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REVIEW

Advancement in nanotechnology for treatment of rheumatoid arthritis: scope and potential applications

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Abstract

Rheumatoid arthritis is a hyperactive immune disorder that results in severe inflammation in synovial joints, cartilage, and bone deterioration, resulting in immobilization of joints. Traditional approaches for the treatment of rheumatoid arthritis are associated with some limiting factors such as suboptimal patient compliance, inability to control the progression of disorder, and safety concerns. Therefore, innovative drug delivery carriers for efficient therapeutic delivery at inflamed synovial sites with better safety assessment are urgently needed to address these issues. From this perspective, nanotechnology is an outstanding alternative to traditional drug delivery approaches, and it has shown great promise in developing novel carriers to treat rheumatoid arthritis. Considering the current research and future application of nanocarriers, it is believed that nanocarriers can be a crucial element in rheumatoid arthritis treatment. This paper covers all currently available pathophysiological aspects of rheumatoid arthritis and treatment options. Future research for the reduction of synovial inflammation should focus on developing multifunction nanoparticles capable of delivering therapeutic agents with improved safety, efficacy, and cost-effectiveness to be commercialized.

Keywords Rheumatoid arthritis · Biological agents · Nanotechnology · Nanocarriers · Targeted therapy · Animal models

Introduction

Rheumatoid arthritis (RA) is a condition of persistent inflammation of the synovium. It is an autoimmune disorder that causes infiltration of β-cells in the synovium, leading to cartilage destruction and erosion of bone (Guo et al. 2018). The rate of occurrence of this disorder among adults (more prevalent in females than males) in developed nations ranges between 0.5 and 1%. The individual suffering from this disease generally experiences disabled mobility, and painful and stiff joints, in addition to mortality in severe cases (Ebel and O'Dell 2021). As per the recorded data of the World Health Organization, RA is identified in individuals of 22–40 years that are active years of employment. Their quality of life is affected (Anita et al. 2021). The earliest diagnosis of RA from the disease onset is 3 to 24 months and by the time it turns out to be more substantial (Law and Taylor 2019). If this condition is left untreated, it leads to gradual bone damage or even fatality (Zhao et al. 2021a). Hence, timely diagnosis is of prime importance for the development of efficient planning which can prevent the destruction of joints, enduring disability, and associated systemic complications (Heidari 2011). Available RA treatment strategy has shown therapeutic effects. Still, due to the risk of dose escalation-induced de-functionalization and therapeutic tolerance, research is shifting towards developing advanced therapies to overcome these drawbacks (Thorne et al. 2017). The current trend in the management of RA mainly incorporates the co-delivery of biological agents and conventional disease-modifying antirheumatic drugs (DMRDs). TNF-α is an essential and new molecular target in treating RA-associated pathogenic environments. The most commonly used therapeutic agents for RA management are TNF-inhibiting

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agents such as etanercept and adalimumab (Zheng et al. 2021). The co-delivery of biological agents and DMRDs shows significant therapeutic efficacy to single delivery of DMRDs. Still, it is also financially an unbearable option for the treatment of RA patients.

Conventional therapeutic agents show restricted application because of poorly soluble behavior, high doses, elevated toxicity, shorter half-life, and non-specific route of administration. Nanotechnology offers a wide range of opportunities to fabricate new drug delivery vehicles that overcome the limitations of conventional dosage forms. Nanotechnology helps in improving the bioavailability, solubilization, half-life, and diffusive properties of drugs leading to optimum treatment choice at a molecular level. Nanotechnology-based drug carrier systems are used to deliver therapeutic agents at targeted synovial sites for their anti-inflammatory activity, which could be achieved by surface modification of carrier systems with stimuli-responsive moiety (Heidari 2011). Additionally, nano-size, along with surface functionalization flexibility, enables the efficient delivery of medicinal agents on desired sites via passive or active mechanisms (Yang et al. 2017). Passive targeting results due to the effective engulfing of nanocarriers by macrophages raised in inflamed synovium. Other mechanisms of target drug delivery in arthritic inflammatory joints are the accumulation of nanoscale drug delivery vehicles via extravasation through leaky vasculature, enhancing permeability retention, and subsequent inflammatory cell-mediated sequestration. These carriers can additionally shield medicinal agents from degradation in the biological environment, thereby providing the release of drugs in a sustained manner and prolonged biokinetics (Anselmo and Mitragotri 2014). These potential benefits of nanocarriers led to the potential application of nanotechnology in RA.

Etiology and pathogenesis

The etiology of RA is complex, with hereditary and environmental variables. However, the disease manifestation mechanism is still unclear. The human leukocyte antigen-DRB1 gene encodes MHC components, the most functional genomic significant risk in RA. A shared epitope (for example, DRB1 0401 or 0404) in the peptide-binding region of alleles has been significantly linked to RA's autoreactive immune responses (Gregersen et al. 1987). Smoking significantly fastens the progression of RA illness. Smoking has been a significant factor for RA, particularly in individuals with a common epitope. A common epitope in smoking individuals has also been demonstrated as a higher risk of RA by a factor of 20 (Källberg et al. 2011). Additional environmental factors, such as periodontitis and silicosis, may contribute to the risk for RA (Sokolove et al. 2016; Akram et al. 2021).

The extraarticular mucosal regions, mainly the intestinal and lungs, are the first targets of inflammation and loss of RA tolerance, resulting in autoimmune (Stolt et al. 2005; Demoruelle et al. 2014). Environmental factors and stressors may produce mucosal damage and stimulate peptidyl arginine deiminase, which encourages post-translational arginine to citrulline modification within proteins, a technique known as citrullination. Smoking cigarettes is a well-known source of citrullination inside the lungs. *Porphyromonas gingivalis* also alleviate the citrullination in periodontitis. The citrullinated peptide link to a common epitope within the MHC protein with greater avidity and rapidly stimulate CD4 T cells.

Consequently, the B lymphocytes are activated, resulting in autoantibodies such as anticitrullinated protein antibodies and rheumatoid factors that identify self-proteins and are harmful during RA (Hill et al. 2003). Rheumatoid factor and anticitrullinated protein antibodies could be detected in the blood as potential biomarkers of RA up to 10 years before the disease progression. These autoantibodies are insufficient to induce illness; however, the specific method by which antibodies target the joints remains unknown. Several immunologic processes, like rising autoantibody levels, epitope distribution, and serum cytokine levels, finally reach a tipping point, resulting in synovial inflammation.

Rheumatoid arthritis has also been linked (Fig. 1) to the regulation of cytokines, infiltration of adaptive and innate immune inflammatory cells into synovium, and complex immune development, which may lead to the activation of complement or direct interaction autoantibodies inside synovial tissues (Arend and Firestein 2012). Additionally, synovitis could be developed by synovial lining growth and the proliferation of fibroblast-like synoviocytes due to the production of pro-inflammatory cytokines such as IL-6, IL-1, MMPs, and TNF-α. Moreover, synovial hyperplasia and secretion of matrix metalloproteinases (MMPs) and cytokines induce cartilage and bone deterioration. The stimulation of osteoclasts by receptor activators of TNF-α, NF-κB ligand, IL-1, and IL-6 could also lead to bone erosions (McInnes and Schett 2011).

Current treatment strategies for rheumatoid arthritis.

Current therapeutic agents used for the treatment of RA are divided into four categories: (i) non-steroidal anti-inflammatory drugs (NSAIDs), (ii) glucocorticoid (GCs), (iii) biological DMARDs, and (iv) non-biological (synthetic) DMARDs. NSAIDs possess immense analgesic and anti-inflammatory properties and show limited application in RA via symptomatic pain relief, swelling, and stiffness of synovial joints (Crofford 2013). Steroid hormones, particularly GCs are

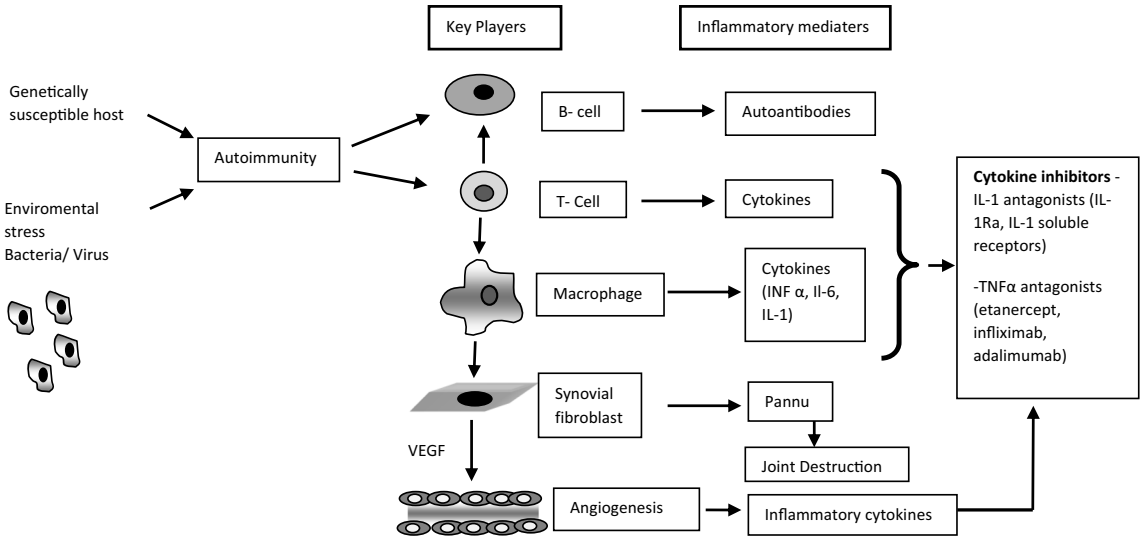

Fig. 1 Aetiology of rheumatoid arthritis

widely used to treat RA because of their potent immunosuppressive, anti-inflammatory activity and inhibition of radiographic erosions at the initial stages of RA. The most effective and widely used therapeutic agents against RA are DMARDs due to their capacity to restrict disease progression with time. DMARDs' anti-inflammatory and inhibitory radiographic progression activities vary from molecule to molecule. DMARD is also combined with GCs as a bridge therapy to prevent adverse effects associated with long-term administration (Townsend and Saag 2004; Buttgereit et al. 2004). Biological DMARDs are an advanced option to treat RA as these agents target the abnormality of the immune system and can effectively alleviate all symptoms of RA in addition to complete reversal of the progression of the disease; hence they advanced the treatment of disorder. Although these agents vary in their structure, nature, pharmacokinetics, targeting moiety, and route of application, they exhibit similar excellent therapeutic outcomes of radiological and clinical therapies (Jain and Lipsky 1997; Münster and Furst 1999). Non-biological DMARDs are a class of chemically synthesized drugs that can also slow the radiographic progression of RA and are also named "slow-acting anti-rheumatic drugs" (Avci et al. 2015). The aforementioned therapeutic approaches available for RA are not adequate to cure it completely; thus, further treatment approaches should be developed to minimize the discomfort, deformities, joint damage, and immobile or painful functionalization of inflamed synovial joints. Some of the newly developed agents useful in RA are biological agents; monoclonal antibodies are advanced therapeutic agents able to down the hyperactive defense system of a living body and treat inflammatory indices (Table 1) (Abbasi et al. 2019). New generation RA therapeutic agents' classification is represented in Fig. 2. These approaches are aimed to provide complete reversal of RA pathology or at least able to restrict the alleviation of disease activity.

Novel nanocarriers employed for management of rheumatoid arthritis

The capability to examine, develop, and manage substances at the atomic, molecular, and supramolecular levels is called nanotechnology. Nanotechnology allows for the formulation of novel drug delivery carrier systems that can improve drug profiles such as bioavailability, cycle half-life, solubility, and diffusivity, resulting in precise therapy at the molecular level. Also, the nanomaterials bring new prospects for targeted and precise disease therapy at the cellular level and simultaneously have the ability to develop future nanomedicine by lowering toxicity associated with the currently available therapeutic substances. The currently available therapeutic options in RA need high doses due to shorter half-life and have limited application due to non-targeted delivery, high toxicity, and low solubility (Oliveira et al. 2018). Nanomaterials are gaining more popularity in biomedicine, particularly diagnostics, and therapy, due to their multi-modality, high drug-loading efficiency, and passive or active targeting properties. In the case of RA, the drug molecules can be delivered preferentially to the synovial inflammation area in a sustained or controlled manner by using nanoscale drug carriers. Thus, nanotechnology can significantly improve traditional anti-RA medications' therapeutic effectiveness by using nanotechnology. Most significantly, nanoparticles provide a stable platform into which many therapeutic and/or diagnostic molecules can be

Table 1 Current treatment approaches for rheumatoid arthritis management

Therapeutic agent	Biomarker	Inferences	Reference
Tocilizumab, sarilumab	IL-6 receptor antibodies or JAK inhibitors	Prevented disease progression	Frade-Sosa et al. (2022)
Propionibacterium freudenreichii	RANKL-induced osteoclast differentiation, TRAP activity	Ameliorates RA in RAW 264.7 cell line and CIA mouse model	Yeom et al. (2021)
Tocilizumab	IL-6, TNF-α	Peripheral ulcerative keratitis associated with RA	Huang et al. (2022a)
Rituximab	B-lymphocytes	Pericarditis occurred in RA joints	Taylan (2022)
Rituximab combined with eltrombopag	B-lymphocytes	Secondary thrombocyte purpura–associated RA disorder	Zhang et al. (2022)
Baricitinib	JAK inhibitors	Improved RA treatment in patients having tolerance to bDMARDs and csDMARDs	Joyo et al. (2022)
Rituximab biosimilar GP2013	B-cells	Chronic inflammatory rheumatic disorders	Avouac et al. (2022)
Abatacept	Costimulation blocker (CD28 mediated T-cell activation)	Controlling inflammation during RA	Alenazy et al. (2021)
Infliximab	TNF inhibitors	RA-associated inflammation and bone erosion	Nakae et al. (2021)
Etanercept	JKAP level, C-reactive protein, ACPAs	Reduced RA risk and inflammation	Salem et al. (2021)
Infliximab biosimilar CT-P13	C-reactive protein	CT-P13 Subcutaneous versus pooled IV treatment arm comparison in adult patients with RA	Combe et al. (2021)
Rosmanol and Carnosol	IL-6, monocyte chemotactic protein 1 (MCP-1) and TNF-α	Swelling, redness, and synovitis decreased the arthritis index score	Li et al. (2021b)
Tanshinone IIA (Tan IIA)	TNF-α induced MMPs and pro-inflammatory cytokines	Inflammatory reactivity inhibition and blocking the destruction of the knee joint in RA-FLSs	Du et al. (2020)
Certolizumab-pegol	TNF-*α*	Higher level of post-treatment tender joint count and VAS scores for pain, fatigue, and global health in pauci-immune in RA	Nerviani et al. (2020)
Adalimumab, etanercept, infliximab	TNF-*α*	CVS disease has a crucial role in modifying the impact of lipid profile and glucose levels dysregulation in RA patients	Corrado et al. (2019)
Liquiritin	IL-1β	RA by reducing inflammation by downregulation of MAPK signaling pathway and angiogenesis	Zhai et al. (2019)

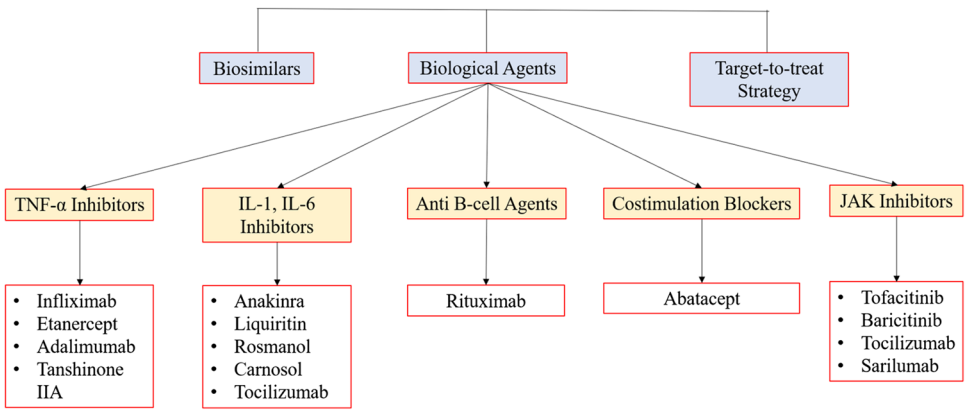

Fig. 2 New-generation biological agents used in rheumatoid arthritis

combined to create synergetic multipurpose nanomedicine (Zhao et al. 2021a). Herein, the key nanocarriers which are having great potential in RA treatment and could be part of future nanomedicine are described in addition to the critical finding in RA research (Table 2, Fig. 3).

Nanoemulsions

Nanoemulsions are colourless, isotropic, biphasic, and kinetically stable. Colloidal dispersions consist of vesicles less than 200 nm in size. Water, amphiphilic molecules, and emulsified oil are the principal components in nanoemulsion formulation (Bernardi et al. 2011). Several studies have shown the application of nanoemulsion in RA. For example, nanoemulsion loaded with citrullinated multiepitope self-antigen and rapamycin (NEs@CitP/Rapa) was fabricated for a targeted co-delivery approach of loaded immunomodulator and self-antigens at ectopic lymphoid-like structures (ELSs) of inflamed synovium, which are created using standard pharmaceutical excipients. In mouse models of RA in previous scientific experiments, the nanoemulsion accumulated well in inflamed paws after intravenous treatment and has an improved anti-inflammatory effect. Research suggested a viable targeted method for inducing immunological tolerance in RA patients (Li et al. 2021a). The experiment was performed to study the effects of bee venom-containing nanoemulsions (Top-NEs) in the collagen-induced model of RA in rats on endothelin-1 serum levels. The serum level of endothelin-1 was efficiently reduced upon treatment with Top-NEs than before treatment in RA-induced rats. Results of the study proved that the prepared Top-NEs could improve endothelin-1 serum level and dermal permeation of bee venom; hence could be applied for drug delivery at the required site to reduce endothelin-1 for RA therapy (Abbasifard et al. 2021). Designed a transdermal gel with Methotrexate-Resveratrol (MTX–RSV) loaded nanoemulsions for RA therapy revealed regulated drug release for up to 48 h. Following that, the nanocarrier combination's anti-inflammatory and prospective anti-arthritic activities were tested in rats, which revealed a $78.76 \pm 4.16\%$ reduction in inflammation and improved anti-arthritic properties. As a result, linking dual delivery with nanotechnology might result in effective therapy alternatives for rheumatic disorders (Poonia et al. 2020). Nanoemulsion comprised of lycopene was constructed and examined in vitro to characterize for therapeutic availability of lycopene. also, an in vivo assessment was done in an RA-induced animal model. The findings confirmed that the prepared nanoformulation of lycopene had significant efficacy compared to traditional lycopene formulations that support its application as an agent capable of reducing inflammation in the cure of RA (Moia et al. 2020). Quercetin (QCT) loaded nanoemulsion-based gel design, modification, and assessment for successful RA management. was developed by Gokhale et al. The QCT- NE formulation was formed using spontaneous emulsification processes. The HIG-82 and RAW 264.7 cells were used to test the cytotoxicity and influence on TNF production. QCT-nanoemulsion depicted a significant inhibitory effect on LPS-induced TNF-α synthesis and has no harmful effect on synoviocytes. Compared to free QCT gel, QCT-nanoemulsion gel revealed sufficient rheological behavior with superior smoothness and better drug penetration. Compared to the free QCT gel, the gel was non-irritating and suppressed paw edema in rats produced by CFA for 24 h. Eventually, the QCT-nanoemulsion gel formulation is an effective topical therapy method for RA (Gokhale et al. 2019). Nanoemulsion containing campul oil, PEG 400, and tween 60 as oil phase, co-surfactant, and surfactant, respectively was synthesized from an aqueous titration procedure, stored at room temperature in a tightly-closed glass vial, and tested for the stability, permeability, and efficacy of mefenamic acid loaded within nanoemulsion. From the findings, it was concluded that the developed mefenamic loaded nanoemulsion possessed considerable physical stability and therapeutic efficacy and could be employed in place of ordinary formulation in RA therapy (Changediya et al. 2021). Mucoadhesive nanoemulsion included rosmarinic acid, and chitosan coating was formulated for drug delivery through nasal administration. After evaluation, it was suggested that the drug-loaded chitosan-coated nanoemulsion sustained drug delivery, longer permeation period, improved mucoadhesive ability, and enhanced penetration of rosmarinic acid via porcine nasal mucosa. The prepared formulation also did not show any toxicity in fibroblasts. These advantages suggest these chitosan-coated drug-loaded emulsions as an effective drug delivery carrier system in RA treatment by nasal route of administration (Fachel et al. 2018).

Solid-lipid nanoparticles

Nowadays, the interest of researchers has increased in nanoparticles composed of lipids like lipid-drug conjugates, nanostructured lipid carriers, and nanoemulsions as drug carriers for the cure of RA. Moreover, SLNs, which contain a solid-lipid matrix, have shown potential in improving the delivery of lipophilic and hydrophilic nature therapeutic agents compared to drug carriers used conventionally (Liu et al. 2008; Mandawgade and Patravale 2008). SLNs are colloidal with a spherical shape with a diameter ranging from 40 to 1000 nm (Sharma et al. 2011). Surfactants surround a high melting point lipid core, forming SLNs. In certain circumstances, the colloidal stability of SLNs is increased with a polymer coating of hydrophilic nature (Naseri et al. 2015). As a solid lipid matrix, cholesterol, solid paraffin behenic acid, stearic acid, glyceryl stearate (mono- and tri-), beeswax, and other lipids are employed (Mishra et al. 2018).

Table 2 Recent nano-carriers for treatment of rheumatoid arthritis

Drug	Nano-carrier	Animal model	Administration route	Silent findings	Reference
Methotrexate	Liposome	CIA model	Intra-peritoneal injection	RA inflammation	Guimarães et al. (2022)
Dexamethasone	Liposomes	CIA model	Intra-articular injection	Reduced inflammation in ankle rheumatic joints	Kulikov et al. (2021)
Celecoxib	Spanlastic nanovesicles	CFA arthritis model	Transdermal gel	Reduced chronic inflammation in RA by reduction of TNF-α, NF-κB, and COX-2 levels	Alaaeldin et al. (2021)
Flurbiprofen	Bovine serum-albumin Nanoparticles coated with hyaluronic acid	AIA rat model	Intra-articular injection	Reduced systemic CRP level with TNF-α & IL-6 serum level induced joint-swelling reduction	Mohamed et al. (2022)
Celastrol	ROS-responsive bilirubin Nanoparticles	AIA rat model	Intravenous injection	Alleviated bone erosion and joint inflammation also suppressed pro-inflammatory cytokines to stop RA progression	Zhao et al. (2022)
Dexamethasone	PLGA-PEG nanoparticles	CFA arthritis model	Intravenous injection	Lipopolysaccharide-induced inflammatory cytokine release is inhibited to prevent joint swelling in RA	Simón-Vázquez et al. (2022)
Infliximab	Hydrogel composite scaffold	CFA arthritis female rabbit model	Transdermal implantation	Improved adipose-derived mesenchymal stem cells survival and proliferation. Also lowered level of inflammatory cytokines	Zhao et al. (2021b)
Dendritic cells	ROS-responsive exosomes	CIA mice model	Intravenous injection	Decreased level of IL-6, TGF-β, TNF-α and regulation of T-cells to cure RA	Lee et al. (2021)
Carvacrol	Tin oxide-chitosan–polyethylene glycol Nanoparticles	CFA arthritis rat model	Intradermal injection	Prostaglandin E2 and cyclooxygenase-2 inhibition	Tian et al. (2021)
Strontium ranelate and sodium chloride	Photothermal-laden methyl cellulose hydrogel	Zymosan-induced arthritis rat model	Intra-articular injection	Inhibited ROS-induced inflammation in RA	Chiang et al. (2021)
Triptolide	pH-sensitive nanoparticles	CIA model	Intravenous injection	Lowered systemic toxicity with preventive action against cartilage destruction and inflammation in RA	Liu et al. (2021)

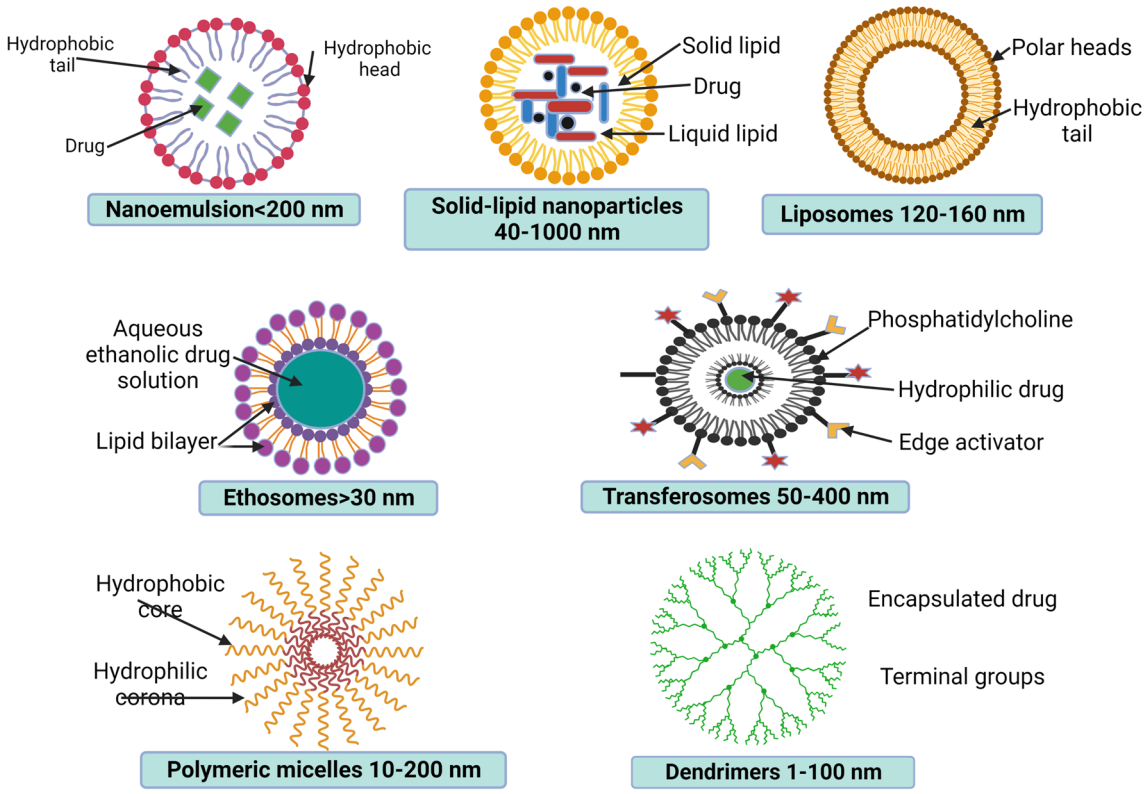

Fig. 3 Various nanocarriers used for delivery of therapeutic agents in the treatment of rheumatoid arthritis

Surfactants, co-surfactants, preservatives, cryoprotectants, and charge modifiers are among the other chemicals utilized to make the SLNs. SLNs have a number of benefits, including excellent physical stability, little skin irritation, regulated drug release, protection against degradation of integrated labile pharmaceuticals, and excellent in vivo tolerability. The therapeutic efficacy of medicines having poor solubility in water can boost by attaching a ligand that targets the specific sites for targeted treatment (Maestrelli et al. 2016). Different types of lipids nanocarriers loaded with naringenin and composed of lecithin chitosan, stearic acid, and stearic-lauric individually were prepared by coprecipitation and hot melt encapsulation process, respectively to improve the in vivo potential of encapsulated poorly soluble flavonoid. The nanocarriers were characterized in vitro for shape, encapsulation efficiency, size, drug release behavior, and in vivo in CFA induced arthritis rat model. All three nanoemulsion formulations exhibited sustained delivery of naringenin, capable of preventing joint deterioration by lowering the Rheumatoid factor and level of major inflammatory cytokines. However, the solid-lipid nanocarriers consisted stearic-lauric were more efficient than the other two formulations due to the synergistic action of lauric acid and stearic acid against inflammation in RA. Conclusively, all prepared formulations were considered effective and non-toxic with enhanced bio-efficacy of naringenin in RA therapy upon oral administration, but nanocarriers prepared from stearic-lauric acid were superior in efficiency for diminishing inflammation; subsequently, lecithin-chitosan and stearic acid nanocarriers (Munir et al. 2021). Leflunomide-encapsulated SLNs coated with chitosan and folic acid subsequently (FA-CS-SLNs) lower the undesired action of leflunomide without negatively affecting its therapeutic potential against RA. The prepared formulation provided a prolonged in vitro drug released profile up to 168 h and enhanced action of joint healing with diminished liver toxicity than conventional leflunomide suspension. The findings accredited the potential of FA-CS-SLNs for active targeting of overexpressed FA receptors in inflamed synovial joints with an intrinsic property of chitosan against RA (Zewail 2021). This work explored the anti-arthritic efficacy of SLN loaded with sitosterol administered in a CFA-induced model of arthritis. The synthesis of sitosterol SLNs was done using a double emulsion solvent displacement process. β-sitosterol-SLN appreciably reduced arthritic index along with paw oedema and it also augmented levels of catalase, superoxide dismutase, and GSH. From the findings of this study, it could be inferred that this formulation exhibited activity against RA thru HO-1/Nrf-2 pathway activation and NF-kB suppression (Zhang et al. 2020). The current study was carried out to design and develop SLNs prepared from conjugation with chondroitin sulfate to co-encapsulate

aceclofenac and methotrexate to manage RA effectively. The resulting SLNs were effective against extremely expressed chondroitin sulfate-linked receptors due to amplified entry of nanoparticles in synovial joints diffused drugs in a sustained fashion. These SLNs also possess the potential for employment in targeted drug delivery for the management of RA effectively (Shilpi et al. 2019). Hyaluronic acid (HA)–coated SLNs incorporated with glucocorticoid prednisolone (PD) were synthesized and named as HA-SLNs/PD for targeted drug therapy in RA therapy. HA-SLNs/PD formulation on intravenous administration in collagen-induced arthritic mice got deposited and possessed a longer circulation period in inflamed synovial joints due to binding of HA to overexpressed hyaluronic receptor CD44 on synovial lymphocytes surface. HA-SLNs/PD considerably prevented cartilage and bone deterioration as compared to drug -loaded SLNs without HA coating and free drug. These HA-SLNs/PD also showed decreased inflammatory cytokines serum concentration, joint swelling, and bone erosion. On the basis of results, these HA-SLNs/PD were suggested as effective and non-toxic for the treatment of inflammation (Zhou et al. 2018).

Liposomes

Liposomes consist of aqueous-cored bilayer vesicles made from a phospholipid. These phospholipids are often employed as pharmaceutical formulations excipients since they are non-toxic and biodegradable (Bulbake et al. 2017; Mohanty et al. 2019). Triptolide-incorporated folate-modified liposomes (FA-TP-Lips) were developed by targeting macrophages for effective and safe Ra therapy. The developed FA-TP-Liposomes were able to encapsulate a larger quantity of drugs with a longer circulation period and also exhibited cellular toxicity, enhanced uptake in cells, considerable activity against inflammation, and osteoclast genesis inhibition during in vivo evaluation. Hence, from the results of this study, it was established that these FA-TP-Lips possessed the ability to longer circulation period of triptolide resulting in significant anti-inflammatory and cartilage protection activity with decreased toxicity in comparison to free triptolide which is a considerable advantage of this system as an effective RA treatment approach (Guo et al. 2022). ROS-responsive liposome (Dex@FA-ROS-Lips) encapsulated dexamethasone was prepared by using synthetic dimeric thioether lipids (di-S-PC) and followed by folic acid surface functionalization. Triggered release of encapsulated Dex due to FA segment and thioesters lipids incorporation minimized cellular toxicity and improved pharmacokinetic profile of loaded agent. In vivo evaluation of these liposomes in an AIA mice model resulted in the deposition of Dex into the inflamed synovial area provided diminished destruction of cartilage, suppression of TNF-α, BAFF, and iRhom2 thereby reduced swelling of joints also exhibited compatibility to systemic fluid as compared to free Dex already available in the market. Thus, RA microenvironment integrated nanomedicine like multifunctional Dex@FA-ROS-Lips could be significantly employed as the newest module for RA management for future clinical purposes (Song et al. 2021). Methotrexate-encapsulated thermal-sensitive flexible liposome (MTFL), which was further immersed in a gel of carbomer (MTFL/Gel), was prepared formulation administered by transdermal route employed for RA therapy. Liposome- loaded agents easily permeated across dermal layers than unloaded form. From the findings, it was established that these liposomes possessed the ability to raise dermal permeation, temperature-sensitive drug release profile, and excellent activity against RA contributing factors when administered along with microwave hyperthermia. These improved properties of MTFL/Gel proposed this as a promising carrier system with enhanced activity for RA therapy (Shen et al. 2021). X et al. prepared triple drug-loaded folate grafted liposomes (FA-lip(DEX + GNRs/ODNs): NF -B decoy oligodeoxynucleotides (ODNs), gold nanorods (GNRs), and dexamethasone (DEX) for RA treatment. The FA-lip(DEX + GNRs/ODNs) was easily absorbed by activated macrophages. FA-lip(DEX + GNRs/ODNs) significantly decreased the release of oxidative factors and pro-inflammatory proteins when combined with laser irradiation during *ex-vivo* studies. FA-lip(DEX + GNRs/ODNs) produced sustained and improved deposition at the inflamed synovium of paws in AIA mice. Level of blood cytokines and Clinical arthritis scores were lowered with cartilage protection from degradation after FA-lip(DEX + GNRs/ODNs) + laser therapy. In conclusion, the triple treatment showed improved efficacy against inflammatory cytokines at synovial joints and was a potential technique for treating RA through several anti-inflammatory pathways (Xue et al. 2020). A pH gradient approach was used to create a new temperature-sensitive liposome formulation loaded with drug sinomenine hydrochloride (SIN-TSL). This formulation exhibited a good drug loading capacity and released drug sensitivity to a faster temperature at 43 °C in comparison to that at 37 °C. These liposomes do not show any cytotoxicity when taken by lipopolysaccharide-activated HUVECs, even efficiently. Furthermore, the investigations in in vivo and in vitro conditions revealed that prepared liposomes showed excellent effectiveness against RA in combination with microwave hyperthermia. Overall, the findings evoked that this combined approach (SIN-TSL with microwave hyperthermia) might be a viable alternative for treating RA symptoms (Shen et al. 2020).

Ethosomes

Ethosomes are lipidic vesicles that are identical to liposomes but have a greater ethanol concentration (10–50%), thus the name "etho-somes" (Parashar et al. 2013). The increase in ethanol content gives these vesicles flexibility, which helps ethosomes penetrate more efficiently through the skin's small channels and increases the mobility of skin lipids (Abdulbaqi et al. 2016; Madhavi et al. 2016). As a result, these "soft vesicles" serve as new drug carriers of vesicular structure for improved distribution to/through the cutaneous pathway. Furthermore, the vesicular lipid system and alcohol blend enhance drug entrapment (Touitou et al. 2000). Ethosome-based gel loaded with naproxen sodium was designed to deliver the loaded agent to the deep skin area for RA treatment. In vivo assessment was employed in a carrageenan-induced paw edema rat model, and results were found as this gel possessed higher efficiency in inhibiting inflammation in paw edema as compared to commercial gel that contained diclofenac sodium. So, the designed formulation could be employed as a choice in place of previous and commercially used therapies for RA (Anjum et al. 2020). Transethosome nanovesicles (TENVs) loaded with dapoxetine hydrochloride (DH) were formulated and administered via transdermal route to retard the adverse effects of DH on oral administration and provide patient compliance. The finding concluded that the prepared TENVs-DH possessed the ability of dermal permeation, desired encapsulation efficiency, better tolerance, and enhanced therapeutic availability of DH also exhibited considerable lowered RANKL level and reduced serum concentration of COMP, IL-6, and anti-CCP. Additionally, normalized synovial fluid and the articular surface were achieved due to the prevention of attenuated alterations in histopathology. Thus, the transdermal TENVs- DH formulation could be successfully used to improve the therapeutic efficacy of DH to cure RA (Salem et al. 2020). Ascorbic acid conjugated transethosomes loaded with sinomenine hydrochloride (AS-TE) were designed to incorporate surface activity against oxidation. The results of this study found that AS-TE comprised efficient potential for encapsulation and permeation of poorly soluble drugs providing increased concentration in synovial fluid. The sedimentation rate of erythrocytes and inflammatory cytokines concentration was diminished significantly, also exhibited requisite antioxidant activity due to enhanced transdermal absorption and accumulation of the drug in the synovial cavity. Therefore, these transethosomes could be applied in the future as a capable TDDS for the management of RA (Song et al. 2019).

Transferosomes

Transferosomes are a new type of vesicular nanoparticle that can transport drugs and through the skin. Transferosomes are often referred to as elastic liposomes, ultra-deformable lipids, or ultra-flexible liposomes because they resemble liposomes. Transferosomes are structurally analogous to liposomes in that they have at lowest one aqueous area covered by a lipid bilayer. Transferosomes, in addition to bilayer lipids, contain edge activators (10–25%), also known as specific surfactants, which contribute to their elasticity. Surfactants such as span 80, tween 80, sodium deoxycholate, and sodium cholate are the most commonly utilized edge activators (Solanki et al. 2016). Edge enhancers are mainly non-ionic or single-chained surfactants that can destabilize the lipidic bilayer and lower surface tension, allowing deformation of vesicles with minimal energy in response to environmental, mechanical force. Edge activator concentrations control vesicle flexibility to improve dermal permeability, permitting these particles to decrease through the dermal membrane beside the transcutaneous gradient before regaining their former diameter (Jain et al. 2017a, b; Srivastava et al. 2017). This process permits transferosomes to pass across the cutaneous tissues via intracellular lipids or transcellular pathways. Transferosomes, like regular liposomes, can contain tiny, mild, and highly hydrophobic and hydrophilic molecules. Transferosomes have been utilized to produce a variety of medicinal compounds, including anti-cancer medicines, NSAIDs, and corticosteroids used to treat RA. Transferosome-based gel entrapped with imatinib (imatinib-TFS-Gel) was synthesized and administered trans-dermally to reduce the frequency of dose administration and undesired effects of conventional imatinib upon oral administration in RA treatment. Drug penetration efficiency of imatinib-TFS-Gel was found to be more during ex vivo studies of skin permeation than simple imatinib-gel. In the rat RA model, the imatinib-TFS-Gel also exhibited more efficiently reduced paw edema than imatinib-gel during in vivo studies. Based on these results, it was suggested that the developed imatinib-TFS-Gel might be employed as a potential system for transdermal delivery of therapeutic agents for RA cure (Taymouri et al. 2021). The therapeutic potential of curcumin by targeted delivery for RA relief was aimed at loading curcumin in transferosomes (Cue-TF). The formulated Cue-TF showed drug delivery in a sustained manner, higher efficiency to encapsulate drug molecules, and improved dermal penetration than the non-transfer of some gel of curcumin during *in-vitro* evaluation. The in vivo evaluation reduced pro-inflammatory cytokines exerting inhibitory NF-κβ mechanisms (Sana et al. 2021). Mixed monoterpenes edge-activated PEGylated transfersomes (MMPTs), including sinomenine (SIN), were formulated to enhance transcutaneous uptake of SIN. These

transferosomes were evaluated for drug delivery in synovial tissues of joint cavities using traditional liposomes as a reference. After examination, it was suggested that SIN-MMPTs penetrated inner dermal layers resulting in an increased concentration of the drug in synovial joints (Zheng et al. 2020).

Nanoparticles

Nanoparticles are colloidal systems with 1 to 100 nm in diameter in which the therapeutic agent is adsorbed, entrapped, or encapsulated in macromolecular components, and possess distinct physicochemical properties, for instance, ultra-small size, high reactivity, surface charge, and large surface area to mass ratio. These unique properties of nanoparticles permit the modification of the fundamental characteristics of the therapeutic agent, such as half-life, immunogenicity drug release characteristics, toxicity, diffusivity, and solubility (Zhang et al. 2008; Lundin et al. 2009). These carriers are used for targeted drug delivery at specific sites in the body by either passive or active targeting mechanisms (Parveen et al. 2012). Therefore, nanoparticles can be a good choice for targeted and effective delivery of anti-rheumatic drugs (Syed and Devi 2019). Nanoparticles comprised of linear β-(1, 3)-glucans from yeast (BYGs) having macrophages targeting efficiency and good biocompatibility were formulated and encapsulated with methotrexate for anti-rheumatic activity. Methotrexate-loaded BYG-based nanoparticles were further grafted with Methoxy poly (ethylene glycol) (mPEG), and cross-linked copolymer (cBP) was made as the final formulation by chemical cross-linking technique. The methotrexate-loaded cBP nanoparticles (cBPM) considerably targeted macrophages in inflamed synovium and reduced the secretion of pro-inflammatory cytokines. Hence, these methotrexate-loaded cBP nanoparticles (cBPM) could be a potential future candidate for alternative and clinically safe treatment of RA (Chen et al. 2022a). The present study aimed to fabricate a nanoparticulate drug carrier based on modified cyclodextrin for the delivery of dexamethasone sodium phosphate to cure RA. Using a double emulsion solvent evaporation process, hydrophobically modified cyclodextrin-based DSP-loaded nanoparticles (DSP-NPs) were formulated. Nanoparticles were 120 nm in size, with outstanding entrapment efficiency and excellent stability. The pharmacokinetic investigations showed EPR that caused enhanced extravasation of nanoparticles into inflamed synovial joints. Pharmacodynamic tests revealed a substantial decrease in paw thickness, inflammatory cytokine level in the systemic circulation, arthritic score, and no adverse effects. These findings imply that DSP-NPs might be an effective treatment for RA (Jadhav and Vavia 2021). In this study, Core–shell nanocarriers loaded with budesonide and glycyrrhizic acid (GA) for co-delivery to treat RA have been created. Gelatin nanoparticles loaded with GA were further coated with amino cellulose-conjugated polycaprolactone (PCL-AC) incorporated budesonide. Formulated nanoparticles showed activity against erythema, inflamed synovium, suppression in bone erosion, and cartilage destruction in the radiological examination, with a reduction in B lymphocyte infiltration and restoring the synovial tissues. The findings imply that dual NPs have a better therapeutic impact on RA than free medicines, which might be due to the delayed and prolonged drug release and the capacity of NPs to regulate inflammatory mediators (Ansari et al. 2021). Co-assembled L-ascorbyl palmitate (L-AP) and N-(carbonyl methoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE-PEG_{2k}) was used for the formulation of Ac2–26 peptides enclosed PEGylated lipid nanoparticles (LDNPs) for treatment of RA in an arthritic rat model. The in vivo evaluation provided biocompatibility, improved stability, and extended circulation period in rat models. It increased deposition at the inflammatory site of prepared ADNPs resulting in the reduction of synovial inflammation. So that these prepared ADNPs could be used for ADNPs pro-resolving medicinal approach for more efficient RA therapy (Qin et al. 2021). Jabbari et al. designed chitosan nanoparticles encapsulated with eugenol nano-size herbal agent compared to methotrexate in neonatal RA. Three treatments, i.e., sham control, methotrexate therapy, and encapsulated eugenol by chitosan nanoparticles, were given to both genders of newborn RA-induced Wistar rats. Noteworthy is the reduction in the expression of FOXO3 protein and MDA serum level that resulted in the group receiving treatment with nanoparticles of eugenol and methotrexate compared to the control groups. Furthermore, MCP-1 and TGF-β genes were suppressed in the group treated with nano-herbal agent nanoparticles. The CIA rats had severe inflammation, synovial hyperplasia, and pannus development. Findings suggested that methotrexate and nanoparticles of eugenol encapsulated in chitosan have a protective impact against RA, most likely due to their anti-inflammatory, antioxidant, and immunomodulatory activity. Nano Eugenol has the potential to produce excellent outcomes against autoimmune illnesses (Jabbari et al. 2020).

Dendrimers

Dendrimers are tree-like macromolecules that are monodisperse, hyperbranched, and three-dimensional and have host–guest entrapment characteristics (Tomalia et al. 1985). Dendrimers without drug loading of polymers of the PAMAM group have been found to have effectiveness against inflammation by suppressing the production of pro-inflammatory cytokines and play a considerable role in the development of several drugs possessing anti-inflammatory activity. As a result, they're one of the best delivery routes for anti-rheumatic medications as they could boost their

anti-inflammatory therapeutic efficacy (Chauhan et al. 2009; Hayder et al. 2011; Durocher and Girard 2016). Oliveria et al. formed poly(amidoamine) dendrimers of the PAMAM group of polymers possessing anti-inflammatory activity and encapsulating chondroitin sulfate (CS) further coated with anti-TNF α-antibodies (Abs). Anti-TNF Abs-CS/PAMAM dendrimer NPs depicted high hemocompatibility and cytocompatibility. Anti-TNF Abs-CS/PAMAM dendrimer NPs demonstrated TNF capture capability, making them promising candidates for novel RA treatment strategies (Oliveira et al. 2021b). Li et al. explored the co-delivery of anti-TNF- siRNA and alpha-tocopheryl succinate (-TOS) for their activity against oxidation and inflammation loaded in poly(amidoamine) dendrimers of generation 5 (G5) that were functionalized with 1,3-propane sultone and gold NPs were entrapped within (Au DENPs). The resulting formulation possesses antifouling properties, and cytocompatibility and could be utilized for targeted delivery of therapeutics that allows administration of serum-enhanced siRNA to macrophage cells (M1-type). Meanwhile, macrophage cells with the linked -TOS have increased anti-oxidation potential. TOS-modified Au DENPs/TNF- siRNA evaluation exhibits their potential to reduce inflammatory and TNF-cytokines secretion that reverses bone erosion and RA lesion. The developed multifunctional nanoplatforms might be used in RA treatment that is both antioxidative and anti-inflammatory (Li et al. 2020). The present study aimed to formulate nanocomposites consisting of nanoGold (Au) focal points with hydroxy-terminated thiolated-dendrons surface functionalization for Au-thiol linkage that results in multifunctional nanoGold-core dendrimer (Au-DEN). The active ingredient was loaded into the core of the dendrimer by conjugation of methotrexate with hydroxyl groups present at the surface of Au-DEN, which resulted in the formation of Au-DEN-MTX-NPs. Methotrexate was used as a targeting ligand and a DMARD to achieve preferentially localized deposition of Au-DEN-MTX-NPs in inflamed synovial tissue via folate receptors activated on this site. Additional loading of a NIR bioactive compound in Au-DEN-MTX-NPs by irradiation with NIR laser gives the photodermal benefits of the prepared formulation. From the evaluation of Au-DEN-MTX-NPs, it was found that these multifunctional targeted NPs might be employed as possible medicines for RA therapy. The method could also be used in other healthcare therapies aimed at reducing inflammation (Pandey et al. 2019).

Polymeric micelles

The nanocarriers having colloidal particles made from the self-assembly of polymers containing blocks of hydrophilic and hydrophilic nature separated by a core shell are called polymeric micelles (Torchilin 2001). Their outstanding and adjustable features make them ideal for medication administration to inflamed joints (Croy and Kwon 2006; Torchilin 2007). The dialysis process made dextran stearate polymeric micelles loaded with methotrexate. In rats, arthritis was caused by Freund's adjuvant injection. The animals were then divided into three groups: model, indomethacin solution, and polymeric micelles. Measurements of the arthritic index, animal paw edema, and biochemical measures such as myeloperoxidase (MPO) activity, lipid peroxidation (LPO), GSH total antioxidant capacity, etc. were used to assess the effects of the designed formulation. Following the injection of indomethacin-loaded polymeric micelles, paw edema was reduced. According to the results of this study, using indomethacin-loaded polymeric micelles reduced symptoms of inflammation, reduced arthritis index, and reduced paw width in arthritic rats in a significant way. Polymeric micelles containing indomethacin solution appreciably lessened the activity of IL-17, MPO, LPO, and IL-1; increased GSH in addition to TAC content; and improved structural changes in the paw tissue (Abdollahi et al. 2021). He et al.'s dual-stimuli responsive polymeric micelles from polyethylene glycol–phenylboric acid–triglycerol monostearate (PEG–PBA–TGMS, PPT) conjugates deliver dexamethasone (Dex) to arthritic joints. In response to an acidic pH and overexpressed MMPs, the release of Dex from PPT micelles is accelerated. The formulation aggregated in arthritic joints in an AIA animal model and demonstrated remarkable therapeutic activity after being administered intravenously. Hence, acting as a viable therapeutic alternative for the successful treatment of inflammatory disorders (He et al. 2021). An amphiphilic graft copolymer consisting of poly(-amino ester)-graft-poly(ethylene glycol) (PAE-g-PEG) was produced (RA). The dialysis approach was used to load methotrexate physically, a hydrophobic medication used to treat RA, into the hydrophobic core of micelles, resulting in excellent encapsulation efficiency. Under the moderately acidic environment, methotrexate was promptly released from PAE-g-PEG micelles. RAW 264.7 cells were unaffected by the micelles and rapidly absorbed them. The formulation was successfully accrued in swollen joints when systemically supplied to CIA mouse models, demonstrating their great targetability to RA. On the whole, PAE-g-PEG micelles might be effective as a carrier for RA treatment (Moon et al. 2020). The present study was carried out to enhance anti-inflammatory activity and oral absorption of celecoxib (CXB) in λ-carrageenan rat models and cell studies by formulating CXB-loaded polymeric micelles. The prepared formulation was further compared with commercially available for its therapeutic efficacy in CFA-induced RA rat models. The results evaluated that the prepared formulation possessed considerable potential against inflammation due to the reduction of nitric oxide, improved bioavailability, and increased suppression of pro-inflammatory cytokines (IL-1β

and TNF-α) release than Celebrex®. Hence, the CXB polymeric micelles could be employed as an intelligent formulation for the treatment of RA- associated inflammation and could evaluate further for clinical application (Choi et al. 2020). Polymeric micelle is constructed using hyaluronic acid (HA) and loaded with curcumin (Cur) as novel polymer-drug composition action against RA. The prepared formulation exhibited exceptional biocompatibility, promoted chondrocyte proliferation, prevented friction-associated cartilage damage, and reduced the effect of vascular endothelial growth factor and inflammatory cytokines. Therefore, the polymeric micelles were proved as a newer potential approach for clinical application in the management of RA (Fan et al. 2018).

Hydrogel

Hydrogels are three-dimensional (3D) networks of hydrophilic polymers that can absorb large volumes of biofluids or liquid (Caló and Khutoryanskiy 2015; Chai et al. 2017). Physical and chemical bridging create hydrogels. Molecular entanglements, ionic, hydrogen bonding, and hydrophobic forces are all used to make cross-linked hydrogels. Biochemical hydrogels are intrinsically cross-linked by strong and irreparable bonds such as redox processes, polymerization, Michael reactions, enzymatic activities, or disulfide-forming events. Hydrogels are among the most commonly used and acceptable biomaterials because of their unique features, such as high-water content, porosity, and flexibility. Furthermore, hydrogels affect living creatures' metabolic activities, and compounds can travel through them (Oliveira et al. 2021a). Several kinds of research were conducted using hydrogels in the therapy of RA. Methotrexate-loaded thermosensitive hydrogel (MTX-HG) poloxamer and polyelectrolyte complexes (MTX-PEC) using hypromellose phthalate and oligochitosan were developed. Prepared MTX-HG and MTX-PEC were associated with each other to develop a newer drug delivery system (MTX-DDSs) encapsulated with methotrexate to treat RA and administered through an intra-articular route. The formulated MTX-PEC-HG and MTX-HG provided sustained drug delivery for an extended period. MTX-PEC-HG and MTX-HG prevented cartilage deterioration and lowered allodynia equally. It could be suggested that the MTX-PEC-HG possesses efficiency in RA recovery with reduced systemic side effects (Agostini et al. 2021). Tyramine-targeted gellan gum hydrogels (Ty-GG) were constructed using horseradish peroxidase crosslinking (HRP) and further encapsulated with betamethasone for safety and specificity enhancement of betamethasone therapy in RA patients. The Ty-GG hydrogels were free from cytotoxicity and unwanted effects on body metabolism and exhibited controlled release of drug and chondrogenic primary cell proliferation. Hence, Ty-GG hydrogels were more therapeutically effective against RA than plain betamethasone and could be employed as a promising approach and substitute for conventional RA therapy (Oliveira et al. 2021c). Transdermal hydrogel was formulated from ibuprofen-loaded pH-sensitive nanoparticles (NPs) having encapsulated ibuprofen (IB) and evaluated its effectiveness in RA therapy. The prepared hydrogel showed 90% encapsulation capability, provided a pH-dependent release of ibuprofen for a sustained period with high dermal penetration efficiency, and exhibited therapeutic action at the desired site in the RA management also free from skin irritation. From the results, it was suggested that the pH-responsive IB-loaded transdermal hydrogel could be employed for the management of RA effectively (Khan et al. 2021). Non-invasive hydrogel for transdermal administration was synthesized using graphene oxide reduced Pluronic® F68 with triptolide encapsulation for RA therapy. The formulated transdermal hydrogels showed 14 h sustained delivery of triptolide and improved bioavailability. So, these hydrogels could be employed as an alternative for invasive (parenteral) and tablet formulation of triptolide in rheumatoid arthritis knee joints (Guo et al. 2021). Acupoint nanocomposite hydrogel comprising triptolide (TP) loaded human serum album nanoparticles (NPs) and 2-chloro-N (6)-cyclopentyl adenosine (CCPA) was synthesized for the co-delivery approach of targeting inflammation and pain associated with RA. Formulated hydrogel provided increased analgesic action at the acupoint, synergistic anti-inflammatory activity, prevented bone deterioration, lowered toxicity to other organs, and re-established Th17/Treg cells balance. Therefore, the prepared formulation of acupoint hydrogel possessed the potential for application in RA recovery as a potential and novel treatment approach due to low toxicity and improved therapeutic effectiveness (Ren et al. 2021).

Theranostics emerges as a promising therapeutic approach

Conventional radiography, ultrasonography (US), computed tomography (CT), and magnetic resonance (MRI) are all imaging diagnostic procedures for RA (MRI). The maximum number of afflicted joints and the length of synovitis are used as imaging diagnostic criteria for RA (Aletaha et al. 2010). Traditional radiography, such as X-ray, is perhaps the most often utilized imaging method for assessing RA joint structural deterioration among other imaging techniques (McQueen 2013). X-rays are convenient and inexpensive, but they pose radiation risks and have little sensitivity for timely identification. CT is beautiful, but it is also pricey, and it cannot detect current inflammations like synovitis and tenosynovitis. Most verification is the process for diagnosing early RA lesions such as synovitis, joint space constriction,

and bone erosion is magnetic resonance imaging (MRI). Still, it is also the most expensive (Wang et al. 2020).

Prenatal recognition of RA remains difficult, however, due to issues in confirming distinctive symptoms at an initial point. In the last two decades, great progress has been made in realizing the benefits of early diagnosis and treatment of RA. Nanoparticles have evolved as an important method for creating innovative drug carriers for the prediction and management of difficult-to-treat diseases like RA (Pirmardvand Chegini et al. 2018). Theranostics, which fully integrate diagnosis and treatment, have increasingly gained study focus in the last decade. It has clear benefits. Firstly, assessment or therapeutic options in tailored medical treatment, real-time monitoring of the treatment method, and partial correlation assessment. The carriers are the foundation for the combination of diagnostic and therapeutic activities. A reliable transportation layout should make it possible to combine diagnostic and therapy more effectively. Nanomaterials with fine size, shape, and surface composition can be an effective carrier to make combining two or more components simple (Lee et al. 2016). As a result, nanoparticles have emerged as one of the most essential and valuable tools for developing multifunctional theranostic probes with high signal strength, effective targeting, and adjustable metabolism dynamics. Biology has a proclivity toward a more dynamic vision, namely theranostics, to bridge the gap between parallel but independent breakthroughs in detection and therapeutics. Nano-theranostics arose from nanotechnology in the formulation of novel theranostic particles, resulting in advancements in theranostics. Liposomes, gold-based nanoparticles, polymeric nanoparticles, Metal oxides and silica-based nanoparticles, exosomes, and magnetic and polymeric-based nanomaterials have also found their place in theranostic applications. Theranostics agents employed in RA management are listed in Table 3 (Madav et al. 2020).

Active targeting to inflamed joints

Despite the leaky vasculature's passive preferring deposition of nanomedicines in affected joints, a better knowledge of the underlying pathophysiology in RA should result in more discrimination biodistribution in inflamed tissues (Table 4). The influx of different inflammatory cells such as FLS, lymphocytes, macrophages, and VEC (Fig. 4), into the synovial joint region mediates cartilage damage and joint inflammation in RA pathogenesis. These cells were typically identified by the presence of a receptor site, such as binding proteins or chemokines, which could be used for potentially hit by including specific ligands into nanocarriers. Because of the lower deposition in normal tissues, combining passive targeting with active biodistribution under inflammatory

Table 3 Theranostic formulations for the treatment of rheumatoid arthritis

Theranostic formulation	Encapsulating agent	Preparation technique	Therapeutic finding	References
Nanoparticles	Albumin-cerium oxide	Biomineralization process conjugated with indocyanine green dye	Controlled RA inflammation with image-guidance	Kalashnikova et al. (2020)
Microbubble	Lapidated Methotrexate	Targeted by microbubble destruction technique	Considerable enhancement in infection-affected areas of RA joints	Zhao et al. (2021c)
PEGylated liposomal	Methylprednisolone hemisuccinate (NSSL-MPS) nanomedicine radiolabelled with [^{89}Zr]Zr(oxinate)$_4$ (^{89}Zr-oxine)	PEGylation and radio-labeling	Lowered inflammation because of higher uptake in occult and inflamed sites detected by PET imaging in K/BxN serum-transfer arthritis (STA) mouse model of RA	Gawne et al. (2020)
iRGD peptide-functionalized echogenic liposomes (iELPs)	Methotrexate and indocyanine green (ICG)	Thin-film hydration method	Ultrasound-triggered release of Methotrexate proved by near-infrared fluorescence imaging also reduced non-desired effects of methotrexate	Wu et al. (2020)
US-triggered perfluorocarbon (PFC)-based Nanobombs	Dexamethasone (Dex) and a shell of folic acid (FA)-grafted polyethylene glycol (PEG)-functionalized phospholipid (PFP-Dex @NDs-PEG-FA)	Thin-film hydration and sonication method	Outstanding activity against inflammation at targeted synovium and joint destruction in collagen-induced SD rat model	Zhu et al. (2019)

Table 4 Targeted formulation for the management of rheumatoid arthritis

Formulation	Therapeutic agent	Mechanism of action	Silent findings	Reference
Exosome	Bone marrow mesenchymal stem cells	Downregulation of NLRP3 expression in macrophages	Bone marrow mesenchymal stem cells (BMSCs) secreted miR-223 microRNA significantly inhibited release of IL-1β, TNF-α, IL-18 and downregulated NLRP3, providing anti-rheumatic activity	Huang et al. (2022b)
Exosomes	Gingival mesenchymal stem-cells	Inhibition of IL-17RA-Act1-TRAF6-NF-κB signal pathway	Inhibited IL-17A and arthritis-induced bone erosion by inhibition of IL-10 in the CIA model	Tian et al. (2022)
Liposomes	Bovine lactoferrin	Inhibition of mitogen-activated protein kinase pathway and NF-κB and binds to TRAF2-TRADD-RIP	TNF-α production suppression in human synovial fibroblasts hence, prevent pannus formation in RA in the SKG mouse model	Yanagisawa et al. (2022)
Extracellular vesicles	Mesenchymal stem cells	Inhibition of paracrine signaling pathway	Improved T cells regulation and reduction in Th 17 polarisation prevents inflammation at knee-joints in an antigen-induced arthritis model	Kay et al. (2021)
Calcium-phosphate based nanoparticles	HIF-1α siRNA	Downregulation of NF-κB, mitogen-activated protein kinase, and hypoxia-inducible factor-1α	Suppressed inflammation in the CIA model by inhibition of RANKL-induced osteoclast formation also prevents bone erosion and cartilage damage	Liu et al. (2022)
pH-responsive calcium carbonate nanosphere	Cell-penetrating poly(disulfide)s	Inhibited CpG-activated joint swelling by inactivation of endosomal toll-like receptors	Prevented bone erosion and inflammation at synovial joints in a CIA rat model	Geng et al. (2022)
Polymeric micelle conjugate	p65 siRNA	NF-κB pathway	Potent activity against macrophage-based cytokines in RA mouse model	Chen et al. (2022b)
Polyethylene glycol-mesoporous silica nanocomposite	Luteolin	RA-FLS cytotoxicity	Prevented cartilage damage and swelling of joints in Freund's adjuvant arthritis model	Pang et al. (2021)

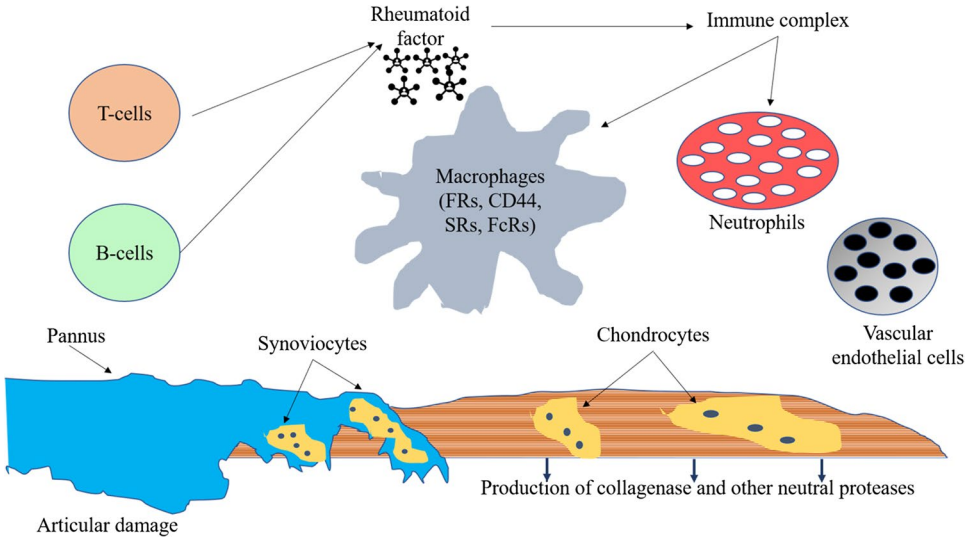

Fig. 4 Active target therapy for rheumatoid arthritis

circumstances would likely result in further dose and frequency reductions (Wang and Sun 2017).

Macrophages

Surface components in the form of molecules on macrophages include mannose receptors, folic acid receptors (FRs), CD44 molecules, Fc-receptors, scavenger receptors (SR), and others. FRs, SRs, and CD44 were amongst the receptors, indicating macrophages that are up-raising on the membrane of active macrophages during the RA. There are at least four isoforms of FRs (α, β, γ, and δ), each with its tissue distribution. FR is normally associated with cancer-targeting, but in the case of RA, it is present on active synovial macrophages (Yang et al. 2016; Varghese et al. 2016; Pei and Yeo 2016). Folate-modified nanocarriers were found to aid macrophage internalization in a receptor-specific way. The ligands of serum albumin, polyanionic macromolecules, and oxidized low-density lipoprotein would be recognized by SR, a glycoprotein present on the surface of macrophages (LDL). The presence of SRs will be increased in an inflammatory milieu, which could ideally promote non-opsonic nanoparticle binding to the macrophage membrane [9]. CD44 is an adhesion molecule found on epithelial cells, activated lymphocytes, macrophages, and tumor cells, among others. CD44-targeted delivery techniques are commonly used in the treatment of cancer. CD44 plays an essential role in the advancement of RA by encouraging the movement of pro-inflammatory cytokines and the activation of numerous effector cells' signalling pathways (Puré and Cuff 2001).

Fibroblast-like *synoviocytes*

Because of their propensity to penetrate and degrade cartilage and synovium, fibroblast-like synoviocytes (FLS) are one of the most important effector cells in the pathophysiology of RA. FLS may also have a role in developing and activating osteoclasts, which leads to bone degradation. Scientists used the phage express technique to identify a synovial fibroblast-homing peptide, HAP-1, that might assist specific internalization into human and rabbit synovial fibroblasts in developing a method for the selective delivery of medicines to synovium. FLS also has a cell surface adhesion molecule called CD44, which can be activated with appropriately aimed ligands like HA (Mi et al. 2003).

Vascular endothelial cells

Angiogenesis, or the production of red blood cells, and vessels in articular tissue, is a process that can contribute to persistent cartilage loss during RA. This neo-vasculature contains many intercellular cell adhesion molecule-1 (ICAM-1), E-selectin, and integrins like v3; thus, it can be used for selective distribution (Koch 2003).

T cells

Aside from the inflammation-related cells discussed above, autoreactive T-cells play a significant role in the process of inflammation. These activated T cells would stimulate monocytes, macrophages, and synovial fibrosis (Boot et al. 2005).

Animal models for rheumatoid arthritis

Up to this point, animal models for arthritis were actively utilized to evaluate and discover pharmacological possibilities for RA and prospective treatments. Issues related to poor clinical research accuracies for experimental medicines (Hay

et al. 2014) and increasing acceptance of an ethical concern underlying the use of experimental animals have prompted many others to doubt the relevance. Thus, it is relevant to evaluate the most widely utilized models based on their pathological significance to real RA and their responsiveness to potential treatment (McNamee et al. 2015).

Collagen-induced arthritis

Insensitive strains of mice and rats, it is caused by vaccination of type II collagen in IFA or CFA, respectively (Trentham 1982; Holmdahl et al. 1989). In collagen-induced arthritis (CIA), both (Th17) and (Th)1 reaction is activated, although the Th17 cell seems to act as a primary pathogenic role (Murphy et al. 2003). In aspects of infiltrating cells within synovial tissue and loss of cartilage and bone, the histopathology of CIA is similar to that of RA. In mice, the susceptibility of CIA is associated with the I-A region of the H-2r and H-2q haplotypes. The I-A chain of genes from susceptible and resistant strains (B10.Q) was analyzed, and it has been discovered that susceptibility was linked to a four-amino-acid pattern within the I-Aβ chain (Nabozny et al. 1994). This type of sequence is found inside an area associated with an antigenic binding peptide, similar to a genetic vulnerability to RA seen in people given by the DRβ chain. The production of arthritis in mice of a C57BL/6(H-2b) origin (Campbell et al. 2000; Inglis et al. 2007) has enabled the use of gene knockout mice, as well as the latest advancement in this will be the establishment of a congenicC57Bl/6N. Q strain, which exhibits arthritis-sensitive qhaplo kind of an MHC class II domain (Bäcklund et al. 2013). The second most used paradigm is rat collagen arthritis, predicated upon the rat counterpart to murine class 1a, specifically MHC class II RT1 complex, with susceptibility as prevalent.

Adjuvant-induced arthritis

This model developed before discovering that some strains of rats acquire arthritis after receiving CFA (PEARSON 1956). Earlier, this was assumed certain mycobacteria constituents cross-linked to joint-specific self-antigens like heat shock proteins (van Eden et al. 1988). Non-antigenic adjuvants, like muramyl dipeptide, IFA, and CP20961, too can cause arthritis, and it's been proposed that such adjuvants might increase responsiveness to self-antigens within the joint (Kohashi et al. 1982). The underlying mechanisms of adjuvant-induced arthritis (AIA) initiation are still not entirely known; however, the reality is that susceptibility is related to particular MHC class genes (Vingsbo et al. 1995; Lorentzen and Klareskog 1996) and also that antibodies to MHC class II and CD4 substances could inhibit ailment underlines the significance of CD4 T cells (Larsson et al. 1985; Holmdahl et al. 1992). Mineral oil and CFA arthritides have distinct processes, with sensitivity to mycobacterial antigen playing a significant role in the former. The distinction between adjuvant and collagen arthritis resistance is more prevalent in adjuvant illness, with MHC having a less but still substantial role. Non-MHC phenotypes, like the Aia1, Aia 2, and Aia 3 areas, play an important role (Joe et al. 2002). The distinction between RA and AIA is that AIA has relatively quick remission, whereas human RA is a chronic illness. In comparison, arthritis caused by lipid pristane (2,6,10,14-tetramethylpentadecane) takes a much more chronic recurrent pattern (Bedwell et al. 1987).

Antigen-induced arthritis

Arthritis caused by antigens is shown in rats, mice, and rabbits after intra-articular infusion of protein antigens (e.g., methylated bovine serum albumin) into knee joints of species that have already been vaccinated with the same antigen (Dumonde and Glynn 1962; Brackertz et al. 1977). The cellular foundation is quite identical to CIA with much more definite sensitization and challenging phases that may be used. This is reliant on CD4 T-cells. Arthritis caused by antigens has histological features comparable to RA, such as synovial lining layer hyperplasia, perivascular infiltration with lymphocytes and plasma cells, lymphoid follicles, pannus, and cartilage erosions. Moreover, repetitive antigen infusions may produce ELS that resembles that found in RA patient subgroups. The erosiveness is linked to an antigen's capacity to attach cartilage. Arthritis caused by antigen on either hand is a monoarticular illness affecting just the treated joint, unlike RA. The paradigm is suitable for investigations using transgenic and gene knockout mice because susceptibility to antigen-induced arthritis is also not MHC class II limited [155].

Bacterial cell wall–induced arthritis

Introducing bacterial cell membrane components into susceptible breeds of rats can cause arthritis that is clinically comparable to human RA. A single intraperitoneal injection of cell membranes can initiate a loop of arthritis aggravation and recovery. The buildup of bacterial cell membrane components within joints is considered to cause arthritis. When the illness has begun, a relapse could be caused by super microbial antigens, which stimulate T lymphocytes with a particular V gene in an antigen-independent way (Schwab et al. 1993).

Spontaneous models

Arthritis develops gradually within mice harboring an altered transgenic-producing human TNF that was dysregulated by replacing the 30 AU area with 30 untranslated regions of

human β-globin gene (Keffer et al. 1991). A synovial cell inside the joint region is also the primary source of transgenic TNFα activation. Transgenic production of a TCR appropriate for a peptide in bovine pancreatic ribonuclease resulted in the K/BxN model. Whenever these mice were mated to NOD base, they acquired arthritis on their own (Kouskoff et al. 1996). Additional research indicated that the emergence of arthritis in K/BxN mice relies on I-Ag7 MHC class II molecules and can be prevented by using non-depleting anti-CD4mAb as a therapy (Korganow et al. 1999; Mangialaio et al. 1999). However, this strongly suggests that illness is caused by CD4β T cells; it was discovered that the existence of B lymphocytes has been necessary for the growth of arthritis (Solomon et al. 2002; Corr and Crain 2002).

Moreover, transitory arthritis may be transmitted in a complement-dependent and FcγR-dependent mode by infusing naive mice with serum IgG in arthritic animals, demonstrating the pathogenic function of autoantibodies under this paradigm (Matsumoto et al. 1999; Solomon et al. 2002; Corr and Crain 2002). The auto antibody' molecular substrate was discovered as glucose-6-phosphate isomerase, a ubiquitous cytoplasmic enzyme in the presence of I-Ag7 MHC class-II components, establishing a natural arthritis paradigm in mice with a single gene mutation producing ZAP-70, a crucial signal transduction protein in T cells. It must have been suggested that disrupted T-cell receptor signaling caused by abnormal ZAP-70 led to thymic excision failures and the development of autoimmune T cells (Matsumoto et al. 1999; Sakaguchi et al. 2003).

Patents and clinical trials

Patent data helps detect technological trends and huge prospects for technology or a specific industry (Raina et al. 2021). As previously indicated, the invention of new medicines and chemicals has resulted in a wide variety of medical conditions and a growth in patentability. Patents on RA were mostly obtained from the Google Patents database by searching for terms like RA, topical therapy, nano-formulation, and so on. Patent observations allow research and development of novel products, medicinal therapies, product licensing, etc. (Table 5) [3]. Technological forecast of novel trends in any industry is done by patent analysis. New anti-rheumatic medications are being created and are conducting clinical studies at different sites to examine their effectiveness for the care and diagnosis of RA symptoms and potential negative effects (Raina et al. 2020). There are a variety of drug compounds, biologics, and combination therapies that have shown promise in clinical studies undertaken by various organizations across the world. Clinical trials are carried out following each country's established medical research regulations. These recommendations primarily cover dose choice, efficacy evaluation, and drug and drug product safety. Clinical trial data is a vital tool for evaluating the potential of medicinal products in humans (Table 6) [3].

Table 5 Patents of rheumatoid arthritis

Patent no	Title	Publication date	Assignee
EP3878441A1	Aloe emodin and ester derivatives thereof for treating sstr2 and/or sstr5 over expressing diseases such as Crohn's disease, rheumatoid arthritis or certain cancers	2021–09-15	Teresa PecerePALU' GiorgioCARLI Modesto
US 20,210,333,276 A1	Compositions and methods for characterizing arthritic conditions	2021–10-28	Augurex life sciences corp
US 20,210,338,614 A1	Use of short chain fatty acids for the treatment and prevention of diseases and disorders	2021–11-04	Temple University of Commonwealth System of Higher Education
US 20,210,338,636 A1	Methods of treating conditions related to the s1p1 receptor	2021–11-04	Arena Pharmaceuticals Inc
US 20,210,338,669 A1	Oral compositions of mk2 pathway inhibitor for treatment of immune conditions	2021–11-04	Aclaris Therapeutics Inc
US 20,210,340,143 A1	Small Molecule Inhibitors of the JAK Family of Kinases	2021–11-04	Janssen Pharmaceutica NV
US 20,210,340,245 A1	Materials and Methods for Treating Juvenile Idiopathic rthritis	2021–11-04	Janssen Biotech Inc
US 20,210,341,491 A1	Rheumatoid arthritis auto-antibody-bound peptide and application thereof	2021–11-04	China Medical University
WO2021195562A1	Oral compositions of mk2 pathway inhibitor for treatment of immune conditions	2021–09-30	Aclaris Therapeutics, Inc
WO2021207508A1	Methods of predicting disease progression in rheumatoid arthritis	2021–10-14	Myriad Genetics, Inc., Crescendo Bioscience, Inc

Table 6 Clinical trials for rheumatoid arthritis

Title	Status	Trial no	Sponsor
INCMNSZ—Rheumatoid Arthritis Cohort	Recruiting	NCT03389711	National Institute of Medical Sciences and Nutrition, Salvador Zubiran
Examination of Efficacy and Safety of Baricitinib in RA Patients	Recruiting	NCT03755466	Shinshu University
Study to Assess the Safety and Efficacy of Enbrel Administered by Sofusa DoseConnect for Rheumatoid Arthritis	Recruiting	NCT04559412	Sorrento Therapeutics, Inc
Development of a Normative Database for Rheumatoid Arthritis (RA) Imaging with Tc99m Tilmanocept	Recruiting	NCT04947137	Navidea Biopharmaceuticals
Safety and Efficacy Study of Human Umbilical Cord-Derived Mesenchymal Stem Cells (BC-U001) for Rheumatoid Arthritis	Recruiting	NCT04971980	Beijing Baylx Biotech Co., Ltd
Early Phase Study to Assess Efficacy and Safety of AZD9567 Versus Prednisolone in Patients with Rheumatoid Arthritis	Completed	NCT03368235	AstraZeneca
A Phase 2 Study of E6011 in Subjects with Rheumatoid Arthritis Inadequately Responding to Biologics	Completed	NCT02960490	Eisai Co., Ltd
A Study Exploring the Safety, Tolerability and Efficacy of a 4 Week Course of INCB018424 in Subjects with Active Rheumatoid Arthritis	Completed	NCT00550043	Incyte Corporation
Study Evaluating ERB-041 With Methotrexate in Rheumatoid Arthritis	Completed	NCT00141830	Wyeth is now a wholly owned subsidiary of Pfizer
Phase IIb Study of Evobrutinib in Subjects with Rheumatoid Arthritis	Completed	NCT03233230	EMD Serono Research & Development Institute, Inc

Future prospects

Rheumatoid Arthritis is a synovium fluid-specific immunological disorder characterized by inflamed and immobilized joints due to the destruction of bone and cartilage, leading to physical disability. Approaches for the treatment of RA for a safe, satisfactory, and complete cure of the disorder are only possible by advanced and innovative research. Treatment strategies with targeted delivery of therapeutic agents at inflamed synovial joints are the primary tool to resolve the issues associated with traditional treatment choices. This strategy also diminishes the side effects when a drug is circulated systematically in the body. Nanocarriers will be helpful in efficient therapeutic drug delivery in a controlled and targeted manner for the treatment of RA. The findings after validating nanocarriers for their drug delivery efficiency and biological safety have revealed that many challenges remain in these systems that are responsible for not providing the complete recovery of RA. Therapies for the treatment of RA in the present era are not successful in achieving patient response, public awareness, and lots of adverse effects. According to some RA therapists, preventive approaches are the only option for reversing the inflammation progression at synovial joints. Understanding the pre-arthritic process and pathophysiology of RA development will play an excellent role in enhancing the potential of nanotechnology against synovium inflammation progression and the destruction of bone and cartilage; hence complete remission of RA can be achieved. Research and finding in animal models of RA are not capable of exactly mimicking a phenotype of disease in the human biological system because RA is more pathogenetic and complicated in humans than in animal models; moreover, it's not applicable practically sometimes to RA patients. In the case of RA, even after the day-to-day improvement and diversification in constitution and functions, nanocarriers are not reached to market because of poor biocompatibility, complicated synthesis, difficulty in scale-up production, and unpredictable in vivo behaviours. Upcoming research should be focused on the scale-up of innovative formulations from laboratory to clinic.

Abbreviations RA: Rheumatoid arthritis; TNF: Tumor necrosis factor; ILs: Interleukins; MMPs: Matrix metalloproteinases; NF-κB: Nuclear factor-κB; MHC: Major histocompatibility complex; NSAIDs: Non-steroidal anti-inflammatory drugs; GCs: Glucocorticoids; DMARDs: Disease-modifying anti-rheumatic drugs; SLNs: Solid lipid nanoparticles; GSH: Glutathione; PAMAM: Polyamidoamine; CFA: Complete Freund's adjuvant; CIA: Collagen-induced arthritis; IFA: Incomplete Freund's adjuvant; AIA: Adjuvant-induced arthritis; ELS: Ectopic lymphoid structures

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Data availability Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

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