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NEW INSIGHTS INTO THE PHARMACOLOGICAL MANAGEMENT OF RHEUMATOID ARTHRITIS

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Abstract: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by synovial inflammation and progressive joint destruction which significantly impairs patients' quality of life and generates substantial socioeconomic costs. Conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate are the cornerstone of RA therapy, particularly for early or mild forms of disease. The newer, biologic DMARDs are a more advanced therapeutic option when conventional DMARDs are not sufficiently effective, or they cause important adverse effects. Targeted synthetic DMARDs are also a recently authorized class of drugs which have the advantage of oral administration. The aim of this review is to provide an overview of rheumatoid arthritis' pharmacological management, focusing on the most important properties of conventional, biologic and targeted synthetic DMARDs and presenting also the current international treatment guidelines. Natural compounds which could be used as adjuvants in the therapy of RA are also detailed.

Keywords: rheumatoid arthritis, conventional DMARDs, biologic DMARDs, targeted synthetic DMARDs, natural compounds

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by synovial inflammation, progressive joint destruction, and various extra-articular manifestations, such as rheumatoid nodules, renal and cardiovascular impairment, pleurisy or anemia (Smolen et al., 2016; Das and Padhan, 2017). Rheumatoid arthritis can affect approximately 1% of the global population, significantly impairing patients' quality of life and generating substantial socioeconomic costs due to chronic disability and comorbidities (Gibofsky, 2012). Over 50% of patients cease professional activities within 5 years of diagnosis, and 10% develop permanent joint deformities within 2 years if untreated (Gibofsky, 2012; Picerno et al., 2015).

The advent of new types of disease-modifying antirheumatic drugs (DMARDs) has revolutionized RA management enabling

remission or lowering disease activity in many patients.

Early diagnosis and effective treatments are critical to prevent irreversible joint damage and improve long-term outcomes (Picerno et al., 2015; Smolen et al., 2016). Nevertheless, the high cost of modern DMARD drugs may limit their availability in developing countries, highlighting the importance of the use of all available therapeutical resources including phytochemical remedies used in traditional medicine which could be significant in certain geographical regions.

This review is aimed at providing an overview of the current understanding of RA, with an extensive emphasis on conventional, biologic and targeted synthetic DMARDs, but also on possible phytotherapeutical alternatives.

2. Materials and Methods

This review used scientific articles written only in English, published between 2015-2025, identified in PubMed, Scopus, Elsevier and Web of Science databases. The search used keywords like "rheumatoid arthritis", "rheumatoid arthritis AND conventional disease-modifying antirheumatic drugs", "rheumatoid arthritis AND biologic disease-modifying antirheumatic drugs", "rheumatoid arthritis AND phytotherapy".

3. Rheumatoid arthritis: epidemiology and pathogenetic mechanisms

Rheumatoid arthritis (RA) has a global prevalence of 0.5-1%, with a male-to-female ratio of 1:2. The prevalence of RA shows a geographical variability with higher values in Western and Northern Europe and North America and lower values in East Asia and Africa, due to genetic and environmental factors (Cross et al., 2014; Smolen et al., 2016). Over the last three decades there has been a significant increase of RA-related incidence rate and RA-related disability-adjusted life years (DALYs), highlighting the significant burden of the disease, which is now considered a significant global health problem (Zhang et al., 2025). Additional comorbidities may complicate the evolution of the disease and also, mortality rates are still higher in RA patients compared with general population, although they have decreased in the last decade (Abhishek et al., 2018).

RA is a complex disease characterized by the interaction of genetic and environmental risk factors which alter the immune tolerance of affected patients (O'Neill et al., 2024). Genetic pre-disposition, particularly the existence of certain Human Leukocyte Antigen alleles (HLA-DRB1), is a major risk factor, present in over 80% of RA patients, being associated with severe disease and bone erosions (Picerno et al., 2015; O'Neill et al., 2024). Environmental factors, including smoking, alcohol consumption, inflammatory diet and infections also contribute to RA's development (Smolen et al., 2016; O'Neill et al., 2024).

The abnormal immune response from RA usually starts in tissues and organs distantly situated from the synovial joints, like the lungs, gums or gastrointestinal tract, where certain proteins are modified by citrullination, carbamylation and acetylation, which later will become the target of autoantibodies (McInes and Schett, 2017). According to multiple evidence, several years before the development of clinical symptoms, patients with RA show increased blood levels of auto-antibodies like rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) but also the lesser discussed anti-carbamylated protein (anti-CarP), and anti-malondialdehyde-acetaldehyde (anti-MAA) (O'Neill et al., 2024). Generally, around 80% of all patients with RA are considered "seropositive", presenting

detectable levels of autoantibodies like RF and ACPA (Wu et al., 2021).

The pathogenesis of rheumatoid arthritis involves a complex immune dysregulation in which aberrantly activated immune cells play a central role, diffusely infiltrating the synovium. In RA, T lymphocytes (CD4+ Th1, Th17) and B lymphocytes drive inflammation, producing pro-inflammatory cytokines (tumor necrosis factor-TNF-α and interleukins IL-6, IL-17) that promote synovial hyperplasia, pannus formation, and osteoclast activation, leading to joint and bone destruction. Additionally, the proinflammatory cytokines can induce acute-phase responses (e.g., elevated C-reactive protein) and may cause systemic complications like anemia (via hepcidin induction), and osteoporosis (via osteoclast activation), contributing to the significant comorbidities of RA (McIness and Schett, 2017; Alivernini et al., 2022).

4. Pharmacological management of rheumatoid arthritis

The drugs used in the treatment of RA are classified in two categories: drugs used for the symptomatic control of the disease (Corticosteroids and Non-steroidal anti-inflammatory drugs-NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) which are able to reduce disease progression (Radu and Bungau, 2021; Brown et al., 2024).

4.1. Symptomatic treatment of RA

The symptomatic treatment of RA is used only for the short-term management of inflammation and pain, consisting primarily of NSAIDs and corticosteroids. NSAIDs act by the inhibition of cyclooxygenases, with a subsequent reduction of prostaglandins level leading to an anti-inflammatory and peripheral analgesic effect. COX-2 selective NSAIDs (celecoxib, etoricoxib) can be used in order to minimize gastrointestinal adverse effects, but the risk of other unwanted effects like thrombotic events requires an assessment of the benefit-risk balance prior to their clinical use (Solomon et al., 2018; Brown et al., 2024).

Corticosteroids have a superior anti-inflammatory potency compared to the NSAIDs, due to their complex mechanism of action which includes the inhibition of arachidonic acid cascade but also the inhibition of several pro-inflammatory cytokines' genes. In RA, corticosteroids are used as a "bridging therapy" for DMARDs until the full development of their effects or associated with DMARDs as an adjunctive treatment (Radu and Bungau, 2021; Brown et al., 2024).

Corticosteroids (prednisone, prednisolone, dexamethasone) can be administered via multiple routes (oral, intravenous, intraarticular) but their use is generally limited in time (up to 3 months) by the development of significant adverse effects which may include hydro-saline retention, osteoporosis, diabetes, cataract, etc. (Singh et al., 2015; Radu and Bungau, 2021).

4.2. Disease modifying anti-rheumatic drugs (DMARDs)

DMARDs act by a variety of immunological mechanisms and are capable of altering the course of RA, promoting disease remission and delaying/stopping joint damage, dramatically improving patient's quality of life. They are classified as:

- conventional DMARDs
- biologic DMARDs
- targeted synthetic DMARDs (Brown et al., 2024).

4.2.1. Conventional DMARDs

Conventional DMARDs were introduced after 1970 and are considered to be the corner-stone of RA therapy, particularly for early or

mild forms of disease, due to their efficacy and large availability. Conventional DMARDs are chemically and pharmacologically diverse, methotrexate, leflunomide, sulfasalazine and hydroxychloroquine being the drugs of choice while d-penicillamine, azathioprine and gold salts are rarely used due to reduced efficacy and significant adverse effects (Radu and Bungau, 2021; Brown et al., 2024).

Methotrexate (MTX), a folate antagonist, is a first-line DMARD due to its efficacy in reducing disease activity and slowing radiographic progression (Brown et al., 2024). The international treatment guidelines recommend methotrexate as the first-line treatment of RA, generally as monotherapy for DMARDs-naïve patients, having better efficacy and a more rapid onset of action than other conventional DMARDs. In combination with a short bridging treatment with cortico-steroids, methotrexate can induce disease remission in approximately 40% of patients (Radu and Bungau, 2021). Associations with other molecules are possible in specific patients when therapeutic improvements are not achieved with MTX alone. Methotrexate inhibits dihydrofolate reductase, reducing DNA synthesis and lymphocyte proliferation, and exerts anti-inflammatory effects via adenosine release (Shinde et al., 2014). Administered mainly orally but also subcutaneously at 7.5–25 mg weekly, methotrexate achieves clinical improvement within 3–6 weeks, with one-third of patients showing radiological stability after 1 year. Adverse effects include hepatotoxicity (elevaited transaminases), leukopenia, and gastrointestinal upset, necessitating folic acid supplementation (1–5 mg daily) and regular monitoring of liver function and complete blood counts every 1–3 months (Visser and Van der Hejde, 2009; Wang et al., 2018).

Leflunomide reduces pyrimidine synthesis via the inhibition of dihydroorotate dehydrogenase, suppressing lymphocyte proliferation. Administered orally at a 100 mg loading dose for 3 days followed by 10–20 mg daily, it is effective in early RA, with clinical benefits within 4–6 weeks and efficacy comparable to methotrexate (Radu and Bungau, 2021; Brown et al., 2024). Adverse effects include diarrhea, hypertension, and hepatotoxicity (elevated transaminases), requiring monthly liver enzyme monitoring for the first 6 months (Alfaro-Lara et al., 2019).

Sulfasalazine, metabolized into sulphapyridine and 5-aminosalicylic acid, reduces inflammation via cyclooxygenase and lipoxygenase inhibition, resulting low concentration of prostaglandins. Dosed at 2–3 g daily, it achieves clinical effects within 6–10 weeks and is often used in early RA or as combination therapy (Brown et al., 2024). Adverse effects include gastrointestinal upset, rash, and hematologic abnormalities (leukopenia), particularly in slow acetylators. It is contraindicated in sulfonamide hypersensitivity or severe renal/hepatic impairment. Regular monitoring of blood counts and liver function is recommended (O'Dell et al., 2002; Brown et al., 2024).

Hydroxychloroquine, an antimalarial drug, modulates immune responses by inhibiting Toll-like receptors (TLRs) signaling and cytokine production. Dosed at 200–400 mg daily, it is used in mild RA or as part of combination therapy, with benefits evident after 2–3 months. It has a favorable safety profile, with rare adverse effects (retinal toxicity with long-term use), requiring annual ophthalmologic screening (Das et al., 2007; Brown et al., 2024).

4.2.2. Biologic DMARDs

Biologic DMARDs are an advanced therapeutic option available when conventional DMARDs are not sufficiently effective or they cause important adverse effects leading to poor patient acceptance. Biologic DMARDs are

generally obtained by recombinant DNA technology, and they target specific immune pathways, being indicated for moderate-to-severe RA, often combined with methotrexate to enhance efficacy (Radu and Bungau, 2021). Several studies have shown that a combined therapy of methotrexate and biologic DMARDs (infliximab, golimumab, adalimumab, etanercept, abatacept) showed an ACR50 response rate of 38% and a remission rate of 18% (Singh et al., 2015). Being directed against a variety of molecular targets, biologic DMARDs are subsequently classified according to the mechanism of action in:

- TNF-α inhibitors (infliximab, golimumab, adalimumab, certolizumb, etanercept)
- IL-1 inhibitors (anakinra)
- B-cell depleters (rituximab)
- Selective co-stimulation modulators (abatacept)
- IL-6 inhibitors (tocilizumab, sarilumab)

(Singh et al., 2015; Radu and Bungau, 2021; Brown et al., 2024).

TNF-α inhibitors act by blocking tumor necrosis alpha (TNF-α), a key proinflammatory cytokine, thus reducing synovial inflammation and joint destruction. Infliximab was the first molecule from its class to be authorized for the treatment of RA at the end of 1990s. It is a chimeric monoclonal antibody which binds to all forms of TNF-α, neutralizing its functions. Infliximab is dosed at 3 mg/kg i.v. every 8 weeks after loading doses and achieves clinical response in 50–60% of patients within 12 weeks (Van Vollenhoven, 2009; Van Vollenhoven, 2016). Golimumab is a fully human monoclonal antibody administered by s.c. or i.v. route at a dose of 50 mg every 4 weeks. It is a newer, better tolerated anti-TNF agent, compared to infliximab and etanercept (Pelechas et al., 2019). Adalimumab is a fully human monoclonal antibody, dosed at 40 mg s.c. every 2 weeks. It showed sustained efficacy over 5 years, with 60% of patients achieving low disease activity (Van de Putte, 2004). Etanercept is a fusion protein obtained by recombinant DNA technology by coupling the human TNF receptor p75 to an Fc fragment. It is dozed at 25 mg s.c. twice weekly or 50 mg weekly and reduces radiographic progression in 70% of patients (Emery et al., 2014). Certolizumab pegol is a PEGylated Fab fragment with long plasma T1/2, dosed at 200 mg s.c. every 2 weeks. It is effective in methotrexate-refractory RA, with rapid onset (2–4 weeks) and is approved also in pregnant women due to the lack of placental transfer (Bonek et al., 2021) (**Table 1**). IL-1 inhibitors are represented by Anakinra, an IL-1 receptor antagonist, dosed at 100 mg SC daily. It has modest efficacy (20–30% response rate) and is less commonly used due to frequent injections and injection-site reactions, being reserved for patients which are intolerant to other biological drugs (Mertens and Singh, 2009).

B-cell depleters are represented by rituximab, a chimeric monoclonal antibody which blocks CD20 epitope on B-cells, reducing their numbers. It is effective in the treatment of RA, as an alternative to anti-TNF agents and is not associated with a significant risk of infections. Rituximab is administered as an i.v. infusion, being particularly effective in seropositive patients (Porter et al., 2016).

The selective co-stimulation modulators are represented by abatacept, a fusion protein that inhibits T cell activation by binding to CD80 and CD86 molecules on the antigen presenting cells (APC), blocking their interaction with CD28 receptor on T cells. It is administered by i.v. route based on body weight (500–1,000 mg every 4 weeks). It reduces disease activity in 50% of metho-trexate-refractory patients, with a favorable safety profile (lower infection risk than anti-TNF agents) (Genovese et al., 2018).

Table 1. Main characteristics of DMARD drugs (Brown et al., 2024; Gao et al., 2024; McInnes and Schett, 2017; Radu and Bungau, 2021)

Class	**Drug**	**Mechanism of action**	**Route of administration**
Conventional DMARDs			
	Methotrexate	Inhibition of dihydrofolate-reductase	oral, s.c.
	Leflunomide	Inhibition of dihydroorotate-dehydrogenase	oral
	Sulfasalazine	Inhibition of nuclear factor kappa-B (NF-kB)	oral
	Hydroxychloroquine	Inhibition of immune activation by reducing TLR signaling and cytokine production	oral
Biologic DMARDs			
	Infliximab	Chimeric mAb against TNF α	i.v., s.c.
	Etanercept	Fusion protein which traps TNF α	s.c.
	Adalimumab	Human mAb against TNF α	s.c.
	Golimumab	Human mAb against TNF α	s.c.
	Certolizumab pegol	Pegylated humanized mAb against TNF	s.c.
	Anakinra	Antagonist of IL-1 receptor	s.c.
	Rituximab	Chimeric mAb against CD20 epitope	i.v.
	Abatacept	Fusion protein of CTLA4 and IgG1Fc	i.v., s.c.
	Tocilizumab	Humanized mAb against IL-6 R	i.v., s.c.
	Sarilumab	Human mAb against IL-6 R	s.c.
Targeted synthetic DMARDs			

	Tofacitinib	Inhibition of multiple JAKs	oral
	Baricitinib	Inhibition of multiple JAKs	oral
	Upadacitinib	Inhibition of JAK1	oral

Note: i.v. - intravenous; s.c. - subcutaneous; mAb - monoclonal antibody; R - receptor; TLR - Toll-like receptor; JAKs - Janus kinases

IL-6 inhibitors are represented by tocilizumab and sarilumab. Tocilizumab is an IL-6 re-ceptor antagonist, dosed at 8 mg/kg by i.v. route, every 4 weeks in patients with moderate-to-severe RA. It reduces inflammation and CRP levels within 2 weeks, with 50–60% of patients achieving remission (Navaro-Milan et al., 2012). Sarilumab is a recently developed drug from the same class, reserved to patients with uncontrolled form of RA (Fleischmann et al., 2017).

The safety profile of biologic DMARDs is superior to conventional drugs, severe adverse effects being rare. Injection site adverse effects were cited by several studies, but they were usually benign. A more significant adverse effect is the risk of serious bacterial or viral infections (Brown et al., 2024). Although the majority of infections in patients treated with biologic DMARDs are caused by common pathogens, in rare cases opportunistic infections were reported, reactivation of tuberculosis and B hepatitis being major concerns. The risk of serious infections also depends on patient's pre-existent comorbidities, use of corticosteroids and disease activity. Therefore, it is recommended that all patients should require a screening for tuberculosis and B hepatitis prior to the administration of biologic DMARDs (Salliot et al., 2009). No sufficient data were collected to present date to indicate if a particular drug from biologic DMARDs class carries an augmented risk of infections, compared to the other representatives. Although some reports have indicated an augmented risk of malignant melanoma in patients treated with TNF-α inhibitors, larger studies have not found any increase in melanoma risk in Europe (Mercer et al., 2017).

The authorization of biologic DMARDs has revolutionized the pharmacological therapy of RA, improving the patient's quality of life, but the high treatment cost poses a significant problem in developing nations. Thus, the recent development of biosimilars for several molecules from this class (infliximab, adalimumab, etanercept) has increased the use of biologic DMARDs in larger categories of patients with RA, worldwide (Brown et al., 2024; O'Neill et al., 2024).

4.2.3. Targeted synthetic DMARDs

The recently authorized drugs from the class of targeted synthetic DMARDs have a small molecular size, being able to act intracellularly by interfering specific cell signaling mechanisms. They are generally represented by Janus kinase inhibitors (tofacitinib, baricitinib, upadacitinib) and have the advantage of oral administration (Singh et al., 2016). Janus kinases family (JAK1, JAK2, JAK3, TYK2) are intracellular proteins located in a variety of immune cells, which act as signal transducers from cytokine signaling, being involved in the activation of transcription processes via JAK/STAT pathway, leading to an inflammatory response. Hence, the

inhibition of Janus kinases with small molecules exerts a significant favorable effect in autoimmune diseases like RA, limiting inflammatory reactions (Singh et al., 2016; Brown et al., 2024).

Tofacitinib and baricitinib are considered first generation drugs, inhibiting multiple types of JAKs while upadacitinib is a second-generation drug, inhibiting only JAK1. The American College of Rheumatology (ACR) guidelines published in 2021 recommend targeted synthetic DMARDs in patients with an inadequate response to conventional antirheumatic drugs. The available data did not show significant differences between biologic and targeted synthetic DMARDs concerning effectiveness in RA (Lauper et al., 2022).

Tofacitinib is a first-generation Janus kinase inhibitor, dosed at 5–10 mg orally twice daily which disrupts cytokine signaling, achieving remission in 30–40% of patients within 4 weeks (Lundquist et al., 2014). The newly authorized baricitinib and upadacitinib are less used in RA, several phase 4 studies being currently ongoing in order to investigate their safety profile (Radu and Bungau, 2021; Brown et al., 2024).

Adverse reactions for targeted synthetic DMARDs include upper respiratory infections, herpes zoster virus infections, hepatotoxicity, and hematologic abnormalities, requiring monitoring of liver enzymes and blood counts. Also, the rate of major adverse cardiovascular events (MACE) and malignancies was higher in patients treated with tofacitinib compared to anti-TNF compounds (Lundquist et al. 2014; Ytterberg et al., 2022).

5. International guidelines and treatment algorithms of RA

The main objectives of RA drug treatment are to achieve remission, preserve joint function, and minimize systemic complications with the ultimate goal of improving patients' quality of life. The international treatment guidelines of the European Alliance of Associations for Rheumatology (EULAR) from 2022 and of American College of Rheumatology (ACR) from 2021 recommend a treat-to-target approach, aimed at rapidly suppressing the inflammatory disease activity with cost-effective drugs which have also a good patient acceptance. The treatment's target would be either a significant remission or a reduction of disease activity evaluated by a disease activity score (DAS) which takes account of the affected joints (Fraenkel et al., 2021; Smolen et al., 2023).

In the early stages of rheumatoid arthritis, both EULAR and ACR guidelines recommend that the drug of choice should be methotrexate used at low doses, in newly diagnosed patients. A bridging short-term treatment with corticosteroids can be administered at the time of the initial diagnosis. Dose escalation protocols could be employed for methotrexate, or another conventional DMARD could be introduced, if needed (Fraenkel et al., 2021; Smolen et al., 2023; Gao et al., 2024).

In patients not reaching their treatment target with conventional drugs, a biologic/targeted synthetic DMARD should be introduced. ACR guidelines equally recommend biologic and targeted synthetic DMARDs, while EULAR guidelines specify that JAK inhibitors should be considered only after an evaluation of pertinent risk factors. Certain modifications of the international guidelines may exist at national level. In the United Kingdom, NICE guidelines recommend that failure of two conventional DMARDs is required ahead of the introduction of a biologic/targeted synthetic DMARD (NICE, 2018).

The choice of the initial biologic/targeted synthetic DMARD is a complex aspect, not very well clarified in the available guidelines. In case of an inadequate response to the initial

drug, subsequent biologic/targeted synthetic DMARDs can be introduced. There is evidence that in case of failure of response to a first TNF-α inhibitor, it is preferable to choose a second biologic DMARD with a different mechanism of action than use another anti-TNF agent (Emery et al., 2015).

The safety profile of a specific molecule and patients' comorbidities also plays a role in the process of DMARD selection. Thus, the potential adverse effects or contraindications could exclude certain treatment options in specific patients, according to the concept of "therapeutic matchmaking" recently introduced in the scientific literature (Konzett and Aletaha, 2024).

6. Natural compounds with antirheumatic properties

Alongside the authorized synthetic drugs used in the therapy of RA, a number of medicinal plants have in their chemical composition potential anti-arthritic constituents, with various mechanisms of action, which are generally well tolerated and could be used as adjuvants (Kaur et al., 2024). Several studies have demonstrated that specific natural compounds can alleviate rheumatic symptoms by targeting inflammatory pathways, offering a holistic approach to disease management, but further research is needed to ascertain their potential role in the therapy of RA.

Boswellic acid (BA), a terpenic compound from *Boswellia serrata* (Burseraceae) can reduce glycosaminoglycan degradation, which could maintain joint integrity and alleviate arthritis symptoms. In preclinical studies, BA reduced cartilage loss, exerting a beneficial role in synovitis, osteoarthritis and other joint disorders by inhibiting 5-lipo-oxygenase (5-LOX), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and cyclo-oxygenase-2 (COX-2) (Safayhi et al., 1992). A meta-analysis of 7 clinical trials enrolling 545 patients with arthritis showed that the administration of Boswellia serrata extract for a mean period of 4 weeks reduced pain and improved joint mobility (Yu et al., 2020).

Quercetin (QU) is a flavonoid present in a variety of plant species and known for its anti-inflammatory properties. In a preclinical adjuvant-induced arthritis model in rodents, QU lowered the production of macrophage inflammatory mediators by regulating NF-kB activity and indirectly inhibiting angiogenesis and cartilage damage (Haleagrahara et al., 2017). In a clinical trial, the administration of quercetin 500 mg/day for 8 weeks in female patients with RA improved clinical symptoms like after-activity pain and morning pain (Javadi et al., 2017).

Epigallocatechin-3-gallate (EGCG), abundant in green tea (*Camellia sinensis*), could also serve as an effective adjunct therapy for RA. Preclinical studies showed that EGCG inhibited pro-inflammatory mediators like PGE2, COX-2, NF-κB and TNF-α (Ahmed, 2010). Also, EGCG suppressed autoimmune arthritis through the modulation of nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, according to another experimental study (Yu G et al., 2020). In a randomized controlled trial enrolling 50 patients with arthritis, a 4-week administration of green tea extract alongside an NSAID agent improved pain control and joint functions (Hashempur et al., 2018).

Peoniflorin, a terpenic glucoside present in paeony (*Paeonia lactiflora*) is a modulator of important intracellular pathways involved in inflammatory processes like MAPK and JAK/STAT, also reducing the level of TNF-alpha and IL-1 (Zhang and Wei, 2020). A meta-analysis of several randomized controlled trials enrolling 463 patients with RA showed

that the administration of total glycosides from peony for 12-24 weeks alongside methotrexate or leflunomide improved clinical outcomes, reducing also the intensity of the adverse effects of the conventional DMARDs (Huang et al., 2019).

Conclusions

Rheumatoid arthritis is a complex autoimmune disease requiring early treatment to achieve remission and prevent disability. Conventional DMARDs, particularly methotrexate, form the backbone of therapy, but newer biologic and targeted synthetic DMARDs are offering a superior control for refractory disease. Despite recent progress, challenges such as high treatment cost or the development of adverse effects warrant new research aimed at developing safer and more accessible therapies for rheumatoid arthritis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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