

From Mechanism to Management: A Comprehensive Review of Rheumatoid Arthritis

Dr. Prashant S. Kumbhar¹, Ms. Aaditi S. Patil^{1*}, Dr. Sanganna C. Burli¹, Dr. Vikas R. Dhole¹

¹Department of Pharmacology, Ashokrao Mane College of Pharmacy,

Peth-Vadgaon, Pin code- 416112, Maharashtra, India.

Correspondence e-mail: aditipatil18802@gmail.com

ABSTRACT

About 1% of people worldwide suffer with rheumatoid arthritis, one of the utmost prevalent chronic inflammatory disorders. They mainly affects the joints, causing angiogenesis, synovial hyperplasia, and the gradual loss of bone and cartilage, which has a major negative impact on both individuals and society as a whole. Because of its complicated pathophysiology, which is still poorly understood, RA is still incurable. Therefore, a multidisciplinary approach is necessary for effective management. Non-steroidal anti-inflammatory medicines, glucocorticoids, traditional disease modifying anti-rheumatic drugs, and biological agents like tumor necrosis factor inhibitors and interleukin 1 receptor antagonists are examples of current therapeutic alternatives that are frequently used to lessen pain and inflammation. However, side effects, toxicity, excessive costs, and insufficient efficacy frequently restrict these treatments. As a result, 60–90% of RA patients look for alternative remedies, especially herbal therapies, which are becoming more and more popular due to their perceived efficacy and safety. Clinical examination, imaging techniques like magnetic resonance imaging or ultrasound, and laboratory are commonly used to diagnose RA. Numerous animal models, such as antigen, antibody, adjuvant, and serum-induced models, as well as genetically engineered animals, have been developed to better understand RA and assess possible treatments. Among these, Complete Freund's Adjuvant-induced arthritis is a commonly used and scientifically proven model for preclinical research on the chronic immunopathological characteristics of RA.

Keywords: Complete Freund's adjuvant (CFA), Diagnosis, Herbal remedies, Pathophysiology, Phytoconstituents, Rheumatoid arthritis.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that distresses joints also other tissues. Its etiology is unknown, and its pathophysiology is complex and multifaceted. RA is characterized by progressive, permanent deterioration to the synovial-lined joints that results in deformity, loss of bone and its function, and joint space. One of the main characteristics of RA is extracellular matrix degradation, which causes the usual breakdown of bone, tendons, ligaments, and cartilage¹. Approximately 1% of people worldwide suffer with rheumatoid arthritis. Environmental and genetic factors that change the course of immunological events are among the many causal agents implicated in the development of RA. An aberrant immune response may be the cause of RA, which eventually results in synovial inflammation and joint degradation. The exact cause of RA's development is still unknown. T cell activation, on the other hand, is crucial because it keeps the T cells' cluster of differentiation intact while also raising the production of several cytokines, such as tumor necrosis factor- α (TNF- α), interleukin 1 (IL), IL-3, IL-6, macrophage migration, and inhibitory factors. All of these inflammatory mediators cause synovial tissue to proliferate, express metalloproteinase and adhesion molecules, and secrete prostaglandins (PGE) and other chemokines. Through remodeling and breakdown, matrix metalloproteinase (MMP) improperly destroys bone and cartilage².

Estimation of clinical characteristics, with signs and symptoms, prognostic test biomarkers, different verdict approaches is vital in the therapy of rheumatoid arthritis. The identification of biomarkers and the application of various imaging techniques are necessary for an appropriate diagnosis. Because they are far more accurate than traditional radiography, tomography techniques such as computed tomography, magnetic resonance imaging, and ultrasound are used to make an early diagnosis³.

Sex hormones, lifestyle, and genetics all have a significant impact on how a disease develops. Animal models that can replicate the conditions and exhibit similarities to the human illness state are required in order to fully comprehend such a disease. Rodent models are useful and crucial for understanding the pathogenic mechanisms of RA in humans. These animal models are crucial for evaluating the potency, effectiveness, and safety of both new and current medications. The most popular models are adjuvant-induced arthritis and collagen-induced arthritis (CIA). The less common animal models are streptococcal cell wall-induced arthritis and proteoglycan-induced arthritis (PGIA)⁴.

Pathophysiology of Rheumatoid arthritis

Although the pathophysiological mechanisms behind RA

are still unknown, a number of ideas have been put forth. The "pre RA phase" refers to immune processes that may occur years before joint inflammatory symptoms appear⁵. Synovitis, an inflammation of the joint capsule composed of the corresponding bones, synovial fluid, and synovial membrane, is a manifestation of autoimmune tissue damage in RA⁶. Both genetic and environmental factors have been shown to have a part in the development of RA, even though the precise cause of the condition is unknown. Like other autoimmune diseases, RA most likely requires two separate events for its initial establishment: first is "the patient's genetic predisposition, which results in the generation of autoreactive T and B cells" and second is "a triggering event, such as bacterial or viral infections or tissue damage, that provides the activated Antigen-presenting cells (APCs) to activate the autoreactive lymphocytes that had previously been produced, disrupting tolerance and leading to the destruction of tissue or organs".

Therefore, a combination of genetic variation, epigenetic change, and environmental factors caused by a stochastic event such as an accident or infection is likely to cause RA in genetically susceptible individuals. Periodontal disease (periodontitis), smoking, obesity, UV radiation exposure, sex hormones, medications, alterations in the gut, mouth, and lung microbiota, and infections are risk factors for the development of RA⁷.

DIAGNOSIS

There aren't any diagnostic criteria for RA. However, the 2010 cataloging criteria may help physicians make a diagnosis even if their primary purpose was to identify homogenous patient populations in RA clinical research^{23, 24}. In an attempt to move the emphasis from late stage phase management to early detection of RA, the 2010 American College of Rheumatology and European League Against Rheumatism classification criteria for RA assess a number of factors, including the number and type of joints involved, and the duration of symptoms. Conditions that a certain score relates to are revealed by the classification system and need to be reexamined throughout time²³.

Autoantibodies are a common feature of autoimmune disorders like RA. RF is not unique to RA, also the anticitrullinated protein antibody is more specific for RA and may contribute to the pathophysiology of the disease. Antinuclear antibody test results may be positive in RA patients, and the test is significant for prognosis in juvenile forms of the disease. Active RA frequently results in elevated CRP levels and ESR; these acute phase reactants are included in the revised RA categorization criteria. ESR and CRP levels can also be used to monitor treatment response and disease activity²⁵.

In the early stages of the disease, RA may only affect one or a few joints. Tendon inflammation, or tenosynovitis, can happen concurrently or even earlier. By displaying hypervascularization of the synovial membrane or enlargement of intra-articular soft tissue, color Doppler sonography or gadolinium enhanced magnetic resonance imaging can detect the existence of tenosynovitis and subclinical synovial inflammation⁶.

Treatment of Rheumatoid arthritis

The primary objective of treatment for a patient with RA is to either achieve full remission within a period of approximately six months in order to prevent joint degeneration, disability, and systemic signs of RA^{6, 26}. Modern treatment approaches offer great disease control, even if RA is incurable. The synthetic medications listed below are used to treat rheumatoid arthritis:

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

In order to promote remission, DMARDs are medications that suppress autoimmune activity and delay or halt joint degeneration. It is best to begin treatment as soon as feasible because DMARDs are slow-acting drugs with a delayed onset of six weeks to six months. Targeted synthetic DMARDs, biologic DMARDs, and conventional synthetic DMARDs are the three categories of DMARDs²⁷. Biologic medications that block cytokines that feed the inflammatory cascade that results in RA symptoms include monoclonal antibodies and recombinant receptors²⁸.

Methotrexate is the most significant of the traditional DMARDs that have been empirically produced. A lesser dose may help patients who are unable to handle this dosage due to side effects. Less than 5% of patients must quit using methotrexate due to side effects^{29, 30}.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs including Coxibs, Ibuprofen, and Naproxen are used to reduce inflammation during the acute phase response. NSAIDs work pharmacologically by blocking cyclooxygenase (COX), particularly COX 2, which is elevated during inflammation. However, PGE inhibition can cause serious adverse effects such as bleeding, gastrointestinal ulcers, renal failure, heart failure, rashes, disorientation, confusion, seizures, etc., thus the risk of injury should be taken into account. COX 2 selective NSAIDs including celecoxib, rofecoxib, and valdecoxib can help prevent some of the side effects^{31, 32}.

Mechanistically, prostanoid biosynthesis inhibition is primarily responsible for NSAIDs' anti-inflammatory effects³³. Prostanoids are second messengers that bind with and activate surface expressed G-protein coupled receptors, thereby influencing a variety of cellular activities. Examples of prostanoids include PGE2, prostaglandin D2, PGE F2, thromboxane A2, and prostacyclin. NSAID use frequently results in renal, hepatic, gastrointestinal, and cardiovascular adverse effects even if it successfully reduces RA symptoms³².

Glucocorticoids

Although NSAIDs have a somewhat higher safety profile, glucocorticoids like prednisone, hydrocortisone, prednisolone, and dexamethasone are more powerful and effective than NSAIDs due to the complex mechanisms behind their anti-inflammatory and immunosuppressive activities. Glucocorticoids are used to treat RA in two main ways: either as additional therapy for active RA that continues even after taking DMARDs, or as bridging therapy for DMARDs before their effects begin. Because

corticosteroid medication causes negative feedback in the control of hypothalamic-pituitary-adrenal axis pulsatility, it is crucial to avoid stopping it suddenly³⁴. In addition to other long-term negative consequences, glucocorticoids can lead to weight gain, water retention, muscular weakness, diabetes, and bone deterioration³⁵.

TNF alpha-inhibitors

The TNF alpha-inhibitors such as Etanercept, Infliximab, Golimumab, Adalimumab, Certolizumab pegol can be used. The Food and Drug Administration authorized Etanercept as the first anticytokine drug for the treatment of RA³⁶. It is the only TNF inhibitor since it is a dimeric fusion protein instead of an antibody. After 36 months of treatment, Etanercept showed both long-term efficacy and a favorable safety profile, according to an open-label study that evaluated the long-term safety and efficacy profile in 549 RA patients³⁷. Infliximab is a human antibody-based chimeric monoclonal antibody that binds to all forms of TNF and neutralizes its biological activity. The administration technique is intravenous infusion. Adhesion molecules, IL-1, IL-6, and IL-8, were reduced in RA patients after infliximab treatment. Medical research indicates that infliximab efficiently inhibits joint degeneration and patients respond to treatment fast³⁸.

Herbal remedies for rheumatoid arthritis

As synthetic RA medications are ineffective and extremely harmful. Furthermore, as they are dissatisfied with the available treatments, 60–90% of RA patients turn to alternative therapies made from herbal sources. Herbal medicines are clearly safer as well as more effective than manufactured pharmaceuticals. Herbal medicines are traditional, offer a great deal of potential, and have a large variety of structural variance compared to produced drug molecules².

Phytoconstituents

Humanity relied on medicinal plants to treat some illnesses prior to the development of synthetic medications. Following are some phytoconstituents which are found to be effective in RA.

- **Flavonoids**

Flavonoids are naturally occurring secondary metabolites found in fruits, vegetables, grains, and herbs⁵⁸.

Quercetin

Hundreds of fruits, vegetables, and herbs contain quercetin, a naturally occurring flavonoid. It demonstrated anti-inflammatory efficacy by reducing the synthesis of macrophage inflammatory mediators by controlling NF- κ B activity, which ultimately led to the inhibition of inflammatory cytokine expression and inflammatory reactions in mice with adjuvant-induced arthritis. By blocking MMP-2 activity, quercetin can prevent the basement membrane from degrading and hence prevent angiogenesis and cartilage injury^{59,60}.

Epigallocatechin-3-gallate

Green tea contains a lot of epigallocatechin-3-gallate, which can be a useful supplemental treatment. Preclinical research has shown that it inhibits inflammatory mediators such as PGE2, COX 2, NF- κ B, interferon- γ , and TNF- α in arthritic joints with CIA⁶¹. Through the nuclear factor Erythroid 2 of the antioxidant route and DCs that produce indoleamine-2, 3-dioxygenase, green tea's epigallocatechin-3-gallate inhibits autoimmune arthritis⁶².

Nobiletin

Nobiletin was able to successfully inhibit the breakdown of aggrecan cartilage in CIA mice. Additional research reveals that it can suppress ADAMTS and mRNA expression in CIA mice and reduce IL-1 β , TNF- α , and IL-6 production in joint tissues in a dose-dependent manner. The inflammation, joint damage, and problems associated with RA are greatly influenced by pro-inflammatory and inflammatory cytokines, among which TNF- α , IL-1, and IL-6 are the main cytokines that promote inflammation⁶³.

Genistein

Soybean seeds are the primary source of genistein, a phytoestrogen and kind of isoflavone. The Akt signaling pathway is a crucial cell transduction system that regulates both cell survival and death. By activating inflammatory cells via the AKT signaling pathway, inflammatory cytokines can contribute to the onset and progression of RA. Genistein can reduce the arthritic index and inhibit synovial hyperplasia in CIA rats. Genistein pretreatment can also lower inflammatory cytokine levels. By modifying the AKT signaling pathway in FLS, genistein may control the imbalance of proliferation and apoptosis in FLS of CIA rats⁶⁴.

- **Alkaloids**

Alkaloids are predicted to become a new class of medications in the treatment of RA since their therapeutic impact is comparable to that of NSAIDs and DMARDs with fewer side effects. Recent experimental and clinical research on the use of alkaloids to treat RA has advanced significantly⁶⁵.

Piperine

The study on piperine and found that it decreased PGE2 production and inhibited MMP-13 and IL-6 expression in a dose-dependent manner. In synoviocytes treated with IL1 β , piperine inhibited the migration of activator protein-1 into the nucleus. Piperine dramatically decreased nociceptive and arthritic symptoms in rats. Piperine's anti-inflammatory properties were demonstrated by histological staining, particularly in the ankle joints⁶⁶.

Cardamonin

In vitro, cardamonin prevented the release of pro-inflammatory cytokines such TNF- α , IL-6, and IL-1 β . In order to ascertain the anti-arthritic effects of cardamonin, particularly on the pain and inflammatory response of RA,

this study was carried out in a rat model of RA. Cardamonin significantly reduced RA induced pain, inflammation, and the progression of joint degeneration in rats, according to histological, behavioral, and biochemical investigations. The plasma levels of TNF- α , IL-6, and IL-1 β were significantly inhibited in cardamonin treated RA rats, according to ELISA data. In the CFA-induced RA rat model, cardamonin shown significant anti-arthritis potential overall⁶⁷.

Berberine

Berberine can stop DCs from proliferating and induce death. DC apoptosis was discovered to be specifically induced by berberine. Berberine reduces anti-collagen antibody, interferon γ , and IL-17 levels, as well as the incidence and severity of RA. This implies that DCs may be a major target for immunosuppressive therapy in RA, and that berberine may inhibit the development of RA through the mechanisms of immunosuppression and anti-inflammation⁶⁸.

- **Polyphenols**

Following are some polyphenols which has been discovered to have both therapeutic and preventative effects on RA.

Resveratrol

Resveratrol could decrease the proliferation of FLS induced by TNF- α in a manner that is dependent on both time and dosage when FLSs from CIA rats are cultured with Res *in vitro*. It is possible that resveratrol significantly lowers the levels of Akt phosphorylation and inhibits the activation of the PBK/Akt signaling pathway, which would reduce the expression of the bcl-xl/bcl-2 related death promoter and lead to apoptosis in RAFLS cells⁶⁹.

Curcumin

Curcumin may, in a dose-dependent way, induce apoptosis and restrict the growth of RAFLS *in vitro*. Curcumin Because Roscoe rhizome extract decreased RAFLS proliferation and triggered apoptosis by elevating the expression of the proapoptotic Bax gene and lowering the expression of the anti-apoptotic Bcl-2 gene, it may have an anti-rheumatic impact⁷⁰. Curcumin has been shown to have a variety of pharmacological actions, including an anti-inflammatory effect⁷¹.

- **Terpenoids**

The terpenoids that have been shown to have therapeutic effects on RA are given below.

Artesunate

In CIA rats, artesunate significantly decreased TNF- α and IL-1 β levels in synovial cells and inhibited their proliferation in a dose-dependent manner⁷². Furthermore, artesunate was able to lessen synovium lesions in AIA rats, and the expression of NF- κ B and bcl-2 in synovium joints significantly dropped after artesunate treatment⁷³.

Geniposide

A geniposide derivative created by esterlysis *in vivo* is geniposidic acid. Geniposidic acid may reduce the level of expression of TNF α and IL-1 β proteins in serum and prevent paw swelling in AIA rats. Additionally, it may promote apoptosis and prevent synoviocyte proliferation by upregulating Bax mRNA expression and downregulating Bcl-2 mRNA expression⁷⁴. Research revealed that high-dose geniposide dramatically decreased serum levels of TNF α and IL-1 β , prevented paw edema in CIA rats, and clearly postponed the onset of paw edema, and had little effect on PGE2 release⁷⁵.

Boswellic acid

Clinical research showed statistically significant improvement in osteoarthritis patients and were well-tolerated with only mild gastrointestinal distress. Boswellic acids antiarthritic properties stem from its suppression of NF-B, COX-2, and LOX-5⁷⁶.

Paeoniflorin

Research revealed that paeoniflorin could lessen paw swelling in AIA rats; additional research revealed that paeoniflorin could inhibit aberrant synoviocyte proliferation and lower the expression of Gi and COX-2 in the synovium as well as the production of IL-1, PGE2, IL-6, VEGF⁷⁷. In CIA rats, reduced paw edema was found after paeoniflorin administration; the generation of cytokines was also lowered⁷⁸.

Model for Rheumatoid arthritis

Since RA is an autoimmune illness that causes joint damage, selecting the appropriate animal model for various *in vivo* studies requires considerable thought. Therefore, when selecting an animal model for RA, careful examination of particular characteristics of the disease and specific knowledge targeted in each study must be taken into account. Animal models of RA, including genetically modified and mutant strains, can be roughly classified as either spontaneous or induced. Treatment with substances including antigens, antibodies, adjuvants, and serum causes RA in animals. CIA, adjuvant-induced arthritis, PGIA, and collagen antibody-induced arthritis are a few types of induced mice models of RA. A variety of mice can develop arthritis as a result of genetic modifications that alter the pathophysiology of the disease⁷⁹.

Among these models, CFA induced rheumatoid arthritis is a standard investigational technique that has been scientifically validated for inducing chronic immunopathological rheumatoid arthritis in lab animals that have pathological mechanisms and cellular immunity responses similar to those of humans⁸⁰.

CFA induced rheumatoid arthritis –

Rat adjuvant arthritis is an experimental model of polyarthritis that has been used extensively for preclinical testing of many antiarthritic drugs that are either already being used as treatments for this condition or are undergoing preclinical or clinical research.

Advantages

Dependable beginning,
Development of strong,
Easily quantifiable results in significant bone resorption,
polyarticular inflammation,
causes the growth of periosteal bone⁸¹.

Induction mechanism

It is a standardized technique that simulates the pathophysiological state in humans. Acute inflammation caused by CFA is associated with,

- a) Persistent edema in several joints brought on by the buildup of inflammatory cells,
- b) Joint cartilage erosion,
- c) Bone destruction^{82, 83},
- d) Mast cell activation,
- e) Leukocyte infiltration,
- f) The release of cytokines and free radicals into the bloodstream,
- g) The quick activation of macrophages,
- h) The release of several enzymes into the bloodstream that significantly contribute to the damage of blood vessels,
- i) Tissue deterioration and fibrosis⁸⁴.

By using the adjuvant model, it is possible to investigate pathological alterations in tissues other than joints and to learn about the action patterns of different kinds of drugs⁸¹.

Phases of induction mechanism

Freund's Complete Adjuvant is a dried, inactivated mycobacterium that primarily stimulates cell-mediated immunity, which in turn boosts the synthesis of specific immunoglobulins. CFA induced arthritis is a primary and secondary chronic arthritis⁸⁵.

- Primary phase: Also referred to as the "inflammatory phase," this stage is in which PGEs produce.
- Secondary phase: This immunological stage is when autoantibodies are produced⁸⁶.

Administration methods

Before beginning experiments, animals should be acclimatized for at least three days. Adjuvant disease can be induced by injecting the synthetic adjuvant using CFA augmented with mycobacterium⁸⁷.

• Sub- or intradermal injection

This technique of administering CFA has been frequently utilized to cause inflammation in rats that resembles rheumatoid arthritis. When CFA was first administered intradermally at the tailbase, it caused a chronic, multi-joint, lapsing-remitting arthritis that lasted for several months. The majority of changes have entailed injecting CFA locally, either into or around the tibiotarsal joint⁸⁸.

• Subcutaneous injection

On the first day, under light ether anesthesia, 0.1 mL of CFA is injected into the subplantar area of the left hind paw⁸⁵. Studying the initial inflammatory response as well as the

immunological response that appears in the contralateral paw and other organs about nine days later is made possible by injection in the footpad⁸⁹. Rats received a subcutaneous injection of CFA into the subplantar area of their left hind paw, which resulted in significant edema (primary lesion) within 30 minutes and peak inflammation within three to four days. Between 12 and 14 days after injection, secondary lesions developed at non-injected areas, such as the non-injected rear paw, forepaws, ears, nose, and tail. In most cases, the CFA induced joint inflammation lasted for 25–28 days⁹⁰. Additionally, it is administered at the base of the tail by subcutaneously injecting 200 µl of CFA emulsion while the rat is under anesthesia⁹¹.

IL-6 expression is crucial in promoting the inflammatory process in the CFA-induced arthritis model, which is frequently used to assess the efficacy of therapies for both acute and chronic inflammation. It was selected because it is similar to arthritis in humans. Heat-killed Mycobacterium tuberculosis and liquid paraffin make up CFA, which causes inflammation by inducing a cellular immunological response and antibody formation. Because CFA closely mimics real arthritic conditions, it is a preferred model over CIA. Rat paw edema provides a sensitive marker for evaluating inflammation and treatment success⁹².

DISCUSSION

Rheumatoid arthritis, a complex inflammatory illness, continues to be a major challenge for researchers and medical professionals. Despite advances in our understanding of the disease's etiology, complete remission is still rare, and the main objectives of current treatments remain to manage symptoms and postpone the disease's progression rather than discover a cure. Due to its chronic nature and systemic manifestations, RA causes considerable physical disability, psychological suffering, and financial burden worldwide.

These drugs effectively reduce joint degeneration and inflammation in a lot of people. However, adverse effects, risk of infection, and high treatment costs limit their long-term use, and they are not always effective.

In recent years, scientists have focused more on herbal and plant-based therapies as potential supplements or alternatives to traditional RA therapy. Herbal compounds contain a range of pharmacological characteristics, including as anti-inflammatory, antioxidant, and immunomodulatory effects, that can target many pathways involved in the pathogenesis of RA. Bioactive substances such as anthraquinones (*Rubia cordifolia* Linn), cardamonin (*Boesenbergia rotunda*), vitexin (*Justicia gendarussa* Burn), flavanoids, and triterpenoids (*Naravelia zeylanica* Linn) have demonstrated efficacy in reducing oxidative stress, inflammatory cytokine levels, and cartilage degradation in preclinical models.

Despite with these promising outcomes, a number of challenges remain before herbal medicines are included into routine clinical practice. There are not sufficient high-quality human trials, and most research is limited to animal or *in vitro* models. Variations in active component amounts, extraction methods, and formulation stability make

standardization difficult. Additionally, a lot of compounds derived from plants have poor pharmacokinetics and bioavailability, which may limit their potential for application in medicine. Therefore, comprehensive clinical research and pharmacological standardization are essential to confirm safety and efficacy.

Preclinical testing of novel RA therapeutics continues to rely heavily on animal models, such as the CFA persuaded arthritis model. Numerous histological also immunological characteristics of clinical RA are replicated in this model, making it possible to investigate molecular pathways and evaluate potential treatments.

In overall, combining modern biomedical research with conventional medical expertise may result in novel approaches to the treatment of RA. Combining evidence-based herbal medicine with traditional medication may improve patient satisfaction, reduce side effects, and improve treatment outcomes. In order to ascertain the therapeutic potential of bioactive phytochemicals in RA, future research should concentrate on discovering them, clarifying their molecular mechanisms, and carrying out controlled clinical trials.

CONCLUSION

Rheumatoid arthritis is still a complicated autoimmune state that requires creative treatment methods outside the traditional pharmaceutical ones. The efficacy, safety, and

accessibility of current biologic and synthetic DMARDs have greatly improved disease management; yet, these limitations underscore the need for supplementary or alternative choices. Several pathogenic pathways in RA may be addressed by the promising anti-inflammatory, antioxidant, and immunomodulatory qualities of herbal and plant-derived substances. However, despite promising preclinical findings, issues include inconsistent bioavailability, a lack of uniformity, and a dearth of high-quality human trials impede translation into clinical practice. To guarantee effectiveness and safety, future research should concentrate on thorough clinical validation, formulation improvement, and molecular mechanism clarification. Patients with rheumatoid arthritis may eventually benefit from more efficient, secure, and reasonably priced treatment alternatives if conventional medical knowledge is combined with contemporary scientific techniques

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ABBREVIATIONS

Sr. No.	Abbreviations	Full form
1	RA	Rheumatoid arthritis
2.	CFA	Complete Freund's adjuvant
3.	TNF- α	Tumor Necrosis Factor- α
4.	IL	Interleukin
5.	PGIA	Proteoglycan-induced arthritis
6.	APC	Antigen-presenting cells
7.	HLA	Human leukocyte antigen
8.	RF	Rheumatoid factor
9.	ACPA	Anti-citrullinated protein antibodies
10.	CRP	C-reactive protein
11.	ESR	Erythrocyte sedimentation rate
12.	DMARD	Disease Modifying Anti-Rheumatic Drugs
13.	CIA	Collagen induced arthritis
14.	FasL	Fas ligand
15.	TRAIL	Tumor necrosis factor - related apoptosis inducing ligand
16.	MMP	Matrix metalloproteinase
17.	MAPK	Mitogen activated protein kinase
18.	NF-K β	Nuclear factor kappa-light-chain-enhancer of activated B cells
19.	COX	Cyclooxygenase
20.	CIA	Collagen induced arthritis
21.	PGE	Prostaglandin
22.	FLS	Fibroblast-like synoviocytes

23.	DC	Dendritic cells
24.	AIA	Adjuvant induced arthritis
25.	LOX-5	Lypoxigenase

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