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SYSTEMATIC REVIEW

A Systematic Review of the Novel Targeted Immunobiological Medications in Rheumatoid Arthritis: Efficacy, Safety, and Innovation

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Abstract:

Introduction:

Over the last half-century, the treatment and management of autoimmune rheumatic diseases have progressively improved, particularly with the contribution of immunobiological or biological therapies known as disease-modifying antirheumatic drugs. Although these agents have been generally efficient in the management of rheumatoid arthritis (RA), some patients experience limited efficacy and non-responsiveness to treatment. In addition, they may cause adverse clinical effects, further aggravating the disease.

Objectives:

Despite advancements in biological therapies, significant clinical needs persist. This review aims to discuss novel treatments, guiding future guidelines and drug discoveries for rheumatoid arthritis.

Methods:

This review follows the 2020 PRISMA statement, utilising PubMed and Google Scholar for literature search and emphasizing recent meta-analyses on the safety and efficacy of targeted immunobiological medications.

Results:

Small molecule inhibitors, whether utilised independently or in conjunction with Methotrexate, have been shown to contribute to effective disease management and have the potential for better adherence to the American College of Rheumatology criteria. Tocilizumab therapy demonstrates a significant reduction in disease activity and improves rates of disease remission when combined with Methotrexate. Investigations of mesenchymal stromal cell therapies have had promising outcomes, improving both cartilage quality (as evaluated by Macroscopic Cartilage Repair Assessment) and joint tenderness and swelling in clinical joint counts. Intra-articular administration of tolerogenic dendritic cells has displayed a capacity to alleviate pain, as measured by Visual Analog Scale scores, and enhance the Disease Activity Score across 28 joints. Resveratrol capsules supplemented with allopathic therapy show potential in reducing TNF-α and interleukin-6 serum levels.

Conclusion:

More investigations and their analysis will improve patient outcomes and reduce adverse effects and the costs involved in developing and obtaining immunobiological drugs. Moreover, assessing the safety and efficacy of anti-RA properties of the bioactive compounds could offer less toxic and more cost-effective natural treatment options.

Keywords: Targeted immunobiology, Rheumatoid arthritis, Autoimmune disease, Bioactive compounds, Efficacy, Safety.

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1. INTRODUCTION

Rheumatoid arthritis (RA) affects about 0.5 to 1% of the general population globally, destroying joints and substantially diminishing the quality of life of patients [1]. Over the last half-century, the treatment and management of autoimmune rheumatic diseases has progressively improved, particularly with the contribution of immunobiological or biological therapies known as disease-modifying antirheumatic drugs (DMARDs) [2]. Although DMARDs have been generally efficient in the management of RA, there remains a significant

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risk of some patients experiencing treatment failure, including limited efficacy and non-responsiveness to treatment. To obtain the maximum therapeutic effectiveness, many rheumatologists recommend combining various therapies for RA patients [3]. Adverse clinical effects associated with DMARDs include diarrhoea, stomatitis, anaemia, exanthema, pneumonia and nephritis, which may further aggravate the disease. Furthermore, early investigations suggest that patients receiving treatment with DMARDS may be at an elevated risk of developing some cancers [4, 5].

Emerging immunobiological interventions for RA primarily target various disease modulators, including proteins, cytokines, and specific cells. These therapeutic approaches offer not only clinical remission but also sustained, enduring efficacy. Nonetheless, significant challenges persist, notably the substantial costs associated with their development and production. Presently, two categories of targeted drugs have exhibited clinical success in RA management: 1) injectable biologic disease-modifying anti-rheumatic drugs (bDMARDs) including Tumour necrosis factor-α (TNF-α) inhibitors, B-cell depletion agents, interleukin-6 (IL-6) blockers and inhibitors of T-cell co-stimulation; and 2) oral targeted synthetic DMARDs (tsDMARDs) such as the Janus Kinases (JAKs) pathway inhibitors [6, 7]. The introduction of novel biological therapies has profoundly transformed the landscape of RA treatment and care for many patients. However, an unmet clinical need exists, as evidenced by a substantial proportion of patients exhibiting limited responses to biological treatments, leading to increased rates of secondary failure [1]. This review aims to explore recent advancements in treatments, offering insights into future guidelines and facilitating the discovery of innovative drugs for RA management.

2. METHODOLOGY

The reporting of this review is in accordance with the 2020 PRISMA statement [8]. Available checklist items [9] are listed below:

2.1. Eligibility Criteria

Non-randomized and randomised controlled trials (RCTs) of male or female adolescents with RA were included, assessing the safety and efficacy of targeting pathways, targeting cytokines and targeting cell medications *vs*. placebo or any other anti-RA agents. Bioactive compounds (polyphenolic compounds, alkaloids, saponins) were included.

2.2. Information Sources

A literature search for all papers related to anti-RA medication was conducted using reliable sources, such as PubMed and Google Scholar Databases, including recent meta-analyses of the safety and efficacy of targeting pathways, targeting cytokines and targeting cells anti-RA medications outcome trials.

2.3. Search Strategy, Selection Process, Data Collection Process

Manual searches by the independent reviewers were performed using the search terms ‘novel anti-RA’, ‘targeting pathways or cytokines or cells’, ‘treatment’ ‘outcomes’ and ‘natural therapy or phytotherapy in RA’. Studies published from 2018 to 2023 were selected as recent advances in the field. In order to provide a scientific base for results discussion, older scientific studies and reviews were also considered. Original papers, high-quality recent research articles, English language, and a focus on novel anti-RA agents were the main eligibility criteria for inclusion.

2.4. Data Items, Outcome Assessment

The efficacy of targeting pathways, targeting cytokines, targeting cells, medications and bioactive compounds was assessed using the American College of Rheumatology (ACR) criteria, ACR 66/68 score, Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire–Disability Index scores, Macroscopic Cartilage Repair Assessment, Visual Analog Scale (VAS) score, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), International Knee Documentation Committee (IKDC) score, European League Against Rheumatism (EULAR) response, clinical markers (the 28-joint count for swelling and tenderness), and serum biochemical markers (C-reactive protein, erythrocyte sedimentation rate (ESR), undercarboxylated osteocalcin, matrix metalloproteinase-3, TNF-α and IL-6). Assessment of the safety of targeting pathways, targeting cytokines, targeting cells, medications and bioactive compounds was performed by the reporting of adverse events: Major Adverse Cardiovascular Events (MACE), tissue fibrosis, vascular signs, venous thromboembolism (VTE), neuromuscular, connective tissue, nervous system (neurogenic), eye, skin disorders, infections, neoplasm, abnormal liver laboratory test, hematologic, and renal function.

2.5. Study Risk of Bias Assessment

The quality of studies was evaluated by assessing the parameters, such as blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data for every single study.

2.6. Study Selection

The search strategy yielded 682 articles, and 572 unique records were screened. About 277 articles were recorded for eligibility. After excluding 295 studies during full-text review, 11 studies were included in the final analysis (Fig. **1** and Table **1**).

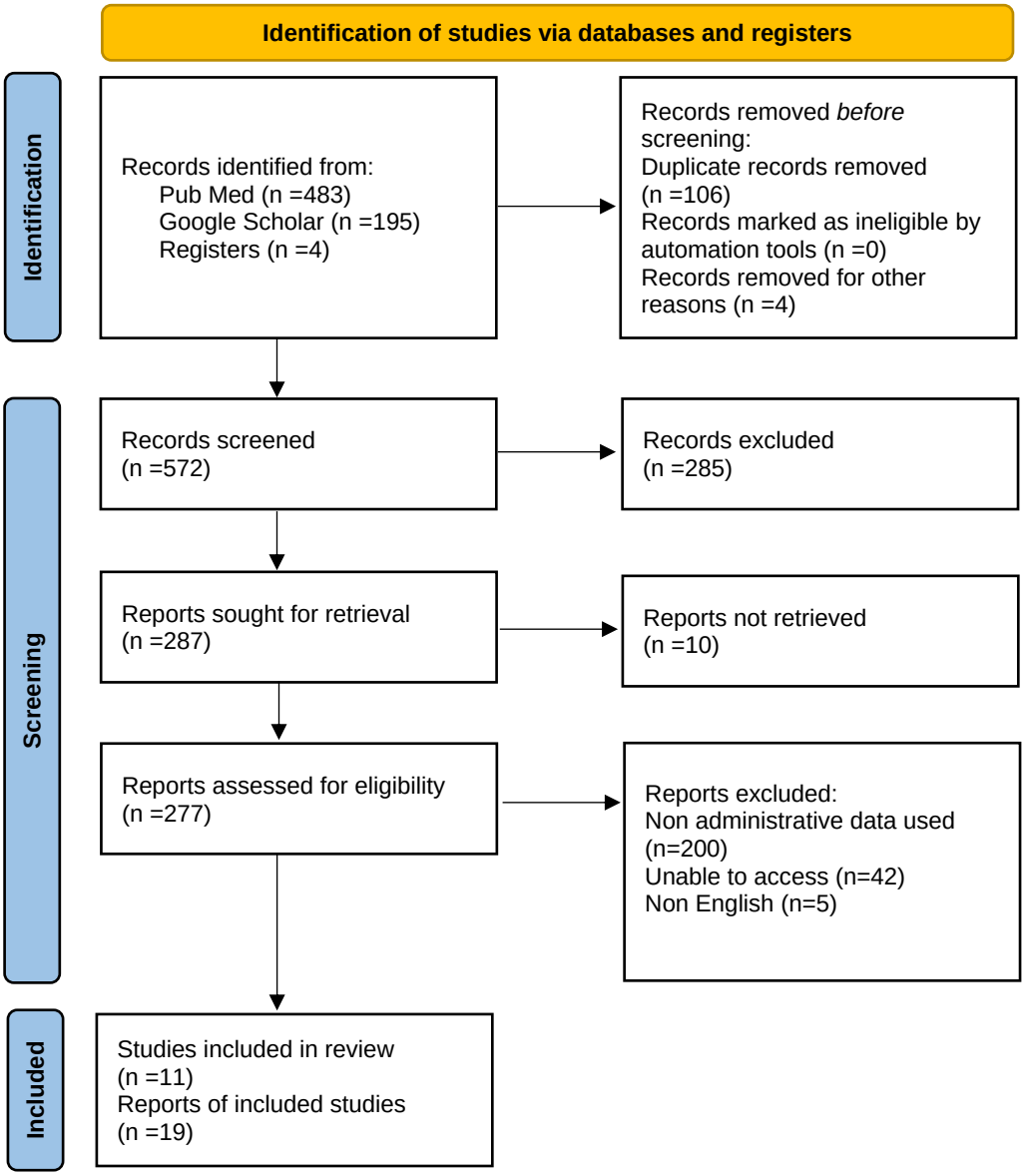

Fig. (1). PRISMA flow diagram for included studies.

Table 1. Overview of included studies.

JAKs Inhibitors					
Author/Year	**Study Type**	**Total Participants (n)**	**Name of the Drugs/ Dose (mg)**	**Comparison Group**	**Duration of Therapy**
Wang *et al.*/2020 [11]	Systematic review and meta-analysis	8982/ 20 RCTs	Tofacitinib/5, 10, Baricitinib/2, 4, Upadacitinib/15, 30	Placebo	4-24 weeks
Sung and Lee/2020 [12]	Meta-analysis	2185/ 4 RCTs	Tofacitinib/5, Baricitinib/4, Filgotinib/200 Upadacitinib/ 15,	MTX	N/A
Liu *et al.*/2022 [13]	Meta-analysis	2290/ 3 RCT	Tofacitinib/5, Baricitinib/4, Filgotinib/200	Placebo, MTX, JAKs inhibitors + MTX	24-52 weeks

(Table 1) contd.....

JAKs Inhibitors					
Author/Year	**Study Type**	**Total Participants (n)**	**Name of the Drugs/ Dose (mg)**	**Comparison Group**	**Duration of Therapy**
Maqsood *et al*./2022 [18]	Meta-analysis	38,574/ 66 RCTs	Tofacitinib/NA, Abrocitinib/NA, Upadacitinib/NA, Baricitinib/NA, Filgotinib/ NA	Placebo/ standard of care	3-48 months
Targeting Cytokines					
Saki *et al*./2021 [21]	Systematic review and meta-analysis	10, 314/15 RCTs	Tocilizumab/4, 8	Placebo	24 weeks
Cell-based therapies					
Lim *et al*./2021 [25]	Phase III RTC	114	UCB-MSCs	Microfracture	48 weeks to 60 months follow-up
Vij *et al*./2022 [26]	Phase I/IIa non-randomized open-label pilot trial	15	adMSCs/ 2×10^8 live cells	-	52 weeks
Kurochkina *et al*./2018 [32]	Control trial	10	DCs/ 1×10^6, 3×10^6, 5×10^6,8×10^6	-	7 days to 6 months follow-up
Willekens *et al*./2021 [33]	Systematic review and meta-analysis	1225/48 reports	MSC, Treg, tolDC,…	Dependent on the type of study	Variable between studies
Bioactive compounds					
Khojah *et al*./2018 [38]	RCT	100	RSV/1 gram + conventional treatment	Control (Regular treatment)	N/A
Dossing *et al*./2023 [41]	Single-centre, double-blind, RCT	100	Colchicine/ 0.5 mg	Placebo	12 weeks

Note: Abbreviations are available in the main text. N/A: Not Available.

2.7. Study Characteristics

2.7.1. Results of Individual Studies and Discussion

The findings of the studies examining novel anti-RA targeted immunobiological agents, bioactive compounds, and their implications are discussed separately. Further, section 5 and the conclusion specifically address the implications of these findings for future research endeavours.

2.7.2. Support

Unfunded.

2.7.3. Competing Interests

Reported.

2.7.4. Availability of data and other materials

Studies included in the review are all peer-reviewed and available in the literature.

3. RESULT AND DISCUSSION

3.1. Targeting Pathways - Small Molecule Inhibitors

JAK enzymes encompass a group of tyrosine kinases categorised into four distinct mammalian subtypes: JAK1, JAK2, JAK3, and Tyk2. These proteins, through linkage with a signal transducer and activator of transcription (STAT) transcription factors, mediate the downstream signalling of cytokine receptors, playing an important role in pathological mechanisms. Due to their ability to modulate this pathway combined with the fact of their oral administration and affordability, JAK inhibitors serve as convenient, targeted, small-molecule therapies capable of moderating various inflammatory pathways involved in the pathogenesis of RA [6, 10]. In their systematic review and meta-analysis of twenty randomised controlled trials including 8982 patients, Wang *et al*. [11] evaluated the safety and efficacy of different JAK inhibitors, including tofacitinib, baricitinib, as well as upadacitinib. They found that various dosing regimens of JAK inhibitors resulted in significantly improved RA control. The highest ACR20 was related to tofacitinib, 10 mg (RR, 2.48; 95% CI, 1.97-3.14; P<.001) and 5 mg (RR, 2.16; 95% CI, 1.81-2.58; P<.001) twice daily compared to placebo. The highest risk of infection was related to tofacitinib, 10 mg, twice daily (RR, 2.75; 95% CI, 1.72 to 4.41; P<.001). In addition, in their review of the comparative study of the safety and efficacy of different JAK inhibitors, Sung and Lee [12] cited a Bayesian network meta-analysis of four randomised controlled trials involving 2185 DMARD-naive patients with RA showing no significant differences in serious adverse events, adverse events (AEs), and withdrawals due to AEs between upadacitinib, baricitinib, tofacitinib and filgotinib. However, it should be noted that ACR50 and ACR70 response rates were significantly higher in these agents compared to methotrexate (MTX).

In terms of combination therapy, many reviews have gathered clinical trial information on various JAK subtype inhibitors administered as monotherapy as well as combination therapy. Most recently, a meta-analysis of 3 trials comprising 2,290 patients was conducted by Liu *et al*. [13], and it was found that, at week 52, JAK inhibitor monotherapy with either tofacitinib, baricitinib or filgotinib resulted in lower response rates (ACR20= 67.74%; RD 0.032, 95% CI: 0.027 to 0.091, ACR50=49.26%; RD 0.050, 95% CI: 0.003 to 0.097 and ACR70=32.26%; RD 0.056, 95% CI: 0.012 to 0.100) compared with their use in combination with MTX

(ACR20=72.69%, ACR50=56.72%; ACR70= 40.40%) in individuals with active RA.

Although, according to Smolen *et al*. [14], JAK inhibitors should be added to continuing regimens, preferably MTX, Gremese and coauthors [15] believe the combination of MTX with JAK1-specific inhibitors may not lead to better clinical outcomes. A systematic review by Emery *et al*. [16] on the effectiveness of monotherapy with JAK inhibitors (tofacitinib, baricitinib) and other biologics for the treatment of RA revealed that, despite most indexes being linked to favourable trends of response rate without many differences, JAK inhibitors plus MTX had higher ACR response due to the greater likelihood of achieving remission and lower disease activity as compared to JAK inhibitor monotherapy.

While enhanced comprehension of aberrant signalling in autoimmunity underscores the potential of small molecule pathway inhibitors as promising orally administered, targeted therapies in RA, the safety profile of JAK inhibitors, akin to other biologic agents, remains controversial. According to reports from the World Health Organisation (WHO) pharmacovigilance database, ruxolitinib, tofacitinib and baricitinib may be associated with infections, musculoskeletal, connective tissue disorders, thromboembolism and neoplasms [17].

Maqsood and colleagues [18], assessing the risk of MACE and VTE following JAK inhibitors treatment, conducted a meta-analysis of 66 randomised controlled trials comprising 38,574 patients with immune-mediated inflammatory diseases. They found that JAK inhibitors may increase the risk of VTE (OR 1.65; 95% CI: 0.97-2.79) and MACE (OR 1.18; 95% CI: 0.83-1.68) compared with control groups. The last could be attributed to an elevation of low-density lipoproteins. However, the mechanisms involved in the pro-thrombotic role of different JAK inhibitors remain disputed [19].

3.2. Targeting Cytokines - Biological Therapies

Cytokines aid in cellular differentiation, act as mediators of inflammation, regulate immune responses and are involved in immune pathologies. For a long time, cytokines have been explored and studied as probable targets for RA therapy due to their direct involvement in the disease process. Pro-inflammatory cytokines, including TNF-α, IL-6, IL-7, IL-15, IL-17, IL-18, IL-23 and granulocyte-macrophage colony-stimulating factors, were found to direct inflammation in RA. Cytokine-targeting therapies, such as anti-TNFα, anti-IL-6 and anti-IL-17, have revolutionised the treatment of RA and provide improved patient outcomes with a realistic outlook for disease remission [2]. These agents are primarily biologics, known for their expensive development process and the need for intravenous or subcutaneous administration. However, a subset of these therapies, like anti-chemokine treatments, fall under the classification of small-molecule agents [20]. Saki *et al*. [21] conducted the inaugural systematic review and meta-analysis involving 15 clinical trials encompassing a total of 10,314 RA patients. This study aimed to evaluate the safety and effectiveness of TCZ, an IL-6 receptor antagonist approved for treating autoimmune conditions, such as RA and systemic juvenile idiopathic arthritis. The findings from the 24-week follow-up demonstrated that TCZ substantially reduced disease activity and, with the addition of MTX, improved disease remission. Moreover, treatment by 4mg TCZ exposed a higher proportion of ACR50 (OR = 4.78; 95% CI: [2.69; 8.51]) and ACR70 (OR = 8.0; 95% CI: [3.23; 19.80]), while RA patients administered with 8mg TCZ obtained a higher proportion of ACR20 (OR = 4.60; 95% CI: [2.35; 9.0]). Also, the highest proportion of DAS28 remission in RA patients was related to combination therapy of TCZ (8 mg) + DMARD (OR = 23.25; 95% CI: [4.32; 125.03]). Adverse events, including infections, ocular complications, skin and subcutaneous disorders, abnormal liver laboratory test results, and nervous system disorders, were notably associated with TCZ at doses of 4 and 8 mg. Despite occurrences of certain adverse events, such as elevated blood pressure and respiratory tract infections, the comparable safety profile and the prompt, sustained effects of this monoclonal antibody indicate its suitability for use in practice. Sarilumab, another recombinant monoclonal antibody targeting the interleukin pathway and approved for treating moderate-to-severe RA in adults, exhibits a safety profile supported by recent trials and post-marketing reports. No new safety issues were identified, underscoring the effectiveness of sarilumab in clinical practice [22, 23].

Regarding the safety of bDMARDs, while the connection between conventional DMARD therapy in RA patients and an elevated overall risk of cancer has been established, the potential for increased cancer risk specifically linked to bDMARDs therapy remains a topic of debate. Evidence suggests that the risk of cancer in these patients might be specific to certain organs, which blurs the impact of DMARDs usage. Conversely, this observation sparks discussions centering on the influence of the RA disease itself in contributing to this risk [5].

3.3. Cells-Based Therapies

Human cells have been established as therapeutic tools in the treatment of RA. Cells that have powerful tolerogenic functions include both non-immune cells, such as mesenchymal stromal cells (MSC) and certain types of immune cells, like tDCs. Clinician researchers have increasingly focused on the immunomodulatory properties of MSCs, characterized by their ability to suppress immune responses and proinflammatory cytokines. This interest is reflected in numerous recent investigations evaluating the efficacy and safety of MSC therapy for RA [24]. A randomised controlled phase III trial, spanning 48 weeks and involving 114 patients with extensive full-thickness cartilage defects, demonstrated that treatment with CARTISTEM significantly improved cartilage grade based on Macroscopic Cartilage Repair Assessment compared to the control group (odds ratio, 16.55; 95% CI, 2.06-133.03; P = 0.001). Although no significant changes were observed in the pain VAS score, WOMAC, and IKDC score at 48 weeks, a follow-up spanning three to five years for 73 of the 114 participants exhibited superior scores compared to those who underwent microfractures. Furthermore, there were no discernible differences in adverse events between the CARTISTEM and microfracture groups [25]. Additionally, a 52-week follow-up of 15 eligible RA patients in a phase I/IIa non-randomized, open-label pilot trial

revealed that a single intravenous administration of autologous, adipose-derived mesenchymal stem cells (adMSCs) significantly improved joint count for both swelling (p = 0.003) and tenderness (p = 0.0008) of joints [26].

Several clinical trials have identified thromboembolism and tissue fibrosis as significant adverse events subsequent to cell injection. Neoplastic, neurogenic and vascular signs were also noted. Among the minor side effects reported in the majority of clinical investigations are fever and localised pain [27]. Conflicting data in published studies exist regarding the therapeutic effects of MSCs in animal models of RA. Some studies indicate no effect or even a worsening of disease symptoms, while others highlight the clear benefits of MSC treatment [28, 29]. While the reasons for these discrepancies remain unclear, it is likely that the differences in the source of MSC and culturing protocols, together with the timing and dose of MSC-based administration, could potentially play a role in determining the efficacy of MSC treatment. For instance, Bačenková *et al*. [30] demonstrated that allogeneic MSC transfer exacerbated inflammatory arthritis, whereas treatment with syngeneic MSCs showed no apparent effect on disease progression, albeit revealing significantly reduced serum IL-17 levels over time. One method of overcoming the challenge of disease exacerbation during MSC infusion is through genetic modification.

Characterised by their ability to present antigens to T-cells in relation to pro-tolerogenic cells, tolerogenic dendritic cells (tDCs) prompt efficient immune responses against various antigens, including self-antigens. These cells can be generated *ex vivo* from peripheral blood monocytes in humans and bone marrow in mice, originating from dendritic cell precursors. Recent advancements in understanding tDCs have led to their use as treatment in autoimmune diseases. Both *in vivo* and *in vitro*, these cells induce tolerance, as elucidated by Spiering *et al*. [31].

In their study, Kurochkina *et al*. [32] evaluated the safety and effectiveness of intraarticular injections of autologous monocyte-derived dendritic cells in patients with RA. The preliminary results demonstrated that DC injections were safe and well tolerated. After one month, there was a reduction in VAS score (p=0.03); at three months, DAS28-ESR was improved (p=0.008; n=10), and a 6-month follow-up of 5 patients showed diminished DAS28-ESR from 5.1to 3.3 (p=0.04).

In their systematic review and meta-analysis, Willekens *et al*. [33] assessed the safety of tolerance-inducing cell-based therapies, examining 48 records. The incidence of severe adverse events was generally low, although due to substantial variations in reporting across studies, the adverse events were not able to be categorised. No signs of immunosuppression or disease exacerbation were declared relating to the use of tDCs in clinical trials.

Despite a surge in the development of cellular therapies for the treatment and management of RA in recent years, several significant challenges persist. The inherent variability in the cellular nature of both MSC and tDC products is a problem in itself. The high costs associated with cell therapies often result in small-scale trials, limiting their applicability and predictive capacity [31]. Fig. (**2**) provides an overview of the efficacy and safety of targeted immunobiologics.

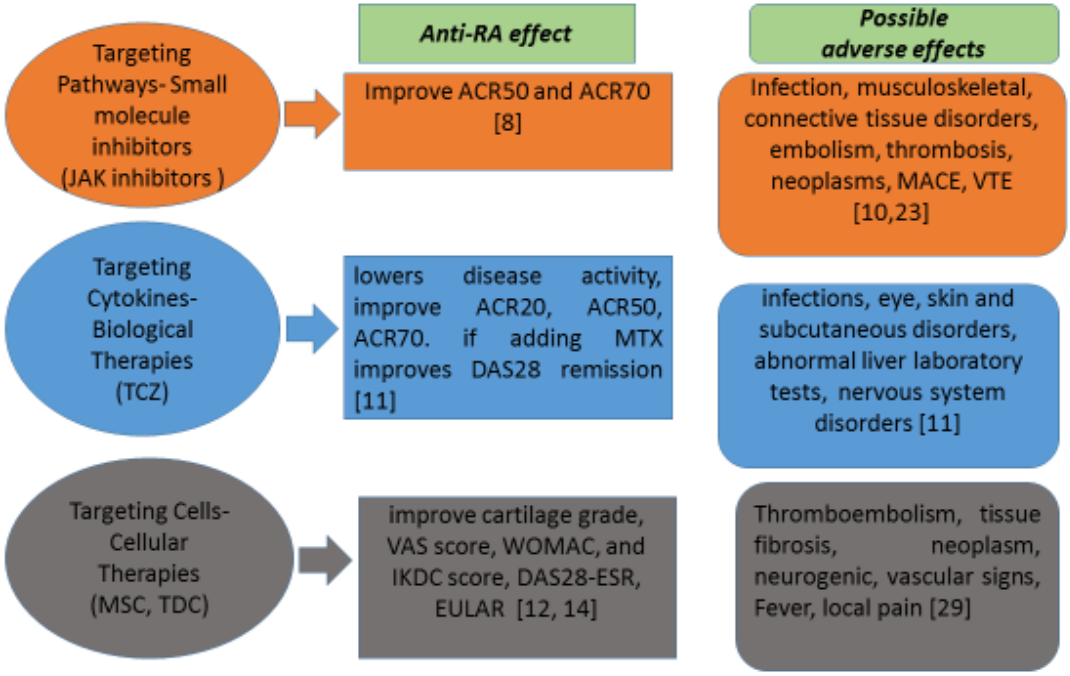

Fig. (2). Overview of the different classes of novel targeted Immunobiological medication used in current approved RA treatments, in ongoing clinical trials and under investigation.

4. BIOACTIVE COMPOUNDS

Historical records attest to the use of phytochemicals in disease treatment, a practice that persists owing to their inherent therapeutic attributes encompassing antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic properties [34]. Conventional therapeutic agents, despite their effectiveness, pose drawbacks such as an increased risk of infection in gastrointestinal, cardiovascular, and nervous system complications, along with high costs. These limitations may hinder their long-term usage and potentially impede achieving a complete therapeutic response [35]. Combining phytochemicals with conventional therapy may create a synergistic, anti-inflammatory and anti-arthritic effect in treating RA while potentially mitigating the associated toxicity [36].

4.1. Polyphenolic Compounds

The anti-inflammatory properties of polyphenols have been well-established in both *in vitro* and *in vivo* studies [37]. In order to assess the anti-RA activity of RSV, being a naturally occurring non-flavonoid polyphenol, Khojah and coauthors [38] conducted a randomised controlled clinical trial involving 100 RA patients. The findings showcased a significant reduction in clinical markers and serum biochemical indicators of RA among 50 patients who received a daily RSV capsule (1 gram) alongside allopathic treatment for three months, compared to the control group, which may be attributed to RSV reducing the serum levels of TNF-α and IL-6. However, regarding the safety profile of polyphenol compounds, it is important to note that their effects are dose-dependent and diverse. Excessive intake might lead to adverse effects, such as the inhibition of digestive enzymes, impact on intestinal microbiota, and influence on drug-metabolising enzymes like CYP isoenzymes, thereby altering the pharmacokinetics of other medications. Additionally, polyphenols could potentially induce hormonal imbalances, mutations, or even carcinogenic effects [39].

4.2. Alkaloids

Li and colleagues [40] extensively discussed the anti-inflammatory effects associated with alkaloids. For instance, administering berberine *via* peritoneal injection at 30 mg/kg showed inhibition of cyclooxygenase enzyme 2 (COX-2) and prostaglandin E2 (PGE2). Oral administration at a concentration of 1.5 mg/ml demonstrated suppression of various interleukins (IL-1, IL-2, IL-8, IL-6), TNF-α and monocyte chemotactic protein-1 (MCP-1). The intravenous injection of lycorine, another alkaloid variant, at 3 mg/kg induced arthritic symptoms in rabbits, with suggested mechanisms involving the suppression of PGE2, IL-6, and the JAK-STAT pathways. Aconitine, a diterpene alkaloid, actively reduces the activation of nuclear factor kappa B (NF-κB) and lowers the levels of inflammatory transcription factor NF-κB, TNF-α, IL-6, and IL-1β. Colchicine, an organic amine alkaloid, has been considered for gouty arthritis treatment by inhibiting neutrophil aggregation in joints, thereby regulating the inflammatory response.

In a recent single-centre, double-blind, randomised, placebo-controlled trial conducted in Denmark, the efficacy and safety of colchicine for osteoarthritis of the hand were assessed. Among 186 eligible participants, 100 were allocated to receive either colchicine (0.5 mg orally) or a placebo twice a day for 12 weeks. The study found that the introduction of colchicine did not effectively alleviate hand pain compared to the placebo group. Additionally, there was a notable increase in adverse events, particularly occurrences of cholecystitis and elevated alanine aminotransferase concentrations, observed in the colchicine group [41]. These findings pose challenges to the safety and efficacy profile of alkaloids, highlighting the need for further preclinical and clinical trials to better understand their potential in treating osteoarthritis and other conditions.

4.3. Saponins

Autoimmune responses in RA disrupt the balance between osteoclastic and osteoblastic bone formation, resulting in bone loss [42]. Recently, attention has turned to exploring the bone-protective potential of saponins. Asperosaponin VI (AVI) has demonstrated effective inhibition of the receptor activator of NF-κB ligand (RANKL) *in vitro*, a key regulator of osteoclast formation and activation. AVI also suppresses osteoclast signalling pathways and exhibits arthritis protection in collagen-induced arthritis (CIA) mice. Moreover, it induces osteoblast differentiation in human umbilical cord mesenchymal stem cells through oestrogen signalling pathways [43, 44]. Research by Zhang *et al*. [45] investigated various ginsenoside monomers (active compounds in ginseng) and found that administering 15 mg/kg of ginsenosides every two days notably reduced arthritis index scores and relieved joint swelling in CIA mice. These ginsenosides downregulated protein expression of TNF-α and IL-6 and reduced activated CD4 + T cells and pro-inflammatory M1-macrophages in the joints of the diseased mice. The primary safety of ginsenoside was assessed by evaluating pathological manifestations of main organs (heart, liver, spleen, lung and kidney) under administration of bioactive substances. Neither morphological nor structural changes were observed, indicating negligible toxicity to normal cells. The safety profile of ginsenosides was assessed by examining pathological changes in vital organs (heart, liver, spleen, lung, and kidney) under the influence of these substances. No observable morphological or structural changes were noted, indicating minimal toxicity to normal cells. Fig. (**3**) illustrates both the anti-RA properties of bioactive compounds and their potential adverse effects. The immunomodulatory properties of polyphenols, alkaloids, and saponins found in plants suggest these compounds are attractive candidates for the treatment of RA. The Nyctanthes arbor-tristis Linn plant is rich in various compounds like alkaloids, phenols, saponins, steroids, proteins, tannins, and flavonoids. Sharma *et al*. [46] recently investigated its potential anti-rheumatoid arthritis (RA) properties. Their study revealed that a plant extract at a concentration of 1 mg/mL exhibited considerable inhibition of protein denaturation (87.63 ± 2.43%) and notably stabilised Human Red Blood Cell Membrane *in vitro* (88.23 ± 2.09%). However, these effects were slightly inferior to those observed with Diclofenac sodium (89.01 ± 1.23% and 91.92 ± 1.69%, respectively). Additionally, docking simulations showed a significant binding affinity of the bioactive compounds of the plant to target proteins, such as cyclooxygenase 2 and TNF-α, effectively inhibiting their activity.

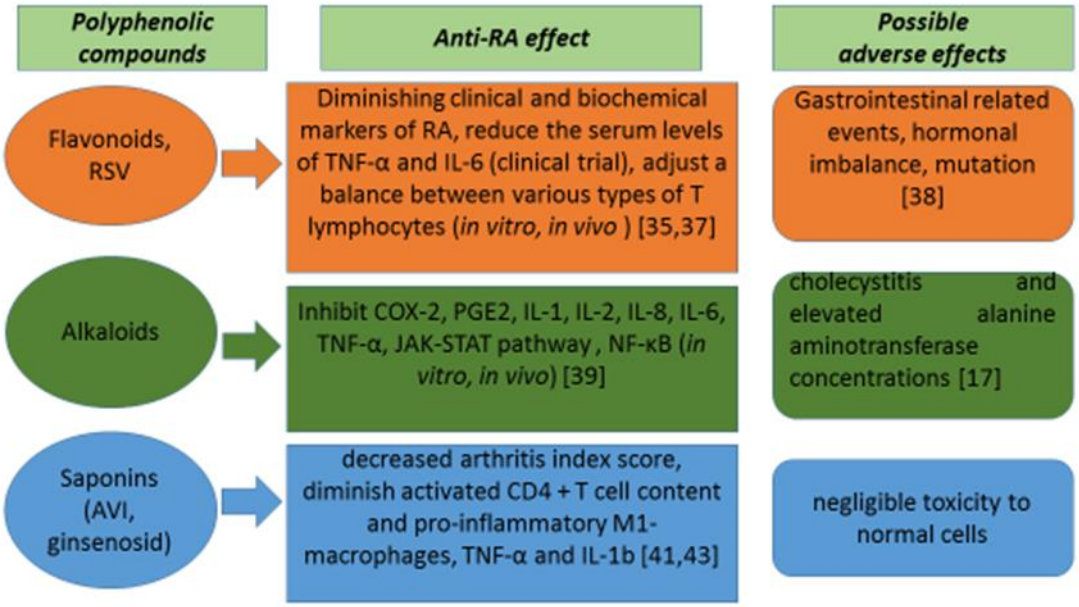

Fig. (3). Overview of the anti-RA effects of natural compounds (polyphenolic compounds, alkaloids, saponins).

5. RECOMMENDATIONS

Around a third of all RA patients fail to respond to any specific biological therapy. Presently, there are no response indicators, and the order in which these therapies are prescribed depends on a given algorithm dictated by National Institute for Health and Care Excellences (NICE) guidelines. Understanding the many diverse RA pathotypes is pivotal in understanding patient responsiveness, and thus, rigorous investigation, requiring significant research and financial investment, is required. In the future, it is anticipated that a more personalised approach will be undertaken, potentially utilising a scoring system based on demographics, biomarkers, and clinical observations to tailor treatment for each patient, aiming to enhance outcomes, minimise adverse effects, and reduce drug development costs. The limited bioavailability of orally administered active natural compounds, such as saponins, might restrict their effectiveness. Hence, a series of interventions are necessary to increase their relative bioavailability.

CONCLUSION

Small molecule inhibitors that target specific intracellular signaling pathways have emerged as vital components in mediating the downstream signaling of pro-inflammatory molecules, presenting a promising avenue for new RA treatments. The landscape of RA therapies has witnessed a revolution, particularly in the approval of biological therapies focused on cytokine targeting. In addition, cellular therapies present a completely different approach to the treatment, with their main advantage being their tolerogenic potential. Cellular therapies may potentially offer brief yet long-lasting courses of treatment. Moreover, exploring the anti-RA properties of bioactive compounds through research endeavours to assess their safety and effectiveness may contribute to the discovery of more cost-effective and less toxic natural treatment alternatives.

LIST OF ABBREVIATIONS

NICE	=	National Institute for Health and Care Excellence
AVI	=	Asperosaponin VI
RANKL	=	receptor activator of NF-κB ligand
CIA	=	collagen-induced arthritis
COX-2	=	cyclooxygenase enzyme 2

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

All the data and supportive information are provided within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

Supplementary material is available on the publisher's website along with the published article.

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