

REVIEW ARTICLE

Rheumatoid Arthritis: Old Wisdom, New Approaches

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ABSTRACT

Globally, arthritis is a leading cause of disability and a chronic illness. Within the hierarchy of the processes involved in RA, inflammatory cytokines play a significant role. Traditional medicine has access to a wide variety of herbal remedies, and scientific studies have helped to clarify how effective these treatments are in managing arthritis. Research and industries specializing in the use of herbal remedies to address a variety of ailments, such as arthritis, have flourished in recent years. It is now simpler to use herbs as an arthritis treatment due to a number of advancements in clinical research in meticulously planned clinical trials. The best chance of a successful therapeutic outcome is achieved with early detection, in particular patients who have well-established risk factors for poor results, including early joint injury, autoantibodies, and high disease activity. The utilization of traditional, biological, and cutting-edge non-biological disease-modifying antirheumatic drugs; they also include the use of nano carriers in order to treat rheumatoid arthritis. Composite indices are used to measure disease activity, and a treatment-to-target strategy is applied. The etiology, pathophysiology, and rheumatoid arthritis prevalence are summarized within this article.

Keywords: Arthritis, Inflammatory cytokine, Pathogenesis, Allopathic treatment, Herbal Drugs, Nanocarriers

Received 14.10.2024

Revised 19.12.2024

Accepted 23.03.2025

How to cite this article:

Varsha J, Sonali M Rheumatoid Arthritis: Old Wisdom, New Approaches. Adv. Biores., Vol 16 (2) March 2025: 422-437.

INTRODUCTION

"The Greek word arthron is where the word arthritis originates, which denotes "joint," and the word it is from latin, which stand for "inflammation." Inflammation in one or more joints is a feature of arthritis.[1] Mostly affecting tiny joints, rheumatoid arthritis (RA) is a symmetrical, long-term inflammatory autoimmune disease that can also affect larger joints, the skin, eyes, heart, kidneys, and lungs. Joint bone and cartilage are regularly damaged, while ligaments and tendons degrade [2]. The entirety of this joint damage leads to deformities also bone erosion, which is usually very painful for the patient. Three components comprise the beginning, clinical progression, and ultimate result of rheumatoid arthritis, or its natural history. The course of rheumatoid arthritis is influenced by the triangle link between the degree of synovitis, the existence of extra-articular illness, and the consequent loss of independence (Figure 1).[3]

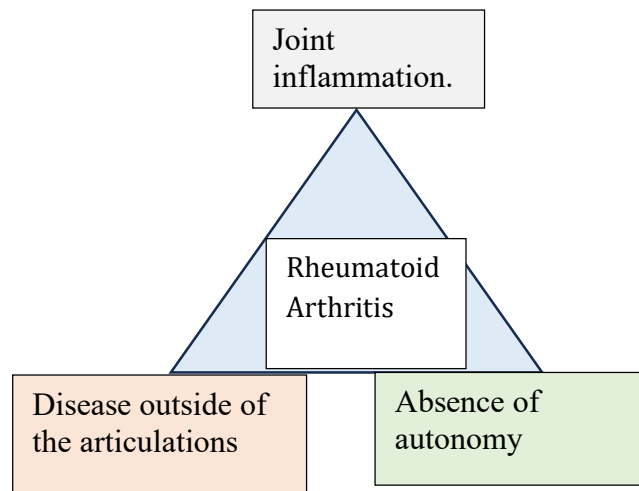


Fig1: Diagram represents a simplified conceptual model of Rheumatoid Arthritis (RA), highlighting three key components contributing to the disease.

The chief complaint of most arthritic patients is joint pain multiple things can contribute to this, including inflammation around the joint, disease-related joint damage, normal wear and tear on the joints, muscle strains from strenuous activities against painful, stiff joints, and tiredness [4]

TYPES OF RHEUMATOID ARTHRITIS

The following are a few of the common forms of arthritis [5]

- **OA, or osteoarthritis:** It is a disease that affects the joints and causes weakness, edema, also lack of motion in the arms and legs.
- **Rheumatoid arthritis (RA):** An autoimmune condition when the body targets its own tissues and cells. Elbows, fingers, thumbs, and knees are the main areas affected.
- **Gout:** This condition is brought on by an elevated uric acid level in the body, which causes joint pain.
- **Ankylosing Spondylitis (AS):** Associated with pain and stiffness, the spine is the most frequently affected area in this disease.
- **lupus Arthritis :** Another autoimmune condition that damages tissue and induces illness is lupus arthritis.
- **Juvenile Arthritis :** The majority of children affected by juvenile arthritis (JA) are 16 years of age or younger. It results in synovial inflammation.
- **Psoriatic arthritis (PA):** This long-term condition causes skin and joint edema. Conjunctivitis, nail pitting, morning stiffness, and lower back pain are symptoms of PA.
- **Fibromyalgia:** It affects women more often than men. Its symptoms include fatigue, pain, insomnia, and stiffness in the morning.
- **Septic arthritis:** Synovial fluid and synovium infections are the cause of this condition. Anorexia, nausea, and exhaustion are some of its symptoms.[6]

PATHOPHYSIOLOGY

There is uncertainty regarding the etiology and pathophysiology of RA. The understanding of RA and its systemic impact on the body is complicated by a combination of biological markers and environmental factors. Adult patients with RA are usually categorized as having either seropositive or seronegative rheumatoid arthritis. Seropositive RA is indicated by blood tests that reveal the existence of antibodies against citrullinated protein antigens (ACPAs) and rheumatoid factor (RF)[7].

Pathogenic autoantibodies against citrullinated proteins are generated by B memory cells within the humoral adaptive immune system of the organism. Targeting pathogens within the body, dendritic cells, T and B cells, and lymphocytes comprise the adaptive immune system. Because they target extracellular citrullinated protein antigens that are created in response to inflammation in bodily tissues and organs, antibodies to citrullinated proteins are extremely specific for RA [8,9].

The, Cytokines' role in the etiology and management of RA particularly in relation to synovitis, has been the subject of extensive discussion. These substances have both pro- and anti-inflammatory properties, which means they regulate the immune responses in charge of cell proliferation, tissue remodeling , and repair. They're split up into two categories:

Th1: stimulates; Immunity mediated by T cells

Th2: controls the humoral reaction (antibody) of B cells.

To keep the immune system healthy and functioning properly, the body must be able to self-regulate the levels of these cytokines. The expression of genes, which is impacted by external factors like infections in the joints, regulates the levels. The RA-related synovitis is caused by a malfunction in the homeostatic functions of cytokines, a cytokine known as interleukins, or an anti-viral biomarker known as interferon, produced in excess or insufficiently.[10]

The relationship between the body's immune response to environmental stimuli is the second element that complicates the start and progression of RA. Numerous risk factors are linked to rheumatoid arthritis, including smoking, infectious agents, periodontal disease, the gastrointestinal microbiome, and unfavorable life events[11]

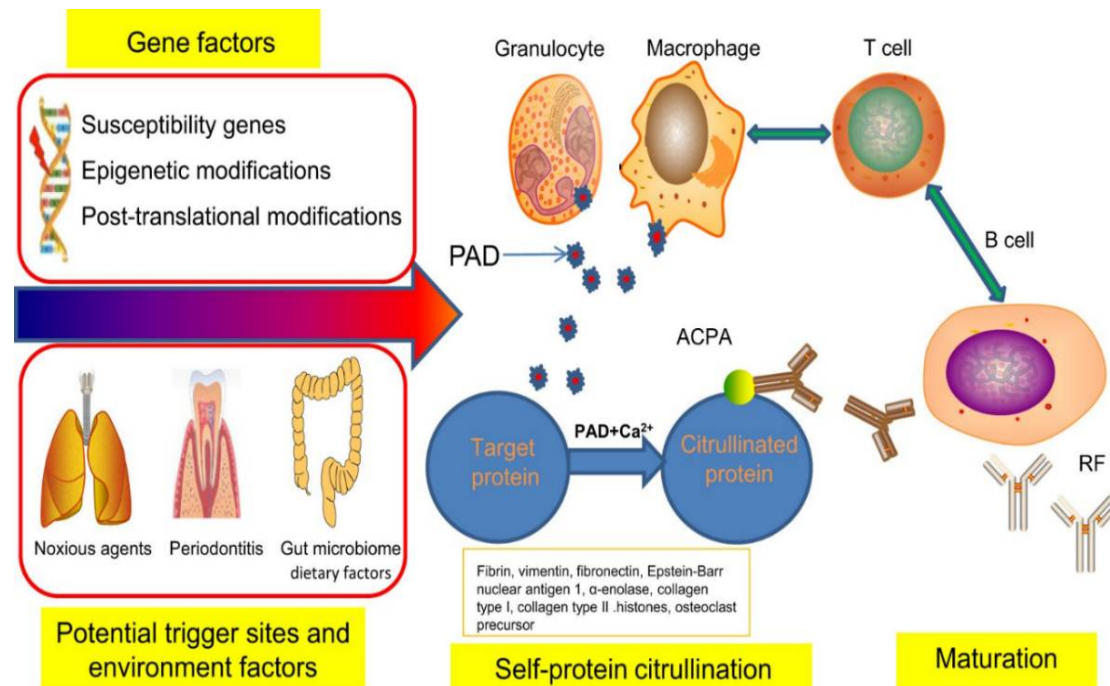


Fig 2: Rheumatoid arthritis pathological mechanism

Rheumatoid arthritis (RA) arises from genetic and environmental factors causing self-protein citrullination, triggering autoantibodies. Lung exposure to toxins, infections, gut microbiota, and diet contribute. PAD enzymes catalyze citrullination, and immune cells secrete them in RA. ACPA antibodies target citrullinated proteins, leading to loss of tolerance and RA development.

PREVALENCE OF RHEUMATOID ARTHRITIS

Due to its close association with the inherited tissue type Major Histocompatibility Complex (MHC) antigen HLA-DR4 (particularly DR0401 and 0404), family history is a substantial risk factor for RA. Men seem to have a slightly later chance of developing the disease than women, with women between the ages of 40 and 50 appearing to have the highest risk [13, 14]. In both sexes, prevalence rose significantly with age, but it was higher in females throughout all age ranges [15]. Between 1980 and 2018, the prevalence of RA worldwide was 460 per 100,000 people, with a 95% prediction interval of 0.06–1.27%. The average prevalence of RA at the point and period levels was 51/10,000 and 56/10,000, respectively. Due to varying methodological approaches and potentially distinct genetic and environmental risk factors, there has been variation in the point- and period-prevalence of RA across continents and countries [16]. The prevalence of RA was greater in urban than rural locations, indicating a possible major role for environmental variables in the development of RA [17].

EPIDEMIOLOGY

Approximately 0.5–1% of people worldwide are thought to have RA, with women being affected by the condition 2-3 times more frequently than males [18]. The risk of developing RA in women is three times higher than in men [19]. It is roughly 2:1 after 60 years of age, but it is 4-5 times higher in women under

50[20]. Age-related increases in RA incidence cause it to peak between the ages of 35 and 50. Roughly three out of every 10,000 people globally are affected by RA annually.

Rheumatoid arthritis affects almost everyone, however it is less frequent in some populations (black people in the Caribbean) and more common in others (such as 56% of certain Native American groups). Rheumatoid arthritis sufferers' first-degree relatives had a twice-higher risk of developing the illness.[21, 22]. Between 0.4% and 1% of people in North America and northern Europe suffer from RA correspondingly, and it comprises 0.3% to 0.7% of Southern European population [23, 24] Inflammatory arthritis, which affects almost 1% of the population nationwide, is also frequently caused by RA [25, 26].

CLASSIFICATION

Criteria	Short tittle	definition
1	Morning rigidity	soreness in the morning over the joints, which should subside after at least sixty minutes. Three or more joints
2	triple or more joint area arthritis	. Doctors have discovered 14 unique locations where soft tissue swelling or fluid buildup has been observed, separate from bone overgrowth: The MTP joints, wrists, elbows, knees, ankles, and bilateral PIP and MCP joints
3	Arthritis of hand Joints	A wrist, MCP, or PIP joint will show signs of swelling as previously described
4	Partial Joint Replacement	Without complete symmetry, bilateral involvement of MCPs, MTPs, or PIPs is acceptable. simultaneous engagement of the same joint regions on both sides of the body [as indicated in (2)]
5	Rheumatoid factor in serum	Physicians observe subcutaneous nodules in bony prominences or juxta articular regions
6	Rheumatoid Nodules	Evidence of high rheumatoid factor levels in the serum or any test where the positive result rate was less than 5% in participants who were healthy controls
7	Modification in radiography	When looking at hand and wrist radiographs, radiographic alterations that are consistent with rheumatoid arthritis include obvious bone decalcification or erosions next to the affected joints; osteoarthritis changes alone are not included in this.

Table 1 : The American Association for Rheumatism first suggested classification standards for RA in 1958 [28]. The Rheumatology's American College updated the 1958 ARA criteria in 1987 [29].

PHARMACOLOGICAL TREATMENT OF RHEUMATOID ARTHRITIS:

In a planned management strategy, four drug classes are usually utilized to treat RA. NSAIDs and corticosteroids, or synthetic anti-inflammatory drugs, lessen pain and inflammation in people with RA. The progression and devastation of the disease are slowed down by DMARDs and biological drugs. The likelihood of impact is higher in women than in males. by Rheumatoid Arthritis, so women who are planning a family or who are pregnant should exercise extra caution when managing their situation because certain arthritis medications can affect fertility and pregnancy.[30] Rheumatoid Arthritis is treated with variety of drugs, such as rituximab, which depletes B cells, abatacept, tocilizumab, anakinra, IL-6 antagonists, etanercept, infliximab, certolizumab, and adalimumab, which modulate T cells and block RA signalling. As a result of using tocilizumab, some adverse effects include headaches, nasopharyngitis, upper respiratory tract infections, and gastrointestinal infections [31] Among the innovative biological medications now in development are those that target IL-17 and the immediate effects of the immune response. Future developments could see a significant role for novel conventional medications with DMARD-like effects [32] Further targets are being investigated, and positive data from clinical trials of the kinase inhibitors SYK and JAK has been reported [33].

Table 2 : Conventional Treatment for Rheumatoid Arthritis

Classification	Name	Mechanism of action	Probable mechanisms	Adverse Effect	Reference
Conventional synthetic DMARDs	Methotrexate	Comparable amount of folate	activities that rely on folate, such as adhesion molecule expression, adenosine signaling, methyl donor production, and reactive oxygen species. The cytokine profiles of eicosanoids and MMPs.	damage to the lungs and increased liver enzyme	[34]
	Leflunomide/ Teriflunomide	An inhibitor of pyrimidine synthesis	NF-kB, kinases, and rapidly dividing cells leukocyte adhesion; DHODH-dependent pathway; interleukins; TGF-β.	Hepatotoxicity, nausea and diarrhea, and hypertension.	[35]
	Sulfasalazine	immunosuppressive and anti-inflammatory	Leukotriene synthesis and chemotaxis; PGE2 and NF-kB activation, cyclooxygenase, adenosine transmission, and inflammatory cytokines (TNF-α, IL-6, IL-1, and)	adverse effects on the hematologic, central nervous system, and gastrointestinal systems.	[36]
	Chloroquine /Hydroxychloroquine	Immunomodulatory effects	Lysosomotropic action, pro-inflammatory cytokines derived from. macrophages, T-cell response, neutrophils, anti-inflammatory effects, Toll-like receptors, and cellular immune responses; cartilage degradation and metabolism	retinal toxicity, adverse effects on the skin, central nervous system, and gastrointestinal tract.	[37]
Biological DMARDs Antibody-based treatment					
TNF-α targeted therapy	Infliximab	TNF-α inhibitor	phagocytosis and pro-inflammatory cytokines, adhesion molecules and chemokines, chemoattractant; function of trig cells; Leukocytes' and synovial fibroblasts, endothelial cells, and osteoclasts.	injection location response to both pneumonia and atypical tuberculosis infection. High blood pressure. Anaphylactoid transfusion reaction, severe.	
	Adalimumab				
	Etanercept				
	Golimumab				
	Certolizumab pegol				[38]
Classification	Name	Mechanism of action	Probable mechanisms	Adverse Effect	Reference
B-cell targeted therapy	Rituximab	B cell reduction	presentation of antigens, complement-mediated destruction of cells, B cell apoptosis, phagocytosis and antibody-dependent cytotoxicity via the Fc receptor gamma, and depletion of CD4+ T cells.	viral reactivation, infection, hypertension, hypogammaglobulinemia, and reactions to vaccinations. start of neutropenia late	
	Ofatumumab			Late-onset neutropenia.	
	Belimumab	suppressors of B cell activity		Anaphylactic shock or severe transfusion reaction	[39]
	Atacicept				
	Tabalumab				
T-cell-focused treatment	Abatacept	CTLA4/CD28 system	Autoantigen recognition; Immune cell infiltrate; T	Infection, malignancy.	[40]

	Belatacept	CD80/CD86	cells activation.		
Interleukin targeted therapy	Tocilizumab	suppression of IL-6	perturbation of the innate and adaptive immune systems; acute-phase proteins.	infections of the skin and soft tissues in particular, high blood cholesterol, transient drops in neutrophil count, and abnormal liver function	[41]
	Canakinumab	IL-1 inhibition	Matrix enzyme; irritant reactions.	neutropenia, cancer, infections, and reactions at the injection site	[42]
	Anakinra				
	Rilonacept				
	Secukinumab	IL-17 inhibition	Function of mitochondria; formation of autophagosomes	There are few safety data regarding infections, nasopharyngitis, candidiasis, neutropenia, and mental health	[43]
Ixekizumab					
Differentiation and growth factors	Denosumab	inhibitor of RANKL	the development and activation of osteoclasts	Numbness, cramping in the muscles, cellulitis, low blood Ca2+ and phosphate	[44]
	Mavrilimumab	GM-CSF inhibitor	Pain pathways are modulated; T helper 1/17 cells are activated, differentiate, and survive; and neutrophils, dendritic cells, and macrophages are.	More investigation is required for the safety file.	[45]
Small molecules					
JAK pathway	Baricitinib	JAK1 and JAK2 inhibitor	T-cell stimulation, the production of cytokines that promote inflammation, synovial swelling, and harm to structural joints.	Further research is necessary to closely monitor any potential side effects, including zoster infection (pre-vaccination is advised) and others.	[46,47]
	Tofacitinib	JAK1 and JAK3 inhibitor			
	Filgotinib	JAK1 inhibitor			
upcoming medication and target	Bruton's tyrosine kinase [49] Toll like receptor [48] transforming growth factor- beta [51] dendritic cell [53] Neuropathways [52] phosphoinositide-3-kinase				

NEED OF HERBAL DRUGS FOR RHEUMATOID ARTHRITIS

There are issues with the safety and efficacy of traditional RA management. Due to adverse reactions to modern medications, patients often consider herbal medicine as a potential treatment option for RA. The study's findings suggest that individuals who experience chronic pain, like those with RA, or who do not respond well to contemporary treatments may want to consider traditional medicine. About 60–90% of people with arthritis use prescription medications [54].

Herbal medicines have been created for over hundreds of years by combining the therapeutic knowledge of generations of physicians who practiced in the traditional medical system [55]. Because the drugs that are currently on the market are either very expensive or have certain side effects, researchers are now very interested in plant-derived medicinal agents [56]. We are blessed by nature with an enormous variety of medicinal plants that can be found all over the world and are a great source of therapeutic substances for treating and preventing a wide range of disorders [57]. Since the beginning of human civilization, herbal remedies have played a significant role in human society's attempts to combat illness [58]. The parts of these herbal plants that are medicinally significant are those that contain chemicals that have a desired physiological effect on the body [59]. The World Health Organization states that 80% of the world's population receives

PLANTS WITH ANTI- ARRTHRYTIC ACTIVITY

1] *Withania somnifera*

Family: Solanaceae

Common Name: Ashwagandha

Chemical Constituent: Withanosides, sitoindisides, alkaloids, Saponins, phenolic compounds and flavonoids.

Uses: Adaptogen, nerve tonic, aphrodisiac, antirheumatic, memory booster, antidiabetic, immunomodulatory

Indian ginseng is a highly significant herb. It has been utilized for more than 3000 years in Ayurvedic therapy. The main plant chemicals with medicinal properties are called withanolides The components of

withanolides are a six-membered lactone ring and a C28 steroidal nucleus with a C9 side chain. nerve tonic, adaptogen, aphrodisiac, memory enhancer, immunodulatory, antidiabetic, antirheumatic agent, and other uses are listed in addition to withanolides 377. January 2019 uses of Research J. Pharm. and Tech. 12(1).

Various investigations are conducted to ascertain the plant's potential anti-arthritis properties. According to a study by Gupta and Singh the degree of arthritis was significantly lessened and the functional recovery of motor activity was enhanced by the inhibition of inflammatory mediators at dose levels of 600 and 800 mg/kg. [61] Khedgikar et al. discovered that the active ingredient withaferin-A increases the expression of mineralizing genes and osteoblast-specific transcription factors, so stimulating osteoblast differentiation and proliferation in Menopausal osteoporosis and bone injury.

In a study conducted by Kiran R. Giri, considerable dose-dependent acute and chronic anti-inflammatory efficacy of carrageenan was observed when compared to hydrocortisone through its ethanolic extract [62].

2] *Vitex negundo*

Family: Lamiaceae

Common Name: Horseshoe vitex, or Chinese chaste tree

Chemical constituent: Nishindine, flavones, luteolin-7, β -sitosterol, phthalic acid.

Uses: anti-inflammatory, analgesic, anticonvulsant, antioxidant and antirheumatic agent

In particular, Southeast Asia makes extensive use of this plant in folk medicine. It comes from South part of India and Myanmar [63]. The main chemical components of the plant are, flavonoids like flavones, iridoid alkaloids like nishindine glycosides, vitamin C, β -sitosterol, benzoic acid, luteolin-7-glucoside fatty acid, vanillic acid phthalic acid, and β -hydroxybenzoic acid [64]. It has antirheumatic, analgesic, anticonvulsant, antioxidant, and anti-inflammatory properties. According to a study by reducing the levels of PGE2, cytokines, IL-17, TNF- α , and ESR, the plant's ethanolic extract showed excellent antiarthritic action at dose levels of 6.25 mg/10 ml, 3.12 mg/10 ml, 1.56 mg/10 ml, and 1.25 mg/10 ml, according to Pandey A et al [65].

3] *Punica granatum*

Family: Lythraceae

Common Name: Pomegranate

Chemical Constituent: Gallic acid, Anthocyanins, Ellagic acid, Tannins, Flavones, Flavonoid Antocyanidins, Sterols, Quercetin, Triterpenoids

Uses: Anti-inflammatory, Anti-carcinogenic, Anti-oxidant, Hypotensive, Hypolipidemic and Anti-diabetic. Many countries, including Southern Asia, Tropical Africa, and India, have widespread access to it. The seeds and juice of the plant were employed in a special tonic to cure rheumatism in Iran's ancient medical system.

The primary chemical component of the plant are quercetin sterols triterpenoids tannins ellagic acid anthocyanins flavones gallic acid [66]. Among the plant's many pharmacological qualities are those that are, anti-diabetic, hypotensive, anti-carcinogenic hypolipidemic, antioxidant and anti-inflammatory. The fruits of the plant showed anti-arthritis action at a dose level of 13.6 mg/kg in a study by Shukla et al., which involved male wistar rats. The fruits did this by suppressing the spectrum of signal transduction pathway [67].

4] *Boswellia serrata*

Family: Burseraceae

Common Name: Salai Guggul

Chemical Constituent: 3-O acetyl 11-keto- β - boswellic acid, Boswellic Acid,

Uses: inflammation, Joint Pain, wound healing

In Ayurvedic medicine, boswellia is a highly important herb that has been used to relieve inflammation and swelling for thousands of years. This plant's oleo-gum resin was utilized in a range of Unani and Ayurvedic remedies to cure a wide range of illnesses. [68] Boswellic acid is the first terpenoid to be separated from the oleo-gum resin. Numerous boswellic acid derivatives have been identified [69] Out of these compounds, 3-O acetyl-11-keto- β -boswellic acid (AKBA) displays the most robust anti-arthritis effects. [70]. 30 patients with osteoarthritis of the knee were chosen by medical researchers in 2003, and a randomized blind placebo controlled trial was carried out. The outcome demonstrated that the patients' arthritis-related range of motion had increased and their swelling had decreased [71]. A combination formulation containing both Glycyrrhiza glabra and Boswellia serrata demonstrated a noteworthy anti-arthritis activity, according to Mishra et al. [72]. According to Sadiq Umar et al., prepared Boswellia

serrata gum resin extract has a protective effect against arthritis, and it has been demonstrated that this effect may be related to immune system modulation [73].

5] *Aloe barbadensis*

Family: Liliaceae

Common Name: Lily of the desert, Curacao aloe

Chemical Constituent: Cinnamic acid, anthracene, anthraquinone, and anthranilic acid

Uses: uterine tonic, fever reliever, spermatogenic, laxative: anti-inflammatory, purgative and, diuretic. Aloe vera cultivation is prevalent in various regions of Europe and many parts of India, notably the northwest Himalayan area. Aloe vera stands out as a crucial plant in traditional medicine. Its key components include anthraquinone, anthracene, cinnamic acid, and anthranilic acid. [74] Aloe vera is utilized in treating a spectrum of skin conditions like eczema, poison ivy, minor cuts, insect stings, and bruises. It serves as a blood purifier, anti-inflammatory, diuretic, uterine tonic, spermatogenic, laxative, purgative, and fever reducer, while also possessing antibacterial and antifungal qualities. The anti-arthritic properties of aloe vera are linked to its anthraquinone compound. Aloe vera is an effective anti-inflammatory and immune system stimulant.[75] When aloe vera extract is applied topically to Sprague Dawley rats with adjuvant-induced arthritis, the rats' inflammation and arthritis decrease

6] *Zingiber officinale*

Family: Zingiberaceae

Common Name: Ginger root

Chemical Constituent: Shogaols, zingerone, and Paradol, gingerol

Uses: nausea, vomiting, diarrhoea, anti-inflammatory, anti-septic

Herb supplements that are highly beneficial include ginger. Though it originated in Southeast Asia, it is now grown in the Caribbean, Africa, Australia, Taiwan, and India. output in India of more than 30%. VOCs, starch, fat, fiber, inorganic matter, and leftover moisture are the components of ginger. Hydrocarbons of monoterpene, sesquiterpene, and oxygenated mono and sesquiterpene's are found in ginger oil.[77] As a carminative, stimulant, aromatic, stomachic, and flavouring agent, ginger is utilized. It is applied to alleviate diarrhoea and nausea. It has additional uses as an antimicrobial, antifungal, anticarcinogenic, antiseptic, antioxidant, and anti-inflammatory [78]. One potent treatment for arthritis-related joint pain that doctors advise using is ginger extract. In [79] Sesquiterpenoids, zingiberene (-), and other constituents make up the majority. Its anti-inflammatory effects are attributed to natural products called sesquiterpene lactones (SLs) [80].

7] *Tinospora cordifolia*

Family: Menispermaceae

Common name: Guduchi

Chemical Constituent: b-sitosterol, cordifolide, cordifol, clerodane furano diterpene, diterpenoid furano lactone, and tinosporidine, tinosporide, tinosporaside

Uses: improves immune system, antiperiodic, antipyretic, antispasmodic, and anti-inflammatory qualities. All over China and the tropical Indian subcontinent, *Tinospora cordifolia* Linn. is found [81]. The primary ingredients include furano diterpene, diterpenoid furanolactone, furano diterpene tinosporidine, tinosporide b-sitosterol, cordifol, , tinosporaside, cordifolide, and columbin are the main ingredients. Improved immune function and increased resistance to infections are two benefits of the plant. The antiperiodic, antispasmodic, anti-inflammatory, and antipyretic qualities of the bitter principle are demonstrated. It is utilized for a number of ailments, including rheumatoid arthritis. At 100 mg/kg, the volume of the paws is decreased in rats with collagen-induced arthritis [82].

8] *Trigonella foenum-graecum*

Family: Fabaceae

Common Name: fenugreek

Chemical Constituent: Betaine isoleucine, 4-hydroxyisoleucine, histidine, leucine, lysine, L-tryptophan, argenine, graecunins, fenugrin B, Fenugreekine, trigofenosides A–G, trimethylamine, neurin, trigonelline, choline, gentianine, carpaine

Uses: antifungal, antioxidant, antihyperlipidemic, anti-obesity, anti-cancer, and anti-inflammatory properties

Native to both India and Northern Africa is *Trigonella foenum-graecum*. There is wide spread use of fenugreek, particularly the seeds and leaves, for tonic purposes, labour induction, inflammation relief, hypertension, malaria, and diabetes. Aqueous fenugreek extract has been shown in studies to have pleiotropic and anti-arthritic properties, which are mediated by a decrease in lipid peroxidation. It also raised the levels of glutathione and superoxide dismutase in the cartilage, preventing cartilage degradation prematurely. These effects were attributed to mucilage or steroidal saponins, such as

trigoneosides, yamogenin, tigogenin, and diosgenin, which were discovered to be present in the extract [83]

Furthermore, fenugreek decreased pro-inflammatory cytokines such as TNF- α , IL-1 α , IL-1 β , IL-2, and IL-6. In an adjuvant arthritis model using female Sprague-Dawley rats, fenugreek mucilage at a dose of 75 mg/kg significantly reduced edema on the 21st day of therapy when compared to the standard medication indomethacin. [84]. Overall, it was clear from these data that fenugreek improved RHA condition by raising antioxidant levels and lowering pro-inflammatory cytokines.

9] *Cinnamomum zeylanicum* L

Family: Lauraceae

Common Name: Dalchini

Chemical constituents: Cinnamaldehyde, Eugenol and pro-anthocyanidin

Uses: Respiratory, digestive, gynaecological ailments

Approximately 250 species make up the genus *Cinnamomum*. High levels of cinnamaldehyde are found in cinnamon bark oil. Plants containing cinnamon bark and leaves are used as a spice, as a plant-based medication, and to make volatile oils. The parts that have been crushed bring out the stronger spicy smell [85]. Research was conducted on animal models of rheumatoid arthritis and inflammation to assess the effectiveness of Type-A procyanidin polyphenols (TAPP) derived from the bark. According to entitlements, TAPP has immunomodulatory and anti-inflammatory properties when used in vitro. Serum C-reactive protein (CRP), cachexia, ankle diameter, and arthritic score levels were among the changes brought about by AIA that were significantly reversed in rats given TAPP therapy [86].

10] *Piper nigrum* L

Family: Piperaceae

Chemical constituents: Volatile oil, Alkaloids, Piperine

Uses: Fever, Cold, Respiratory Problems and Pains

Many traditional medical systems make extensive use of this plant in order to address a variety of ailments, such as fever, colds, and respiratory problems, and pains. Piperine's analgesic and antiarthritic properties were observed in rat models of arthritis and edema caused by carrageenan. The active component of *Piper nigrum*, piperine, has been demonstrated to have anti-inflammatory effects on fibroblast-like synoviocytes obtained from rheumatoid arthritis patients in vitro that were stimulated with interleukin 1 β (IL1- β). Ankle joints with noticeably reduced inflammatory areas were shown by histological staining [87].

11] *Angelica sinensis* (Oliv.)

Family: Apiaceae

Common Name: Female ginseng

Chemical Constituent: Ferulic acid, Z-ligustilide, Butylidenephthalide

Use: therapy for cancer as well as erythema, acne, sinusitis, colds, headaches (particularly migraines), and toothaches

It is packed full of polyphenols. Research has demonstrated that the ethyl acetate component of this herb reduces RHA-FLS proliferation, MAPK, and RANKL-mediated osteoclastogenesis in addition to having apoptotic effect against pleomorphic immune cells [88,89,90]. Moreover, it was found that the ethyl acetate extract of *Angelica sinensis* reduced the inflammation associated with rheumatoid arthritis by inhibiting the proliferation of synovial fibroblasts in rheumatoid arthritis as well as the mRNA and protein expression of MMP-1, MMP-3, and COX-2; this also included the production of PGE2, the phosphorylation of ERK-1/2, p38, and JNK (c-Jun N-terminal kinase), and NF-kB activation mediated by IL-1 β .

12] *Commiphora mukul*

Family: Burseraceae

Common Name: Guggul, Balsamodendron mukul and *Commiphora wightii* Bhandari,

Chemical Constituent: Guggulsterol I-V, Z-guggulsterone, E-guggulsterone, and Z-guggulsterol.

Numerous studies have demonstrated the anti-inflammatory qualities of guggul [92, 93, 94]. The oleoresin fraction of guggul has potent anti-inflammatory and anti-arthritic effects, with an effective minimum dose of 125 mg/kg body weight. It was found that the crude water extract of oleo gum resin could suppress the acute rat paw edema caused by carrageenan. The granuloma pouch test revealed that it inhibited the formation of granulomas as well. Without having any discernible effect on the initial phase, the extract in adjuvant arthritis very successfully suppressed the secondary lesions. In ovariectomized rats, bone resorption is inhibited by a methanol extract of the dried exudate of *C. mukul*. [95] The inhibition of hyperimmune reactions may be one of its mechanisms of action. TNF-alpha, IL-1 beta, and IL-2 are downregulated as a result of the inhibition of MAP kinases by crude extract and pure

compound isolated from *C. mukul* [96]. From *C. mukul*, a crystalline steroidal compound with anti-inflammatory properties was isolated. In both human clinical trials and experimental animals [97], pure gum guggul demonstrated a hypolipidemic effect. Patients with knee osteoarthritis have reported positive results from *C. mukul* [98]. The new triterpenes myrrhanol A and myrrhanone A, which are derived from guggul-gum resins, showed a potent anti-inflammatory effect in mice with adjuvant-induced air pouch granuloma [99]. The results of the study showed that a 50% crude resin extract and hydrocortisone had less of an anti-inflammatory effect than myrrhanol A.

13] *Camellia sinensis* (L.) O. Ktze:

Family: Theaceae

Common Name: Green tea

Chemical Constituent: epigallocatechin, caffeine, tannins, catechin, and epicatechin

Many health advantages are associated with this plant. Tea's antimicrobial properties help lower the risk of cardiovascular disease and cancer, among other benefits. One herbal remedy for respiratory conditions like asthma is theophylline, a chemical found in tea (100). Strong antioxidants can be found in tea thanks to a polyphenol called epigallocatechins [101]. In rats with collagen-induced arthritis, green tea greatly decreased inflammation and the inflammatory cytokines TNF- α & γ -interferon along with COX-2. Total immunoglobulin G elevation and green tea decreased the amount of antibodies specific to collagen (102). Current studies suggest that black tea extract may have antiarthritic effects in both clinical and experimental contexts. A reduction in the levels of PGE2, TNF α , IL-1 β , and IL-6 in the blood was observed in rats treated with Freund's complete adjuvant-induced arthritis, when black tea water extract was applied (103).

14] *Coriandrum sativum*

Family: Apiaceae

Common Name: Cilantro

Chemical Constituent: Linalool, Geraniol, Citronellol, Borneol

Use: stomachic, tonic, carminative, diuretic and stimulant. anti-bacterial, anti-oxidant, anti-carcinogenic
This plant, which is cultivated all over India and contains volatile oil in its seeds, fruits, and leaves, is herbaceous and used medicinally. These essential oils—geraniol, citronellol, borneol, and others—make up the chemical composition of the plant [104]. This plant's essential oil, cineole, has anti-rheumatic and anti-arthritic properties [105]. As a carminative, diuretic, stimulant, stomachic, and tonic, the plant is helpful. It possess antibacterial, anticarcinogenic, and antioxidant properties. According to a study published by Nair V et al., the reduction of paw edema in male wistar rats caused by formaldehyde and CFA techniques through the suppression of pro-inflammatory cytokines and TNF- κ was detected at dose levels of 8, 16, and 32 mg/kg of the hydroalcoholic extracts of the seeds. Therefore, the investigation proved that the herb had anti-arthritic qualities [106].

15] *Cuscuta reflexa*

Family: Cuscutaceae

Common Name: dodder Plant, devil's hair

Cuscuta reflexa is a parasitic medicinal plant that is used to treat a range of ailments. It is also commonly referred to as the devil's hair or dodder plant. Licorice, mannitol, sitosterol, lycopene, apigenin-7- β -rutinoside, 6-7 dimethoxy coumarin, quercetin, hyperoxide, propenamide, reflexin, lutein, cuscutin, cuscotalin, kaempferol, and kaempferol-3 O-glucoside are just a few of the many phytoconstituents that are contained in it [107]. Anti-oxidant, anti-inflammatory, anti-pyretic, anti-diabetic, and antimicrobial agents are among its uses [108]. Strong anti-inflammatory properties characterize it. This plant has a significant impact on arthritis, according to several studies. Ethanolic extract of *Cuscuta reflexa* has a strong anti-arthritic effect, according to Damerakonda Kumaraswamy et al.'s report [109]. This plant exhibits significant anti-arthritic activity, according to Vennila et al. [110].

NANOCARRIERS FOR MANGEMENT OF RHEUMATOID ARTHRTIS

Due to its non-invasive nature and patient-friendly ease of application, topical delivery, also known as transdermal drug delivery, has received much attention lately. Along with its resistance to stomach pH and enzymes that inactivate medications, the cutaneous route of drug delivery also has the advantage of not requiring hepatic first pass metabolism, sustained activity, dose flexibility, and less adverse effects [111]. Still, a barrier to the wider use of transdermal drug delivery routes is the drugs' minimal permeation via the stratum corneum. The stratum corneum, the outermost layer of the epidermis surrounded by lipid layers, is composed of corneocytes, or dead keratinized cells. This means that the stratum corneum, which functions as a strong, flexible membrane that is impermeable to water, limits the diffusion of drugs. To improve medication permeation, researchers have experimented with a variety of

technologies, including electroporation [115], microneedle [114], sonophoresis [113], and iontophoresis [112].

In this sense, the question with topical conventional formulation has been solved by the use of nano formulations, such as solid lipid nanoparticles, ethosomes, niosomes, liposomes, and nanoemulsions [116]. These formulations are usually integrated into a gel base to enhance penetration and attain a longer residence time for an efficacious reduction of inflammation caused by RA [117].

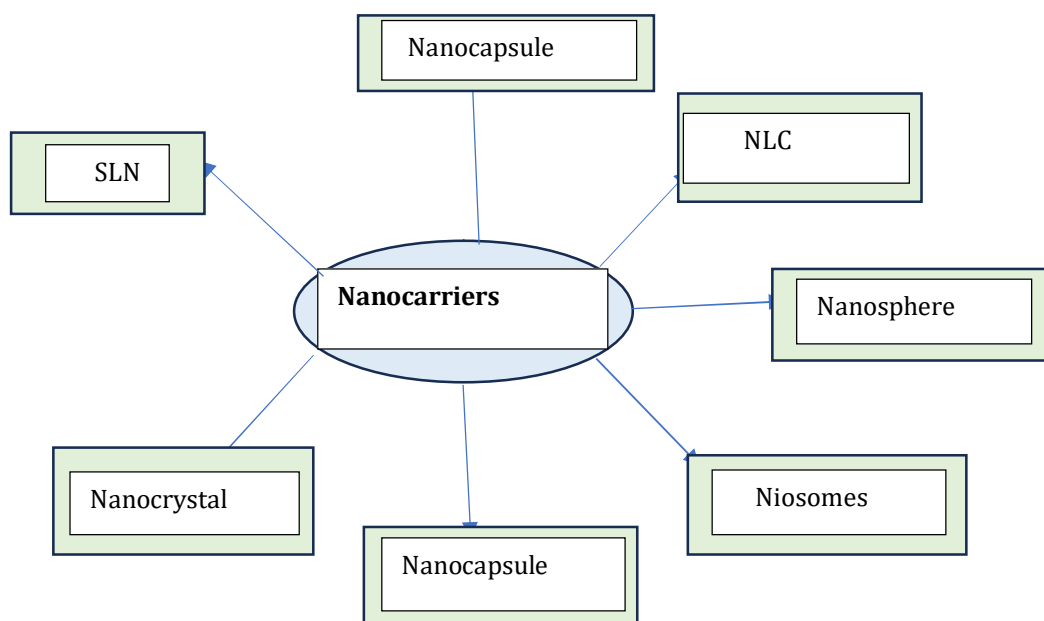


Fig 3 : Nanocarriers for Rheumatoid arthritis

CONCLUSION

In conclusion, rheumatoid arthritis (RA) is an autoimmune disease that damages and inflames joints. As a result, it is a significant global health burden. Herbal medications and novel nanocarriers hold promise for improving the management of RA symptoms, even though traditional pharmaceutical treatments have drawbacks. Incorporating these strategies could result in safer and more effective treatment options; therefore, more study and clinical validation are necessary to improve RA management and patient outcomes.

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