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(REVIEW ARTICLE)

Rheumatoid Arthritis and novel carrier systems in diagnosis and treatment: An AI generated review

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Abstract

Rheumatoid arthritis (RA) is a debilitating autoimmune disease that primarily affects the small joints of the hands and feet, leading to chronic inflammation, pain, and progressive joint damage. This inflammatory condition results from an overactive immune response, where CD4+ T cells, B cells, and macrophages infiltrate the synovium, triggering an aggressive immune attack on healthy tissues. Conventional treatments, including non-steroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs, provide symptomatic relief but often come with significant side effects and limited long-term efficacy. Recent advancements in targeted therapy and nanomedicine have revolutionized RA treatment, offering innovative drug delivery systems designed to magnify therapeutic outcomes while lessen systemic toxicity. Emerging approaches, such as polypeptide nanogels, exosome-based therapy, silk fibroin hydrogels, and ROS-responsive polymeric micelles, hold great promise in improving drug bioavailability and precision targeting of inflamed joints. Moreover, novel strategies like macrophage repolarization, solute carrier nutrient transporters, and dendritic nanotheranostics are reshaping the landscape of RA therapeutics by modulating immune responses at a cellular level. This comprehensive review highlights the latest breakthroughs in RA treatment, emphasizing the potential of nanotechnology, biomaterials, and personalized medicine in addressing the limitations of traditional therapies. By integrating cutting-edge drug delivery mechanisms and immune-modulating strategies, these advancements open the way for a more effective, safer, and patient-centric approach to managing rheumatoid arthritis.

Keywords: Polymeric Nanoparticles; Exosomes; Nanogel; Nanoemulgel; Nanothernostic Agents

1. Introduction

Rheumatoid arthritis (RA) is a symmetric polyarticular arthritis characterized by inflammation in small arthrodial joints of the hands and feet. The aggressive tissue front known as the pannus also causes inflammation in the synovium, the joint's lining. CD4+ T cells, B cells, and macrophages invade the synovium and may group into distinct lymphoid aggregates with germinal centers. Recent studies show that Europe and North America have higher rates of arthritis than developing nations. Data from developing countries is only becoming available, with the World Health Organization and International League of Associations for Rheumatology working together to collect data for countries like the

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Philippines, China, Malaysia, Indonesia, and rural South Africa.[1] A systematic review of population-based studies (including 60 studies) showed 0.51% (1955-2015) as a worldwide period prevalence of RA.[2]

RA's autoimmune and inflammatory nature causes the immune system to mistakenly target healthy cells, resulting in inflammation in affected body parts. Depending on the severity of symptoms and the duration of rheumatoid arthritis, patients may take non-steroidal anti-inflammatory drugs (NSAIDs), steroids, biologic agents, and disease-modifying anti-rheumatic medicines (DMARDs), or a combination. Currently, multiple drugs are being used to treat arthritis (RA) patients.[3] The most widely used class of drugs is NSAIDs, which target and suppress prostaglandins through inhibition of cyclooxygenase (COX) enzymes.[4] These drugs can cause various symptoms, including renal, hepatic, and cardiovascular toxicity. Some COX-2-selective agents can cause myocardial infarction and stroke.[5]

The second major class of antirheumatic drugs is biologics and DMARDs, which belong to two categories: chemical and biological. Methotrexate (MTX) is one of the gold standards of therapy for RA, and it is a chemical DMARD that can suppress proinflammatory cytokines and modulate the levels of specific MMPs. Adenosine, a chemical DMARD, exerts its anti-inflammatory properties by inhibiting proinflammatory cytokine production, attenuating neutrophil trafficking, and suppressing Th17 cell differentiation while stimulating Regulatory T cells (Treg) differentiation.[6]

Biological DMARDs include monoclonal antibodies targeting tumor necrosis factor (TNF)-α and interlukin-6 (IL-6) receptor (anti-TNF-α), which inhibit these two cytokines that promote RA pathogenesis. Anti-TNF-α is currently the standard of care for RA patients, but approximately 10-30% of patients do not respond to initial treatment and 23-46% lose responsiveness over time.[7]

Corticosteroids are another group of biologic DMARDs used for RA therapy, which suppresses inflammation by binding to the glucocorticoid receptor and transcription of multiple genes that inhibit several inflammatory pathways. An established corticosteroid known for its potent anti-inflammatory and immunosuppressive effects is prednisolone.[3,5] However, corticosteroids have unwanted side effects, including osteoporosis, peptic ulcer, and increased rates of infections.[8]

2. Drug delivery approaches in diagnosing/treating RA

JinWu JianGu capsule (JWJG) a Chinese herbal medicine, was studied for its anti-inflammatory effects on RA in rats. JWJG Capsule (JWJGC) was given to rats with collagen-induced arthritis (CIA) and was reported to lower Reactive oxygen species (ROS) levels, restore balance, and decrease inflammatory markers. It also had an effect on lipid metabolism, downregulating lipids associated with ferroptosis and inhibiting ferroptosis via modifying glutathione/glutathione peroxidase 4 expression. The results indicate that JWJGC improves RA by modulating the SLC7A11/GSH/GPX4 pathway in M1 macrophages.[9] JWJG repressed ADCY10, reduced cAMP/RANKL, and obstructed inflammation and osteoclastogenesis, with a prominent reversing in RA symptoms. Researchers state that it can be presented as a possible novel therapeutic stratagem for preventing or even reversing bone damage and refining the quality of life for RA patients.[10]

Exosomes, a form of extracellular vesicle, are lipid particles that contain a variety of substances such as nucleic acids, proteins, and DNA. They can be employed as both a diagnostic biomarker and a therapeutic agent in RA. These bilayered particles are naturally discharged into the extracellular periphery by numerous cells, including malignant cells. Exosomes have unique features, allowing them to be employed as vectors and carriers of biological and medicinal particles such as medicines for delivery to specific locations. The proteins and RNAs contained in circulating exosomes in B-cell malignancies are thought to be interesting sources for diagnostic and prognostic biomarkers, as well as therapeutics. Exosomes has been investigated in diagnosing of arthritis rheumatoid[11]. Targeting solute carrier nutrition (SLC) transporters in rheumatoid arthritis requires enhanced expression of these SLC transporters in order to meet a high demand for energy or biomolecules. SLC transporter families act as metabolic gates for cells, transporting various nutrients including glucose, amino acids, vitamins, neurotransmitters, and inorganic/metal ions. SLC-mediated transmembrane transport in RA fibroblast like synoviocytes (FLS) differs from osteoarthritis in terms of epigenetic landscapes.[12]

Polypeptide nanogel was prepared using hyaluronic acid (HA) -conjugated, redox-responsive poly amino acid nanogels (HA-NG) to deliver tacrolimus (TAC) specifically to inflamed joints. The nanogels' disulfide bonds enable controlled TAC release in response to high intracellular glutathione (GSH) levels in activated macrophages, prevalent in RA-affected tissues. *In vitro* results demonstrated that HA-NG/TAC significantly reduced TAC toxicity to normal macrophages and showed high biocompatibility. *In vivo*, HA-NG/TAC accumulated more in inflamed joints compared to non-targeted NG/TAC, enhancing therapeutic efficacy and minimizing side effects. Therapeutic evaluation in CIA mice revealed HA-

NG/TAC substantially reduced paw swelling, arthritis scores, synovial inflammation, and bone erosion while suppressing pro-inflammatory cytokine levels. HA-NG/TAC is a promising drug delivery method for RA, potentially leading to safer and more effective therapeutic uses.[13] Zhu et al. presented a cationic peptide dendrimer nanogel with deoxyribonuclease I conjugation to treat RA, which reduced Toll like Receptor-9 signalling pathways and RA symptoms in collagen-induced arthritic animals.[14]

Curcumin Cyclosporine Loaded Nanoemulgel was investigated in a lipopolysaccharide-induced RAW 264.7 cell culture model and found that the drug-loaded nano emulsion Carbopol gel reduced IL-6 and TNF levels, decreased prostaglandin E2, and increased anti-inflammatory cytokine (IL-10) levels. The gel effectively reduced paw oedema and arthritic symptoms in a rat model by improving medication topical penetration.[15]

Targeting solute carrier nutrient (SLC) transporters in rheumatoid arthritis involve increased expression of these SLC transporters to meet a high demand for energy or biomolecules. SLC transporter families are nutrient transporters and serve as 'metabolic gates' for cells by mediating the transport of several different nutrients such as glucose, amino acids, vitamins, neurotransmitters, and inorganic/metal ions. In Rheumatoid Arthritis , FLS , SLC-mediated transmembrane transport is one pathway associated with different epigenetic landscapes between RA and osteoarthritis, thus SLC family offer the promise of future therapeutic targets for RA.[16] Metabolic pathways can also be used to identify RA-specific targets that include SLC transporters, enzymes, and transcription factors, to advance innovative therapeutic agents.[17]

Osteoclasts, generated *in vitro* from peripheral blood cells of patients with RA were fewer which could be linked to rheumatoid inflammation. RA activity was the best predictor of osteoclast characteristics, limiting their ability to predict treatment resistance and erosions. However, the erosive phenotype of RA was related with resistance to apoptosis of peripheral blood cells (PBMC) derived osteoclasts, a parameter that was unaffected by RA activity and remained consistent in patients throughout time. The utility of osteoclast characteristics in defining long-term RA phenotype is notices in this study.[18] Osteoblast role in the pathogenesis of rheumatoid arthritis.[19] Denosumab reduces bone destruction in RA but does not affect joint inflammation or cartilage damage, requiring combination therapy. Its optimal role in RA treatment remains unclear, necessitating further research.[20] Current and future arthritis treatment aims to combine inflammation control with structural protection .Targeting osteoclasts may enhance joint preservation and ensure long-term structural integrity in inflammatory disease.[21]

Liposomes encapsulating Ginsenoside compound K[22], dexamethasone[23], mesenchymal stem cell based biomimetic liposomes[24], gold hybrid nanoparticles encoded with Coenzyme Q10[25] and many such antirheumatic agents have been successfully prepared, characterised, evaluated *in vivo* for targeted therapy proving to alleviate inflammation resulting as therapeutic potential in treating RA.

Ufasomes have been explored in the treatment of inflammation in RA. It is a dermal drug delivery system designed to localize MTX in the synovial joint using fatty acid vesicles, surfactants and Carbopol gel. In conclusion, when compared to either aqueous solution or regular liposomes, ufasomes made with oleic acid enhanced the *in vitro* skin delivery of MTX. The increased buildup of MTX in the skin may aid in improving the drug's targeting and opening up new possibilities for the current, well-regulated topical administration of MTX in the treatment of RA.[26]

Dendritic nano theranostic have been investigated to address the issue of over expression of target protein by conjugating the drug with antibodies. Anionic carbosilane dendrimer with a fluorochrome on its surface, which forms a conjugate with antibodies, including infliximab, to target TNF-α, a cytokine often overexpressed in autoimmune disorders like rheumatoid arthritis was synthesises. The study also investigated whether the antibody's integrity and functionality are affected by the coupling process. Nanotechnology, particularly dendrimers, offers a promising way to improve RA treatments, including biological therapies leading to new treatment options.[27] Enhancement in pre-dendritic cells (DC) in peripheral blood forecast RA treatment resistance stating that pre-DC could have pathophysiological significance to RA treatment response.[28] Another study presents a novel theranostic nanoparticle composed of albumin-cerium oxide conjugated with indocyanine green for targeted treatment and imaging of rheumatoid arthritis. The nanoparticles exhibit strong reactive oxygen species scavenging, reprogram pro-inflammatory macrophages, and accumulate in inflamed joints. In a mouse model, it showed therapeutic effects comparable to methotrexate. Imaging confirmed precise delivery and localization to affected areas.[29]

Macrophage repolarization as a targeted therapy for RA Macrophage is reported by researchers. Polarization plays a crucial role in the development of rheumatoid arthritis. In arthritic joints, M1 macrophages overexpress folate receptors. To target this, we engineered folic acid-modified liposomes (FA-Lips) to encapsulate triptolide (TP) for RA therapy. FA-Lips showed significantly better internalization in LPS-stimulated RAW 264.7 cells compared to standard

liposomes. In an adjuvant-induced arthritis rat model, FA-Lips selectively accumulate in inflamed paws, improving treatment efficacy and lowering toxicity. They target M1 macrophages and promote their repolarisation to M2. Our findings indicate that TP-loaded FA-Lips effectively deliver targeted therapy for RA through macrophage repolarization, highlighting activated M1 macrophages as key targets for intervention. The reduction of M1 macrophages and their transition to M2 phenotypes were essential for alleviating inflammation in arthritic joints, with TP-loaded FA-Lips showing lower systemic toxicity. Overall, targeting activated macrophages in the joint microenvironment presents a promising strategy for relieving the symptoms and delaying the progression of RA.[30] In RA, activated macrophages drive inflammation and cartilage damage. Fc gamma receptor (CD64) directed immunotoxins can selectively induce apoptosis in synovial macrophages, which express higher CD64 levels than blood monocytes.[31] Monocytes and macrophages drive RA inflammation by activating T-cells and releasing pro-inflammatory cytokines. An imbalance favouring M1 over M2 macrophages sustains inflammation in blood and synovium.M1 macrophages promote osteoclastogenesis, leading to bone erosion. This creates a cycle of chronic inflammation and joint destruction.[32]

Silk fibroin in-situ hydrogel infused with Sesbania Sesban L. extract, known for its anti-inflammatory properties and beneficial for managing rheumatoid arthritis has been inspected. The hydrogels were created through spontaneous gelation at varying temperatures, and their characteristics—including morphology, gelation time, viscosity, gel strength, stability, drug loading capacity, drug release rate, and *in-vitro* anti-inflammatory activity were thoroughly evaluated. The gel was non-toxic to the RAW 264.7 cell line and showed comparable anti-inflammatory effects to the free extract, particularly in reducing nitric oxide levels warranting further investigation as a potential treatment for rheumatoid arthritis.[33] Hydrogels of tyramine-modified gellan gum with silk fibroin via horseradish peroxidase, with encapsulated betamethasone, increased therapeutic efficacy in handling of RA.[34]

Stimuli-responsive polymeric nanomaterials have transformed medication delivery for this chronic condition of RA. Research shows that targeted drug delivery systems can enhance treatment effectiveness while reducing the side effects associated with traditional anti-RA medications. Nanoparticles that respond to external or internal stimuli—like temperature, pH, or specific biomolecules—offer a precise drug delivery alternative. These systems enable the controlled release of therapeutic agents at the right site and time, improving efficacy and minimizing systemic side effects. The versatility of responsive materials allows for diverse nanoparticle structures, enabling tailored drug delivery solutions for individual patients. Additionally, exploring transdermal delivery methods may enhance patient compliance and treatment outcomes. However, challenges remain, including the limited number of drugs suitable for this approach.[35] In a study Aceclofenac nanoparticle loaded transdermal hydrogel was developed for RA treatment, offering sustained drug release at inflamed sites. Compared to conventional therapy, nano-carriers improve efficacy by reducing oral administration side effects and dosing frequency.[36] PEGylated lecithin chitosan nanoparticles enhanced leflunomide delivery for rheumatoid arthritis, showing improved stability, small size, and high drug encapsulation leading to better therapeutic effects and safety.[37]

ROS-responsive berberine polymeric micelles (BPseP) / nanoparticles were studied. *In vivo* results have demonstrated that BPseP significantly reduces inflammation, cytokine production, and even bone destruction compared to berberine. BPseP effectively restores the balance between suppressive and effector immune cells. Treg, which are a crucial subset of suppressor T cells believed to mitigate RA and prevent autoimmune diseases, were notably upregulated by BPseP, while the activity of CD8+ effector T cells was diminished. Importantly, in addition to its suppressive effects on FLS-RA, BPseP is capable of modulating and restoring immune equilibrium in RA. ROS-responsive micelles preferentially target the mitochondria of inflamed tissues to eliminate affected cells, demonstrating tenfold greater efficacy than berberine. Future advancements in the targeting efficiency of responsive micelles could be achieved by incorporating targeting antibodies, such as anti-TNF, to facilitate binding with RA-affected cells.[38] Researchers have developed ROS/pH-responsive micelles for targeted RA therapy. These micelles accumulate in swollen joints via the extravasation through leaky vasculature and subsequent inflammatory cell-mediated sequestration effect and selectively release the drug in inflamed cells. *In vitro* and *in vivo* studies confirmed their biocompatibility, anti-inflammatory effects, and inhibition of RA progression.[39] RGD-modified polymeric micelles improved the targeted delivery of low-dose methotrexate and nimesulide, enhancing therapeutic effects in rheumatoid arthritis and showing promise for clinical use.[40] Breathing micelles (BM) that inhale NO and exhale CO to regulate inflammation have also been developed. BM reduces proinflammatory cytokines and outperforms dexamethasone in RA treatment by depleting NO, deactivating inducible NO synthase, and activating heme oxygenase-1.[41] Table 1 enlists the various carrier systems and approaches investigated in treating Rheumatoid Arthritis.

Table 1 Various carriers and approaches in treating Rheumatoid Arthritis

Carriers	Mechanism	Role
JinWu JianGu Capsule (JWJGC)**[9]**	Regulates the SLC7A11/GSH/GPX4 pathway in M1 macrophages, reduces ROS levels, and restores balance in lipid metabolism.	Reduces inflammation and ferroptosis in RA.
Exosomes[12]	Serve as vectors for delivering biological and medicinal particles (nucleic acids, proteins, and drugs).	Enhances targeted drug delivery, immune modulation, and potential for vaccine development.
Polypeptide Nanogel (HA-NG)[14]	Uses redox-responsive bonds to release drugs in response to high GSH levels.	Targets inflamed joints, improves drug bio availability, and reduces toxicity.
Solute Carrier (SLC) Nutrient Transporters[17]	Mediate nutrient transport to meet high energy and biomolecule demand in fibroblast-like synoviocytes.	Potential target for modulating metabolic activity in RA.
Osteoclast-Derived Precursors**[21]**	Reduced osteoclast generation from PBMCs in active RA patients.	Potential for predicting disease activity and treatment resistance.
Ufasomes[26]	Fatty acid vesicles enhance drug penetration and stability in the synovium.	Improves topical drug delivery and targeting of inflamed joints.
Dendritic Nanotheranostic**[27]**	Antibody-conjugated dendrimers target TNF-α and facilitate targeted delivery.	Enhances targeted delivery and immune response modulation.
Macrophage Repolarization (FA-Lips)**[31]**	Folic acid-modified liposomes target M1 macrophages and promote transition to M2 phenotype.	Reduces inflammation and improves therapeutic efficacy.
Silk Fibroin Hydrogel**[33]**	Infused with Sesbania Sesban L. extract for anti-inflammatory activity.	Provides controlled release, improves drug stability, and reduces inflammation.
Stimuli-Responsive Polymeric Nanomaterials**[35]**	Respond to external/internal stimuli (e.g., pH, temperature) for controlled drug release.	Enhances site-specific drug delivery and reduces systemic toxicity.
ROS-Responsive Berberine Polymeric Micelles (BPseP)**[38]**	Targets mitochondria in inflamed tissues, modulates immune balance.	Reduces inflammation, increases drug accumulation, and improves therapeutic outcome.

3. Conclusion

Rheumatoid arthritis (RA) remains a challenging autoimmune disease that significantly impacts patients' quality of life, requiring continuous advancements in treatment strategies. While conventional therapies such as NSAIDs, corticosteroids, and DMARDs provide symptomatic relief, their long-term efficacy is often hindered by adverse effects and resistance. The emergence of innovative therapeutic approaches, including nanotechnology-based drug delivery systems, exosome therapy, and macrophage-targeted treatments, offers new hope for more effective and safer interventions.

By leveraging precision medicine, researchers are now able to design highly targeted therapies that enhance drug bioavailability, minimize toxicity, and address the root causes of inflammation at a cellular level. Advanced drug carriers, such as polypeptide nanogels, silk fibroin hydrogels, and ROS-responsive micelles, have shown remarkable potential in improving therapeutic outcomes by ensuring controlled drug release and sustained action within inflamed joints. As science continues to push the boundaries of RA treatment, the future holds immense promise for transforming disease management. The integration of nanomedicine, immunotherapy, and personalized approaches will not only provide better symptom control but may also pave the way for disease modification and remission. With ongoing research and

clinical advancements, the goal of achieving long-term relief and improved quality of life for RA patients is becoming increasingly attainable.

Compliance with ethical standards

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