

Review Article

From osteoarthritis to rheumatoid arthritis: re-exploring the molecular pathways and therapeutic potential of diacerein

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ABSTRACT

Diacerein, an anthraquinone derivative, is emerging as a promising disease-modifying agent in rheumatoid arthritis (RA), because of its potent anti-inflammatory and chondroprotective actions. Unlike nonsteroidal anti-inflammatory drugs, which primarily inhibit cyclooxygenase enzymes, diacerein suppresses interleukin-1 β , a central mediator of synovial inflammation and cartilage degradation. It also modulates tumor necrosis factor- α and matrix metalloproteinases, thereby alleviating pain, decreasing inflammation, and preserving joint structure. This review of clinical and preclinical studies highlights the therapeutic potential of diacerein in RA management, focusing on its molecular mechanisms, clinical outcomes, and combination strategies with disease-modifying antirheumatic drugs (DMARDs) or biologics. Recent advances in drug delivery, including nanoparticle-based and sustained-release formulations, have further enhanced its bioavailability and efficacy. Diacerein effectively decreases joint swelling and stiffness, while demonstrating a superior gastrointestinal safety profile to nonsteroidal anti-inflammatory drugs. However, its slow onset of action and moderate efficacy as a monotherapy limit its standalone use. Combination therapy with DMARDs or biologics appears to potentiate its therapeutic benefits. Overall, diacerein is a valuable adjunctive agent in RA treatment. Further studies are warranted to optimize dosing regimens and delivery systems to improve clinical outcomes.

Keywords: Diacerein, Rheumatoid Arthritis, Molecular Pathways, Disease-Modifying Antirheumatic Drugs (DMARDs), Chondroprotection, Anti-inflammatory

1. INTRODUCTION

Rheumatoid arthritis (RA), a systemic autoimmune disorder, affects primarily the synovial joints, and results in persistent inflammation, discomfort, stiffness, and ultimately joint destruction. The pathophysiology of RA includes a combination of genetic predisposition and environmental factors, including infections and smoking [1, 2]. Genetic susceptibility to RA is strongly associated with HLA-DRB1 shared epitope alleles, which confer an approximately 3–5-fold increased risk of disease development, particularly in the presence of environmental triggers such as smoking [3, 4]. At the molecular level, RA is driven by dysregulated immune activation involving T lymphocytes, B cells, macrophages, and fibroblast-like synoviocytes (FLS), thus resulting in excessive

production of pro-inflammatory cytokines, notably tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6. Persistent cytokine signaling promotes synovial hyperplasia, pannus formation, and progressive joint destruction [5]. A defining characteristic of RA is the generation of autoantibodies, including rheumatoid factor and anti-citrullinated protein antibodies, which contribute to the creation of immune complexes that intensify inflammation and harm joint structures [6].

Current therapeutic strategies include nonsteroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (DMARDs), and biologic or targeted synthetic DMARDs. Although these agents have substantially improved disease outcomes, their use is limited by delayed onset of action, incomplete remission rates, infection risk, long-term safety concerns,

and high costs. Therefore, adjunctive therapies targeting complementary inflammatory pathways are of interest [7-12]. Biologics, although efficacious, might elevate the risk of severe infections and are often costly [13]. Despite advances with DMARDs and biologics, many patients fail to achieve sustained remission, highlighting the need for adjunctive therapies [13]. Conventional DMARDs require many weeks to months to exhibit efficacy, and they pose considerable adverse effects that can potentially lead to cessation. Biologics pose risks including heightened vulnerability to infections, and their cost potentially restricts their availability [14, 15].

Attaining disease remission with monotherapy poses several problems, primarily because of the intricate, multifaceted characteristics of various illnesses. Monotherapy frequently inadequately addresses the comprehensive range of illness causes, thus resulting in partial remission or recurrence [16, 17]. In chronic disorders such as cancer, tumor cell heterogeneity may lead to some cells exhibiting resistance to the only drug used in monotherapy, thus resulting in therapeutic failure. The emergence of medication resistance is a critical issue; over time, infections or cancer cells can acclimate to the monotherapeutic agent and decrease its effectiveness [18, 19]. Furthermore, monotherapy may inadequately regulate the immune system or other biological processes implicated in disease development, and therefore have constrained efficacy. These limitations highlight the need for combination therapies addressing many facets of disease biology to achieve more sustained and thorough remission [20].

Diacerein, an anthraquinone-derived medication, has garnered interest as a treatment agent for RA, because of its anti-inflammatory and disease-modifying characteristics. It functions primarily by obstructing the IL-1 receptor, a crucial mediator in the inflammatory mechanism of RA, thus decreasing the production of pro-inflammatory cytokines and restraining the inflammatory response [21, 22]. Diacerein also influences cartilage deterioration by preventing the synthesis of matrix metalloproteinases (MMPs), which facilitate joint breakdown [23]. Moreover, diacerein has analgesic qualities that alleviate discomfort associated with the condition. Nonetheless, despite its prospective advantages, its application may be constrained by adverse effects such as gastrointestinal problems and delayed onset of action; consequently, careful patient supervision is required [24].

As discussed in the Introduction, osteoarthritis (OA) derived evidence provides mechanistic support but not direct proof of disease-modifying activity in RA. In OA, disease modification refers primarily to slowing cartilage degeneration, whereas in RA, it entails suppression of systemic autoimmune inflammation, prevention of bone erosion, and long-term preservation of joint structure. Accordingly, OA-derived evidence should be considered as providing mechanistic support rather than direct evidence of disease-modifying antirheumatic activity in RA.

2. DIACEREIN'S MECHANISM OF ACTION

Diacerein suppresses IL-1 β -mediated signaling through the pathogenesis of RA and other autoimmune disorders. Therapeutic inhibition of IL-1 β has therefore emerged as an important anti-inflammatory strategy. Agents such as anakinra, a recombinant IL-1 receptor antagonist, exemplify this approach by directly blocking IL-1 signaling, and thereby decreasing synovial inflammation and joint damage in RA [25].

Beyond direct receptor antagonism, several experimental agents have been shown to suppress IL-1 β production through modulation of inflammasome activation and transcriptional regulation. Itaconate derivatives and nscapine are two examples of compounds that block the generation of IL-1 β by specifically targeting the NLRP3 inflammasome or associated signaling pathways, and have shown notable anti-inflammatory benefits in inflammatory arthritis preclinical models [26, 27]. Itaconate and its derivatives, including 4-octyl itaconate, inhibit NLRP3 inflammasome activation and consequently decrease IL-1 β production [28]. In Mouse model of inflammatory arthritis, treatment with 4-octyl itaconate has been found to decrease synovial IL-1 β levels by approximately 40–60% and to significantly attenuate joint inflammation scores [29]. Similarly, nscapine, an alkaloid derived from *Papaver somniferum*, has shown pronounced anti-inflammatory activity by markedly decreasing IL-1 β levels and other inflammatory mediators, thereby reinforcing the therapeutic relevance of IL-1 β -targeted interventions [30, 31].

RA is characterized by a complex interplay between innate and adaptive immune responses. Antigen-presenting cells activate T lymphocytes, which subsequently stimulate macrophages and B cells via cytokines including TNF- α , IL-1, IL-2, and interferon- γ . These mediators promote osteoclast activation, cartilage degradation, and bone erosion, whereas B-cell differentiation into plasma cells leads to autoantibody production that further perpetuates inflammation [32].

Diacerein exerts therapeutic effects primarily by suppressing IL-1 β -mediated signaling within this inflammatory cascade. By inhibiting IL-1 activity, diacerein decreases chondrocyte damage, osteoclast activation, and synovial inflammation, and consequently attenuates joint destruction associated with RA (Figure 1) [33, 34].

3. DIACEREIN IN COMBINATION THERAPY

After oral administration, diacerein is rapidly deacetylated to its active metabolite, rhein, which reaches peak plasma concentrations approximately 2.5 hours after administration. Dietary factors influence its pharmacokinetics, and high-fat meals enhance its bioavailability. Rhein is eliminated primarily via renal excretion, and it has a plasma half-life of approximately 4–9 hours [35, 36].

Although diacerein is not classified as a conventional DMARD, its use in combination with established

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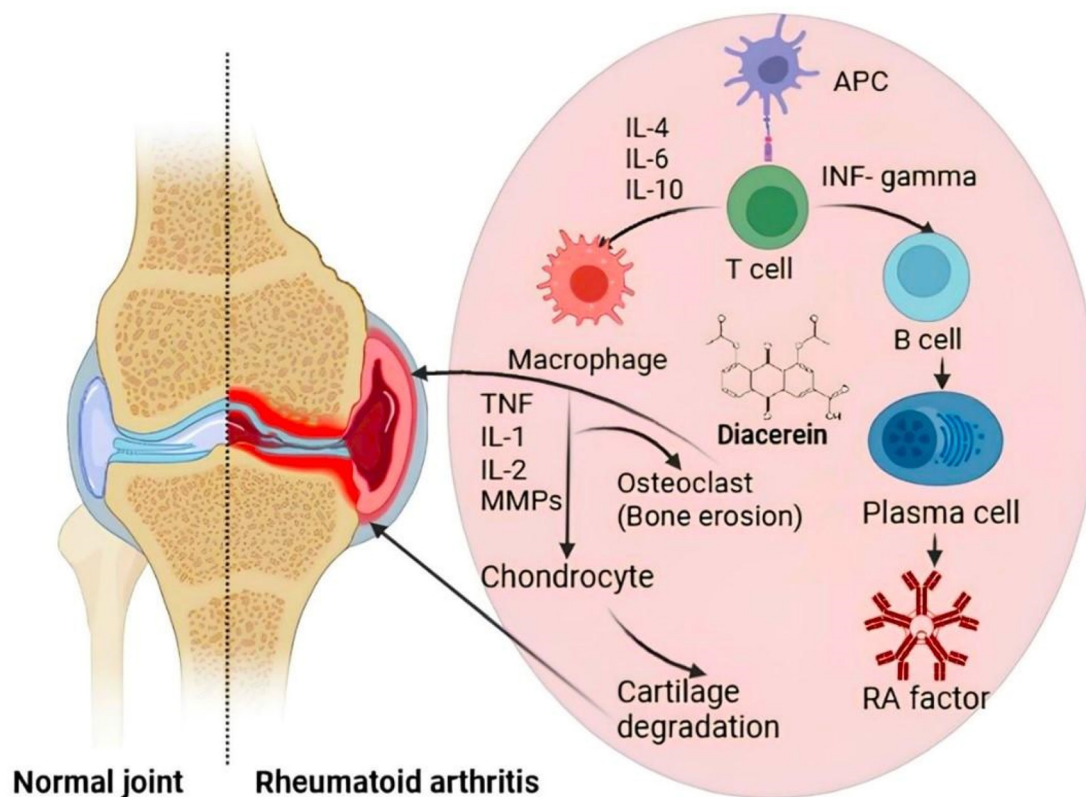


Figure 1 | Role of diacerein in rheumatoid arthritis (RA). A normal joint is compared with an arthritic joint affected by inflammation.

antirheumatic therapies has been explored. Because concomitant administration with NSAIDs may increase the risk of gastrointestinal adverse effects, tolerability monitoring during combination therapy is important. Given the limited data on pharmacokinetic and pharmacodynamic interactions between diacerein and other RA medications, further investigation is necessary [33, 37-39].

Regulatory considerations have also influenced the clinical use of diacerein. The European Medicines Agency has issued warnings regarding risks of severe diarrhea and hepatotoxicity, and has recommended dose reduction in older patients and immediate discontinuation after onset of significant gastrointestinal symptoms. These safety concerns are particularly relevant when diacerein is used as part of combination therapy in chronic inflammatory diseases [40, 41].

4. MOLECULAR PATHWAYS MODULATED BY DIACEREIN

Diacerein modulates multiple intracellular signaling pathways involved in inflammation, synovial activation, and joint degeneration. Among these, the

mitogen-activated protein kinase (MAPK) pathway plays a central role in RA pathogenesis by regulating inflammatory gene expression and cartilage degradation through the activation of p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase. Diacerein, by selectively inhibiting JNK activation, leads to the suppression of c-Jun/AP-1-dependent transcription and a consequent decrease in pro-inflammatory mediator production. This targeted inhibition contributes to its anti-inflammatory and chondroprotective effects [42, 43]. The regulatory role of diacerein on MAPK signaling, particularly JNK inhibition, is schematically illustrated in Figure 2.

Beyond MAPK modulation, diacerein interferes with the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, a key mediator of cytokine-driven inflammation in RA. Activation of this pathway after cytokine binding to cell surface receptors results in JAK-mediated phosphorylation of STAT proteins, STAT dimerization, and nuclear translocation, wherein pro-inflammatory gene transcription is initiated [44]. Diacerein suppresses STAT phosphorylation, thereby preventing STAT activation and nuclear signaling, and subsequently decreasing transcription of inflammatory genes and attenuating

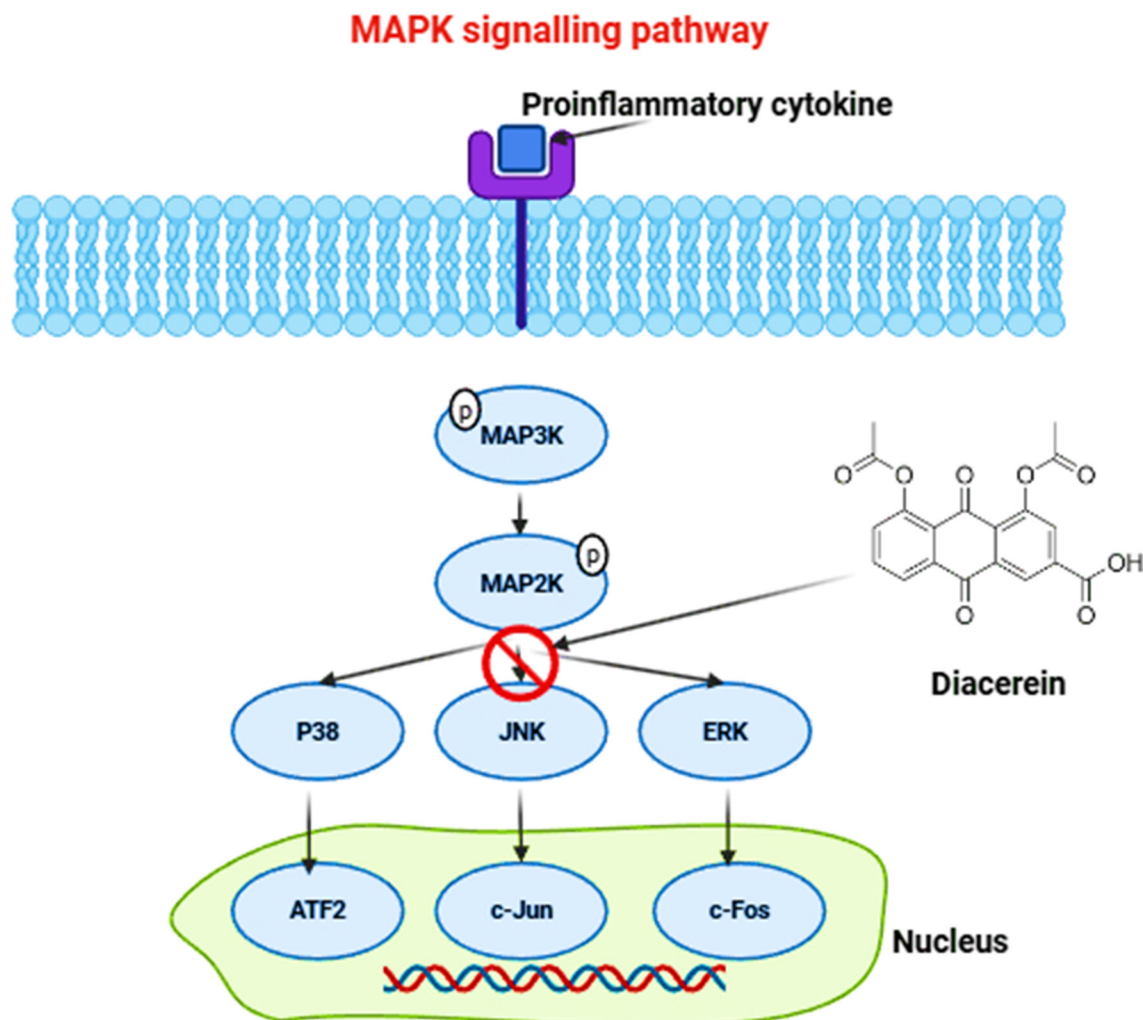


Figure 2 | MAPK signaling pathway and the inhibitory effect of diacerein on JNK activation.

cytokine-mediated responses in RA [45, 46]. The inhibitory effect of diacerein on JAK–STAT signaling is summarized in [Figure 3](#).

Diacerein also modulates Wnt signaling pathways that contribute to inflammatory and degenerative processes in joint tissues. The canonical Wnt/ β -catenin pathway regulates cellular proliferation, differentiation, and inflammatory responses through β -catenin stabilization and nuclear translocation after Wnt ligand binding to Frizzled and LRP co-receptors [47, 48]. Diacerein inhibits β -catenin accumulation and nuclear translocation, thereby suppressing Wnt-dependent transcriptional activity. This mechanism contributes to its anti-inflammatory and anti-degenerative effects, particularly in pathological conditions involving aberrant Wnt signaling, such as RA and OA [48, 49]. The canonical Wnt pathway and its modulation by diacerein are depicted in [Figure 4](#).

Beyond canonical signaling, the non-canonical Wnt pathway plays critical roles in RA pathogenesis by regulating cytoskeletal organization, FLS activation, and inflammatory mediator production independently of β -catenin. Activation of this pathway involves Wnt ligand binding to Frizzled receptors and co-receptors such as ROR2, and subsequently leads to downstream signaling through Rac1/JNK and RhoA/ROCK pathways [50, 51]. In RA, non-canonical Wnt signaling promotes synovial inflammation, pannus formation, and progressive joint destruction through sustained FLS activation and cytokine release [52]. Diacerein attenuates these pathological processes by suppressing IL-1 β -driven inflammatory signaling and inhibiting JNK/AP-1 activation, thereby decreasing FLS-mediated synovial inflammation and joint damage [33, 53]. The role of non-canonical Wnt signaling in RA and its modulation by diacerein is illustrated in [Figure 5](#).

JAK-STAT signalling pathway

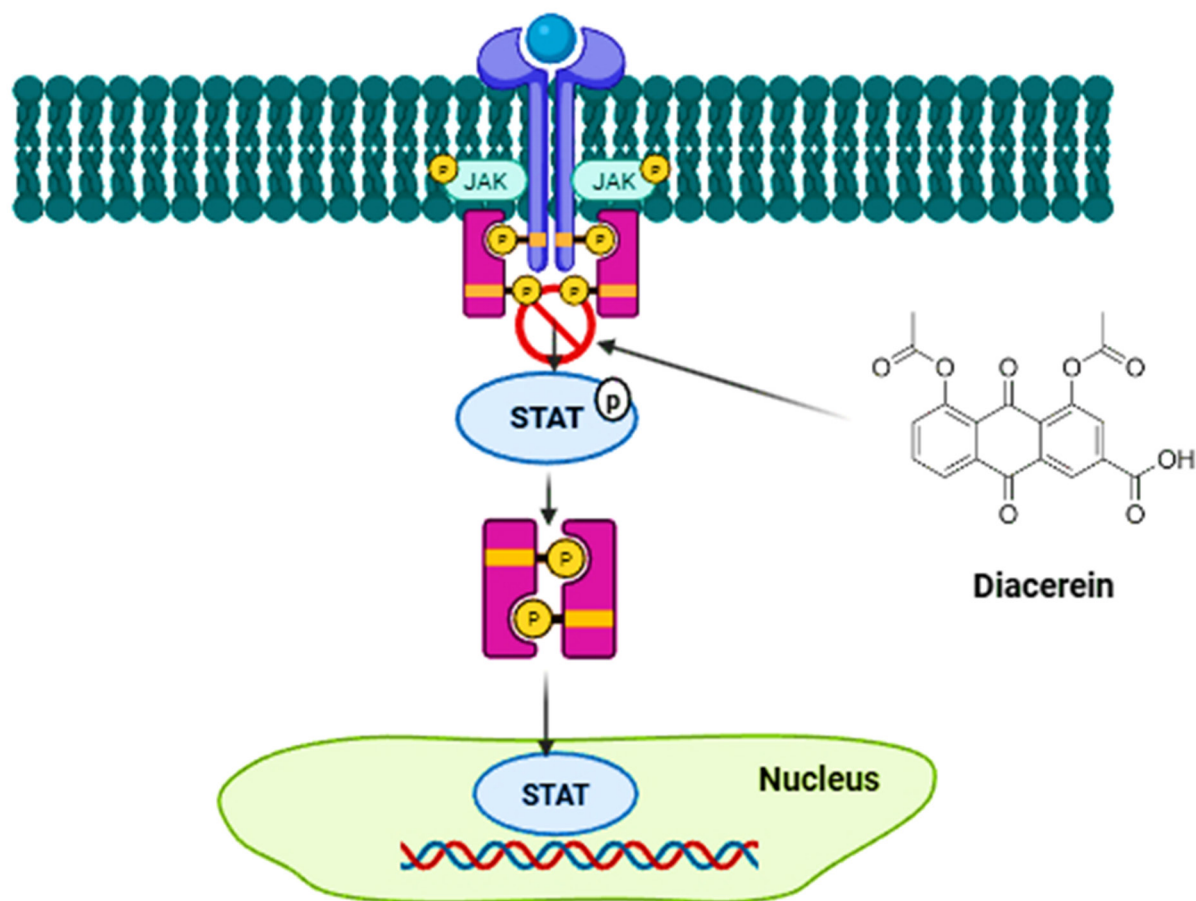


Figure 3 | JAK-STAT signaling pathway and the inhibitory effect of diacerein.

At the level of cartilage homeostasis, diacerein exerts protective effects on chondrocytes by modulating apoptosis, oxidative stress, and autophagy-related pathways. Experimental studies have shown that diacerein decreases chondrocyte apoptosis by suppressing pro-inflammatory mediators and downregulating inducible nitric oxide synthase and cyclooxygenase-2 expression [54]. Additionally, diacerein alleviates oxidative stress by decreasing reactive oxygen species generation and enhancing antioxidant enzyme activity in chondrocytes exposed to inflammatory or oxidative insults [55]. Diacerein has also been shown to promote autophagy through activation of the AMP-activated protein kinase pathway, a process essential for maintaining chondrocyte survival under stress conditions [56, 57].

Although these anti-inflammatory and chondroprotective actions suggest disease-modifying potential at the level of joint tissue, they do not constitute the broad immunomodulatory effects required for disease modification in RA.

5. DIACEREIN AND ITS ANTI-INFLAMMATORY EFFECTS IN RA

Diacerein, a synthetic anthraquinone derivative, has been investigated for its possible effects on synovial fluid and tissue inflammation, particularly in OA [58]. Diacerein modulates synovial inflammation by suppressing macrophage- and fibroblast-like synoviocytes via IL-1 β , TNF- α , prostaglandin E2, and MMP production [33]. Diacerein has been found to inhibit the production of pro-inflammatory cytokines in synovial cells, thus mitigating synovial inflammation, and to decrease the production of MMPs, enzymes implicated in cartilage breakdown, thus potentially protecting joint integrity [59]. Moreover, the anti-inflammatory characteristics of diacerein treatment include decreased levels of inflammatory mediators, such as prostaglandin E2. Diacerein has been suggested to have advantageous effects on synovial inflammation and tissue integrity in OA. However, validation of these effects in RA requires

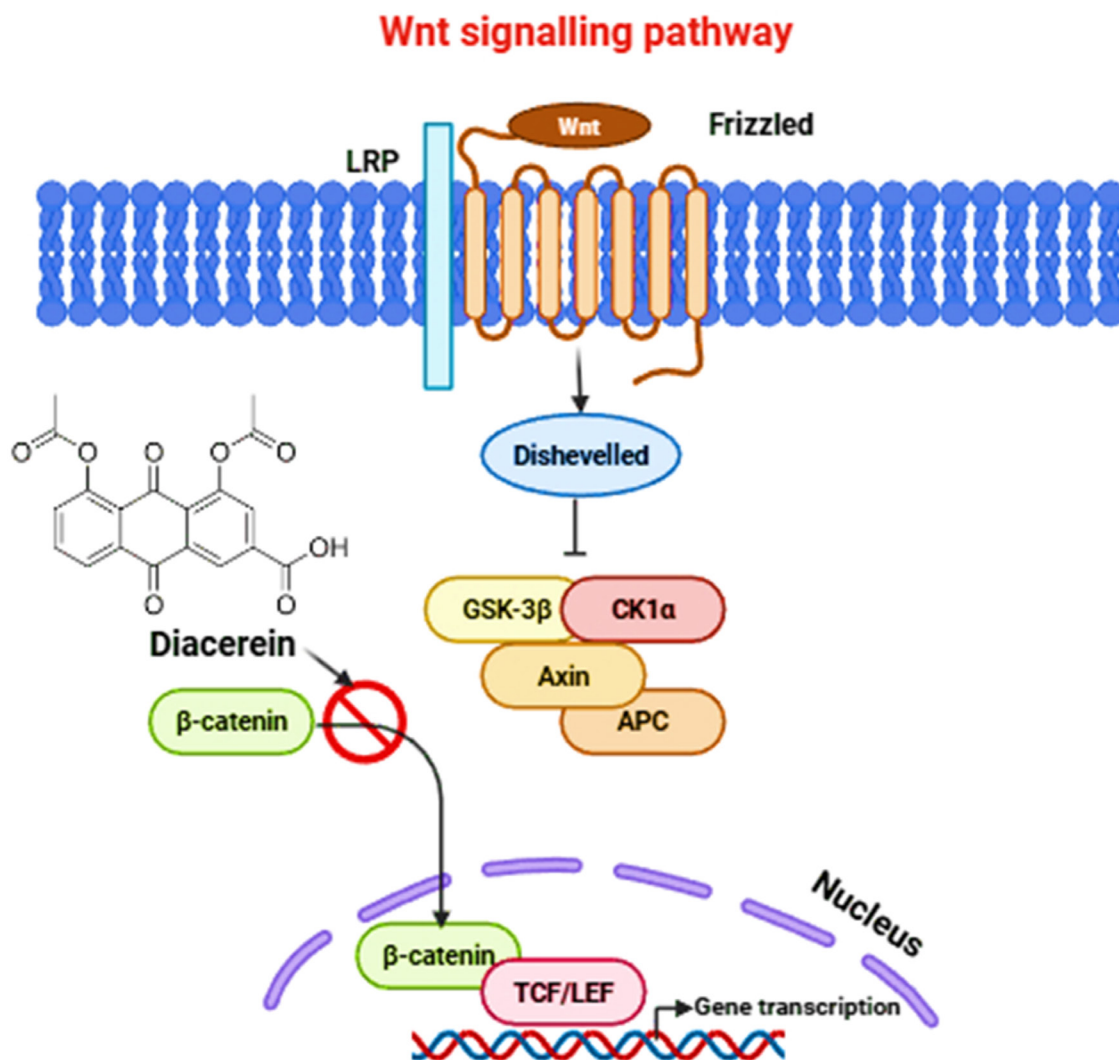


Figure 4 | Wnt signaling pathway and the inhibitory effect of diacerein on β -catenin activity.

adequately powered randomized controlled trials with radiographic and disease activity endpoints over at least 12–24 months [60]. RA involves a highly interconnected immune signaling network in which macrophages, T cells, B cells, natural killer cells, and synovial resident cells collectively sustain inflammation and joint damage. Activated macrophages release key pro-inflammatory cytokines such as $\text{TNF-}\alpha$, IL-1, and IL-6, which in turn drive fibroblast-like synoviocyte activation, chondrocyte dysfunction, and osteoclast-mediated bone resorption [61]. T-cell subsets (Th1, Th17, and Treg cells), regulated through co-stimulatory signals (CD80/CD11a/CD3), produce cytokines including IL-17 and GM-CSF, which further amplify synovial inflammation and osteoclastogenesis [62]. B cells contribute through antigen presentation and autoantibody production, whereas dendritic cells reinforce immune activation [63]. **Figure 6** also highlights multiple therapeutic targets within this network,

such as $\text{TNF-}\alpha$, IL-1, IL-6, IL-17, IL-15, IL-18, IFN- γ , and co-stimulatory molecules, illustrating how biologics and targeted agents disrupt specific signaling pathways, and consequently attenuate immune activation and prevent structural joint damage in RA.

Figure 6 shows the complex immune signaling network in RA and the targeted therapies used to modulate immune responses. Various immune cells, including macrophages, T cells, B cells, Natural killer (NK) Cells, dendritic cells, chondrocytes, and osteoclasts, contribute to RA pathogenesis through release of cytokines ($\text{TNF-}\alpha$, IL-1, IL-6, IL-10, IL-15, IL-17, IL-18, and IFN- γ). Several biologic drugs, such as abatacept, efalizumab, fontolizumab, orelizumab, rituximab, and others, target specific molecules (CD11a, CD80, CD3, CD19, and CD20) and consequently inhibit inflammation and immune activation, thereby decreasing joint damage in RA [64].

Wnt signalling pathway (Non-Canonical)

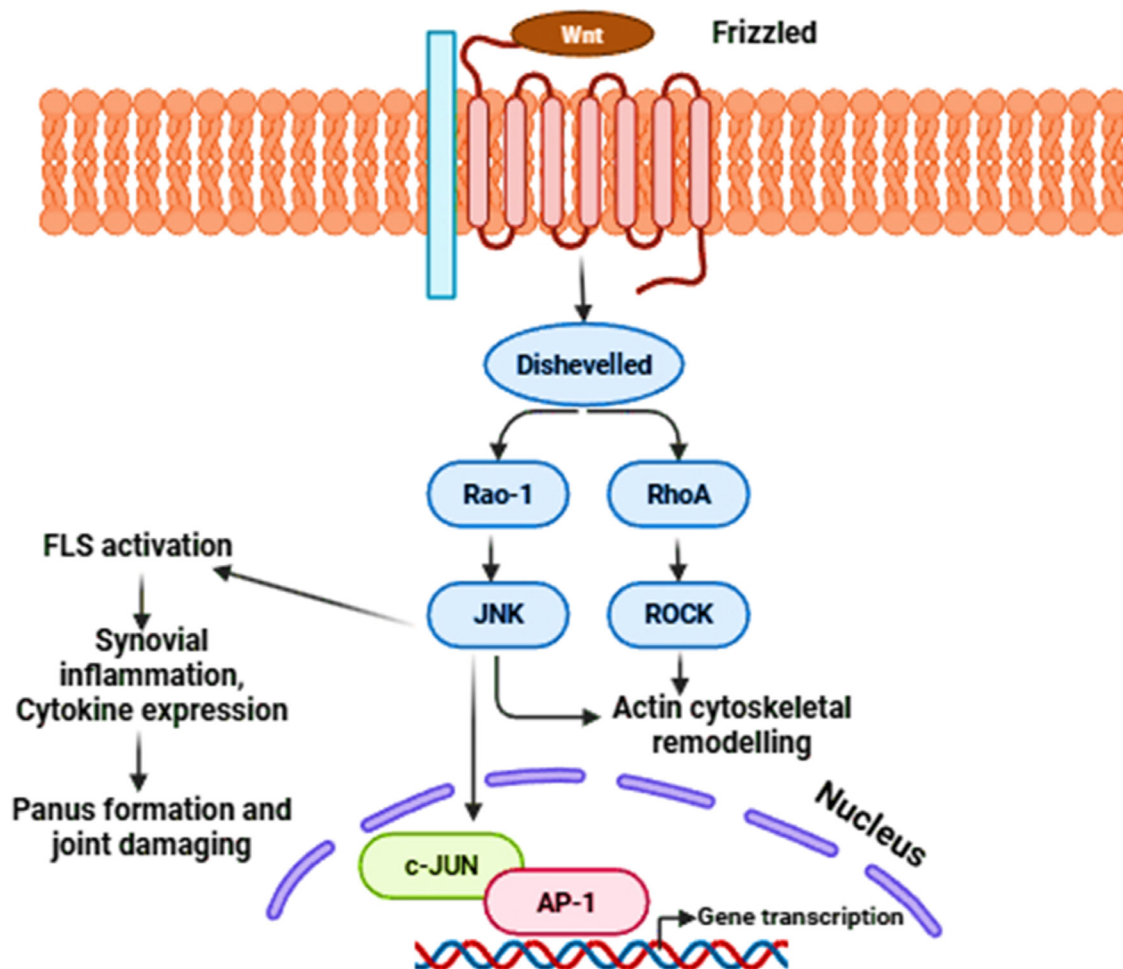


Figure 5 | Non-canonical Wnt signaling pathway and its role in FLS activation, contributing to joint inflammation and damage.

6. EFFECTS ON CARTILAGE PROTECTION AND JOINT REMODELING

MMPs, particularly MMP-13 (collagenase-3), are crucial in the degradation of extracellular matrix constituents such as collagen in cartilage. MMP-13 overactivity has been associated with OA advancement, because of its effectiveness in destroying type II collagen [65, 66]. Diacerein and its metabolite rhein have been demonstrated to limit MMP production and activity, thereby diminishing the breakdown of cartilage matrix components [23]. This inhibitor aids in preserving the structural integrity of cartilage by averting excessive degradation [67]. Beyond MMP inhibition, diacerein protects the cartilage through modulating inflammatory pathways: it inhibits the synthesis of pro-inflammatory cytokines, such as $\text{TNF-}\alpha$, which are recognized to enhance MMP expression and facilitate

cartilage destruction [68, 69]. Diacerein decreases catabolic activity in the joint environment by downregulating these cytokines. Moreover, diacerein has been reported to affect subchondral bone remodeling [70, 71]. In OA, subchondral bone experiences structural alterations that facilitate disease progression [70]. Diacerein's anti-inflammatory properties influence the subchondral bone and aid in normalizing bone remodeling processes, thus potentially decreasing sclerosis and enhancing joint functionality [72].

In animal studies, diacerein has shown potential advantages in maintaining joint integrity. Diacerein suppresses the synthesis of pro-inflammatory cytokines, including $\text{IL-1}\beta$ and $\text{TNF-}\alpha$, which are crucial in RA pathophysiology [73]. Clinical evidence of diacerein's effectiveness in RA remains scant, in comparison to its well-documented application in OA [74]. Only a few small clinical studies (in <100 patients) have evaluated

Immune signalling network in rheumatoid arthritis

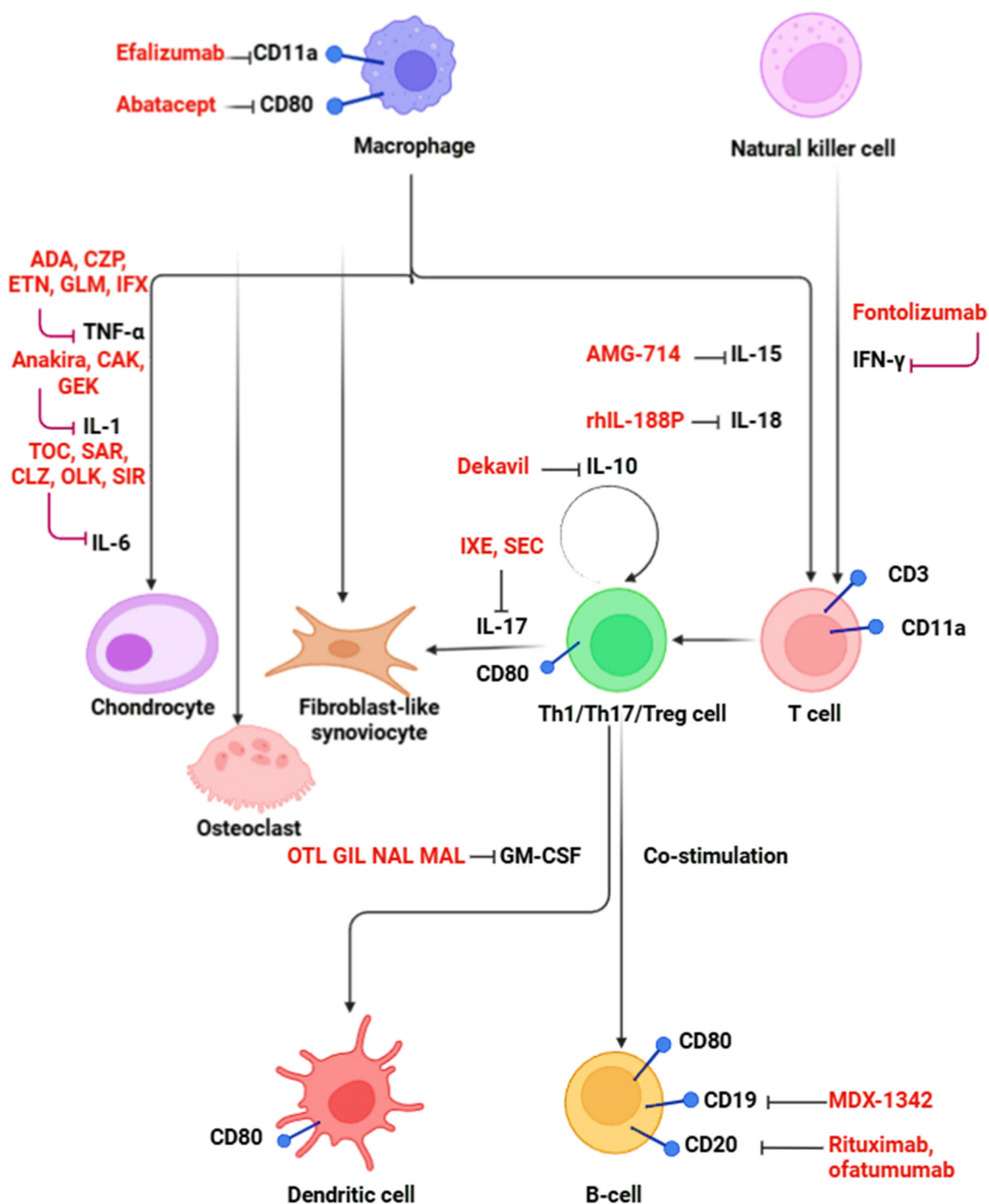


Figure 6 | The complex immune signaling network in RA and the targeted therapies used to modulate immune responses.

diacerein in RA, and have indicated modest improvements in pain scores and inflammatory markers, without definitive evidence of structural joint preservation [75].

Despite their distinct etiologies, OA and RA converge on IL-1β-driven synovial activation and matrix degradation; therefore, a mechanistic rationale exists

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for evaluating diacerein beyond OA. These shared pathways provide a biological rationale for exploring whether agents that are effective in OA, such as diacerein, might exert adjunctive benefits in RA.

In OA models, diacerein inhibits MMP-13 and decreases cartilage degradation. Given that MMP-13-mediated collagen breakdown and IL-1 β signaling have also been implicated in RA-associated joint damage, a mechanistic rationale exists for exploring diacerein in RA.

7. CLINICAL EFFICACY OF DIACEREIN IN RA

Evidence of diacerein's effectiveness is more limited in RA than OA. Pflugbeil et al. have thoroughly assessed pharmacological interactions in the management of inflammatory joint illnesses, encompassing RA and psoriatic arthritis [40]. That study emphasized the importance of understanding the pharmacokinetics and therapeutic applications of several antirheumatic drugs, including diacerein, despite a focus on drug-drug interactions. Although diacerein is considered a DMARD, its efficacy with respect to other DMARDs, including biologics and small molecules, has not been thoroughly demonstrated in RA [39]. Standard dosage protocols for diacerein in OA recommend initial administration of 50 mg once per day, which may be increased to 50 mg twice daily, depending on patient tolerance and clinical response. Because data regarding diacerein use in RA are insufficient, dose regimens customized for patients with RA are not well-defined [75]. Clinical effects, including pain alleviation, functional improvement, and enhanced quality of life, have been demonstrated in OA investigations; however, analogous data in populations with RA are limited. In RA treatment, DMARDs are fundamental to therapy [76]. Conventional DMARDs, such as methotrexate (MTX), and contemporary biologic medicines, including TNF inhibitors, have been established to effectively decrease disease activity and avert joint deterioration [14, 77].

Accordingly, application of the term "disease-modifying" to diacerein in RA should be interpreted cautiously and should not be construed as indicating its equivalence to conventional or biologic DMARDs, which directly target systemic immune dysregulation and structural joint damage.

Although diacerein has demonstrated consistent anti-inflammatory and chondroprotective effects, current evidence supports diacerein as an adjunctive rather than disease-modifying therapy in RA. Few randomized controlled trials have evaluated diacerein in RA, most of which had modest sample sizes, short treatment durations, and heterogeneous patient populations. Although improvements in disease activity indices, such as Disease Activity Score 28 (DAS28) and European League Against Rheumatism (EULAR) response criteria, have been reported, those studies were not powered to assess long-term structural joint preservation

or sustained remission. Across available RA trials, diacerein has been found to produce modest improvements in DAS28 (~ 0.8 – 1.2 units) and higher EULAR moderate response rates than placebo treatment, but the outcomes were inferior to those achieved with biologic or targeted synthetic DMARDs.

Importantly, clinical evidence supporting diacerein in RA, in contrast to OA, is limited. Whereas OA trials have consistently demonstrated symptomatic and structural benefits, RA studies remain limited and have shown only modest clinical effects. Therefore, OA-derived clinical outcomes should not be directly extrapolated to RA but instead should be considered supportive evidence warranting further investigation.

8. COMBINATION WITH CONVENTIONAL DMARDS

8.1 Methotrexate plus diacerein

8.1.1 Efficacy and safety of diacerein in patients with RA with inadequate response to MTX. In vitro studies have shown that diacerein decreases the synthesis and activity of pro-inflammatory cytokines, including IL-1 β and TNF- α ; suppresses IL-1 β -induced nuclear factor- κ B activation; and decreases synovocyte MMP-13 synthesis. Therefore, diacerein might have disease-modifying properties in RA, through decreasing inflammation and joint destruction [78]. A randomized, double-blind, placebo-controlled study has assessed the effectiveness and safety of diacerein in patients with RA who had an unsatisfactory response to MTX. The American College of Rheumatology 20% improvement criteria (ACR20) response at week 24 was comparable between the diacerein and placebo groups (65% vs. 45%, $p = 0.20$). Nonetheless, treatment response according to EULAR criteria was markedly superior in the diacerein group, in which 75% exhibited a moderate response, in contrast to 25% of the placebo group ($p = 0.002$). Moreover, the Disease Activity Score 28 (DAS28) showed greater improvement, signifying a decrease in disease activity, in the diacerein group. Although the occurrence of adverse events was similar in both groups, chromaturia was more prevalent in the diacerein group (40% vs. 10%, $p = 0.03$). This trial indicated that diacerein might enhance disease activity in patients with RA who inadequately respond to MTX, while maintaining a tolerable safety profile [79].

8.1.2 Combination therapy with diacerein and MTX. A randomized, double-blind, placebo-controlled, multicenter phase II trial has evaluated the effectiveness and safety of incorporating diacerein into MTX treatment for patients with early RA who had unsatisfactory responses to MTX. The trial included patients with active early RA who had received consistent MTX treatment for at least 4 weeks while still demonstrating disease activity. Participants were randomly assigned to receive either 50 mg diacerein or a matched placebo twice daily, together with their existing MTX regimen, for 24 weeks.

The principal endpoint was ACR20 at week 24, and secondary endpoints comprised the EULAR response criteria, Minimal Clinically Important Improvement in pain, and Patient Acceptable Symptom State. At week 24, 13 patients in the diacerein group and nine patients in the placebo group had an ACR20 response ($p = 0.2036$). Good or moderate EULAR response was achieved in 15 patients in the diacerein group and five patients in the placebo group ($p = 0.0016$). The Disease Activity Score 28 (DAS28) exhibited an increase from baseline of 1.26 ± 1.37 in the diacerein cohort and 0.85 ± 1.17 in the placebo cohort ($p = 0.1199$). Therefore, including diacerein in MTX treatment might improve therapeutic outcomes in patients with early RA [80].

8.1.3 Comparative efficacy of diacerein and NSAIDs. A meta-analysis of controlled clinical studies evaluating diacerein for OA therapy has revealed comparable efficacy between diacerein and NSAIDs in the management of knee OA throughout the treatment duration. Diacerein demonstrated a substantial carryover effect: its analgesic-sparing impact lasted as many as 3 months beyond the termination of therapy and offered extended relief. In contrast, NSAIDs did not demonstrate this enduring advantage, because their effects often decreased after therapy cessation. The extended analgesic effect of diacerein indicates that it might provide a more sustainable solution than traditional NSAIDs for pain management in patients with OA, thus providing potential benefits in long-term therapy approaches for knee OA [43, 81].

9. LIMITATIONS OF CURRENT EVIDENCE AND RESEARCH GAPS

Despite compelling preclinical and mechanistic evidence supporting the anti-inflammatory and disease-modifying potential of diacerein, clinical data in RA remain limited and inconclusive. One major limitation is the small number of randomized controlled trials conducted specifically in RA, most of which have involved small sample sizes, short follow-up durations, and heterogeneous patient populations. These factors significantly decreased study statistical power and limited the ability to draw definitive conclusions regarding long-term efficacy, structural joint protection, and disease remission.

A critical gap in the literature is the absence of large, multicenter phase III clinical trials evaluating diacerein as a standalone or adjunct DMARD in RA. In contrast, OA has benefited from extensive clinical evaluation, because of diacerein's classification as a symptomatic slow-acting drug for OA and its primary chondroprotective indication. RA research has historically prioritized agents targeting TNF- α , IL-6, JAK-STAT pathways, and B-cell depletion; consequently, commercial and academic interest in repurposing diacerein for RA might have been limited.

Furthermore, safety concerns, particularly gastrointestinal intolerance and hepatotoxicity warnings issued by regulatory authorities, have constrained long-term RA trials requiring long-term treatment. This aspect is particularly relevant in populations with RA that frequently receive combination therapy, thereby increasing the risk of cumulative toxicity. Another notable gap is the lack of validated biomarkers to identify RA patient subgroups that might preferentially benefit from IL-1 β -targeted therapies such as diacerein.

A major limitation in positioning diacerein for RA is the absence of large, multicenter phase III clinical trials specifically designed for RA. Because most available data originated from OA studies or small RA cohorts, the generalizability of the findings is limited. In addition, regulatory safety concerns, particularly gastrointestinal intolerance and hepatotoxicity warnings, have constrained long-term trials in RA populations that typically require long-term therapy. These limitations underscore the need for well-powered trials and biomarker-driven patient stratification before diacerein can be broadly recommended in RA management.

10. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Future studies should assess diacerein's efficacy in RA while carefully monitoring its common adverse events and long-term safety. Table 1 shows guidelines for dosages and adverse effect management, as well as the regular monitoring crucial for clinical use of diacerein.

Diacerein, an anthraquinone derivative exhibiting anti-inflammatory and chondroprotective effects, has recently been investigated for its potential uses beyond OA [93]. Its effectiveness in treating RA, diabetes-related OA, and neuropathic pain has been examined. Moreover, diacerein's function in regulating inflammatory pathways has attracted attention for possible applications in treating inflammatory bowel disease and other chronic inflammatory disorders [94]. Current clinical trials are evaluating its safety and efficacy in these novel therapeutic domains, to broaden its clinical use. Researchers are exploring innovative delivery strategies to increase diacerein's bioavailability and mitigate the gastrointestinal adverse effects that have constrained its conventional oral administration [94, 95].

Diacerein, a selective IL-1 β inhibitor, has been explored for its potential in combination therapy and precision medicine. Its synergistic effects with various anti-inflammatory drugs have been investigated, to improve treatment results in illnesses such as OA and inflammatory bowel disease [96]. Moreover, investigations have focused on pinpointing genetic markers to predict individual patients' reactions to diacerein and enable personalized treatment approaches. These findings highlight diacerein's potential in enhancing combination treatments and precision medicine strategies [97, 98]. Moreover, diacerein regulates the activity of MMPs,

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Table 1 | The safety profile of diacerein compared with other RA drugs.

Medication/drug class	Common adverse events	Long-term safety considerations and monitoring requirements	References
Diacerein	• Gastrointestinal effects: diarrhea (common, particularly during initial weeks), loose stools • Urine discoloration: yellow or pink due to metabolite excretion (clinically insignificant) • Cutaneous reactions: rash, pruritus, or eczema (less frequent) • Hepatic effects: elevated liver enzymes	• Regular monitoring of liver function tests recommended, because of hepatotoxicity risk • Not recommended in patients ≥ 65 years of age, because of elevated risk of severe diarrhea and dehydration • Dose titration advised: initiation at 50 mg once daily with gradual escalation to 50 mg twice daily to decrease gastrointestinal intolerance	[82, 83]
Methotrexate	• Gastrointestinal disturbances: nausea, vomiting, or diarrhea • Hepatotoxicity: risk of liver injury with long-term use • Hematological toxicity: bone marrow suppression leading to anemia, leukopenia, or thrombocytopenia • Pulmonary toxicity: rare cases of methotrexate-induced pneumonitis	• Mandatory routine monitoring of liver function tests and complete blood counts • Contraindicated in pregnant patients or those with significant liver disease • Folic acid supplementation recommended to decrease adverse effects • Careful dose adjustment and patient surveillance required for long-term use	[84-86]
NSAIDs (e.g., ibuprofen, naproxen, and celecoxib)	• Gastrointestinal toxicity: dyspepsia, peptic ulcers, or gastrointestinal bleeding • Cardiovascular events: elevated risk of myocardial infarction and stroke, particularly with long-term use • Renal effects: diminished renal perfusion and potential nephrotoxicity	• Long-term use associated with elevated gastrointestinal, cardiovascular, and renal risks • Caution advised in older patients and those with renal impairment, cardiovascular disease, or history of peptic ulcers • Periodic renal function and blood pressure monitoring recommended	[87-89]
Biologic DMARDs (e.g., TNF- α inhibitors: etanercept, adalimumab, and infliximab)	• Infections: elevated susceptibility to bacterial, fungal, and opportunistic infections (including tuberculosis reactivation) • Injection-site reactions: pain, erythema, or swelling • Hypersensitivity reactions: rare but potentially severe allergic responses	• Mandatory screening for latent tuberculosis and hepatitis before therapy initiation • Long-term monitoring for malignancies, autoimmune complications, and serious infections required • Continued assessment of immune status required during therapy	[90-92]

enzymes that decompose extracellular matrix constituents and facilitate tissue damage in autoimmune disorders. Diacerein may aid in maintaining joint integrity and function in people with RA through multiple biological activities [52]. Moreover, diacerein's antioxidant characteristics might alleviate oxidative stress, a major aspect involved in the advancement of autoimmune disorders. The identified molecular targets indicate that diacerein might be a promising therapeutic drug for the management of RA and potentially other autoimmune illnesses [99].

11. CONCLUSION: REVEALING THE FULL POTENTIAL OF DIACEREIN IN RA TREATMENT

Diacerein, an innovative therapeutic drug for RA, has demonstrated significant healing potential in the management of this chronic inflammatory disorder. RA involves chronic joint inflammation resulting in pain, edema, rigidity, and ultimately joint deterioration.

Diacerein functions principally by decreasing the action of IL-1, a pro-inflammatory cytokine implicated in RA pathophysiology. By addressing this crucial mediator of inflammation, diacerein has promise in alleviating the detrimental effects of RA on the joints, decreasing discomfort, and enhancing functionality for patients. Diacerein has shown considerable efficacy in clinical studies, by decreasing inflammatory indicators, including C-reactive protein, and enhancing physical function; therefore, it might provide a valuable therapeutic option for managing RA. In the transition to personalized medicine in RA treatment, diacerein might potentially be integrated into a customized strategy in which therapy is modified according to individual patients' disease characteristics. Comprehensive investigations of its pharmacokinetics, ideal dose, and prolonged effects might enable diacerein to become fundamental in RA treatment, by improving patient quality of life and alleviating disease burden. To fully achieve this promise, continued clinical trials and research will be essential to

refine its roles in RA care and the future treatment of autoimmune diseases.

Based on current evidence, diacerein should be considered an adjunctive anti-inflammatory and joint-protective agent rather than a true DMARD in RA.

According to currently available clinical evidence, diacerein should not be considered a first-line disease-modifying antirheumatic drug in RA. Instead, it appears to have a potential role as an adjunctive therapy in combination with conventional DMARDs, particularly in patients with inadequate response or intolerance to standard treatments. Further large-scale clinical trials are required before its roles in RA treatment algorithms can be definitively established.

DATA AVAILABILITY STATEMENT

No data were generated in this article.

ETHICS STATEMENT

No direct interactions with human or animal subjects were involved. Therefore, ethical approval and informed consent were not required.

AUTHOR CONTRIBUTIONS

Subarnarekha Maitra contributed to the writing of the original draft, as well as resource gathering, method design, investigation, and conceptualization. Sreemoy Kanti Das and Tathagata Roy were responsible for visualization and supervision. Dibya Sinha, Maitreyee Mukherjee, and Susanta Paul contributed to formal analysis and data curation, ensuring the accuracy and integrity of the study.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported herein.

CONSENT FOR PUBLICATION

The authors have consented to the publication of this article. All authors have reviewed and approved the final version of the manuscript, and have agreed to its submission for publication. We confirm that the work is original, does not contain any conflicting interests, and adheres to ethical guidelines. All co-authors have provided consent for publication.

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