolerability of apremilast in OA populations remain understudied, highlighting the need for extended-duration trials.

Conclusion

Apremilast has a strong mechanistic rationale for OA therapy. It potently suppresses pro-inflammatory mediators, such as TNF, IL-6, IL-17, IL-1α, protects chondrocytes, inhibits angiogenesis in various tissues, and reduces oxidative stress. Preclinical studies demonstrate cartilage-protective effects, suggesting potential disease-modifying properties. However, clinical evidence in humans remains limited, with no proven efficacy in OA to date for symptom relief. Further clinical investigation is needed to determine whether apremilast could be repurposed as a disease-modifying or symptomatic treatment for OA, particularly in combination therapy strategies.

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