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New and Emerging Therapies Related to Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by inflammation in synovial joints, leading progressively to pain, joint deformities, and diminished mobility. Current pharmacological management of RA includes nonsteroidal anti-inflammatory medications (NSAIDs), glucocorticoids (GCs), conventional disease-modifying anti-rheumatic drugs (DMARDs), and biologic DMARDs (bDMARDs), which primarily alleviate pain and inflammation. However, these agents are often associated with several side effects, such as immunosuppression, neurological complications, risk of developing multiple sclerosis, and lymphoma in certain patients. Recent advances have led to the development of new therapies that may offer greater effectiveness with fewer side effects. In this review, we highlight both recently explored therapies and therapies under investigation. The literature search was conducted using PubMed and Scopus, employing the names of specific therapies as keywords. Information on the ongoing and completed trials was obtained from the National Library of Medicine database. Promising new therapies include biosimilar-based infliximab and etanercept, mesenchymal stem cell therapy, Janus kinase (JAK) inhibitors, and plant-derived compounds such as mangiferin and cinnamic acid. Additional therapies currently under investigation involve ASITI-RA, macrophage repolarization, CAR-T cell therapy, extracellular vesicles, photobiomodulation, and nanomedicine. These emerging therapies are ushering in a more targeted, patient-specific approach, with improved therapeutic responses and fewer side effects, and are deviating from a generalized symptom-management approach.

Keywords: rheumatoid arthritis; biosimilars; mesenchymal stem cells; immunotherapy; macrophage repolarization; nanomedicine.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease with inflammatory symptoms in synovial joints and occurs symmetrically, leading to progressive disability [1]. The prevalence of RA estimated globally in adults is observed between 0.5 to 1%. A study shows that the annual medical expenditure is ₹44,700 for RA in tertiary care private multi-speciality hospitals in Tamil Nadu [2]. RA has a higher prevalence in females than in males and tends to manifest more commonly in younger individuals. The clinical symptoms include damage to cartilage and bone, and dysregulation of joint function [3]. RA involves the pathogenesis of pro-inflammatory and anti-inflammatory mediators secreted by interactions among various immune cells [4]. Some similar disorders, viz. lupus erythematosus, psoriatic arthritis, and

fibromyalgia, are also diagnosed by X-rays and laboratory tests. Since RA is incurable, it burdens individuals and society [5]. RA is a multifactorial disease involving genetic risk, environmental factors, and microbiome interaction, because of which the aetiology of RA remains incompletely understood [6,7]. Among the environmental contributors to RA, tobacco use plays a predominant role, while genetic influences include genetic predisposition, advanced age, female sex, and the HLA genotype [8].

The pathogenesis of RA involves two primary subtypes, distinguished by the presence or absence of anti-citrullinated protein antibodies (ACPAs) (Figure 1). Calcium-dependent enzyme peptidyl-arginine-deiminase (PAD) catalyses the citrullination. It converts the positively charged arginine to a polar form, but after post-translational modification, it converts it to the neutral amino acid citrulline. Around 67% of individuals with RA test positive for ACPAs, which not only aid in diagnosing early, undifferentiated arthritis but also help predict the progression to RA. The positive form of ACPAs of RA has a more aggressive clinical phenotype as compared to the negative form of ACPA of RA because some studies show that the negative form of ACPA of RA is associated with different genetic patterns and differential responses of immune cells to citrullinated antigens from the positive form of ACPA [9]. Human leukocyte antigen-DR4 and -DRB1 present on chromosome 6 are associated with the genetic factor of RA [10]. Other studies, such as genome-wide association, show additional genetic signatures at more than 100 loci, with the STAT4 gene and the CD40 locus involved in RA risk [8,11].

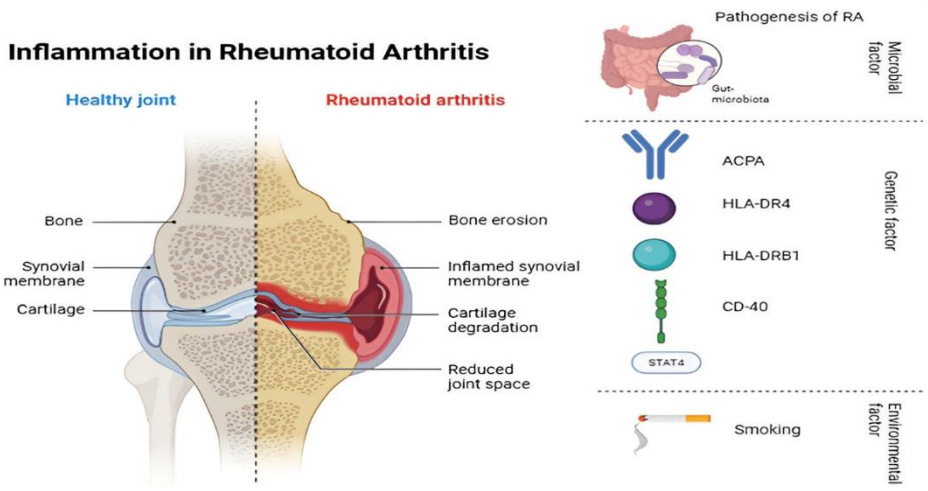


Figure 1. Inflamed joint as observed in RA and its pathogenesis. Original figure created by the authors using BioRender.

One approach to managing RA involves the use of nonsteroidal anti-inflammatory medications (NSAIDs), glucocorticoids (GCs), conventional disease-modifying anti-rheumatic drugs (DMARDs), and biologic DMARDs (bDMARDs) [4]. NSAIDs are used to reduce chronic musculoskeletal pain and acute pain by blocking the production of prostaglandins (PGs), but they differ in their chemical classes. The mechanism of blocking is by inhibiting the activity of the enzyme PGG/H synthase, also called cyclooxygenase (COX). There are two isoforms of COX, i.e., COX-1 and COX-2, which differ in their tissue distribution and regulation. COX-1 is involved in normal physiological conditions and plays a role in the production of PGs involved in homeostatic functions, whereas during inflammation and other pathologic conditions, COX-2 is upregulated [12]. Glucocorticoids play a key role in RA because of their ability to reduce inflammation and suppress the immune response. Some clinical trials and observational studies show that glucocorticoids not only provide short-term

benefits (bridging the time until DMARDs take effect) but also help prevent radiologic progression of disease. At the same time, there are some reported side effects such as osteoporosis and osteoporotic fracture, peptic ulceration, cataract, infections, diabetes, and Cushing's syndrome [13]. DMARDs have two forms called csDMARDs (conventional synthetic disease-modifying anti-rheumatic drugs) and bDMARDs (biological disease-modifying anti-rheumatic drugs). Methotrexate, hydroxychloroquine, and sulfasalazine are used as csDMARDs. Tumour necrosis factor-alpha (TNF) inhibitors, the CD80/CD86 co-stimulation inhibitor abatacept, the interleukin-6 (IL-6) inhibitors, the CD-20 depleting agent rituximab, and an anti-IL1 antibody are classified as bDMARDs [14].

A significant section of the human population is afflicted with RA. There has been a substantial improvement in the treatment approach over the past two decades. DMARDs have become the standard treatment, with methotrexate considered the cornerstone of therapy. Despite methotrexate being the drug of choice, 30-50% patients do not respond to it and often show side effects like immunosuppression, neurological derangements, and development of multiple sclerosis and lymphoma. [15]. The prospect has been to personalise the treatment approach to RA. Although factors linked to poor outcomes in RA are well recognized, they often fail to predict how a patient will respond to therapy reliably. New studies are focused on identifying additional biological and genetic markers, such as ACPA, C-reactive protein (CRP), and HLA-DRB1, that can be targeted at early stages of the disease [16].

This review aims to provide a comprehensive overview of the evolving therapeutic landscape of rheumatoid arthritis (RA), with a particular focus on novel and emerging treatment strategies that extend beyond conventional pharmacological interventions. The objective is to synthesize current evidence from preclinical and clinical studies, identify therapeutic innovations, and discuss their potential to overcome the limitations of traditional therapies (Figure 2).

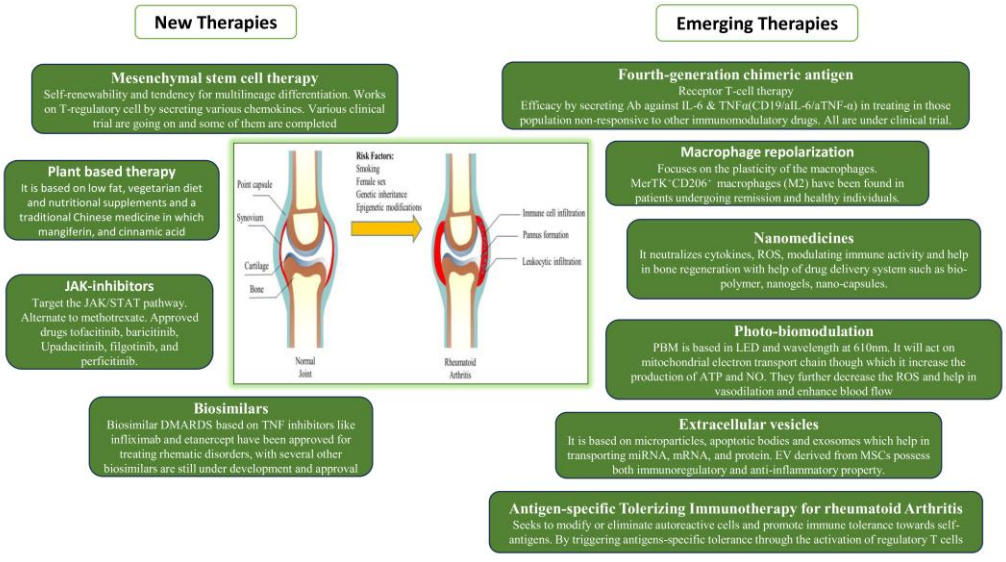


Figure 2. An insight into the new and emerging therapies for RA. Original figure created by the authors using BioRender.

2. Methodology

A comprehensive literature search was conducted using PubMed and Scopus databases to identify recent studies on newer and emerging therapies for RA. Keywords employed for the search were "therapy based on RA", "new therapy for RA", and specific therapy names

such as mesenchymal stem cell therapy for RA, plant-based therapy, CAR-T cell therapy, photobiomodulation, and extravascular therapy in RA. Information on clinical studies, completed and ongoing trials, was obtained from the National Library of Medicine (NIH) database. This review included original research articles, clinical trials, and peer-reviewed papers related to novel and emerging therapies for RA. Both preclinical and clinical studies evaluating therapeutic efficacy, safety, and mechanism of action were considered. Only articles published between 2015 and 2025 with full text availability were retrieved and included. Studies focusing solely on conventional treatments, non-peer-reviewed studies, duplicates, and those not available in English were excluded. We ensured that we included only high-quality, relevant, and up-to-date information on newer therapeutic approaches for RA, although available clinical data were limited primarily to MSC, plant-based, and CAR-T cell therapies.

3. New Therapies

3.1. Biosimilars.

Biosimilars are biologic medications that have the same treatment risks and benefits as their original biologics and are safe and effective in the treatment of various diseases, including RA [17]. Biosimilar DMARDs based on TNF inhibitors, such as infliximab and etanercept, have been approved for the treatment of rheumatic disorders, while several other biosimilars are still under development and awaiting approval [18].

CT-P13 was among the earliest infliximab biosimilars to receive approval, supported by findings from two clinical trials: the phase I PLANETAS study involving 250 patients and the phase III PLANETRA study with 606 participants. Both studies compared CT-P13 and reference infliximab administered at different dose levels. The PLANETAS study used 5 mg/kg as the primary endpoint, while the PLANETRA study used 3 mg/kg intravenously in combination with methotrexate [19,20].

BOW015 is another infliximab biosimilar. The clinical trials carried out on BOW015 and reference infliximab, administered at 3 mg/kg intravenously to 189 patients receiving combination therapy with methotrexate, showed promising outcomes. Ranbaxy Laboratories Ltd. has been granted approval to market BOW015 in India under the trade name Infimab [21].

ZRC-3197 is the first approved biosimilar of adalimumab and has been approved for use in the treatment of RA, juvenile inflammatory arthritis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS) [21]. No differences in aggregation or in the profile of low-molecular-weight fragments have been detected between reference adalimumab and ZRC-3197 [22].

HD203, a biosimilar of etanercept, is produced by recombinant DNA technology in Chinese hamster ovary cells. Similar pharmacokinetic profiles of HD203 and reference etanercept have been reported in Phase I studies [23, 24]. SB4, another etanercept biosimilar seeking market authorization, has been developed by a South Korean pharmaceutical company [21].

3.2. Mesenchymal stem cell therapy.

The origin of mesenchymal stem cells (MSCs) was initially identified in the bone marrow of mice by Friedenstein [25]. MSCs have the capacity for self-renewability and the tendency for multilineage differentiation. It is found in many tissues, such as endometrial polyps, bone marrow, menstrual blood, oviducts, adipose tissue, etc. (Figure 3) [26].

The pathogenesis of RA is based on cells of the innate immune system (HLA-DR+ macrophages and dendritic cells), which are detected in the synovial fluid of RA patients as pro-inflammatory markers. These macrophages are responsible for activating T-cells, which then activate B-cells, leading to the inflammatory response [27].

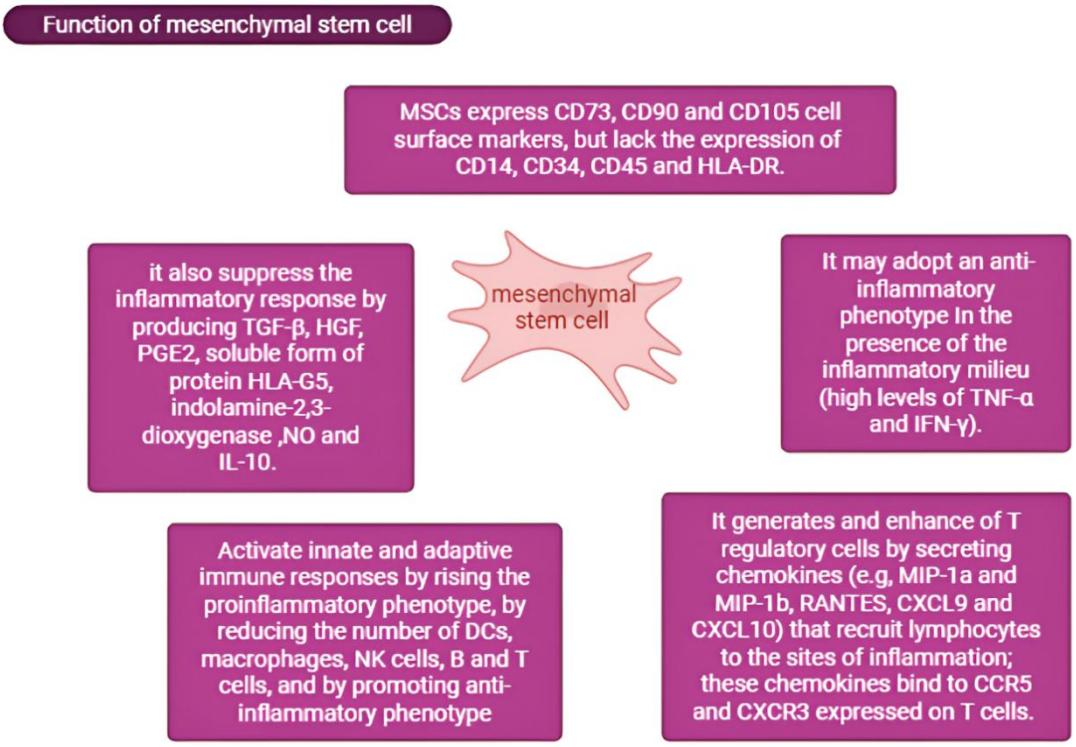


Figure 3. Function of mesenchymal stem cells (MSC).

Based on data obtained from NLM, there are 18 clinical trials, 9 of which are completed and published. The 1st clinical study was started in 2009 and examined the clinical study in 60 patients who had knee osteoarthritis by intra-articular injection of bone marrow mesenchymal stem cells (BM-MSCs). All patients were randomly assigned to cohorts. Control group A received only routine medical therapies and a placebo injected into the knees. Group B received mesenchymal stem cells in addition to routine medical therapy. The examination included WOMAC questionnaires, DAS28 scoring, radiographic assessments, and biochemical analyses (NCT01873625) [28].

Another study was done on refractory RA patients from 2011 to 2013 to identify the safety of I.V. administration of allogeneic adipose-derived mesenchymal cells (eASCs) with the objective to determine the dose-limiting toxicity and side effects on those patients who received at least one DMARD and the clinical and functional effect of eASCs (NCT01663116) [29].

Some other ongoing studies include NCT04170426, NCT06888973, and NCT03828344, based on autologous adipose-derived stem cells (AdMSCs), mesenchymal stem cell infusion in patients with autoimmune diseases, and the safety and tolerability of a single intravenous infusion of BX-U001 in refractory RA, respectively (Table 1).

Many preclinical studies have shown that allogenic transplantation is more effective than autologous transplantation of MSCs. However, some reported studies indicate that both transplantations are safe and effective for refractory RA. The therapeutic effects of MSC treatment have been observed to persist for up to 3 years, indicating its long-term safety and efficacy [27].

Table 1. Clinical trials based on Mesenchymal stem cells (MSC), Plant-based therapy, and CAR-T cell therapy.

NCT ID	Interventions	Primary outcome measures	Phases	Study status	Conclusion
Mesenchymal stem cell therapy (MSC)					
NCT03333681	Biological: Autologous mesenchymal stem cells	Effect of mesenchymal stem cells therapy on the percentage of regulatory T cells, Percentage change in regulatory T cells from baseline, which is analyzed by fluorescence-activated cell sorting (FACS), at 0 and 6 months follow-up	Phase1	Completed (2016-2018)	Autologous bone marrow-derived MSCs ameliorate the severity and activity of refractory RA [30]
NCT05925647	Drug: Messenchymal stem cell secretome|DRUG: Placebo	Rheumatoid Arthritis Disease Activity, Disease Activity Score 28-joint count (DAS28) before and after therapy, and the change of disease activity score in patients at 1 month	Phase1 Phase2	Completed (2022-2023)	Results not yet published
NCT02643823	Biological: hUC-MSC + DMARDs|DRUG: DMARDs	Severity of adverse events, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), 12 months	Phase1	Unknown (2016-2017)	No Results published
NCT01873625	Biological: mesenchymal cell transplantation|BIOLOGICAL: placebo	Rheumatoid Arthritis Disease Activity, Disease Activity Score 28-joint count (DAS28) before and after therapy. The change in the disease activity score of patients at 1 month	Phase2 |Phase3	Completed (2009-2011)	Safe and well tolerated, with a trend towards clinical efficacy with improvements in WOMAC, VAS, gelling time, and pain-free walking distance [28]
NCT01985464	Biological: Umbilical cord mesenchymal stem cells	Number of participants with adverse events, 12 months	Phase1 |Phase2	Unknown (2013-2020)	No results published
NCT01547091	Biological: Umbilical Cord-Derived Mesenchymal Stem Cells (UC-MSCs)| Drug: Rheumatoid Arthritis With Disease-Modifying Drugs (DMARDs)| Biological: UC-MSC+DMARDS	Safety of MSC treatment. Adverse events will be recorded in a patient or clinical investigation subject who administers MSC and will be evaluated for a causal relationship with the treatment, six months after the administration.	Phase1 Phase2	Unknown (2013-2014)	Safe, TNF-α, and IL-6 levels decreased, the proportion of Tregs increased, and a clinical improvement was observed. The therapeutic effect lasted 3-6 months, and repeated infusions increased the efficacy [31]
NCT04170426	Biological: autologous adipose-derived stem cells	Adverse events and severe adverse events. The total number of adverse events and severe adverse events related and non-related to AdMSCs will be recorded to indicate the safety and tolerability, 52 weeks	Phase1 |Phase2	Not yet recruiting (2023-2026)	Study Ongoing
NCT03798028	Biological: UC-MSCs	Improvement of blood hemoglobin (HGB, +10g), forced vital capacity (FVC, +0.5%), and carbon monoxide diffusing capacity (DLCO, +10%) compared to baseline was observed over 24 weeks.	nan	Unknown (2017-2020)	No results published
NCT05003934	Biological: AlloRx	Safety (adverse events), Clinical monitoring of possible adverse events or complications, Four-year follow-up	Phase1	Recruiting (2021-2026)	Study Ongoing
NCT03067870	Biological: Stem Cell Transplantation	Evaluation of Pain Reduction measured by VAS scaling, measured by VAS scaling, 1 month	Phase1	Unknown (2016-2022)	

NCT ID	Interventions	Primary outcome measures	Phases	Study status	Conclusion
NCT04971980	Drug: hUC-MSC infusion (BC-U001)	Adverse events (CTCAE 5.0), vital signs, CBC, biochemistry, coagulation, urine analysis, pregnancy test, cardiac rate (ECG), assessed from day 1 to 28±3 days for patients' convenience.	Phase1 Phase2	Active not recruiting (2021-2025)	Study Ongoing
NCT01663116	Genetic: Stem cells|Genetic: Placebo	The number of adverse events and severe adverse events, total number of adverse Events and severe adverse events, related and non-related to the medication, will be recorded as a measure of tolerability and safety. A 6-month follow-up after the first administration	Phase1 Phase2	Completed (2011-2013)	The intravenous infusion of Cx611 was, in general, well tolerated, without evidence of dose-related toxicity at the dose range and time period studied [32]
NCT06888973	Biological: Mesenchymal Stem Cells|OTHER: Placebo	Safety was assessed by DLT, spirometry, and adverse events using NCI CTCAE criteria across multiple durations: 48 hours to 52 weeks.	Phase1 Phase2	Enrolling by invitation (2025-2026)	Study Ongoing
NCT03828344	Biological: hUC-MSC suspension| Biological: Placebo	Frequency of Adverse Events (AE) and Serious Adverse Events (SAE), Total number and rate of AEs and SAEs, related and non-related to BX-U001 infusion, will be recorded as a measure of tolerability and safety, 12 months after infusion	Phase1	Not yet recruiting (2025-2027)	Not started yet
NCT03691909	Biological: HB-adMSCs	Total Number of Adverse Events and Serious Adverse Events, Total number of Adverse Events and Serious Adverse Events across all subjects over 12 months., 12 months	Phase1 Phase2	Completed (2018-2020)	Single, intravenous administration of autologous adMSCs is safe and efficacious for improvement in joint function in patients with active RA. [33]
NCT00953485	Biological: Allogeneic Mesenchymal Stem Cells (AlloMSC)	Sjögren's syndrome disease activity index, Monthly	Phase1 Phase2	Unknown (2009-2011)	MSC treatment directed T cells toward Treg and Th2, while suppressing Th17 and Tfh responses, and alleviating disease symptoms. [34]
NCT03618784	Biological: FURESTEM-RA Inj|OTHER: sterile saline	Safety of FURESTEM-RA Inj. - number of adverse events, Evaluate the number of adverse events. Safety of FURESTEM-RA Inj., 4 weeks follow-up after treatment	Phase1 |phase2	Completed (2018-2022)	No results published
NCT04615455	Drug: ASCs| Drug: Cryostor CS10	Ocular Surface Disease Index (OSDI), The OSDI is a valid and reliable instrument for measuring dry eye disease severity, 4 months after treatment	Phase2	Completed (2020-2023)	Reduces the risk of injury to the eye and adjacent structures and makes a precise transcutaneous injection possible. [35]
NCT06805448	Drug: MSC| Drug: Saline Water (Control)	Change in unstimulated whole saliva flow rate by sialometry, from baseline to 4 months after treatment	Phase1 |phase2	Recruiting (2025-2025)	Not yet started
NCT01413061	Procedure: Subtalar Arthrodesis	Fusion Rate (%) (as determined by CT assessment), Fusion Rate (%)(as determined by CT assessment), 6 months post-op	nan	Completed (2010-2018)	No results published
NCT02926300	Biological: stem cells	all kinds of adverse events which occur during the clinical study, Safety outcome, 114 weeks	nan	Unknown (2015-2021)	No results published
Plant-Based Therapy					
NCT06305936	Other: Intervention with a 100% plant-based diet	Plant-based diet intervention feasibility/fidelity assessed by objective measures, questionnaires, acceptability, recruitment, retention, and adherence—all outcomes evaluated over 3 months for	nan	Recruiting (2024-2024)	In process

NCT ID	Interventions	Primary outcome measures	Phases	Study status	Conclusion
		protocol and participant engagement.			
NCT03580681	Other: Plant-based diet| Dietary_supplement: Supplement	Pain, disease activity, and mood were evaluated: visual analog scale (0–100%) for pain, joint scores for disease activity (remission <2.6, severe >5.1), BDI-II for mood (0–63), changes assessed from baseline at 4 months.	nan	Completed (2018-2020)	The Disease Activity Score-28 (DAS28) decreased from 4.5 to 2.5 (P < .001) in the Diet phase and from 3.2 to 2.9 (P = .41) in the Supplement phase (between-group P = .01). [36]
NCT03417648	Other: Plant-based diet| Other: Supplement	Pain was assessed by VAS (0–100%), disease activity by joint count (painful/swollen/tender), and mood by BDI-II; changes in pain, disease activity, and mood were measured from baseline at 4 months.	nan	Completed (2018-2018)	The mean number of swollen joints decreased from 7.0 to 3.3 in the Diet phase (P = .03) and increased from 4.7 to 5 in the Supplement phase (P = .63; between-group P = .047) [36]
NCT01700881	Other: Plant-based diet| Other: Supplement	Pain (VAS), disease activity (joint count), mood (BDI-II), and depression (CESD-R) were assessed; changes in pain, disease activity, mood, and depression from baseline were measured at 4 months.	nan	Completed (2012-2020)	The dietary intervention was associated with symptomatic improvements. [36]
NCT03856190	Other: Fasting and plant-based nutrition| Other: Standard Nutrition Counselling	Health Assessement Questionnaire (HAQ), Change from Baseline in the HAQ after 12 weeks, range from 0 to 3, with higher values meaning a higher grade of disability, date of inclusion (baseline), day 7, after 6 and 12 weeks	nan	Terminated (2019-2021)	Both dietary approaches had a positive effect on RA disease activity and cardiovascular risk factors in patients with RA. [37]
NCT05911880	Behavioral: Plant-based diet for 14 days in patients with rheumatoid arthritis.	A plant-based diet reduces DAS28 scores by an average of **1.5 points** at 14 days, signifying improved disease activity in rheumatoid arthritis patients. This change represents a clinically meaningful shift toward lower disease severity.	nan	Recruiting (2021-2024)	Pilot study suggested that a short-term plant-based dietary intervention may modulate circulating miRNAs and improve clinical and biochemical parameters in RA patients.[38]
NCT04262505	Behavioral: Mediterranean Diet Group|BEHAVIORAL: Healthy Eating Group	Quality of life will be measured using the RAQoL (1–30 scale; higher scores = worse QoL) and physical function by HAQ-DI (0–3 scale; 3 = severe disability), assessed at baseline, mid-, and post-intervention over 12 weeks.	nan	Completed (2020-2021)	Adhering to the MedDiet and Irish Healthy Eating Guidelines resulted in improvements in RA patient-reported outcomes. [39]
NCT06842316	Other: 1 blood sample, 40 mL (collection during a blood test, part of the standard of care for this disease)	The primary outcome is to evaluate how blood cells from IMID patients respond to different pCB extracts by measuring changes in inflammatory cytokines and gene expression in specific immune cells, using ELISA and transcriptomic analysis from a single baseline blood sample.	nan	Recruiting (2025-2026)	Ongoing
CAR-T cell therapy					
NCT06503237	Drug: Anti-CD19 CAR T-cells will be given IV at split doses.	Safety outcomes include AE listings, summaries, treatment-emergent lab abnormalities, and the All Treated analysis set data, covering up to two years.	nan	Recruiting (2023-2026)	Ongoing
NCT06503224	Drug: Anti-BCMA and CD19 CAR T-cells will be injected	Adverse events and lab abnormalities were summarized using All Treated analysis data,	nan	Recruiting (2024-2028)	Ongoing

NCT ID	Interventions	Primary outcome measures	Phases	Study status	Conclusion
	intravenously on a one-time basis.	covering treatment-emergent outcomes for up to two years.			
NCT06947460	Drug: CD19-BCMA CAR T-cells infusion	Dose-limiting toxicity (DLT), incidence, and type of dose-limiting toxicity(DLT) within 28 days of CD19-BCMA CAR-T infusion. 28 days, Adverse events (AEs), Total number, incidence, and severity of adverse events (AEs) within 30 days of CD19-BCMA CAR-T infusion, 30 days	Phase1 |phase2	Recruiting (2025-2026)	Ongoing
NCT06201416	Biological: SBT777101	Incidence, nature, and severity of adverse events [Safety and Tolerability], Day of treatment to end of follow-up period (48 weeks)|Incidence and nature of dose-limiting toxicities (DLTs), Death, CRS, ICANS, vital organ toxicity, hematological toxicity, Day of treatment to end of DLT evaluation period (28 days)	Phase1	Recruiting (2024-2026)	Ongoing
NCT06947473	Drug: umbilical cord blood CD19-BCMA CAR T-cells infusion	Dose-limiting toxicity (DLT), incidence and type of dose-limiting toxicity (DLT) within 28 days of umbilical cord blood CD19-BCMA CAR-T infusion, 28 days|Adverse events (AEs）, Total number, incidence, and severity of adverse events (AEs) within 30 days of umbilical cord blood CD19-BCMA CAR-T infusion, 30 days	Phase1 Phase2	Not yet recruiting (2025-2026)	Ongoing
NCT06549296	Drug: RD06-04 CAR T-Cell Injection	The incidence of adverse events (TEAEs), serious adverse events (SAEs), and adverse events of particular concern (AESI) during treatment, 2 years	Early Phase1	Recruiting (2024-2027)	Ongoing
NCT06548607	Drug: RD06-04 or RD06-05 CAR T-Cell Injection	The incidence of adverse events (TEAEs), serious adverse events (SAEs), and adverse events of particular concern (AESI) during treatment, 2 years	Early Phase1	Recruiting (2024-2027)	Ongoing

3.3. JAK-inhibitors.

Janus kinases (JAKs), comprising various isoforms including both homodimers and heterodimers, are a family of intracellular, non-receptor tyrosine kinases lacking a transmembrane domain and are involved in signalling pathways such as the JAK/STAT pathway [40]. JAKs are cytokine receptors associated with ligands like interferons (IFNs), interleukins (ILs), and several other polypeptides [41,42]. The STAT pathway gets activated on phosphorylation of the tyrosine residue. This phosphorylation can be catalysed by ligand-activated receptors with intrinsic tyrosine kinase activity, as well as by receptors lacking intrinsic tyrosine kinase activity, such as epidermal growth factor (EGF) receptors and JAKs [42,43].

JAK inhibitors are a class of oral medications that have recently been approved for use. These medications are an alternative for patients exhibiting a lack of sustained remission in response to methotrexate or experiencing toxicity and adverse effects [44]. The approved JAK inhibitors are tofacitinib, baricitinib, upadacitinib, filgotinib, and peficitinib [45]. Tofacitinib and baricitinib were the first JAK inhibitors to receive approval [46].

Tofacitinib was approved by the Food and Drug Administration (FDA) in 2012 at a recommended dose of 5 mg bd and 5 mg qd for patients with moderate liver impairment or moderate to severe kidney impairment [47]. Tofacitinib works by inhibiting the activation of JAK, preferentially JAK1 and JAK3, and to a certain extent JAK2 by competing with ATP to bind to the active site of the kinase domain [48,49]. Some of the prominent side effects reported include invasive fungal infections (cryptococcosis and pneumocystosis), bacterial (active tuberculosis), viral (herpes zoster), and other infections caused by opportunistic pathogens [50].

Baricitinib was the second JAK inhibitor to receive approval from the EMA in 2017, at a recommended dose of 4 mg and 2 mg qd [46]. Baricitinib selectively inhibits JAK1 and JAK2 and was approved by the FDA in 2018 at a recommended dose of 2 mg qd, but the 4 mg dose was not approved due to concerns about thromboembolism [51, 52]. Other issues reported included upper respiratory tract infections, urinary tract infections, and transient changes in haematological parameters [53].

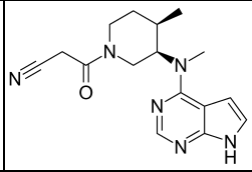
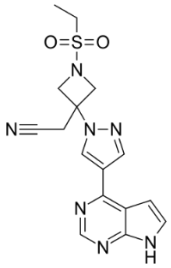
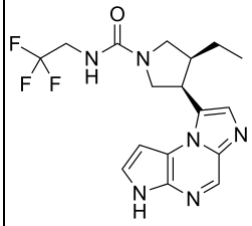
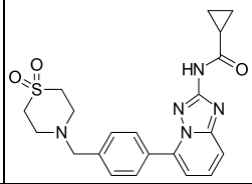
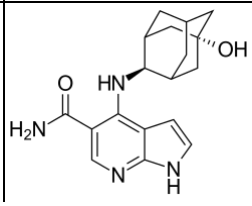
Upadacitinib received FDA approval in August 2019 for the treatment of moderately to severely active RA with the recommended dose of 15 mg qd. It shows greater selectivity for the inhibition of JAK1 cytokine activity than JAK2 [54]. Some adverse effects include upper respiratory tract infections, nasopharyngitis, and urinary tract infections [55].

Filgotinib is the oral JAK inhibitor to have received the most recent approval from the European Union (EU) and Japan in 2020. In the EU, it has been recommended for patients suffering from RA who do not show the anticipated response to one or more DMARDs. In Japan, filgotinib is recommended for the treatment of RA patients who have not responded adequately to conventional therapies. Filgotinib shows selective inhibition of JAK1 activity [56]. The use of filgotinib has also been found to be associated with changes in haematological parameters and a decrease in serum CRP [57]. It has not yet received FDA approval due to testicular toxicity risks observed in animal trials [58].

Peficitinib, a recently developed JAK inhibitor with selectivity for JAK3, has received approval for the treatment of RA in Japan, South Korea, and Taiwan. In the Japanese clinical setting, the recommended daily dose is 150 mg, with the possibility of reducing to 100 mg based on individual patient response and tolerance [45,59].

Although the use of JAK inhibitors has gained significant traction in recent years, concerns regarding the risks of major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) have prompted the FDA to issue black box warnings for tofacitinib, baricitinib, and upadacitinib. While patients with RA are inherently predisposed to a higher risk of cardiovascular disease and thromboembolic events, the association of elevated cardiovascular risk with JAK inhibitors was unexpected, as traditional DMARDs, such as methotrexate and TNF inhibitors, are known to reduce the incidence of MACE significantly. In the FDA-mandated Oral Rheumatoid Arthritis (ORAL) Surveillance trial, an increased risk of pulmonary embolism was observed in patients receiving JAK inhibitors compared to those treated with TNF inhibitors. However, other studies have not consistently replicated these findings. Nevertheless, as a precautionary measure, JAK inhibitor administration is generally avoided in high-risk patient populations, and both healthcare professionals and patients have been provided with specific safety recommendations by the FDA [60].

Table 2. JAK inhibitors are approved in different countries.

JAK inhibitor	Structure	JAK selectivity	Developing company	Brand name	Approved by	References
Tofacitinib		JAK1 & JAK3 (some JAK2)	Pfizer Inc.	Xeljanz	FDA (2012) EMA (2017) Japan (2013)	[46,47,49]
Baricitinib		Primarily JAK1 & JAK2	Eli Lilly	Olumiant	FDA (2018) EMA (2017) Japan (2017)	[46,51,52]
Upadacitinib		JAK1	AbbVie	Rinvoq	FDA (2019) EMA (2019) Japan (2020)	[44,54]
Filgotinib		JAK1	Galapagos NV	Jyseleca	EMA (2020) Japan (2020)	[44,56]
Peficitinib		JAK3	Astellas Pharma	Smyraf	Japan (2019) Taiwan (2020) South Korea (2020)	[44,45,59]

3.4. Plant-based therapy of RA.

Plant-based therapy for RA was primarily started in 2012, which was based on low-fat, vegetarian diets and certain nutritional supplements that can help reduce pain and reduce the need for pain medications for some people (NCT01700881). Plant-based clinical trials for RA are complete, and some are ongoing, as shown in Table 1.

Another study is based on the plant Baihu-Guizhi decoction (BHGZD), which is utilized as a traditional Chinese medicine. Researchers identified bioactive compounds, such as mangiferin (MG) and cinnamic acid (CA), as inhibitors of NF-κB via TLR4/PI3K/AKT signalling, leading to suppression of NLRP3 inflammasome activation and decreased secretion of IL-1β and IL-18. Two cell lines were used, i.e., RAW264.7 and MH7A cells, for the drug treatment; both cell lines were studied in six distinct groups. The 1st group was the normal control group, who had no stimulation or treatment. The 2nd group was used to stimulate the cells by exposing them to different concentrations of LPS and ATP to induce a cellular model. In the 3rd group, after stimulation, 28.53 μg/ml of BHGZD was used for 24 h. At the same time, the 4th group received a combination of both MG+CA bioactive compounds at concentrations of 1.69 ng/ml MG and 0.13 ng/ml CA for 24 hours, which mirrors their levels in a 5 μg/ml BHGZD formula. In the 5th and 6th groups, both bioactive compounds were individually used at the same concentration, which were used in combination for the same duration. Analysis of

the CCK8 assay shows that no toxicity was observed at this level, and flow cytometry analysis shows that MG, CA, and the two-BAC combination treatment prominently reduced the marker for cells that stain necrotic, dead, or membrane-compromised, i.e., PI. Hence, it demonstrates that treatment with BHGZD, MG, CA, and the two-BAC combination effectively counteracted the rise in FLICA-positive RAW264.7 cells and TUNEL-positive MH7A cells triggered by LPS/ATP stimulation [61].

4. Emerging Therapies

4.1. Antigen-specific tolerizing immunotherapy for rheumatoid arthritis (ASITI-RA).

Antigen-specific immunotherapy aims to modify or eliminate autoreactive cells and to promote immune tolerance to self-antigens. By triggering antigen-specific tolerance through the activation of regulatory T (T_{reg}) cells, either by using tolerogenic peptides alone or in combination with cells or nanoparticles, it is possible to reprogram autoreactive immune cells and achieve long-term immune tolerance. In RA, autoantibodies are primarily of two types: rheumatoid factors (RF), which target the Fc portion of immunoglobulins, and ACPAs, which recognize self-proteins that have undergone post-translational modification [62]. Most current RA treatments focus on relieving pain and managing symptoms after the disease has already developed. In contrast, ASITI-RA targets early intervention, aiming to halt disease progression before it advances, as studies have shown that some individuals exhibit distinct serological markers several years before the onset of clinical symptoms [15,63].

A recently concluded randomized phase I trial of antigen specific tolerizing immunotherapy with peptide/calcitriol liposomes in ACPA+ rheumatoid arthritis that evaluated the effects of low, medium, and high doses of DEN-181 (single ascending dose of liposomes encapsulating 40 μg/mL CII + 400 ng/mL calcitriol) on peripheral blood CII(self-peptide collagen $II_{259-273}$)-specific and bystander Cit64vimentin59–71–specific (Cit-Vim–specific) autoreactive T cell responses, cytokine profiles, and ACPA levels in 17 HLA-DRB1*04:01$^+$ or *01:01$^+$ ACPA$^+$ rheumatoid arthritis patients receiving methotrexate therapy reported DEN-181 to be well tolerated and modulated immune responses in rheumatoid arthritis. Treatment reduced Cit-Vim–specific T cells, increased CII-specific PD-1$^+$ (programmed cell death 1$^+$ antigen-specific) T cells, and was associated with improved disease activity, decreased autoantibody and inflammatory cell levels, and enrichment of naïve and CCR7$^+$ (C-C chemokine receptor type 7) T cells, indicating induction of tolerogenic immune pathways [64].

Therapeutic challenges for antigen-specific immunotherapy involve choosing the right antigen to target, minimizing off-target effects, and determining the most suitable stage of the disease for treatment [65]. Moreover, even though some of the most commonly associated self-antigens with RA are known, self-antigens tend to transform through epitope spreading as the disease progresses, because of which the treatment needs to be tailored [66].

4.2. Macrophage repolarization.

Macrophages play a central role in coordinating responses within both the innate and adaptive immune systems. They perform essential functions such as engulfing harmful microbes, presenting antigens to other immune cells, and releasing a range of cytokines. Through these activities, they help defend the host, control inflammation, clear dead cells, and support tissue healing within a balanced immune environment. In RA, monocytes expressing

the chemokine receptors CCR2 and CX3CR1 respond to signals from fibroblast-like synoviocytes (FLS), which produce the ligands CCL2 and CX3CL1. This interaction facilitates the accumulation of macrophages within the synovial tissue and amplifies the release of pro-inflammatory cytokines and chemokines, thereby contributing to the persistence of inflammation in the joint environment [67].

Under the influence of specific stimuli and microenvironments, macrophages can differentiate into classically activated, pro-inflammatory (M1) macrophages or alternatively activated, anti-inflammatory (M2) macrophages. M1 macrophages are responsible for killing pathogens and antigen-presenting and are activated by microbial components or cytokines, while M2 macrophages are responsible for the resolution of inflammation and tissue repair and are induced by IL-4 or IL-6 secreted by other immune cells [68].

An imbalance in the M1/M2 macrophage ratio has been found to be associated with RA. Patients with RA have shown an elevation in the M1/M2 ratio. M1 macrophages induce the production of reactive oxygen species (ROS), which are responsible for the destruction of cartilage and synovial joints [69].

This treatment approach focuses on the plasticity of the macrophages. For instance, $MerTK^{+}CD206^{+}$ macrophages (M2 macrophages) have been identified in patients in remission and in healthy individuals. Cellular metabolic reprogramming, which induces MerTK+ macrophages and reduces M1 numbers, is a promising approach [70]. Currently, none of the approved treatment modalities directly target M1 macrophages; instead, they target cytokines and other inflammatory factors. Drugs targeting M1 macrophages, such as H22 (scFv)-MAP and Mavrilimumab, are in preclinical and phase II clinical trials, respectively [69].

4.3. Fourth-generation chimeric antigen receptor T-cell therapy (CAR-T).

Based on previous studies, the pathogenesis of RA involves the secretion of cytokines such as IL-6 and TNFα [14]. For the inhibition of these chemicals, the fourth-generation CD19-targeted CAR-T cells show efficacy by secreting antibodies against IL-6 and TNFα (CD19/aIL-6/aTNFα) in treating D2T RA. As compared to other biological DMARDs, CAR-T cell therapy has better results in 30% of the population who did not respond to several cycles of immunomodulatory drugs [1].

CAR-T cells contain a patient's T-cell, which is harvested from leukocytes. Its genetic modification involves transduction by a viral vector, which helps in the expression of CAR construction. To increase its therapeutic number, the modified T-cell went for ex vivo expansion. To create a suitable environment before engraftment of CAR-T cells, patients generally undergo lymphodepleting chemotherapy. After that, the CAR-T cells are infused into patients, and they proliferate and become effective upon encountering target antigens [71].

The initial clinical studies were started in 2023 in the Affiliated Hospital of the University of Science and Technology of China with NCT06503237. The intervention was intravenous infusion of anti-CD19 CAR-T cells in split doses in 18 patients with refractory RA. Before IV infusion of anti-CD19 CAR-T cells, they had to receive chemotherapy for lymphodepletion with cyclophosphamide and fludarabine. The estimated date of completion is 03/26. Another recruiting study of NLM based on CAR-T cell is Anti-BCMA and CD19 CAR-T cells, RD06-04, BIOLOGICAL: SBT777101, RD06-04 or RD06-05 CAR T-Cell Injection CAR-T Cell with NCT06503224, NCT06549296, NCT06201416, and NCT06548607, respectively.

4.4. Extracellular vesicles.

Extracellular vesicles (EVs) are membrane-enclosed microparticles (also referred to as microvesicles), apoptotic bodies, and exosomes that have been established to be involved in transporting microRNA (miRNA), mRNA, and protein [72]. Based on biogenesis, EVs can be largely classified into three classes. Microvesicles/microparticles/ectosomes are generated due to outward budding and division of the plasma membrane. Exosomes that originate within the endosomal system are released when multivesicular bodies merge with the plasma membrane. And apoptotic bodies that are expelled as cell blebs during apoptosis. Proteomic profiling (or protein composition) is one of the most accepted methods of distinguishing between the types of EVs, but there is no single specific marker to distinguish between them clearly. Once considered to be specific to exosomes, Tetraspanins CD9, CD63, and CD81 have now also been reported in microvesicles and apoptotic bodies [73].

Cell-secreted EVs, located within the synovial fluid and cartilage extracellular matrix, play key roles in orchestrating joint morphogenesis and sustaining joint homeostasis [74]. Research indicates that diverse types and functions of EVs are associated with various joint disorders, with disease-specific surface marker patterns of EV also being identified [75]. The involvement of extracellular vesicles in RA has been proposed to encompass roles such as antigen presentation and immune complex formation by proteins like vimentin, fibrin, fibronectin present in the membrane, that get citrullinated and lead to inflammation by activating innate and adaptive immune system; destruction of extracellular matrix (ECM) by carrying catabolic proteases like hexosaminidase D, β-glucuronidase which cause the breakdown of ECM leading to cartilage destruction and elevated inflammation; delivery of miRNAs that alter inflammation response; inflammation by stimulating the production of TNF-α, IL-6, IL-8 and mPGES-1 (microsomal prostaglandin E synthase 1). EV-based immune complexes have been found to be associated with elevated inflammation [72,74]. EVs derived from FLS of RA patients contain a membrane-associated form of TNF-α, which activates NF-κB signalling in recipient FLS, thereby enhancing inflammatory responses and contributing to the resistance of synovial T cells to apoptosis [76]. The total plasmatic EV concentration has been found to be increased in RA patients in comparison to healthy controls across multiple studies, while another study conducted on 41 RA patients found no difference in total plasmatic concentration between seronegative and seropositive RA [77,78]. Instead, elevated levels of CRP and ESR were found to be associated with seropositive RA [78].

There are various cellular sources of EVs, varying characteristics, and their prospective therapeutic roles according to their cellular sources. EVs derived from bone marrow MSCs possess both immunoregulatory and anti-inflammatory functions. They suppress the proliferation of T and B lymphocytes while promoting the generation of regulatory T cells and regulatory B cells. EVs originating from adipose-derived MSCs are known to influence cytokine secretion and modulate T cell proliferation. In contrast, EVs from umbilical cord-derived MSCs contribute to immune regulation by directing macrophage polarization toward the anti-inflammatory M2 phenotype and affecting T cell responses.

Regarding tissue repair, adipose-derived MSC-EVs support regeneration of both bone and cartilage, whereas umbilical cord MSC-EVs primarily facilitate cartilage regeneration. EVs released from macrophages influence the balance between M1 and M2 macrophage phenotypes and modulate inflammatory responses. Dendritic cell-derived EVs possess immunosuppressive effects, and granulocyte myeloid-derived suppressor cell-derived EVs

induce regulatory T cell production and suppress proliferation of T helper 1 cells, while neutrophil-derived EVs exhibit macrophage and FLSs modulation and synovial inflammation inhibition [4].

In RA, extracellular vesicles can serve as biomarkers; for instance, the levels of $CD41^+$ EVs were found to be significantly elevated in the synovial fluid of RA patients, while $CD41^+$ EVs remained undetected in 19 of the 20 patients suffering from osteoarthritis [79]. EVs, due to their cellular origin, are well-suited for application as drug delivery systems. Therapeutic agents or biomolecules can be loaded into EVs either during their biogenesis or following their release from donor cells. While EV-based drug delivery has not yet been applied in RA treatment, this strategy has been successfully explored in other disease contexts [80].

4.5. Photobiomodulation (PBM).

PBM includes light-emitting diodes (LEDs), and its wavelength lies in the red and infrared spectral range, especially at the 610 nm wavelength. It induces the acceleration of TNF-α, which leads to the regression of nuclear translocation of NF-κB and NLRP3 inflammasome activation. It decreases the production of autoantibodies and pro-inflammatory cytokines in serum. Suppression of NLRP3 also activates caspase 1, which helps in pyroptosis [81]. The mechanism associated with it is that the photon released by PBM is absorbed by cytochrome c oxidase (CCO). It is located in the inner mitochondrial membrane and is the fourth component of the mitochondrial electron transport chain. Absorption of a photon by CCO causes an electronic transition from a low to a high energy level, which leads to the release of an electron. It will cause photooxidation of CCO and photodissociation of CCO. Photooxidation leads to an increase in electron transport, which increases ATP production. After photodissociation, CCO releases NO, increasing oxygen binding and respiration rates. NO will help in vasodilation and increase the blood flow. PBM also inhibits the production of COX-1 and MMP-13, which are responsible for pain and degradation of extracellular matrix components. There are limited clinical studies on PVM; most of them show effective clinical approaches for RA patients. So that PVM has no agreements on PVM treatment. However, it needs more future clinical trials, which will ensure the effects of different wavelength ranges, dosages, treatment durations, and their safety and efficacy [82]. PBM also acts as an analgesic, which helps in reducing pain and swelling by decreasing ROS [83,84]. The advantage of PBM therapy is that it is non-invasive, painless, inexpensive, and shows no side effects after prolonged use [85].

4.6. Nanomedicines.

Nanomedicine refers to the use of nanotechnology for diagnosing, treating, or preventing diseases. This field encompasses a range of nanoscale therapeutic systems, including drug-encapsulated liposomes, nanoparticles, polymer-based micelles, nanogels, and nanocapsules. Additionally, structures such as polymer-drug and polymer-protein conjugates, as well as antibody-based therapies, are categorized as nanomedicines [86]. Nanomedicine specifically targets clinical applications of nanotechnology with a patient-focused approach. In contrast, nanobiotechnology explores fundamental biological processes such as molecular mechanics and electrochemical signalling, typically using nonhuman models for basic research. The first generation of nanomedicines can be classified into several classes, such as

polymer-drug conjugates, block copolymer micelles, and nanocrystals, each with distinct physicochemical features and spanning different size ranges in the nanoscale [87].

Nano-therapies for RA take advantage of the shared characteristics between inflamed joints and tumour microenvironments to enhance targeted drug delivery. Their clinical effectiveness relies on harnessing the Enhanced Permeability and Retention (EPR) effect to localize treatment at disease sites [88]. Nanoparticle-based therapies for RA aim to reduce inflammation by neutralizing cytokines, inducing apoptosis in inflammatory cells, scavenging reactive oxygen species (ROS), modulating immune activity, and aiding bone regeneration. Delivery strategies often employ biomimetic nanoparticles that mimic natural biological structures, helping them evade immune detection and more precisely accumulate in inflamed tissues [89].

Nanoparticle-based drug delivery systems enhance therapeutic outcomes through both passive and active targeting mechanisms. Passive targeting relies on the abnormal characteristics of inflamed tissues, enabling nanoparticles with high permeability to concentrate at these sites. In contrast, active targeting involves functionalizing nanoparticle surfaces with specific ligands that bind to receptors on inflamed cells, allowing for more accurate and efficient drug delivery [90]. While nanotechnology holds significant potential, its long-term effects on human health remain unclear. Regulatory agencies struggle to develop appropriate safety standards and testing methods for these novel materials, leading to challenges in their clinical approval. Additionally, the potential for nanoparticle accumulation in organs over time raises concerns about chronic toxicity [89].

5. Conclusion

While existing therapies for treating RA have improved the prospects of remission, a major lacuna exists for patients who are either non-responsive or show adverse effects in response to the conventional treatments. The therapeutic landscape of RA is undergoing a paradigm shift, from symptom management to precise, immune-modulatory, and regenerative strategies. These new and emerging therapeutic interventions offer promising alternatives that align with the principles of personalised medicine and address the limitations of traditional treatments. Novel immunological approaches such as ASITI-RA, macrophage repolarization, and CAR-T cell therapy offer personalised strategies, particularly for drug-resistant RA. Non-pharmacological approaches such as photobiomodulation and plant-based diets, along with nanomedicine and extracellular vesicle research, offer additional avenues to improve patient quality of life. Although these treatments offer an optimistic perspective, the progress in targeted therapies has not kept pace with the growing clinical need in RA care. Furthermore, a transition towards personalized medicine may increase treatment costs due to high development and manufacturing costs, thereby compartmentalizing treatment and exacerbating health inequity. A more robust take on the translation of these therapies from laboratory to bedside is required. RA, being an autoimmune disorder, possesses the challenge of sharing similar pathways with other autoimmune disorders, thus further complicating the entire process. Therefore, a concerted effort is needed not only to target therapies but also to ensure equitable access to high-quality, affordable healthcare for all patients.

Author Contributions

Conceptualization, J.K. and R.M.; methodology, J.K. and R.M.; writing—original draft preparation, J.K., R.M. and M.K.; writing—review and editing, M.K.; supervision, M.K.; project administration, M.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ACPAs	Anti-Citrullinated Protein Antibodies
AdMSCs	Autologous Adipose-derived Stem Cells
ASITI-RA	Antigen-Specific Tolerizing Immunotherapy for Rheumatoid Arthritis
ATP	Adenosine Triphosphate
bDMARDs	biological Disease-Modifying Anti-Rheumatic Drugs
BHGZD	Baihu-Guizhi
CA	Cinnamic Acid
CAR T-cell	Chimeric Antigen Receptor T-cell
CCO	Cytochrome C Oxidase
COX	Cyclooxygenase
CRP	C-Reactive Protein
csDMARDs	conventional synthetic Disease-Modifying Anti-Rheumatic Drugs
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
eASCs	Allogeneic Adipose-derived Mesenchymal Cells
ECM	Extracellular Matrix
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
EU	European Union

Abbreviation	Definition
EVs	Extracellular Vesicles
FDA	Federal Drug Administration
FLS	Fibroblast-Like Synoviocytes
HLA	Human Leukocyte Antigen
IL	Interleukin
JAKs	Janus Kinases
MG	Mangiferin
miRNA	microRNA
MSCs	Mesenchymal Stem Cells
NLM	National Library of Medicine
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PBM	Photobiomodulation
PGs	Prostaglandins
RA	Rheumatoid Arthritis
ROS	Reactive Oxygen Species
STAT	Signal Transducer and Activator of Transcription
TNF	Tumor Necrosis Factor
VTE	Venous Thromboembolism

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