

Review

Rheumatoid Arthritis Has Won the Battle but Not the War: How Many Joints Will We Save Tomorrow?

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Abstract: Rheumatoid arthritis refers to joint diseases of unclear etiology whose final stages can lead to unbearable pain and complete immobility of the affected joints. As one of the most widely known diseases of the joints, it serves as a study target for a large number of research groups and pharmaceutical companies. Modern treatment with anti-inflammatory drugs, including janus kinase (JAK) inhibitors, monoclonal antibodies, and botanicals (polyphenols, glycosides, alkaloids, etc.) has achieved some success and hope for improving the course of the disease. However, existing drugs against RA have a number of side effects which push researchers to elaborate on more selective and effective drug candidates. The avant-garde of research, which aims to develop treatment of rheumatoid arthritis using antisense oligonucleotides along with nonsteroidal drugs and corticosteroids against inflammation, increases the chances of success and expands the arsenal of drugs. The primary goal in the treatment of this disease is to find therapies that allow patients with rheumatoid arthritis to move their joints without pain. The main purpose of this review is to show the victories and challenges for the treatment of rheumatoid arthritis and the tortuous but promising path of research that aims to help patients experience the joy of freely moving joints without pain.

Keywords: rheumatoid arthritis; joints; inflammation; antisense oligonucleotides



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1. Introduction

Examination of European and North African skeletal remains has revealed that ancient people suffered from different forms of arthritis: osteoarthritis, gout and spondyloarthritis [1,2]. Paleontological analysis of samples dating back several millennia show characteristic features of rheumatoid arthritis (RA) among indigenous tribes in North America [1,3]. A severe climate is a known factor responsible for rheumatoid arthritis [4,5], which may explain these paleontological findings.

One of the first statements in describing the details of RA was recorded in the doctoral dissertation of the French physician Augustin Jacob Landré-Beauvais [6,7], written in 1800. He defined this symptom and proposed the term aesthetic gout. Alfred Garrod, an English scientist, first used the term ‘rheumatoid arthritis’ in 1859 [8].

Rheumatoid arthritis (RA) is a difficult to treat disease. This disease is characterized by synovial inflammation (synovitis), which affects bone turnover and the ability of bone to adapt to bone tissue when replacing the cartilaginous matrix with mineralized bone [9]; it also leads to degeneration of bone tissue [10]. Patients with this disease experience pain in their joints, accompanied by stiffness, which limits their mobility. In addition, over time, this disease can destroy both cartilage and bone; limited mobility becomes active disability and may lead to deformed joints. Along with deformity, extra-articular manifestations such as vasculitis and scleritis can also be observed [11,12].

Among common risk factors, cigarette smoking has the strongest association with RA [13–16]. Tobacco smoking, does not cause rheumatoid arthritis but leads to a worsening

of the disease by means of citrullination of tissue proteins [17,18]. Interestingly, Jiang et al. reported that the impact of cigarette uses on the development of RA increased only when smoke was inhaled from cigarettes, but not when tobacco products containing nicotine were chewed, which suggests that nicotine is not significantly involved in the pathogenesis of RA [16,17].

As mentioned above, RA is the most common autoimmune inflammatory arthritis, with incidence of 0.5–1.0% in the northern hemisphere population [19,20]; annually, it occurs in 24–45 people per 100,000 [21]. The disability that attends rheumatoid arthritis is serious and debilitating. An extensive review showed that within 2–3 years of onset, approximately one-third of sick people with rheumatoid arthritis stopped working because of the disease; by 10–15 years after onset, almost two-thirds (50–60%) may be unable to work [22,23]. In addition to deterioration of patients' health, this leads to adverse effects in the global economy [24,25].

The juvenile form of the disease that occupies a significantly higher incidence in comparison with other inflammatory diseases of the joints is a particularly serious problem in children. In some, it may affect vital organs; this, coupled with the inevitable side effects from therapeutic manipulations lead to a deterioration in the health of the entire body [26,27]. Many causes predispose both children and adults to the disease, including heredity, poor hygiene, environmental exposure, poor nutrition, trauma, lactation that lasts a long time, pregnancies, grief, tuberculosis, etc. Among adults, women are more susceptible than men. Worldwide, a large number of organizations share the goals of finding treatments for RA and combating its spread, including the Rheumatology Research Foundation (US) [28], the French Society for Rheumatology (France) [29], and the New Zealand Association of Rheumatologists (NZ) [30] and others.

There is no single cause of rheumatoid arthritis, and its prognosis remains uncertain [31]. But microbiological infections, genetic and environmental factors play a special role in the development of RA. Meta-estimates of the regional prevalence of rheumatoid arthritis in low- or middle-income countries were 0.4% (Southeast Asia), 0.37% (Eastern Mediterranean), 0.62% (Europe), 1.25% (North, Central, and South America), and 0.42% (Western Pacific). A formal meta-analysis cannot be performed for sub-Saharan Africa due to limited data. No significant difference in the prevalence of RA was found between urban and rural areas. While the prevalence of the disease in low- and middle-income men was 0.16%, it climbed to 0.75% in women, a statistically significant difference [32]. Hormones and genetic (X-linked) factors may explain the more frequent occurrence of rheumatoid arthritis among women [33]. For example, estrogens, which control the body's immune response, can lead to autoimmune diseases [34]. To explain gender bias, scientists have shown that women with RA exhibit non-random X chromosome inactivation (XCI), which can cause autoimmunity. It is believed that this error correlates with the presence of a shared epitope and the duration of the disease. Premature immuno aging, characterized by shorter telomere length, is also associated with the presence of SE [35]. An RA study cohort comprising primarily women (77.1%) demonstrated the tendency of the disease to affect middle-aged women; in this study, the median age at diagnosis was 58.7 years and at death was 74.8 years [36]. The mortality risk for patients of either sex with RA is higher than for the general population. Previous studies have confirmed a mortality rate 1.29- to 2.03-fold higher. That being said, while the specific cause of death differs from country to country [37], the main causes of death included an increased incidence in circulatory system, oncological, and respiratory system diseases [36,38]; dementia; and diabetes [39].

2. A Mystery That Still Needs to Be Deciphered

Although assimilation of knowledge in the study of pathogenesis of RA is still incomplete, this disease is widely accepted as an immune-mediated disorder. That immune cells play an important role in the pathogenesis of RA has been shown by studies in which treatment with anticytokine agents, for example a neutralizing Abs against TNF- α , soluble TNF receptor fusion proteins, or rIL-1 β receptor antagonists resulted in the successful

suppression of joint inflammation [40]. Agents that target cytokine-driven immune processes are among the most important clinical treatments used to manage disease in RA patients [41]. Disease-modifying antirheumatic drugs (DMARDs), which are divided into synthetic (sDMARDs) and biological (bDMARDs), are widely used [42]. There are also new targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) such as JAK inhibitors [43], IL-6R inhibitors [44], and anti-CD20 antibodies [45]. TsDMARDs are small molecules that provide protection against pro-inflammatory cytokines, compared to bDMARDs which can block specific extracellular molecules [46]. However, future studies are needed to monitor the risk-benefit ratio, given the increased risk of infectious diseases and thromboembolism, among others. Now, every year there are new medicines that are able to fight this insidious disease. And although there is no way to completely cure rheumatoid arthritis at this time, the goal of treatment implies remission and reduction of side effects [47–49]. In addition, international guidelines on management have been developed that improve the quality of treatment of the disease, based on such treatment principles as a strict control strategy and a targeted approach to treatment [50].

There are three pronounced determinants that can describe the clinical picture of RA: the inflammatory process (swelling, pain, stiffness during movement); the proliferative-destructive process (destruction of joints); and the enzymatic collagenolytic process (primary necrotism) [51]. The intensity of pain is directly related to the activity of the disease as a whole [52]. The pathogenesis of RA has different etiologies of origin. Since the early 1980s, it has been assumed that the spread has a genetic link [53], including exposure to various chemicals on the respiratory tract [54]. There are a variety of ways to counteract RA, and one of the first measures is dietary nutrition, since there are already a number of scientific justifications that show an advantage in combating the disease and lead to a reduction in symptoms [55].

The pathogenesis of the studied disease involves a complex interconnection between B cells, CD4+ and CD8+ T cells, and dendritic cells [56]. Because B cells undergo isotype switching, they are more capable of supporting the inflammatory cascade. In addition, the rheumatoid factor (RF), a group of autoantibodies with the ability to respond to Fc of human IgG, behaves like heterophilic antibodies and cross-reacts with other types of antibodies [57,58]. The participation of the RF in the formation of the immune complex can lead to further fixation of the complement and the involvement of cells that cause inflammation such as macrophages, neutrophils, and lymphocytes. This leads to tissue damage and provides positive feedback for the production of even more autoantibodies. At the moment, a long list of causes for rheumatoid arthritis has been identified, including epigenetic, genetic, hormonal, reproductive, neuroendocrine and comorbid host factors [59].

It appears that macrophage-derived cytokines, for example, tumor necrosis factor alpha (TNF- α) and IL-1 β , are critical to the mediation of inflammatory synovitis; however, it has also been suggested that synovial T cells participate both in triggering the disease and in contributing to the development of the disease in RA. Significant infiltration of the synovial tissue by T lymphocytes has been observed frequently in RA [60]. However, little is known about the direct action of T cells in the development of pathogenesis. While the synovial T cells observed in RA are mainly classified by type of memory type: CD4+ CD45 RO [61] with a pro-inflammatory Th1 phenotype. Compared to TNF- α and IL-1 β , the classical Th1 T-cell-derived cytokine IFN- γ is also rarely seen in rheumatoid joints [62].

Scientists believe that T cells-produced cytokine IL-17 participates in the RA development. IL-17 is frequently produced by T cells clones taken from patients with RA, and it was shown that IL-17 is found in abundance in the synovial fluids of RA patients [63]. Therefore, it comes as no surprise that T cells specifically predisposed to antigen have been shown to be efficacious in the medication of rheumatoid arthritis. Generally, these data suggest that T cells are quite significant albeit their still incompletely understood role in the pathogenesis of RA.

A typical 'Western' diet, rich in calories and insufficient in fiber, increases the risk of disease [64]. However, the intake of omega-3 fatty acids has been led to a reduction

in risk of RA. Investigation of the link between diet and immune diseases has shown that nutritional factors can function as environmental triggers in genetically predisposed individuals. In RA, these triggers set in motion a cascade of events [65] that includes the elaboration of chemokines and cytokines (soluble immune mediators) by cells of joint tissue, such as synovial macrophages, synovial fibroblasts, and chondrocytes, resulting to joint damage and deformity [64,66].

Recently, we began to better understand the etiology of this disease [67]. For instance, we have learned that RA is a heterogeneous disease that, according to the data combining genetic risk factors and autoantibodies, can be classified positive and negative for anti-citrullinated protein antibodies (ACPA). Some critical immune responses manifest very early in RA patients. For example, elevated C-reactive protein levels, ACPA, and RF are detected in some patients years before the clinical symptoms are seen [68].

Studies have been conducted based on function enrichment analysis, which shows that the RA-related modules were significantly enriched in immune-related actions [69]. Hub genes were then identified as candidate genes. This analysis of scientists showed that the expression levels of candidate genes are significantly associated with the immune microenvironment of RA, which in the future may lead to earlier detection of RA disease. A number of other studies have reported that expression quantitative trait loci (eQTL) analysis has revealed dynamic variations in eQTL effects in the context of immunological conditions as well as cell types. These cell type-specific and context-dependent eQTLs showed significant enrichment in genetic variants associated with immune diseases, and they affect cell types, genes and environments associated with disease [70].

It has also been proven that an increase in pre-DC (dendritic cell precursors) in peripheral blood predicted RA treatment resistance. Pre-DC could have patho-physiological relevance to RA treatment response [71].

Moreover, the identification of important cytokine signaling pathways taking part in disease progression along with synovial studies have demonstrated the importance of both adaptive and innate immune responses [72]. The increase in knowledge concerning the pathophysiology of this disease has significantly expanded specific treatment options. Currently we possess a wide range of therapeutic options ranging from established drugs such as steroids and disease-modifying anti-rheumatic drugs to targeted therapies that aim to inhibit particular cells or cytokines [73].

The introduction of drugs that inhibit pro-inflammatory cytokines heralded a significant shift in the progress of the treatment of RA, particularly those that target (TNF- α). Measurement of the amount of this cytokine in the peripheral blood of patients with RA has been used to assess the severity of the disease [74].

3. Achieving Movement without Pain

In addition to adalimumab, drugs such as methotrexate [75], etanercept [76,77], prednisone [78], and leflunomide [79] quite often used in the treatment of RA. These drugs have been in use longer, and for a variety of conditions. Their side effects are also serious and must be considered.

According to EULAR (European alliance of associations for rheumatology) recommendations the biologic and targeting synthetic drugs should be used only after treatment with methotrexate [80]. Methotrexate is the first-choice treatment among most patients [81]. Treatment with methotrexate reduces inflammation but also degrades cartilage. It is unknown whether these clinical responses to methotrexate are evidence of a specific mechanism of action or merely a common final pathway. While it is possible that changes in the production of PGE2 and levels of TIMP 1 may represent the downstream effects of methotrexate on the formation of IL-1 and IL-6, respectively, no conclusive evidence exists to support this. Some of these changes are also observed following treatment with nonsteroidal anti-inflammatory drugs, and the methotrexate-specific pathways have yet to be elucidated [82]. In addition, the number of side effects—some severe—associated with methotrexate are many: nausea, headaches, fatigue, mucositis and hair loss, cytopenia,

interstitial lung disease (ILD pneumonitis), and drug-related liver diseases (fibrosis and cirrhosis of the liver) [83]. Unfortunately, the exact mechanisms of methotrexate toxicity remain unclear [84] (Table 1).

Table 1. Comparative characteristics of drugs against RA.

Drug	Characteristic	Mechanism of Action	Side Effects
Adalimumab	A blockbuster product based on monoclonal antibodies.	The inhibition of TNF- α	Including the risk of developing serious infections, particularly of the lungs [85–87], the development of deep fungal infections [88,89].
Methotrexate	FDA approved folic acid antagonist [90].	Inhibits enzyme AICAR transformylase; acts as an antifolate antimetabolite; leads to suppression of T cell activation, downregulation of B cells, increased sensitivity of activated CD-95 T cells.	Nausea, headaches, fatigue, mucositis and hair loss, cytopenia, ILD pneumonitis, and drug-related liver diseases (fibrosis and cirrhosis of the liver).
Prednisone	Corticosteroid with anti-inflammatory properties.	Promotes conformational changes in the DNA-binding domain, which leads to a displacement of the receptor into the nucleus [91]; action is the binding of prednisone to the glucocorticoid receptor, it promotes conformational changes in the DNA-binding domain, which leads to a displacement of the receptor into the nucleus; anti-inflammatory process is transrepression, in which glucocorticoids prevent the interaction of transcription factors.	Ecchymosis, cushingoid features, parchment-like skin and sleep disturbance [92].
Leflunomide	Anti-rheumatic drug, (teriflunomidum, or A77 1726) [93].	In reversible manner inhibits dehydroorotate dehydrogenase [93].	Gastrointestinal disorders (diarrhea), elevated liver function tests, abdominal pain, nausea/vomiting, allergic reactions, and reversible alopecia [94–96].

Prednisone is another drug used to treat RA. It is a corticosteroid with anti-inflammatory properties and immunosuppressive activity [91,97]. The mechanism of action is the binding of prednisone to the glucocorticoid receptor; it promotes conformational changes in the DNA-binding domain, which leads to a displacement of the receptor into the nucleus. In the latter, various genes are activated, including anti-inflammatory genes [91]. Among these are the genes encoding annexin-1 (formerly known as lipocortin 1), I α B (NF κ B inhibitor), IL-10, and the anti-inflammatory protein MAPK-phosphatase-1. This process, called transactivation, is responsible in part for the anti-inflammatory action of glucocorticoids. Another mechanism involved in the anti-inflammatory process is transrepression, in which glucocorticoids prevent the interaction of transcription factors such as AP-1 and NF κ B with DNA, thereby eliminating the formation of pro-inflammatory cytokines. This transactivation and transrepression inhibit the formation of inflammatory mediators, supporting the powerful anti-inflammatory effect of glucocorticoids [98].

The undesirable effects of corticosteroids are doses and time dependent and vary depending on the drug administered [99]. Some adverse effects follow a linear dose-response pattern, where the incidence increases together with dose increases (ecchymosis, cushingoid features, parchment-like skin and sleep disturbance). Other adverse effects may instead ensue a threshold dose-response pattern, where the probability of the disease only becomes elevated beyond a distinct threshold value (weight gain and epistaxis at prednisone doses greater than 5 mg daily, glaucoma, depression, hypertension at prednisone doses greater than 7.5 mg daily, etc.) [92].

Patients with RA are often prescribed anti-rheumatic drug leflunomide whose primary aim is to reduce swelling and inflammation in the affected joints [97]. The active metabolite of leflunomide (teriflunomidum, or A77 1726) in reversible manner inhibits dehydroorotate dehydrogenase, a step limiting the rate of de novo pyrimidine synthesis [93]. This results in a reduction in the level of circulating pyrimidines and affects their availability for DNA and RNA synthesis, which in turn has an effect on the spreading of immune cells as well as the expression of inflammatory cytokines. Leflunomide inhibits the capacity of T lymphocytes to promote monocytes through direct cell-cell contact in vitro.

Results from a Phase II clinical trial of leflunomide in patients revealed that A77 1726 binds to plasma protein with great efficiency (>99%) [100]. In studies conducted on animal models, leflunomide has been demonstrated to be extremely effective in the treatment of both adjuvant [101,102] and collagen induced arthritis [93,103]. The leflunomide metabolite A77 1726 adjusts lymphocyte proliferation both in vitro [104] and in vivo [105] (it is an equally efficacious immunoregulator of CD4+ and CD8+ T cell proliferation when induced by mitogens mediated by cell surface receptors). Currently, two specific mechanisms of action have been found for A77 1726: inhibition of tyrosine kinases and de novo inhibition of pyrimidine nucleotide biosynthesis at the end of G1 (growth). The most common undesirable effects of leflunomide treatment were gastrointestinal disorders (diarrhea), elevated liver function tests, abdominal pain, nausea/vomiting, allergic reactions, and reversible alopecia [94–96].

Due to the highly complex interaction among genetics and epigenetics, truly individual therapy for RA is impossible at this time. Currently, standard therapeutic algorithms are used, but they are unable to consider the individual characteristics of the patient [73].

Difficulties arise in treatment and prevention; for example, it is not always possible to control the degree and activity of the disease, despite the use of several drugs with different mechanisms of action. The type of RA, which is difficult to treat, is called D2T, which is a heterogeneous and multifactorial disease [106,107].

4. Botanicals as a Beacon of Hope on the Horizon

Herbal preparations used in humans demonstrate their effectiveness in the treatment of rheumatoid arthritis (Table 2). One of the main positive effects is anti-inflammatory and antioxidant activity [108–110]. For example, such an herb as *Boswellia* spp., which has been used in Ayurvedic medicine since ancient times. Activity of boswellic acid and other active natural compounds of *Boswellia* spp. includes inhibition of microsomal prostaglandin E2 synthase-1 (PGE2) and 5-lipoxygenase, reducing the production or activation of inflammatory mediators such as matrix metalloproteinase (MMP)-9, MMP-13, cyclooxygenase (COX)-2, and nitric oxide (NO) and also has analgesic and anti-arthritis effects [104,105]. It has been found to reduce the number of osteophytes by attenuating inflammatory mediators such as C-reactive protein and hyaluronic acid [111–113]. Research by scientists has demonstrated the safety of using *Boswellia serrata* R. [112]. However, knee-related activities of daily living and quality of life did not improve significantly [114].

Polyphenols constitute an alternative direction of using natural compounds against rheumatoid arthritis. Application of an extract from *Curcuma* spp. containing polyphenol curcumin also showed its anti-inflammatory and antioxidant actions [115,116]. Curcumin inhibits the production of inflammatory mediators, such as a variety of MMPs, tumor necrosis factor-alpha (TNF- α), interleukin (IL)-8, IL-1, NO, via diminishing the activation

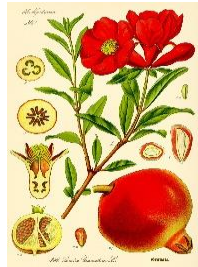
of MAPK signaling pathways protein kinase B (Akt) and NF- κ B [117,118] and leads to a decrease in prostaglandin synthesis [119]. Studies have shown that when compared with the treatment of ibuprofen, turmeric showed more effective results [120], and compared with diclofenac, a small number of side effects [121]. The dried plant *Matricaria chamomilla* L. has been used for many centuries in the treatment of joint pain [122,123]. The plant contains several phenolic compounds: apigenin, patuletin, luteolin, and glycosides [124] that reduce inflammation by reducing the levels of cytokines and PGE2, which play a role in the pathogenesis of arthritis. Epigallocatechin-3-gallate (EGCG), a catechin monomer that has antioxidant and anti-inflammatory effects, is isolated from tea leaves [125]. Green tea extract can inhibit the expression of IL-1 β -induced chemokines. This was studied in an experiment with rats having arthritis [126,127].

Date seeds of *Phoenix dactylifera* L. are a well-known traditional Moroccan remedy for pathological conditions involving inflammation such as RA [128]. The wild pomegranate *Punica granatum* L. has been used as a traditional medicine for various conditions, including pain and inflammation [129]. Pomegranate demonstrated potential inhibition of NO as well as reduction in paw edema in carrageenan-induced mice after administration of 100 mg/kg [130]. Pomegranate juice is one of the natural products that has also shown promising results in clinical trials for the treatment of RA symptoms, which may also be due to polyphenolic compounds with antioxidant and anti-inflammatory effects [131].

Glycosides from different plants show anti-inflammatory effect during rheumatoid arthritis. The root of *Paeonia lactiflora* P. has been used in Chinese medicine since ancient times. Inhibition of the production of leukotriene B4, PGE2, ROS, NO, and other pro-inflammatory mediators by paeoniflorin and total glucosides of paeony has been proven [132]. Combined treatment using this plant and methotrexate has shown beneficial effects in RA with fewer side effects [133]. Decoctions from *Eremostachys laciniata* (L.) are also used for arthritis [134–136]. It is assumed that the iridoid glycosides of this plant exhibited an anti-inflammatory effect. *Curculigoorchioides* G. contains curculiglycoside, which improves arthritis symptoms in rats [128] induced by collagen type II (CIA) and reduces levels of inflammatory factors (TNF- α , IL-1 β , IL-6, IL-10, IL-12 and IL-17A). Its antiarthritic molecular mechanism may be related to the JAK/STAT/NF-Kb signaling pathway [137]. Extracts from the root of *Tripterygium wilfordii* Hook F. also has an immunosuppressive effect and inhibits the expression of pro-inflammatory mediators and cytokines, adhesion molecules and matrix metalloproteinases by macrophages [138–140]. However, adverse reactions have been reported in the form of episodic severe toxicity [141–143].

Alkaloids of some plants show promising results against rheumatoid arthritis too. Synomenine, which is contained in the Chinese medicinal stem *Sinomenium acutum* Thunb., is used in the treatment of rheumatic diseases [144,145]. Synomenine can phosphorylate p62 Ser351, degrade Keap1 and increase Nrf2 expression, and play a role in protecting against bone destruction by increasing p62 expression and activating the p62-Keap1-Nrf2 axis. Research shows that sinomenine has an immunoregulatory effect on RA [146–148]. Dry root of *Aconite kusnezoffii* Reichb. (caowu) has been used for many years to treat RA and relieve joint pain due to its anti-inflammatory properties. Pharmacological studies have shown that diterpenoid alkaloids (mesaconitine, hypaconitine, neolin, talatizamine) are responsible for the main biologically active effects of *A. kusnezoffii* and provide a promising strategy for RA therapy [149,150]. The Radix Linderae, the dry roots of *Lindera aggregata* (Sims) Kosterm. contain the alkaloid norisoboldine (NOR), which has anticancer activity [151]. Also, studies [152,153] have shown that NOR can inhibit bone and cartilage destruction in antigen-induced arthritis (AIA) rats by downregulating the expression of RANKL, IL-6, PGE2, and MMP-13 via the p38/ERK/AKT/AP-1 pathway.

Table 2. Common botanical remedies used to treat and prevent RA.

Plant	Mechanism of Action	Appearance
<i>Boswellia</i> spp.	Inhibition of microsomal prostaglandin E2 synthase-1 (PGE2) and 5-lipoxygenase [104,105].	
<i>Curcuma</i> spp.	Inhibits the production of inflammatory mediators (MMPs), tumor necrosis factor-alpha (TNF- α), interleukin (IL)-8, IL-1, NO [117,118] and leads to a decrease in prostaglandin synthesis [119].	
<i>Punica granatum</i> L.	Inhibition of NO as well as reduction in paw edema in carrageenan-induced mice after administration of 100 mg/kg [130].	
<i>Paeonia lactiflora</i> P.	Inhibition of the production of leukotriene B4, PGE2, ROS, NO [132].	

In recent years, scientists have agreed that a mixed herbal decoction can actively manifest itself in the fight against RA. For example, wutou decoction which consists of ephedra, peony, astragalus, licorice and Sichuan aconite [154]. In a study, wutou decoction was shown to effectively inhibit the expression of iNOS, TNF- α , and IL-6. Another example would be GuiZhiShaoYaoZhiMu Decoction (GSZD), which consists of *Ramuluscinnamomi*, *P. lactiflora* root, *Radix GlycyrrhizaePreparata*, *Ephedra* sp., *Anemarrhenaasphodeloides* Bunge root, *Atractylodesmacrocephala* and *Zingiber officinale* [155,156]. Combination treatment with GSZD and methotrexate was more effective and safer than RA treatment with methotrexate alone [157].

Thus, there is strong evidence that botanicals can help with rheumatoid arthritis, triggering anti-inflammatory and antioxidant activity and decreasing or stopping the speed of biochemical reactions, leading to less pronounced disease. The main disadvantage is that it requires long-term treatment, especially when achieving the goal of pain relief, and adverse reactions can occur [158,159]. Nevertheless, glycosides, polyphenols, alkaloids and other natural compounds produced by plants are very helpful and can strengthen the effect of traditional drugs, or even substitute them in some conditions.

As herbal extracts and nutritional supplements become more popular, research on the potential benefits of herbal supplements for arthritis is growing [160,161]. Modern pharmacological preparations make it possible to relieve the pain and symptoms of RA, as well as improve the quality of life. Concerns about the safety and cost of traditional arthritis treatments have fueled interest in natural remedies. In addition, the difficulty in treating chronic arthritis pain has led to research into herbal therapies. Herbs may offer a complementary or alternative method of effective and safe treatment [162]. The use of herbal medicines among arthritis patients is on the rise, and around 60–90% are expected to seek complementary and alternative medicine options.

In our opinion, the use of botanicals preparations is appropriate in early stages of the disease or when a period of remission begins. In the latter case, botanicals are best used in combination with synthetic and biological drugs (Figure 1). On the contrary, solely synthetic and biological drugs are better in acute stages of the disease.

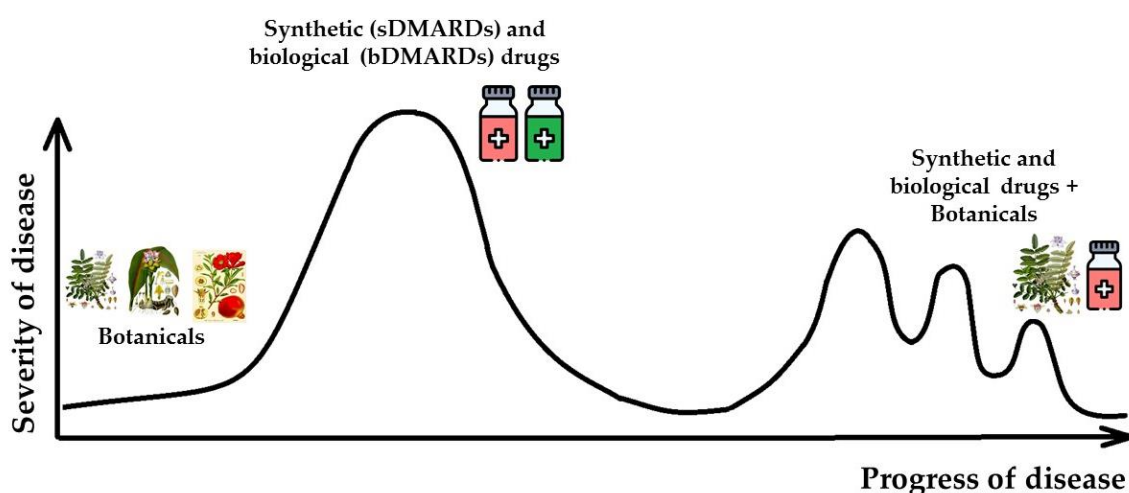


Figure 1. Possible scheme for the use of anti-rheumatoid preparations in different phases of disease development.

There is a widespread belief among scientists that herbs and their extracts can provide a safe and fairly effective complementary therapeutic approach to the treatment of rheumatoid arthritis [163,164]. Scientific research proves that from a pharmacological point of view, natural plant extracts or mixed plant compounds effectively regulate the human immune system to alleviate RA by inhibiting pro-inflammatory cytokines [165].

5. But How Many Joints Will We Save Tomorrow?

Science is always moving forward and actively developing, making new methods of treatment available to human beings.

Today, different approaches exist that help reach successful regeneration, ranging from a gene-manipulated stem cell laden scaffold for cartilage regeneration [166] to a material-free cell therapy [167]. A promising strategy in medicine is the use of antisense techniques. Antisense technology has been widely and thoroughly explored. The perspective of antisense technology is that specific DNA or RNA can connect to target mRNA and afterward turn the ‘undesired’ gene off. According to complementarity principle, designed DNA or RNA molecules target mRNA of interest, effectively resulting in the degradation of the target mRNA or blocking initiation of translation [168,169].

Oberemok’s research group conceptualized and conducted research with the phosphorothioate antisense oligonucleotide (ASO) Cytos-11 that targets TNF- α mRNA. Cytos-11 selectively lowered levels of TNF- α in the peripheral blood and reduced swelling of joints in rats with RA with an efficacy similar to that of adalimumab. Generally, Cytos-11 was well tolerated by the rats, showing a low frequency of immunological reactions. Obtained

results showed the potential of ASO to be used in combination with other drugs or as a monotherapy [170].

In an attempt to develop oligonucleotide therapy aimed at synovitis (an inflammatory disease of the synovial membrane of joints or ligaments with the accumulation of inflammatory effusion in the cavity), modulation of the phenotype of activated proliferative inflammatory synovial fibroblasts using antisense oligonucleotides was documented. For example, antisense oligonucleotides developed by Nakazawa et al. targeting the Notch-1 protein have been reported to inhibit both basal and TNF- α -caused proliferation of human synovial fibroblasts isolated from the synovial membrane of a patient with RA [171,172]. It has also been reported that antisense knockdown of the PTPN11 gene that encodes SHP-2 (a known proto-oncogene) inhibits the migration and survival of synovial fibroblasts [171,173]. Consequently, oligonucleotides targeting lncRNAs, which interfere with regulation in the tissues of an arthritic joint, can provide new therapeutic strategies triggering epigenetic factors involved in joint inflammation [171,174]. It is important to note that since oligonucleotide therapy is based on a particular gene sequence, it is expected that oligonucleotides will work specifically on the target gene and may thereby be less prone to causing non-targeted effects or adverse side effects. Actually, the same basic chemical composition of oligonucleotides and the safety profile determined for oligonucleotide therapy in the clinic show evidence that the failure of late-stage clinical trials with drugs of this class may be less common than with monoclonal antibodies [171].

In another study carried out using human cells, a 20-mer-modified ASO with methoxyethyl protection (ISIS 104838) has been investigated, which showed pronounced efficacy, good tolerance, and drug stability during Stage 1 clinical trials. Its pharmacological effect was found to be a dose-dependent, linear, specific reduction in the synthesis of TNF- α by leukocytes in peripheral blood after stimulation with lipopolysaccharide *ex vivo*; in addition, the highest concentration of ASO in the plasma proportionally and predictably coincided with the dose [170,175].

To us, an additional advantage of antisense technologies in the fight against RA is that treatment with antisense oligonucleotides shows great promise in ending the unbearable pain that accompanies rheumatoid arthritis. These oligonucleotides have proven to be effective pain blockers in other different diseases: nerve injury-induced neuropathic pain [176], spinal muscular atrophy and severe infantile neurological disorder [177], and postoperative pain [178].

In the future, better treatment for rheumatic diseases is indeed possible through the use of new methods of genetic engineering or cell therapy, such as autologous stem cell transplantation [179,180] and CAR-T-cell therapy [179,181]. Although these therapies are currently still risky and costly, the need for effective methods of therapy for autoimmune diseases is urgent, which is why other avenues should be explored as well. In the future, a new goal may be to find a cure, not just remission, for the disease [179].

While there is currently no cure for RA, the treatment aims to expedite diagnosis and promptly achieve a state of low disease activity [182]. Vaccinations may enable the early prevention of RA. Recently, immunization with the protein 14-3-3zeta (ζ), which is involved in T-cell polarization and IL-17A signal transduction, has been shown to suppress arthritis in 14-3-3 ζ knockout inflammatory arthritis rat models by the suppression of IL-1 α levels and amplified collagen production [183]. In another approach, peptide vaccine CEL-4000 utilizes an MHC class-II specific ligand to activate regulatory responses and subsequently trigger the polarization of T helper cell 2 (Th2) [184].

Another promising approach, DEN-181 immunotherapy, introduces liposomal technology to inject collagen II as a liposome-encapsulated antigen together with calcitriol in patients with ACPA-positive RA. Results from a Phase 1 trial have shown that in addition to its effect on antigen-specific T-cells in RA patients, DEN-181 established a good safety profile. Any specific effects of DEN-181 on the prevention of RA will be investigated in future trials [73].

Great progress has been made in the field of disease monitoring and diagnostics. Potential biomarkers or cytokine panels promise to allow earlier diagnosis and treatment monitoring tracking [185]. With ever-improving high-resolution imaging techniques and the widespread availability of ultrasound, RA can be found at a very early stage, allowing even minor disease progression to be assessed [73].

Funds have already begun to appear for predicting the outcome of therapy and treatment of the disease [186]. With the help of artificial intelligence, it is possible to investigate changes in arthritis using X-rays [187] and can be used in silico trials to develop new treatments [188]. These new technologies using computerization will help to make more accurate predictions for patients for the future. The P4 (predictive, preventive, personalized and participatory) medicine approach has also appeared for early diagnosis of the disease and prevention [189].

Thanks to innovative methods, new opportunities appear in the fight against rheumatoid arthritis. Cuproptosis is an innovative method of treatment of rheumatoid arthritis, which is based on the application of the principle of pneumatic compression of the air bag using special equipment. First, cuproptosis in multiple immune cells may be suppressed, and this suppression contributes to their over-proliferation in RA. Secondly, several essential regulatory genes of cuproptosis have been identified to be associated with multiple RA processes, such as aberrant fibroblast-like synoviocytes (FLS) proliferation and inflammatory processes in various immune cells. Cuproptosis is a safe and non-invasive method of treatment that does not require the use of medications or surgical interventions. Well-designed preclinical experiments and clinical trials are still required for in-depth studies of cuproptosis and its associated genes in the context of RA, which still present a significant challenge. However, it is a research direction with great potential [190].

Another innovative method is the use of gene therapy technology. An innovative method of treating rheumatoid arthritis using histone modification is a reliable alternative to traditional approaches. Histones are proteins that pack DNA inside a cell and regulate gene activity. Histone modification consists of changing the chemical structure of these proteins, which allows you to control the activity of certain genes. Found that in PDGF-induced FLS, the expression of Jumonji C family of histone demethylases (JMJD3) was increased through the Akt signaling pathway, and the proliferation and migration ability of FLS was weakened after inhibition or silence of JMJD3, and the symptoms of DBA/1 mice by collagen-induced arthritis were alleviated [191]. Recent research has shown that histone modifications may be involved in the development and progression of RA. Studies have found that specific histone modifications, such as histone acetylation and methylation, are associated with increased inflammation and joint destruction in RA [192].

In recent years, a method of treating rheumatoid arthritis based on the use of phosphates has been developed. Studies have shown that phosphates can have an anti-inflammatory effect by reducing the production of inflammatory cytokines. They are also able to improve the function of the immune system. Dexamethasone sodium phosphate (DSP) is another anti-inflammatory and immunosuppressive glucocorticoid known to be used frequently in treating RA by decreasing cytokines expression and impeding functions of leukocyte, fibroblast and endothelial cells. Delivered using the beta-cyclodextrin nanocarriers (DSP-loaded H- β CD nanoparticles) was effective for RA in the AIA rat model. Thus, the use of nanocarriers has overcome the limited applications of DSP alone in chronic diseases and has been reported to be able to reduce arthritic score, paw thickness, and cytokine level [193].

It is obvious that today medical preparations have achieved better results in the treatment of RA (Figure 2). However, herbal preparations also have potentially high prospects but have not yet been fully disclosed. Joint application of both botanicals and medical preparations, may bring us to new era of RA treatment, safe and efficient for patients.

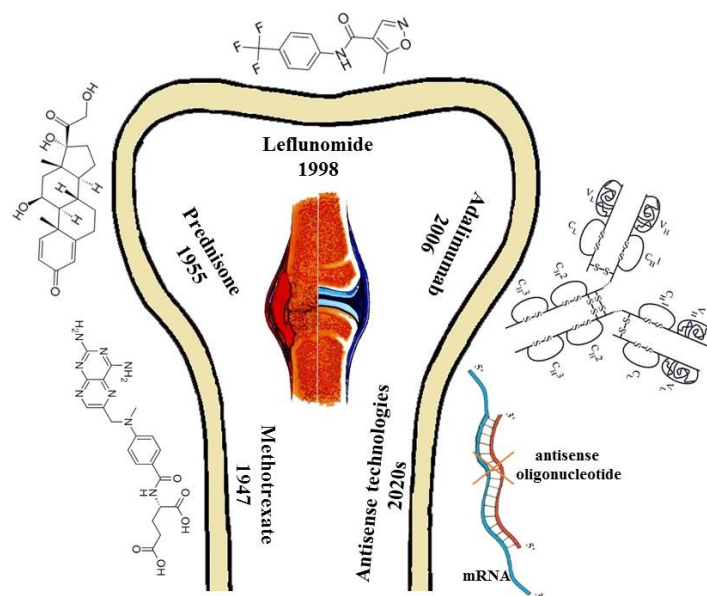


Figure 2. The evolution of medicines for the treatment of rheumatoid arthritis: beginning from methotrexate to prednisone, leflunomide, adalimumab and ending with antisense oligonucleotide.

6. Conclusions

Rheumatoid arthritis does not kill quickly but today it looks like a sentence to a hard-to-treat disease. This, coupled with the many different factors that can trigger RA, may explain why this disease is not treated successfully, with continued high incidence. Now the range of drugs is extensive, and nevertheless has its negative sides. Namely, side effects such as nausea, headaches, fatigue, allergic reactions, and hair loss.

A beacon of hope on the horizon is the use of botanicals (polyphenols, glycosides, alkaloids, etc.) and antisense technologies, which have already proven themselves in a number of studies on the treatment of rheumatoid arthritis [194], as well as on the relief of pain in the treatment of diseases such as neurological dysfunction.

Two other useful proactive strategies are vaccination and early diagnosis of the disease, both of which can help prevent and forestall the development of any disease that has already begun. As far as treatment of ongoing disease, the ideal drug has not yet been found, and all of those in use have their side effects. But the prospects for the treatment of rheumatoid arthritis, despite its tortuous solutions, are bright, with promising areas of research fueled by people determined to help these patients. Though today's battle is lost to rheumatoid arthritis, humanity prepares its joints for the win in the war for movement without pain.

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