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Pathogenesis and treatment of rheumatoid arthritis with focus on herbal therapeutic approaches (Review)

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Abstract. Rheumatoid arthritis (RA) is a disease in which the body cells are unable to recognize their own components; the condition is termed an autoimmune disorder. It is an inflammatory disease and the lining of the joints is mainly affected, which is known as synovial inflammation. This leads to pain, stiffness, numbness, fever and oedema; due to these symptoms, affected individuals are unable to perform daily tasks. The condition is more commonly reported in females compared to males. Several advancements in diagnostics, clinical tests and allopathic medications have been achieved for the treatment of RA; these include disease-modifying anti-rheumatic drugs and non-steroidal anti-inflammatory drugs, corticosteroids, which are being used in patients with RA patients. However, although patients experience symptom relief with these treatments, these treatments are also associated with adverse side-effects. Therefore, in an aim to identify safer treatments with minimal or no side-effects, focus is being placed towards ayurvedic and herbal medicines. Some plants have been reported to possess anti-inflammatory activity, which may be beneficial for the treatment of RA. However, research is still ongoing for a number of the unexplored plants with anti-inflammatory and anti-arthritic activity. Examples of such substances include drugs, natural compounds and herbal extracts. In the coming years, it is expected that more herbs will be available commercially for the treatment of RA. With a focus on herbal therapies, the present review discusses the current therapy paradigms and aims to provide a thorough investigation of the pathophysiological factors causing RA. The present review also discusses the integration of phytochemicals into contemporary rheumatology, new developments in herbal pharmacology, and the difficulties in standardization, bioavailability and clinical validation. Further high-quality clinical trials, mechanistic investigations and translational research are necessary to establish safety profiles, optimise therapeutic formulations and facilitate regulatory approval. The present review attempts to close the gap between modern evidence-based therapy and traditional herbal knowledge by synthesising recent scientific material, opening the door to a more individualised and integrative approach to treating RA.

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Contents

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by chronic inflammation, primarily affecting the synovial joints. It is a debilitating condition that can lead to joint deformities, functional impairment and a diminished quality of life. RA is distinguished by its unique immunopathology, involving the infiltration of inflammatory cells into the synovial membrane, leading to the destruction of articular structures. Of note 15-20% of the Indian population suffers from this disease. Females are three-fold more prone to developing RA than males (1). This condition typically manifests between the ages of 35 and 60 years, with periods of remission and aggravation. A condition known as juvenile RA, is comparable to RA, but does not have the rheumatoid factor. It affects young children, even those <16 years of age (2) (Fig. 1).

The exact aetiology of RA remains complex and multifactorial, with a combination of genetic, environmental and immunological factors contributing to its onset and progression. The hallmark of RA is the persistent inflammation of the synovial lining, leading to synovial inflammation, and subsequent cartilage and bone destruction. In RA, synovial hyperplasia is the main cause of bone damage; it involves the abnormal proliferation (excessive growth) of the synovial membrane, the specialized connective tissue lining the inside of joints, tendons and bursae. It is a hallmark of inflammatory joints and significantly contributes to joint damage and dysfunction. Chronic inflammation, immune dysregulation, genetic factors and angiogenesis lead to synovial hyperplasia (4). Immune cell infiltration refers to the accumulation and migration of immune cells (such as T-cells, B-cells, macrophages and others) into the synovial membrane of affected joints. This process is a hallmark of RA and plays a central role in driving inflammation, joint damage and the progression of the disease. In RA, the synovial membrane becomes inflamed and swollen due to the infiltration of immune cells. This inflammation leads to the formation of a thickened synovial tissue known as the 'pannus', which invades cartilage and bone (5).

This inflammatory cascade involves the dysregulation of various cytokines, including tumour necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1. The immune response in RA is not confined to the joints, as systemic manifestations can affect organs, such as the skin, heart, lungs and blood vessels. Clinically, RA presents with symmetrical polyarthritis, involving multiple joints on both sides of the body. Morning stiffness, swelling and pain are common symptoms, and if left untreated, the disease can progress to irreversible joint damage. Early and accurate diagnosis is crucial for implementing timely interventions to attenuate or halt disease progression. Extra-articular signs including keratitis, pulmonary granulomas (rheumatoid nodules), pericarditis/pleuritis, small artery vasculitis and other non-specific extra-articular signs are possible in poorly managed or serious conditions (6). The underlying cause of RA remains unknown, despite the fact that several biomolecular pathways have been postulated. The dysregulation of citrullination causes the generation of anti-citrullinated protein antibodies (ACPAs). The immunological reaction against self-antigens is aided by these autoantibodies, which causes joint injury and synovial inflammation (7,8)

In addition to providing a thorough discussion of contemporary treatment approaches, with an emphasis on herbal therapy, the present review discusses the pathophysiology of RA. In addition to discussing standard pharmaceutical treatments, including biologics, small-molecule inhibitors and targeted therapy, the present review also summarises the molecular and immunological pathways that underlie the progression of RA (9,10). Furthermore, the present review also highlights new developments in herbal medicine. The difficulties encountered in incorporating herbal remedies into conventional RA care are also discussed, and possible directions are suggested for further investigation. The present review attempts to present a comprehensive discussion of RA treatment by combining the most recent scientific data, highlighting the possible contribution of herbal remedies to improving therapeutic results.

2. Factors affecting rheumatoid arthritis

Genetic factors. RA is generally categorised into two subtypes: 'Seropositive' and 'seronegative' disease. Seropositivity is characterised by elevated serum levels of the autoantibodies rheumatoid factor (RF) and the recently identified ACPAs. Multiple factors have strongly demonstrated that the development of RA is significantly influenced by genetic makeup. One of these factors is the overall higher rate of RA in families;

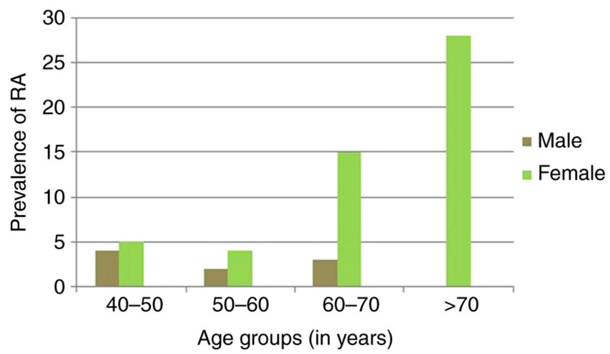

Figure 1. Graph illustrating the global prevalence of RA of different age groups until 2020 (3). RA, rheumatoid arthritis.

it is estimated that 40-50% of seropositive RA is caused by familial risk, with first-degree relatives (FDRs) bearing the highest risks.

A group of alleles in the major histocompatibility complex that encode amino acid sequences that indicate structural similarities in the human leukocyte antigen (HLA) peptide-binding groove have been dubbed the 'shared epitope', or SE, collectively (11). The notion of the 'shared epitope' was first proposed by Gregersen *et al* (12) in 1987 and it has a well-established association with RA that is positive for the ACPA. These alleles are the most potent genetic risk factors. It is believed that SE alleles collectively account for up to ~40% of the hereditary risk of RA; however, some research indicates a lower contribution. The HLA class II area on chromosome 6, which has the highest risk effect for a number of autoimmune disorders, including RA, may have genetic variations. However, as the strongest genetic propensity to RA is linked to the inheritance of specific HLA-haplotypes, the HLA association in RA is unique and different in and of itself. Genetic marker HLA-DRB1 alleles, particularly DR4 and DR1, define molecules with a five-amino acid 'shared' motif (QKRAA, QRRAA, or RRRAA in positions 70-74 of the DRB1 chain) that encodes the positively charged P4 peptide-binding pocket. This motif has come to be known as the shared epitope (SE) (12). Notably, in addition to the HLA-DRB1 gene, three other statistically significant HLA loci are also independently linked to RA susceptibility: Two associations within HLA class I genes (amino acid position 77 of HLA-A and amino acid position 9 of HLA-DPB1, another HLA class II gene. Using HLA and non-HLA risk alleles, Zhang *et al* (13) created RA genetic risk scores (GRS) and conducted a phenome-wide association study, examining the association between the RA GRS and phenotypes using multivariate generalised estimating equations that controlled for age, sex and the initial five main variables. Out of 20 phenotypes, 13 (65%) were immune-mediated conditions, including multiple sclerosis, granulomatosis with polyangiitis, polymyalgia rheumatica and type 1 diabetes. They also discovered a novel collaboration in coeliac disease, where the HLA and non-HLA alleles had strong associations in opposite directions (13). The processes of autoimmunity and autoinflammation in the recently identified inborn errors of immunity (IEIs) have been outlined by Sogkas and Witte (14), and they may be pertinent to the pathophysiology of rheumatic illnesses. Differentiating patients with RA with an underlying IEI can become a key issue therapeutically in daily clinical practice, particularly as it is becoming more well acknowledged that IEIs can present as a well-classified rheumatic illness. Unusual extraarticular manifestations in RA may help identify rheumatic patients with an underlying IEI through genetic testing, in addition to clinical or laboratory evidence of immunodeficiency, such as hypogammaglobulinemia or altered B-cell development (14).

Environmental factors. There are several dietary, lifestyle and environmental factors that have been linked to RA; however, tobacco exposure is the key factor. Numerous studies have discovered odds ratios of links between smoking and RA, and it is estimated that 20-30% of risk factors for RA involve exposure to smoke. However, there are a number of aspects of the smoking-RA association that may act as mediators of the elevated risk for the development of RA. The main finding is that smoking is most strongly linked to ACPA-positive RA, particularly when the SE is present. Furthermore, even when RA is not present, smoking has long been linked to the occurrence of RF. The implication is that RA may be caused by biologic interactions among these variables. Although there are numerous other local and systemic effects of tobacco use that may affect immunity, it has been suggested that smoking may increase citrullination, which, in the presence of the proper genetic background, results in the presentation of citrullinated proteins and the generation of ACPA (15). In addition to exposure to tobacco smoke, numerous studies have consistently revealed a link between occupational silica/dust exposure and RA, specifically ACPA-positive RA (16). The risk of RA has also been disparately associated with a number of dietary or other factors, including supplements or drugs (17). These include a higher risk of developing RA due to a decreased intake of vitamin D and antioxidants and a higher diet intake of sugar, sodium, red meat, protein and iron. Additionally, in the FDRs of RA patients who did not have classifiable RA at the time of the study, the self-reported consumption of omega-3 fatty acid supplements and fatty acid biomarkers revealed that higher blood levels of fatty acids and increased intake were linked to a lower risk of RF and ACPA positivity (18). Furthermore, the risk of RA has been linked to healthy lifestyles, such as a lower body mass index and healthier diets that are generally high in fruits, whole grains, and vegetables and low in sugar and animal fats, but these definitions vary throughout research (19). Laragione *et al* (20) examined the effects of a high-magnesium diet in two distinct mouse models of collagen-induced arthritis and RA induced with KRN serum. The high-magnesium diet group was notably protected with decreased joint damage and arthritis severity, as well as the decreased expression of IL-1β, IL-6 and TNF-α. Additionally, the high-magnesium group had higher numbers of $Foxp3^+$ Treg cells and IL-10-producing T-cells. They represent a new role for magnesium in suppressing arthritis, in expanding Foxp3+ T reg cells, and in the production of IL-10, and demonstrate that these effects are mediated by the intestinal microbiome. Their findings suggest a novel approach to altering the intestinal microbiome to treat RA and other autoimmune and inflammatory diseases (20).

Immune system dysregulation. Immune system dysregulation plays a central role in the etiology of rheumatoid arthritis (RA), which is an autoimmune disease characterized by chronic inflammation and joint destruction. The immune system fails to distinguish self from non-self, leading to the recognition of self-antigens as foreign. Proteins modified by citrullination (conversion of arginine to citrulline) are misidentified as threats. This results in the development of autoantibodies, such as RF and ACPAs, which are hallmarks of RA. Dysregulated immune cells release excessive pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6. This affects the recruitment of inflammatory cells (e.g., macrophages and neutrophils) and increases synovial inflammation and hyperplasia (pannus formation). Immune dysregulation leads to the chronic inflammation of the synovial membrane. Proliferating synovial tissue invades cartilage and bone, which causes bone resorption in which osteoclast activation by cytokines [e.g., receptor activator of NF-κB ligand (RANKL)] leads to bone erosion (21).

As one of the main pro-inflammatory cytokines in RA, TNF-α, has been shown to increase inflammation by upregulating TNFR II, activating the NF-κB pathway, and causing RA-fibroblast-like synoviocytes (FLS) to secrete RANKL for osteoclast formation. Likewise, in RA, macrophages are the primary source of IL-1, which triggers potent and rapid inflammatory reactions. Furthermore, RA is partially caused by chemokines, including IL-8, monocyte chemoattractant protein-1 and C-X-C motif ligand 13, as well as other inflammatory factors, such as IL-12, IL-15, IL-18, IL-32 and granulocyte-macrophage colony-stimulating factor. These cytokines contribute to the pathogenic inflammatory environment within the synovium by forming a complex network with one another, even though they cannot directly cause RA (22).

3. Diagnosis of rheumatoid arthritis

The early diagnosis and identification of short-term inflammatory arthritis that progresses to chronic RA in the future can be challenging in normal clinical procedures. More patients with inflammatory arthritis have a moderate-to-high disease activity, and some experience aggressive joint deterioration and systemic consequences, compared to a small number of patients who may experience spontaneous remission and others who may have a mild disease history with slow progression. Consequently, there is a need for imaging evaluations and/or laboratory biomarkers that would be more useful in the early detection of illness.

The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) categorisation criteria for RA included acute phase reactants and ACPAs, particularly at elevated levels, which are linked to aggressive illness. The revised classification criteria for RA were established by the ACR and the EULAR in 2010. These criteria replaced the older 1987 ACR criteria to improve the early diagnosis and classification of RA. This system assigns a score from 0 to 10, with a score of ≥6 classifying a patient as having definite RA (23). Therefore, meeting these requirements encourages doctors to begin the right treatment as soon as possible to prevent irreparable harm. To further enhance the diagnosis of RA, novel biomarkers are still required, even with the high diagnostic value of RFs and ACPAs. Recently, a number of new autoantigens and antibodies have been discovered that could help with early diagnosis and forecast the future progression of the disease. Imaging methods, particularly ultrasound (US), may enhance the early detection of RA in addition to clinical symptoms and serological testing, particularly in individuals who test negative for the disease (24).

High resolution multiplanar images of soft tissue, cartilage and bone profiles can be obtained using US. The early diagnosis and monitoring of chronic arthritis can benefit from the careful evaluation of the smallest structural changes made possible by the high resolution of the most recent generation of US technology. The extent and distribution of the different characteristics of cartilage degradation can be thoroughly analysed using US. The most striking illustration of the devastation that chronic arthritis can cause is bone erosions. Due to the high sensitivity of US, bone erosions as minimal as a tenth of a millimetre can be found. The most sensitive morphological biomarkers to forecast the occurrence of erosions later on are most likely the loss of sharpness and subtle abnormalities of the bone pattern at the points to interact with the synovial pannus (25).

For the diagnosis of RA, the most specific serological indicators are ACPAs. According to recent research, the ACPA responses of patients with RA vary widely and are polyclonal. Enzyme immunoassays (EIAs) detect and measure immunologic reactions by using the catalytic properties of enzymes. One heterogeneous EIA method used in clinical analyses is the enzyme-linked immunosorbent test (ELISA). One of the reaction's components is covalently or nonspecifically adsorbed to the surface of a solid phase, like a plastic bead, magnetic particle, or microtiter well, in this kind of test. The separation of bound and free-labeled reactants is made easier by this connection (26). The basis of gene microarray technology is the capacity to deposit a wide variety of DNA sequences on a tiny surface, often a glass slide (commonly called a 'chip'). The various DNA fragments are grouped in rows and columns so that each fragment's identification may be determined by where it is located on the array (27).

A variety of analytical methods based on ELISA and microarray technologies have been used so far, allowing for the accurate early detection of RA due to its diverse response. As regards the former, an ELISA technique was created based on chimeric fibrin/filaggrin synthetic peptide that is extremely sensitive and specific for RA detection when compared to healthy controls and those with other chronic illnesses (28).

Following this technological requirement, the development of electrochemical immunosensors using nanostructured materials, specifically, multiwalled carbon nanotube (MWCNT)-polymer composites, offers the potential for the creation of low-cost, high-sensitivity point-of-care diagnostic devices when certain biomarkers are available, as in this instance. This makes use of a quartz crystal microbalance that has been altered by carbon nanotubes (CNTs), which have been further coated with a synthetic peptide receptor (29). Additionally, a citrullinated specific peptide receptor and a MWCNT-polystyrene (PS) composite transducer are used to create a basic electrochemical immunosensor. Rabbit sera that had already received the citrullinated peptide vaccination were used to evaluate the performance of the device, and human sera from patients with RA were used for additional testing. The advantages of this method are demonstrated by its simplicity in transducer manufacture, covalent modification with the peptide receptor, miniaturisation, and need for inexpensive, basic equipment (30).

4. Pathogenesis of rheumatoid arthritis

The pathogenesis of RA involves complex interactions within the immune system, leading to chronic inflammation and joint damage. RA is considered an autoimmune disease, meaning that the immune system mistakenly targets and attacks the body's own tissues, particularly the synovium (lining of the joints) (31). The exact trigger for this autoimmune response is not yet fully understood, although it is believed to involve a combination of genetic susceptibility and environmental factors. It has been shown that immunological activities, known as the 'pre-RA phase', may take place years before signs of joint inflammation become apparent. Peptide arginine deiminases performs a post-translational alteration known as citrullination on these proteins containing arginine residues, converting them to citrulline (32). Furthermore, cytokine release that may result in joint inflammation and modified self-antigens can be triggered by joint abnormalities, such as synovial hyperplasia or synovial infections (33). Citrullinated proteins (vimentin, type II collagen, histones, fibrin, fibronectin, Epstein-Barr nuclear antigen 1 and α-enolase) are no longer recognised by the immune system as self-structures because of the susceptibility genes HLA-DR1 and HLA-DR4. Antigen-presenting cells are activated dendritic cells that take up antigens in order to start an immune response (34). The entire complex moves to the lymph node, where $CD4^+$ helper T-cell activation occurs. Moreover, B-cells in the germinal centre of the lymph node are stimulated by T-cells in a reciprocating and sequential signalling mechanism known as co-stimulation (35).

The human leukocyte antigen D-related B1 gene (HLA-DRB1) is the most relevant disease-susceptible gene according to genome-wide analysis of single nucleotide polymorphisms in rheumatoid arthritis patients. Other disease-susceptible genes were also found. TNF-α-induced protein 3, cytotoxic T-lymphocyte antigen-4, signal transducer and activator of transcription (STAT)4, C-C motif chemokine ligand 21 and peptidyl arginine deiminase 4 are among these genes. ACPAs are extremely associated with this particular disease, and in individuals who test positive for anti-CCP antibodies, a breakdown of bone or cartilage is more likely to develop (36).

On the other hand, common environmental factors, including smoking, gingivitis and gut bacterial flora can alter the epigenome and demethylate DNA and histones, which triggers the production of pro-inflammatory cytokines (37). Air pollution, which is defined as a mixture of gases (nitrates, ozone, sulphur dioxide and carbon monoxide) and suspended particulate materials (PMs) of different sizes, has recently drawn increased attention to the field of RA. Air pollution may play a role in the aetiology of RA through a few different molecular pathways. Inhaled PM can produce free reactive oxygen species (ROS) that can trigger NF-κB), which in turn triggers T-helper cell type 1 (Th1) to release IL-1 and IL-6, as well as TNF-α. These cytokines stimulate resting monocytes

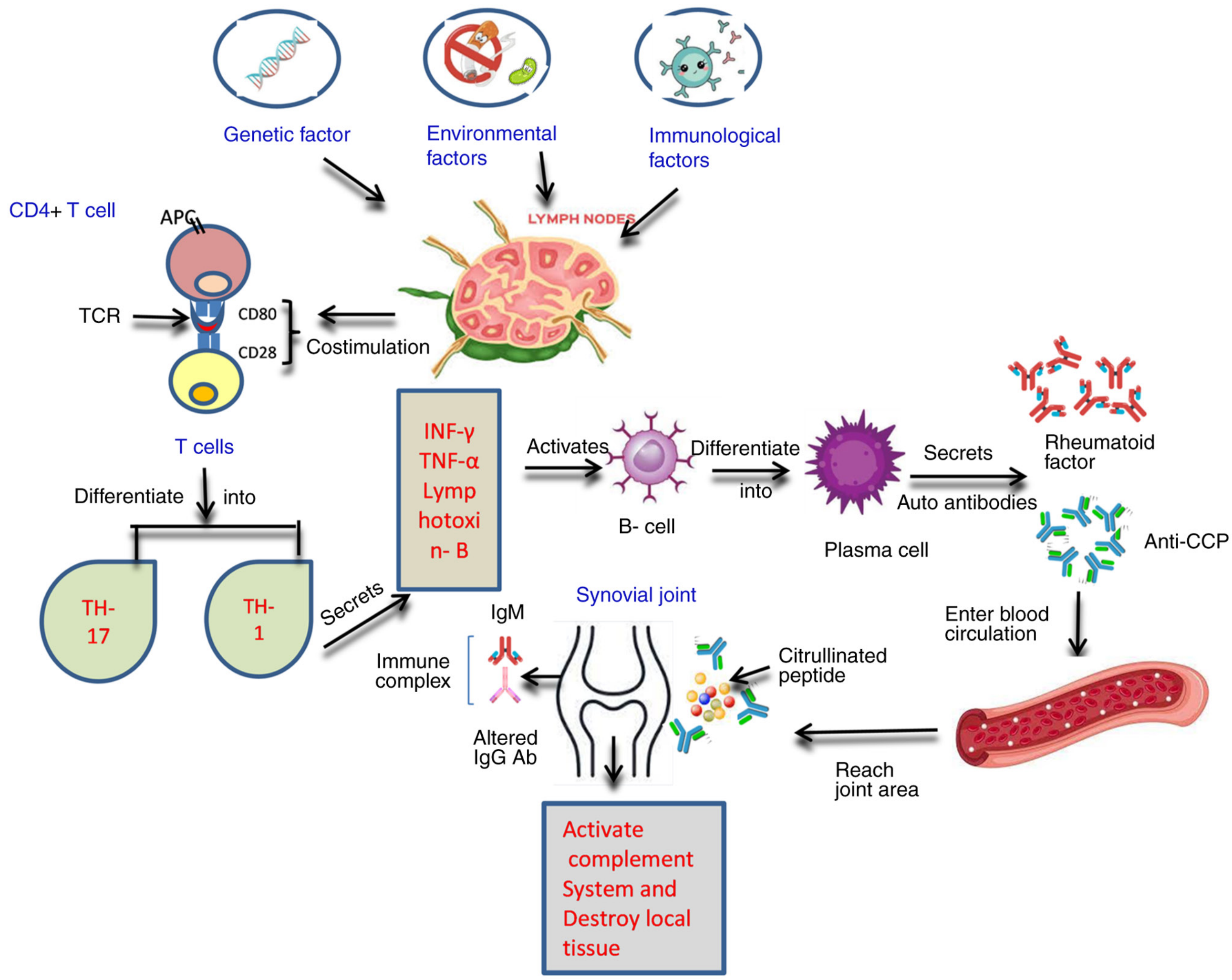

Figure 2. Mechanisms of the pathogenesis of rheumatoid arthritis mediated by chronic inflammation.

to develop into mature dendritic cells. Furthermore, dendritic cells provide auto-antigens to self-reactive T-lymphocytes, triggering the latter to migrate to target tissues and enhance joint inflammation. Furthermore, ROS contribute in the citrullination of arginine amino acid residues into citrullinated peptides, hence promoting systemic inflammation and chronic lung disease. Biochemical events produce ACPAs, which bind to cellular Fc receptors and activate complement to initiate an immune response that causes bone degradation and inflammation in the joints (38).

In RA, the synovium, which lines the joints, becomes inflamed due to the increased presence of immune cells and inflammatory cytokines. Inflammation in the synovium leads to the release of enzymes, such as matrix metalloproteinases, which contribute to the degradation of cartilage and bone (39). Chronic inflammation results in the formation of a thickened layer of synovial tissue (pannus). Pannus invades and erodes the cartilage and bone within the joint, causing structural damage. The ongoing inflammatory process, combined with the action of enzymes and cytokines, leads to the destruction of cartilage, bone, and other joint structures. Joint damage contributes to pain, swelling, and loss of function. In addition to joint involvement, RA can have systemic effects, affecting other organs and tissues. Systemic inflammation may contribute to conditions, such as rheumatoid nodules, vasculitis, and an increased risk of cardiovascular disease (40). RA is a chronic condition characterized by persistent inflammation, with periods of exacerbation (flares) and remission. The chronic nature of the disease can lead to cumulative joint damage over time if not effectively managed (41) (Fig. 2).

5. Therapeutic approaches for rheumatoid arthritis

The therapeutic approaches for RA aim to reduce inflammation, alleviate symptoms, attenuate joint damage and improve the overall quality of life of patients. The main goal of treating RA is to inhibit the disease and induce remission as soon as possible after diagnosis, ideally before joint destruction occurs (42). The non-pharmacological approaches aim to decrease the level of pain, reduce depression and anxiety and enhance mobility. Polyunsaturated fatty acids (PUFAs) have gained increasing attention in the field of depression and anxiety. Docosahexaenoic acid and eicosapentaenoic acid in the series of omega-3 fatty acids are the two components of PUFAs which have been examined for their anti-depressant properties and also to minimize anxiety (43). Other helpful measures include surgery, physical therapy, occupational therapy and rest. Joint surgery is limited to the most advanced phases of RA. Surgical techniques relieve discomfort and help joints function again (44).

The novel treatment alternatives have been successful in minimising symptoms, delaying the course of the condition and averting consequences. Non-steroidal anti-inflammatory drug (NSAIDs), such as ibuprofen, cyclooxygenase (COX)-2 inhibitors and naproxen, are used in the acute phase response to lower inflammation and therefore discomfort. The pharmacological effects of NSAIDs are mediated through inhibition of COX, namely COX-2, the levels of which are increased during inflammation (45).

Although the suppression of prostaglandins may result in severe adverse effects, such as bleeding, gastrointestinal ulcers, renal failure, heart failure, rashes, dizziness, confusion, seizures, etc., the risk of injury should be taken into account. Due to the intricate mechanisms underlying their anti-inflammatory and immunosuppressive actions, glucocorticoids (GCs), such as prednisone, hydrocortisone, prednisolone and dexamethasone are more potent and effective than NSAIDs, although NSAIDs have a slightly better safety record (46). Weight gain, water retention, muscle weakness, diabetes, bone weakening and other long-term adverse effects are associated with the use of GCs. disease modifying anti-rheumatic drugs (DMARDs) are pharmacological medicines that decrease autoimmune activity and delay or prevent joint deterioration in order to induce remission. DMARDs are divided into three categories as follows: Biologic DMARDs (bDMARDs), targeted synthetic DMARDs (tsDMARDs) and conventional synthetic DMARDs (csDMARDs). Depending on the mechanisms through which they function, genetically altered protein molecules known as bDMARDs are categorised into multiple types, such as TNF-α inhibitors, B-cell depleters, B-cell receptor inhibitors, antagonists of CD28 on T-cells, IL-1 inhibitors, IL-6 inhibitors, IL 12/23 inhibitor, IL-17 inhibitors. One of the main obstacles preventing patients from receiving bDMARDs is the high cost of biologics (46-48). Kartnig *et al* (49) used a novel *ex vivo* model culture system that enabled high-content microscopy to characterise a palette of RA-specific small compounds and biologicals with various mechanisms of action along with defined control stimuli. By using this screening approach, they were able to identify known RA-related characteristics linked to certain treatments, such as B-cell depletion following *ex vivo* rituximab treatment and cell-to-cell contact-dependent lymphocyte activation (49). He *et al* (50) provided an overview of the possible processes underlying the impact of total glucosides of paeony (TGP) on the expression level of blood inflammatory cytokines in animal models of RA. Clinically, TGP tablets have been used extensively to treat RA with good effectiveness and safety records. Their research revealed that TGP can lower serum levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 and raise serum levels of anti-inflammatory cytokines like IL-10 when compared to the control group of the RA animal model. This has an anti-inflammatory effect by controlling and enhancing inflammatory cytokine levels, which in turn helps to alleviate the disease (50).

If methotrexate is not contraindicated, it is advised to be the initial standard pharmacological therapy delivered following a diagnosis of RA, even though more than ten conventional synthetic DMARDs have been approved. Compared to other traditional synthetic DMARDs, it is the most effective. Gastrointestinal and liver issues are among the side-effects associated with the use of methotrexate (51). In Japan, an all-case surveillance study of 5,000 patients receiving infliximab over a 6-month period found that 1,401 patients experienced adverse reactions, and 308 patients experienced severe adverse reactions. These included 108 patients with bacterial pneumonia, 25 with interstitial pneumonia, 22 with pneumocystis pneumonia and 14 with tuberculosis (52). On the other hand, targeted synthetic DMARDs are defined as inhibitors against Janus tyrosine kinase (JAKs), which are intracellular signalling molecules like cytokines. The drugs tofacitinib, baricitinib, peficitinib, upadacitinib and filgotinib have varying degrees of selectivity for various JAK isoforms and are used to treat RA. Strict screening should be followed prior to their use, as well as strict monitoring throughout treatment. Patients with severe infections, liver, kidney, or blood cell abnormalities should not use JAK inhibitors. Additionally, long-term safety in terms of the development of infections such as herpes zoster and malignant tumours such as lymphoma need to be demonstrated (53-55) (Table I).

6. Mechanisms of action of therapeutic agents

NSAIDs. The COX enzyme is inhibited by NSAIDs, which is their primary mode of action. Arachidonic acid must be converted by cyclooxygenase in order to produce prostacyclins, prostaglandins, and thromboxanes. The absence of these eicosanoids is considered to be the cause of the therapeutic effects of NSAIDs. In particular, prostaglandins produce vasodilation, raise the hypothalamic temperature set-point, and contribute to anti-nociception, whereas thromboxanes aid in platelet adhesion (70). COX-1 and COX-2 are the two COX isoenzymes. The body constitutively expresses COX-1, which contributes to renal function, platelet aggregation and the preservation of the lining of the gastrointestinal tract. COX-2 is inducibly expressed during an inflammatory reaction rather than constitutively expressed in the body. The majority of NSAIDs inhibit both COX-1 and COX-2 and are nonselective. However, because they only target COX-2, COX-2 selective NSAIDs (such celecoxib) have a different profile of side effects. Crucially, since COX-2 primarily contributes to inflammation and COX-1 is the primary mediator for maintaining the integrity of the gastric mucosa, COX-2 selective NSAIDs ought to reduce inflammation without endangering the gastric mucosa (71).

The gastrointestinal mucosa, cardiovascular system, hepatic system, renal system and haematological system are all known to be negatively affected by NSAIDs. The inhibition of COX-1, which stops the production of prostaglandins that shield the gastric mucosa, is probably the cause of the negative effects in the stomach. The reason for the negative effects on the kidneys is that COX-1 and COX-2 promote the synthesis of prostaglandins, which are involved in renal haemodynamics. Because nonselective NSAIDs have antiplatelet activity, haematological side-effects are likely. Usually, this antiplatelet effect is only problematic if the patient has a history of GI ulcers or other conditions that affect platelet function. Anaphylactoid reactions affecting the skin and pulmonary systems, such as

Table I. List of common FDA-approved anti-rheumatic drugs, year of discovery and their side-effects.

Serial no.	Drugs	Mechanisms of action	Year	Common side-effects	(Refs.)
1.	Acetylsalicylate (aspirin)	Inhibits cyclooxygenase activity	1897	Tinnitus, hearing loss, and gastric intolerance	(56)
2.	Corticosteroids	Upregulation of anti-inflammatory genes	1929	Bone-thinning, weight gain, diabetes, and immunosuppression	(57)
3.	Methotrexate (csDMARDs)	Inhibits activity of dihydrofolate reductase (DHFR)	1947	Gastrointestinal and liver issues	(58)
4.	Sulfasalazine (csDMARDs)	Reduces inflammation	1950	Gastrointestinal and central nervous system toxicity, rash, liver function abnormalities and infertility	(59)
5.	NSAIDs	Inhibits cyclooxygenase activity	1961	Nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding	(60)
6.	Infliximab (bMARDs)	Blocks the activity of TNF-α	1998	Pneumonia, lymphoma and tuberculosis	(61)
7.	Leflunomide (csDMARDs)	Inhibits dihydroorotate dehydrogenase (DHODH)	1998	Diarrhea, nausea, headache, rash, itching, loss of hair and body weight, hypertension, chest pain, palpitation, infection, and liver failure	(62)
8.	Adalimumab (bDMARDs)	Blocks the activity of TNF-α	2003	Skin reactions, latent infections, and cardiac failure	(63)
9.	Abatacept (Costimulation modulator)	Blocks interaction of CD28 on T-cells	2005	Headache, hypertension, dizziness, gastrointestinal disorder	(64)
10.	Tocilizumab	Inhibit signalling of IL-6 receptors	2010	Hypertension, hyperthyroidism, diarrhoea, gastric ulcers, leukopaenia	(65)
11.	Golimumab	Neutralize TNF to prevent inflammation	2013	Sinusitis, bronchitis, dizziness, hypertension, paraesthesia	(66)
12.	Tofacitinib	Inhibits JAK pathway and reduces inflammation	2016	Diarrhoea, nausea, headache, anaemia	(67)
13.	Baricitinib	Inhibits JAK pathway and reduces inflammation	2018	Upper respiratory tract infections, acne vulgaris, headaches, urinary tract infections, and folliculitis	(68)
14.	Upadacitinib	Inhibits JAK pathway, cytokine signalling	2019	Fever, cough, nausea, pharyngitis, sinusitis	(69)

DMARDs, disease-modifying anti-rheumatic drugs; csDMARDs, conventional synthetic DMARDs; NSAIDs, non-steroidal anti-inflammatory drugs; bDMARDs, biologic DMARDs; TNF, tumor necrosis factor; JAK, Janus tyrosine kinase; IL-6, interleukin-6.

urticaria and aspirin-exacerbated lung disease, are among the other mild side-effects (72).

DMARDs. The mechanisms through which each DMARD functions differ, yet they all eventually disrupt important inflammatory cascade pathways. For instance, methotrexate suppresses cell-mediated immunity, decreases neutrophil adhesion, inhibits neutrophil leukotriene B4 synthesis, suppresses fibroblast adenosine release, inhibits local IL-1 production, lowers IL-6 and IL-8 levels, and inhibits the expression of the synovial collagenase gene. Other drugs in this family function by preventing lymphocytes from proliferating or by causing them to malfunction. Leflunomide prevents lymphocyte proliferation by inhibiting dihydroorotate dehydrogenase, which in turn prevents pyrimidine production. By inhibiting oxidative, nitrative, and nitrosative damage, sulfasalazine exerts its anti-inflammatory actions. However, the relatively modest immunomodulatory drug hydroxychloroquine blocks the intracellular Toll-like receptor 9 (73).

While the negative effects of the majority of traditional DMARDs are similar, each drug has a few distinct side-effects. Diarrhoea and rash are frequent side-effects of hydroxychloroquine. Retinopathy/maculopathy is an uncommon but severe side-effect of hydroxychloroquine that occurs with a larger cumulative dose. The adverse effect profile of sulfasalazine, leflunomide and methotrexate is comparable. All of these substances have common side-effects, including rash or allergic reaction, bone marrow suppression, hepatotoxicity, gastrointestinal distress (diarrhoea, nausea and stomach pain), and an increased risk of common and occasionally serious infections. Leflunomide and methotrexate can both result in baldness. Liver cirrhosis, folic acid deficiency, and interstitial lung disease are other side effects specific to methotrexate. Weight loss, peripheral neuropathy, and hypertension are all side effects of leflunomide. Gastrointestinal distress is a very real danger with sulfasalazine. An elevated risk of common and dangerous infections, such as bacterial, fungal, and viral infections, is the most worrisome side effect of all biologic DMARDs. Hepatitis B/C, herpes zoster and tuberculosis can also reactivate. Biologic DMARDs have infrequently been linked to hepatotoxicity and bone marrow suppression (74).

Corticosteroids. The biological effects of corticosteroids are diverse and include immunosuppressive and anti-inflammatory properties. Leucocyte mobility and, to a lesser extent, leucocyte function are significantly impacted by them. Generally speaking, they impact cellular functions more than humoral ones. Prostaglandins, leukotrienes, and other metabolites of arachidonic acid, as well as certain cytokines such as IL-1, are inhibited by these (75).

GCs a subtype of corticosteroid, use a variety of methods to achieve their potent immunosuppressive and anti-inflammatory actions. Almost all primary or secondary immune cells are impacted by GCs at the cellular level. They interfere with leukocyte, fibroblast and endothelial cell activities, restrict the generation and effects of humoral factors, and prevent leukocyte traffic and access to the site of inflammation (76).

There are numerous potential side effects of corticosteroid medication. Weight gain and Cushinghoid traits, such as moon face, hirsutism, skin atrophy, bruises, posterior subcapsular cataract, mood swings, and osteoporosis, are more frequent side effects associated with prolonged treatment. Some of the negative consequences are more severe and might need to be watched: elevated blood glucose, particularly in diabetic patients, hypertension, and heightened vulnerability to infection and avascular bone necrosis (77).

Conventional synthetic disease-modifying antirheumatic medications (csDMARDs) were the first line of treatment for RA in the past. Biological or targeted synthetic DMARDs were then added. But since each patient responds differently to treatment, it is acknowledged that a one-size-fits-all strategy is inadequate. By customising RA treatment according to each patient's distinct genetic, serological, and clinical characteristics, personalised medicine seeks to provide more efficient and focused therapeutic approaches. This change is fuelled by developments in machine learning, pharmacogenomics, and biomarker research, all of which support a more customised strategy for managing RA (78). In contrast to the conventional 'one-size-fits-all' approach, personalised medicine seeks to customise treatment plans for each patient. Biomarkers in RA assist physicians in determining which individuals are most likely to experience severe symptoms, predicting which patients will benefit from particular treatments, and reducing the possibility of side-effects.

Tools such as the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI) and the Disease Activity Score in 28 Joints (DAS28) are frequently used to measure disease activity. As they offer a standardised, quantitative method of tracking the course of RA and the effectiveness of treatment, these tools are very helpful for personalised medicine. While CDAI is useful for making clinical choices in real time when test findings aren't immediately available, SDAI, with its CRP component, provides a measurement that is more sensitive to inflammation. Doctors can more accurately adapt therapy, such as adding biologics, changing dosages, or even decreasing drugs in cases of remission, by routinely monitoring SDAI or CDAI scores.

Additionally, these indices are employed in clinical trials to assess the effectiveness of novel drugs and make sure that treatment goals (such as 'treat-to-target' tactics) are being reached. The objective of customising RA treatment for each the particular condition of each patient is advanced in practice by SDAI and CDAI, which aid in bridging the gap between clinical observations and molecular-level insights from biomarkers (79).

Based on response and development, these objective metrics aid in directing therapy modifications. ACPAs and RF are two examples of serological markers that shed light on the prognosis and severity of the disease. Compared to RF, ACPAs are more specific and frequently linked to more severe forms of the illness. Variants in the HLA-DRB1 gene are one example of a prognostic biomarker that aids in predicting the severity of the disease and the possibility of joint injury. The 14-3-3η protein is another new prognostic indicator that has been connected to accelerated disease progression. As they help determine which medications are most likely to be effective for a given patient, predictive biomarkers are essential to personalised medicine. For instance, the response of a patient to TNF inhibitors such as infliximab or adalimumab may be affected by specific polymorphisms in the Fc gamma receptor gene. Serum medication levels and inflammatory cytokines such as IL-6 and TNF-α are examples of pharmacodynamic biomarkers that provide real-time information about how a drug is functioning in the body. In the event that the current treatment proves ineffective, these biomarkers allow therapists to adjust dosages or change medicines (80). Additionally, by identifying patients who are susceptible to side effects, safety biomarkers aid in the prevention of adverse medication reactions. For instance, TPMT gene variations can alert against thiopurine medication toxicity, and liver enzyme levels are tracked throughout methotrexate treatment. Incorporating biomarkers into RA treatment expedites medication development while also personalising care. In order to increase success rates and expedite the approval of novel treatments, pharmaceutical companies now plan clinical trials that concentrate on particular patient subgroups found using biomarkers. Furthermore, precision medicine is being pushed by cutting-edge technologies, such as AI-driven data analysis and multi-biomarker disease activity assays, which detect a combination of inflammatory indicators. Additionally, liquid biopsies, which monitor inflammatory chemicals in the blood, are becoming increasingly popular as real-time disease monitoring methods (81).

The development of combination medicines suited to certain immunological profiles, the expansion of pharmacogenomic databases and the improvement of predictive algorithms are the main areas of ongoing research. It is anticipated that

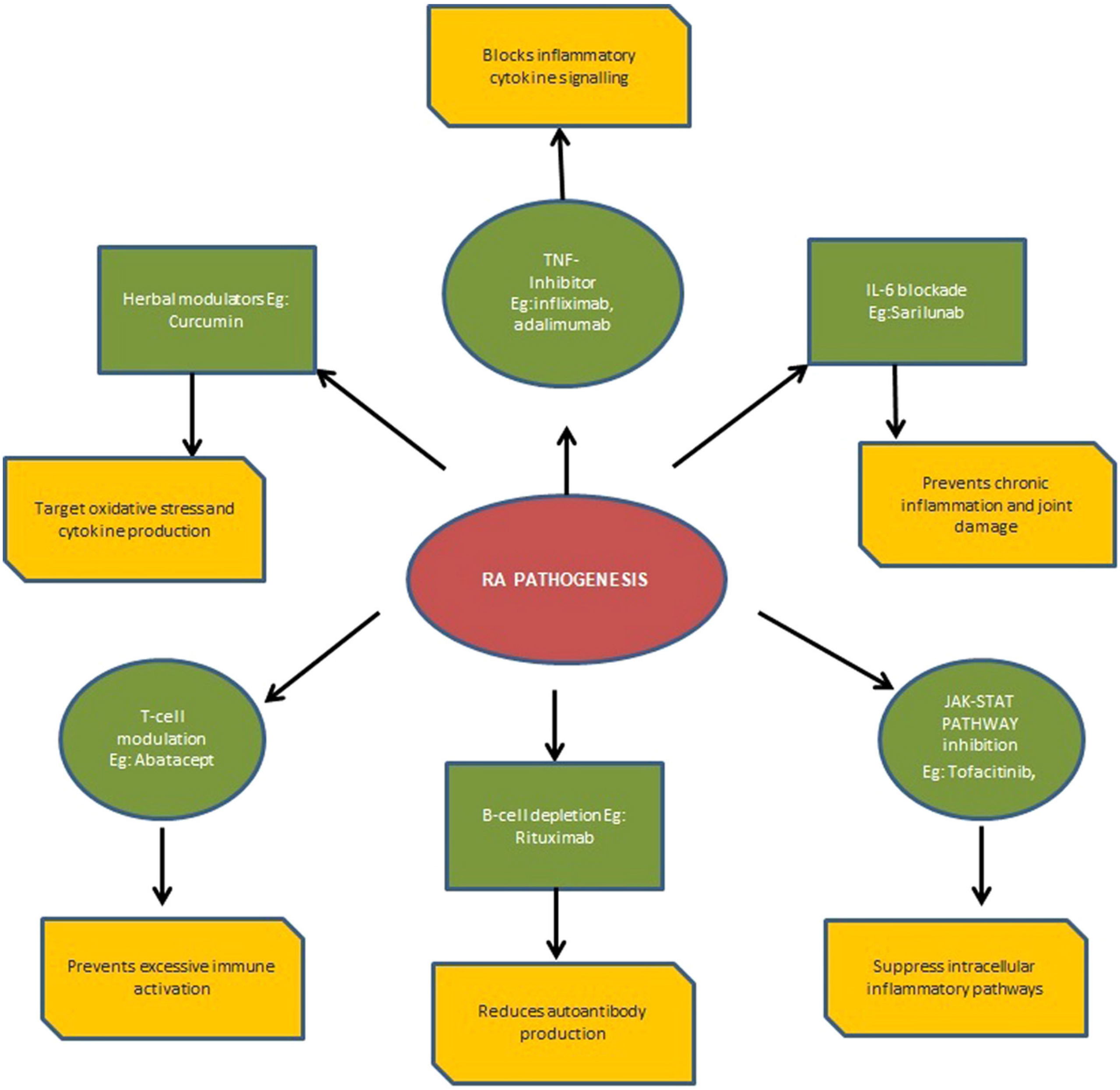

Figure 3. Clinical targets in the treatment of RA and its associated mechanisms. RA, rheumatoid arthritis.

the management of RA will be redefined as precision medicine becomes more widely available and is incorporated into clinical guidelines and standard practice (82).

The increasing complexity of modern diseases necessitates a shift towards natural origin approaches in drug discovery, as they offer rich sources of pharmacologically active compounds. In contrast, the limitations of available pharmacophores, which are often based on synthetic molecules, become apparent. These synthetic pharmacophores may not fully capture the intricate interactions between biological system and natural compounds, leading to reduced efficacy and increased side-effects. By embracing natural origin approaches, researchers can tap into the vast chemical diversity of plants, animals and microorganisms, unlocking novel pharmacophores that can effectively target complex diseases mechanism (83). This paradigm shift has the potential to revolutionize drug discovery, enabling the development of more effective, safer, and sustainable therapeutic agents that harmonize with the human body's natural process (Fig. 3).

7. Novel perspectives in herbal approaches

RA conventional treatments have several issues with safety and effectiveness. A number of patients seek out complementary and alternative medicine (CAM) solutions as a means of managing this incapacitating illness due to the adverse effects of synthetic medications. Studies have shown that individuals with chronic pain and those who are not pleased with their present care are very inclined to opt for CAM. It is estimated that 60-90% of individuals with arthritis use CAM. There is a need for research on the safety and effectiveness of herbal medicines as individuals with RA are becoming more interested in them. RA is treated using a multidisciplinary strategy aimed at reducing inflammation, easing discomfort and restoring joint function. Herbal medicines that interact with inflammatory mediators have become increasingly popular in the treatment of rheumatoid arthritis (84).

Herbal remedies are often perceived as more 'natural' compared to synthetic medications. Some individuals prefer herbal treatments as they feel more comfortable with substances derived directly from plants (85). In some cases, herbal remedies may be associated with fewer side-effects compared to certain conventional medications. Cultural and traditional beliefs may influence the preference for herbal remedies. In some cultures, traditional herbal medicine has a long history of use and is deeply rooted in local practices (86,87). They are sometimes seen as part of a holistic approach to health, addressing not only the symptoms but also focusing on overall well-being and lifestyle changes. They may be more readily available and accessible to some individuals, particularly in regions where conventional medications may be less accessible or more expensive. Natural product consumption may be advantageous for RA patients in the context of antioxidants. Since there is currently minimal research available in this area, there is conflicting evidence regarding the role of antioxidants in RA. However, the value of antioxidants in reducing inflammation is well-established, which explains why natural products' antioxidant properties are frequently assessed and typically come first *in vitro* evaluations before their anti-inflammatory properties (88).

Some herbs have been reported to have curative properties for RA. For example, *Evolvulus alsinoides* (IC50 value, 3.462 mg\ml) using aqueous solvent (89), *Drynaria quercifolia* using methanol (IC50 value, 16.90 μg) and aqueous (IC50 value, 20.24 μg) as solvents for studying their anti-inflammatory properties (90), *Alpinia galanga* with hexane (IC50 value, 800.52 μg\ml), ethyl acetate (IC50 value, 475.87 μg\ml) and methanol (IC50 value, 364.31 μg\ml) as solvents (91), *Kaempferia galangal* with hexane (IC50 value-831.82 μg\ml), ethyl acetate (IC50 value-492.75 μg\ml) and methanol (IC50 value-424.44 μg\ml) as a solvents (91). *Boswellia serrata* essential oil with methanol (IC50 value-7.514%) as a solvent for studying its anti-inflammatory properties (92).

Recent studies have identified a number of herbs that may have therapeutic benefits for RA, providing information on potential future treatments. The major ingredient of turmeric, curcumin, has been thoroughly investigated for its immunomodulatory and anti-inflammatory qualities. It suppresses pro-inflammatory cytokines that are essential to the pathophysiology of RA, including TNF-α, IL-6, and IL-1β by altering leukotriene pathways (93). In their review, Deng *et al* (94) revealed two distinct macrophage phenotypes: Classically activated M1 macrophages produce cytokines, chemokines, and various inflammatory agents that worsen inflammation, whereas alternatively activated M2 macrophages reduce inflammation and promote tissue repair. During the development and course of RA, an imbalance in the M1/M2 macrophage ratio is crucial. The major ingredient of turmeric, curcumin, has potent immunomodulatory properties and is used to treat a number of autoimmune conditions, including RA (94). Curcumin is a natural substance that helps RA patients with their symptoms because of its strong effectiveness, low cost and few adverse effects. Curcumin has been shown to have therapeutic promise in slowing the course of RA, which may be related to its ability to decrease macrophage migration, promote macrophage polarisation towards the M2 phenotype and inhibit cytokines produced by M1 macrophages (94).

Boswellia serrata, sometimes known as Indian frankincense, has also been shown to lessen joint inflammation. Epigallocatechin gallate, one of the polyphenols found in green tea, has demonstrated potential in preventing oxidative stress and inflammation (95). Furthermore, the immunosuppressive and cartilage-protective properties of ginger, ashwagandha and *Tripterygium wilfordii* (Thunder God Vine) have been studied, opening up new possibilities for integrative therapy approaches. Thunder God Vine is a traditional Chinese medicinal herb that has strong immunosuppressive and anti-inflammatory effects. RA and other autoimmune illnesses have been treated with it for decades. It is one of the most promising herbal alternatives to traditional treatment for RA due to recent scientific investigations into its mechanisms of action, therapeutic potential and clinical efficacy. It inhibits the synthesis of important inflammatory mediators, including IL-6, IL-1β and TNF-α. These cytokines play a significant role in the inflammation and cartilage degradation linked to RA (96).

Triptolide and celastrol, two of the active ingredients of *Tripterygium wilfordii*, control T-cell and B-cell activity, lowering the creation of autoantibodies and inflammatory reactions. In particular, triptolide has been demonstrated to restore immunological homeostasis by promoting the expansion of regulatory T-cells (Treg) and inhibiting Th17 cell development. The inhibition of the NF-κB and JAK/STAT signalling pathways, which are essential for the transcription of inflammatory genes in the pathophysiology of RA, are the mechanisms through which *Tripterygium wilfordii* exerts its potent anti-inflammatory effects. Research has shown that triptolide inhibits RANKL, a crucial component in the bone loss associated with RA, hence preventing osteoclast development and bone resorption (97).

Research on complementary and alternative medicine techniques that could improve traditional RA treatments is made possible by these plants. Targeting FLS, which are crucial in the degeneration of joints linked to RA, is one intriguing avenue. To specifically stop inflammatory signalling, inhibitors of particular pathways are being developed, such as cadherin-11 and JAK inhibitors (98). Since dysbiosis has been connected to autoimmune illnesses, such as RA, altering the gut microbiota is another intriguing approach. Microbiome-targeted treatments and probiotics may help control immune responses and enhance therapeutic results. Adaptive and precision medicine methods are changing the way RA treatments are studied and used in clinical trials. The possibility of successful treatment responses is increased by the classification of patients based on genetic, serological, and molecular profiles made possible by biomarker-driven clinical trials. To guarantee a more thorough assessment of therapy efficacy, trial techniques are increasingly integrating wearable technologies, real-world data integration, and patient-reported outcomes (99).

In order to maximise RA management, combination therapy trials are also investigating the synergistic benefits of small molecules, biologics, and complementary therapies,

Table II. List of herbs indicating their used parts and solvents for anti-rheumatic properties.

Serial no.	Herb	Used part	Solvent	Curative property/active against	(Refs.)
1.	*Abrus precatorius*	Root, leaf, flower, fruit	Methanol	Anti-rheumatic, cough, cold, fever	(101)
2.	*Alpinia conchigera*	Rhizome	Ethanol	Analgesic and anti-inflammatory	(102)
3.	*Alchornea cordifolia*	Leaf	Aqueous and methanol	Anti-inflammatory: Conjunctivitis	(103)
4.	*Azadirachta indica*	Leaf	Ethyl acetate, hydro alcoholic extract	Anti-inflammatory, antipyretic, antimalarial, anti-tumour, antiulcer, antidiabetic, antifertility	(104)
5.	*Butea frondosa*	Roots and leaves	Aqueous	Anti-inflammatory	(105)
6.	*Boswellia serrata*	Oleogum resin	Petroleum ether	Cancer, inflammation, arthritis, asthma	(106)
7.	*Cistus laurifolius*	Leaf	Ethanol	Anti-Inflammatory	(107)
8.	*Cyperus rotundus*	Tubers	Methanol	Anti-inflammatory, cervical cancer, liver, menstrual disorders	(108)
9.	*Justicia gendarussa*	Leaf	Ethanol	Fever, hemiplegia, rheumatism, arthritis	(109)
10.	*Pistacia khinjuk*	Leaf	Aqueous, methanol	Anti-inflammatory	(110)
11.	*Glycyrrhiza glabra*	Roots and rhizomes	methanol	Anti-inflammatory, antiulcer, antimicrobial	(111)
12.	*Strychnos potatorum*	Seed	Aqueous	Anti-inflammatory, diabetes, gonorrhoea	(112)
13.	*Urtica pilulifera*	Leaf	Methanol	Inflammation, bronchitis and cancer	(113)
14.	*Polygonum viviparum*	Rhizome	Methanol	Anti-inflammatory and anti-arthritic activity	(114)
15.	*Hibiscus platanifolius*	Leaf	Aqueous	Hyperlipidemic, diabetes, anti-arthriic	(115)
16.	*Annona squamosa*	Root	Alcohol and aqueous	Anti-bacterial, anti-fungal, anti-inflammatory, anti-diabetic	(116)
17.	*Salix sps*.	Bark	Aqueous	Antioxidant, anxiolytic activity and hypocholestrolemic effect	(117)
18.	*Zingiber officinalis*	Rhizome	Aqueous	Anti-inflammatory, antioxidant, digestive aid, anti-microbial	(118)
19.	*Sinomenium acutum*	Stem	Aqueous	Anti inflammatory, anti arthritic, analgesic, anti-oxidative, anti tumor	(119)
20.	*Trigonella foenum graecum*	Seed	Petroleum Ether	Anti-inflammatory, anti-diabetic, anticancer, gastro-protective	(120)
21.	*Coriandrum sativum*	Fruit	Petroleum Ether	Anti-inflammatory, antioxidant, anti-diabetic, carminative, diuretic	(120)
22.	*Pistacia atlantica*	Leaf	Methanol and aqueous	Wound healing, anti-inflammatory, antioxidant, anti-microbial	(121)
23.	*Carica papaya*	Leaf	Ethanol	Anti-hypertensive, anti-inflammatory, antioxidant, anti-microbial, anticancer	(122)
24.	*Ajuga remota*	Leaf	Hexane	Malaria, diarrhoea, fever, kidney disease, oedema	(123)
25.	*Oxygonum sinuatum*	Leaf	Methanol	Pain and inflammation, cough remedy, skin infection	(124)

such as herbal remedies. These research avenues have the potential to transform the treatment of RA by offering more individualised, efficient, and patient-focused therapy approaches as personalised medicine develops (100). An increasing number of herbs are being studied and reported by researchers for indicating their anti-inflammatory properties with their curative properties in the table given below (Table II).

8. Conclusion and future perspectives

RA is one of the most common diseases worldwide that affects a large number of individuals. In modern times, individuals typically lead unhealthy lifestyles without sufficient exercise or consuming a balanced diet. Thus, this disease also affects the younger generations. NSAIDs, steroid, and other medications are among the several treatments for arthritis that are accessible. These therapies have severe adverse effects, but can help with pain relief and disease control to some degree. Patients with RA are currently being treated using herbal therapies instead of pharmaceutical ones. Therefore, for the traditional Indian medical system, quality control and standardisation need to be strengthened. As regards the use of natural plant extracts or mixed herbal compounds in the treatment of RA, specific studies and clinical data are available. Pharmacologically speaking, these compounds efficiently control the immune system to reduce RA symptoms by primarily blocking pro-inflammatory cytokines. However, less knowledge is known about the immunological mechanism underlying RA and its pathophysiology at this time. Thus, further fundamental research is required to support the use of herbs in the treatment of RA, and a large-scale clinical investigation will facilitate the advancement of plant extracts as RA therapy medications. A personalized, integrative approach combining conventional and herbal therapies may offer a more holistic RA treatment strategy. While conventional therapies remain the cornerstone of RA management, herbal medicine presents a valuable complementary approach with promising therapeutic potential. Advancing research in this area could lead to safer, more effective, and personalized treatment options, ultimately improving patient outcomes and quality of life.

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Authors' contributions

AB was solely responsible for the conceptualization of the study topic, performing the literature review and writing the manuscript. RV designed the scope and structure of the review. LG and RV supervised the overall preparation and guided the direction of the review. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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