

Overview of Rheumatoid Arthritis and their treatment approaches

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ABSTRACT

The immune system plays an essential role in the human body systems. It works as a guard and protects the body from various diseases. The hypersensitivity of the immune system leads to allergy and other autoimmune diseases. Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by inflammation, swelling, and redness of the affected joints. It also affects blood vessels and lymphatic tissues. The main purpose of the treatment of rheumatoid arthritis is to eliminate the symptoms of the disease or to slow down the development of the disease. Presently many types of drugs are used for the treatment of this disease like disease-modifying antirheumatic drugs (DMARDs), glucocorticoids, and non-steroidal anti-inflammatory drugs (NSAIDs). Long term usage of these drugs causes many adverse effects. The use of plants for the treatment of the disease causes no side-effects. India has blessed with an enormous wealth of medicinal plants. Since ancient times, herbal drugs are employed for the remedy of several disorders in India. The present review summarizes the prevalence statistics, mechanism of action, types of rheumatoid arthritis, and synthetic as well as herbal approaches for the treatment of rheumatoid arthritis.

Keywords: Autoimmune system, Arthritis, Rheumatoid Arthritis, Herbal plants

I. INTRODUCTION

Autoimmune System

The immune system of the human body acts as a double-edged sword that can either heal or harm our physiological process. In a healthy person, the immune system can differentiate between the self and the nonself and destroys only those tissues that it recognizes as “nonself”.

Autoimmune disorders are formed in the body, as an outcome of the inappropriate immune response against its one tissue. Failure of this system

to acknowledge the body’s normal constituents as “self” will end in inflammation, and tissue damage. [1]

The gene defect that caused the immune system to attack the body and create an autoimmune disease could cause another autoimmune disease. These include rheumatoid arthritis, multiple sclerosis, autoimmune thyroids, Sjogren's syndrome, and others.

Rheumatoid Arthritis

Arthritis is made up of two different words Latin and Greek. In Greek word is “Arthron” signifies joint and in Latin words “Its” specifies inflammation. Thus arthritis is normally viewed as a disease rather a collection of medical problems collectively termed as “Arthritis”. Nearly forty-seven million adults and 300000 children suffer in the US alone. [2]

Arthritis is normally produced inflammation of the joints. Mainly it can affect one joint or multiple joints. Inflammation is a process in which the body’s WBC and immune proteins help protect us from infection and foreign substances such as bacteria and viruses. [1]

Generally bone moves or twists on a similar piece have to maintain functional flexibility. During movement the ligament acts on plastic bands to help keep the bones in the same place. Under all situations whether in resting or moving, ligament always holds the same place. Cartilage tissue covers the bone surface to prevent direct rubbing thus smoothens the limb movement without causing pain or bone erosion due to friction. [3]

PREVALENCE STATISTICS

The incidence and prevalence of RA generally rise with increasing age until about age 70, then declines. [4] [5] From 2013–2015, an estimated

54.4 million US adults (22.7%) annually had ever been told by a doctor that they had some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia. The age-adjusted prevalence of arthritis among adults reporting no leisure-time physical activity (23.6%) is significantly higher than the prevalence of arthritis among adults who report meeting physical activity recommendations (18.1%). Arthritis can be a barrier to physical activity, and inactivity is associated with conditions such as cardiovascular disease, diabetes, obesity, and functional limitations. [6][7]

MECHANISMS OF RHEUMATOID ARTHRITIS

Activation of different pathways in the course of rheumatoid joint destruction. In early synovitis, Toll-like receptor signaling triggers the release of chemokines from synovial cells. As a

consequence, both cytokine-dependent and cytokine-independent pathways are activated, resulting in the activation of synovial fibroblasts during early rheumatoid arthritis. The cytokine-independent pathway is characterized by the expression of the endogenous retroviral transposon L1 that induces several important activators, including p38 δ , which is the protein responsible for the induction of specific matrix-degrading enzymes. Current therapies are not assigned to inhibit this pathway, mediated by the activated rheumatoid arthritis synovial fibroblasts. The individual contribution of each pathway to the disease in a given patient might, therefore, be responsible for the limited effectiveness of current drug therapies using biologic agents. Under the influence of additional triggers such as hypoxia, both pathways enhance joint destruction during the destructive phase of the disease. L1, retroviral transposon L1; TLR, Toll-like receptor.

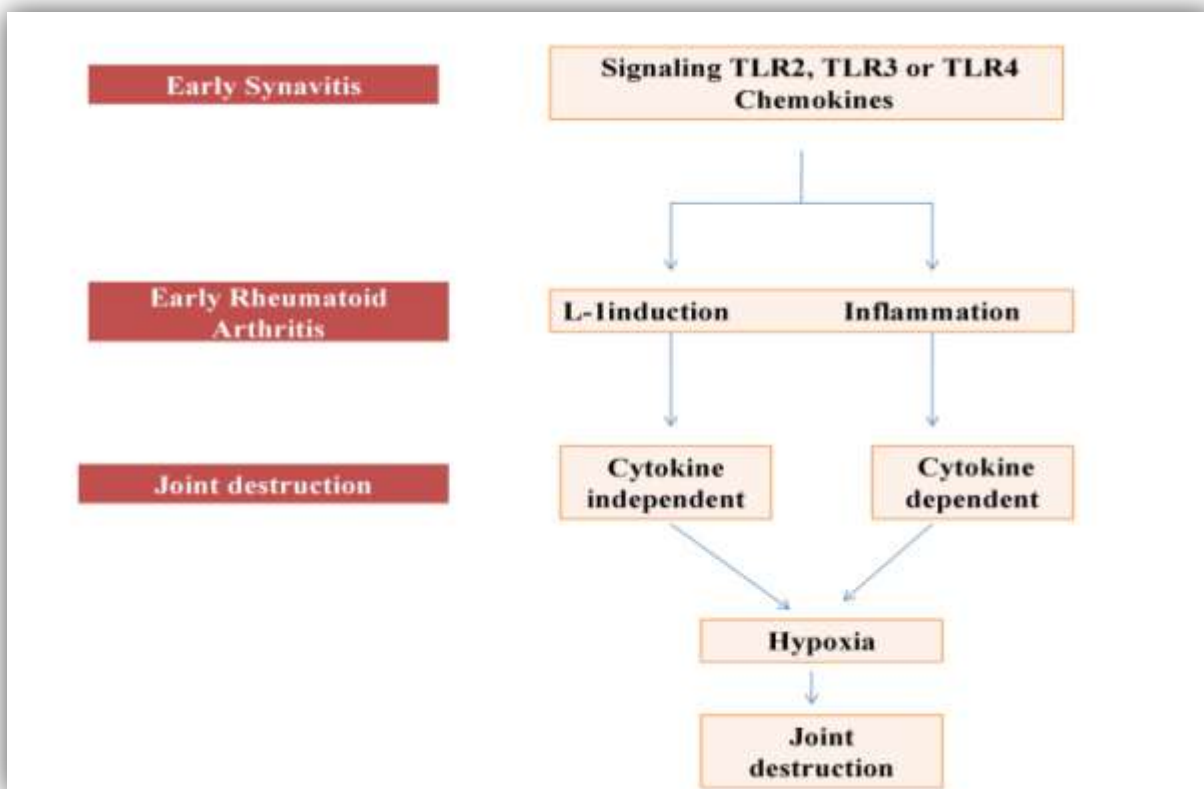


Figure 1: Mechanisms of Rheumatoid Arthritis

SYMPTOMS

Arthritis is the most common symptom of pain stiffness and swelling around the joints Some types of arthritis are the autoimmune disease affects your whole body like Rheumatoid arthritis cause, not just pain and stiffness, but fever loss of appetite and fatigue.[8]

1. Osteoarthritis (OA)
2. Rheumatoid arthritis (RA)
3. Gout
4. Ankylosing Spondylitis (AS)
5. Lupus arthritis (LA)
6. Infectious arthritis (IA)
7. Juvenile arthritis (JA)
8. Psoriatic arthritis (PA)
9. Fibromyalgia

TYPE OF ARTHRITIS

Table 1: Different forms of Arthritis

Types of arthritis	Description	Symptoms	Location of symptoms	Time of day	Age of onset	Reference
Osteoarthritis (OA)	Known as the “wear and tear” type of arthritis and is associated with factors such as aging, injury, or obesity	Joint stiffness, pain, and decreased range of motion.	Usually affects weight-bearing joints (i.e., back, hip, knee) as well as the neck, small finger joints, and big toe	Most commonly affects middle-aged and older people	An estimated 27 million people have osteoarthritis in the US	[9] [10] [11] [12]
Rheumatoid arthritis (RA)	Autoimmune arthritis	Joint pain, swelling, and stiffness, decreased range of motion, fever, fatigue, and loss of energy can also occur	Often causes swelling in pairs of joints—especially smaller ones (both hands, both ankles, etc.)	Usually occurs between 30 and 60 years of age, though can occur at any age	Approximately 1.3 million people have RA in the US	[13] [14] [15] [16] [17] [18]
Gout	It is also categorized as a form of arthritis affecting the bone joints	Joint pain, swelling, and stiffness, fingers or ankles creating inflammatory gouty condition.	Gout is a painful and debilitating disease caused by the uric acid / urate crystal deposition within the joints like toes	Most common form of inflammatory joint disease in men aged ≥40 years	Approximately 2.6 million people have Gout in the US	[19] [20] [21]
Ankylosing Spondylitis (AS)	A type of autoimmune arthritis that mostly affects the back and hips.	Low back pain and stiffness, as well as tenderness or pain where tendons or ligaments attach to bones.	Mostly affects the joints of the spine and also where the spine attaches to the hips.	Most often begins from the late teens to 35 years	An estimated 0.2% of people in the US have ankylosing spondylitis.	[22] [23] [24]
Lupus arthritis (LA)	Autoimmune arthritis.	Joint and muscle pain,	Meaning that it bacterial	About 15 to 20 percent of	Approximately 1.5 million	[25] [26]

		swelling, and stiffness.	infection a wide part of the body, including the joints, kidneys, skin, blood, brain and other organs.	all systemic lupus erythematosus cases develop before the age of 18 years.	people in the U.S have lupus	
Infectious arthritis (IA)	Autoimmune disorder.	Joint pain, swelling, and stiffness, Knee, elbow, shoulder and hip Predominate decreased range of motion.	Septic arthritis is inflammation of a synovial membrane with purulent effusion into the joint capsule, due to infection.	Usually affect an disease that that can develop in older age.	There is an estimate of 20,000 cases of septic arthritis per year in the United States.	[27] [28] [29] [30]
Juvenile arthritis (JA)	Juvenile arthritis (JA), also known as pediatric (autoimmune) rheumatic disease.	Many common symptoms, like pain, joint swelling, redness and warmth.	Affect the musculoskeletal system, but joint symptoms may be minor or nonexistent. Juvenile arthritis can also involve the eyes, skin, muscles and gastrointestinal tract.	Usually affect an Disease that can develop in children under the age of 16.	Nearly 300,000 children – from infants to teenagers – in the U.S. have some form of arthritis.	[31] [32]
Psoriatic arthritis (PA)	A type of autoimmune arthritis associated with psoriasis (a disease that causes red, scaly patches on the skin).	Joint pain, swelling, and stiffness, as well as tenderness or pain where tendons or ligaments attach to bones. Red, scaly patches of skin often on the elbows, knees, and scalp.	Usually affects the ankles, knees, fingers, toes, and lower back.	Usually occurs between 30 and 55 years of age. Skin symptoms often appear first.	Between 6% and 42% of all people in the US with psoriasis have Psoriatic arthritis	[33] [34] [35] [36]
Fibromyalgia	Fibromyalgia is a condition associated with widespread amplified chronic pain in different parts of the	Symptoms such as fatigue, non-refreshed sleep, memory problems and mood changes, all	It is considered an arthritis-related condition. It is often found as a comorbid condition in people who have different	Fibromyalgia can develop at any age, including in childhood	Fibromyalgia affects more than 3.7 million Americans.	[37] [38]

	body at different times	strongly impact the quality of life for these patients.	forms of arthritis like osteoarthritis, rheumatoid arthritis, lupus, and inflammatory bowel diseases.			
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II. TREATMENT METHODOLOGY

Arthritis treatment focuses on relieving symptoms and improving joint function. We have to be compelled to try several different treatments or combinations of treatments before you establish what works best for you.

Medications

The medications used to treat arthritis vary depending on the kind of arthritis. Commonly used arthritis medications include:

- **Painkillers:** These medications help reduce pain but haven't any effect on inflammation. An over-the-counter option includes acetaminophen.
- For more severe pain, opioids might be prescribed, such as tramadol, oxycodone, or hydrocodone. Opioids act on the central nervous system to relieve pain. When opioids are used for an extended time, they'll become habit-forming, causing mental or physical dependence.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs):** NSAIDs reduce both pain and inflammation. Over-the-counter NSAIDs include ibuprofen (Advil, Motrin IB, others) and naproxen (Aleve). Some types of NSAIDs are available only by prescription.
- Oral NSAIDs can cause stomach irritation and will increase your risk of heart failure or stroke. Some NSAIDs are also available as creams or gels, which can be rubbed on joints. [39]
- **Counterirritants:** Some varieties of creams and ointments contain menthol or capsaicin, the ingredient that makes hot peppers spicy. Rubbing these preparations on heal your aching joint may interfere with the transmission of pain signals from the joint itself.
- **Disease-modifying antirheumatic drugs (DMARDs):** Often used to treat autoimmune disease, DMARDs slow or stop your system from attacking your joints. Examples include methotrexate (Trexall, Rasuvo, others) and hydroxychloroquine (Plaquenil). [40]

- **Biologic response modifiers:** Typically utilized in conjunction with DMARDs, biologic response modifiers are genetically engineered drugs that specialize in various protein molecules that are involved within the immune and their response.
- There are many types of biologic response modifiers. Tumor necrosis factor (TNF) inhibitors are commonly prescribed. Examples include etanercept (Enbrel, Erelzi, Eticovo) and infliximab (Remicade, Inflectra, others).
- Other medications target other substances that play a role in inflammation, such as interleukin-1 (IL-1), interleukin-6 (IL-6), Janus kinase enzymes, and certain types of white blood cells known as B cells and T cells. [41][42]
- **Corticosteroids:** This class of medicine, which incorporates prednisone (Prednisone Intensol, Rayos) and cortisone (Cortef), reduces inflammation and suppresses the system. Corticosteroids will be taken orally or are often injected directly into the painful joint. [43]

Therapy

Physical therapy will be helpful for a few forms of arthritis. Exercises can improve range of motion and strengthen the muscles surrounding joints. In some cases, splints or braces may be warranted.

Surgery

If conservative measures don't help, your doctor may suggest surgery, such as:

- **Joint repair.** In some instances, joint surfaces are often smoothed or realigned to scale back pain and improve function. These sorts of procedures can often be performed arthroscopically — through small incisions over the joint.
- **Joint replacement.** This procedure removes your damaged joint and replaces it with a synthetic one. Joints most commonly replaced are hips and knees.

- **Joint fusion.** This procedure is more often used for smaller joints, like those within the wrist, ankle, and fingers. It removes the ends of the 2 bones within the joint then locks those ends together until they heal into one rigid unit.

DRUG USED IN TREATMENT OF ARTHRITIS

1. Synthetic agents:

- **NSAIDS:** Aspirin, Ibuprofen, Diclofenac, Naproxen, Firoxicam, Etoricoxib
- **DMARDS:** Methotexate, Azathioprine, Sulfasalazine, Chloroquine & Hydroxychloroquine, d-Penicillamine

2. Biologics:

- TNF- alfa antagonist- Etanecept, Infliximab
- IL-1 antagonist- Anakinva.
- T-cell modulating agent- Abatacept
- B-lymphocyte depletory- Rituximab

3. Glucocorticoids: Prednisolone, Triamcinolone. [44][45]

Table no 2: List of available dosage forms for the treatment of rheumatoid arthritis

S. No.	Drugs	Delivery approaches	Importance	Toxicities	References
NSAIDS (Nonsteroidal anti-inflammatory drugs)					
1.	Diclofenac	Liposome Pellets Microcapsules Microspheres Nanocomposites Soft gels Suppositories Pharmacosomes	Enhance skin delivery Increase bioavailability Better efficacy Good targeting efficiency Prolonged action Acceptable side-effect Avoid gastric irritation High drug loading	Upset stomach, nausea, heartburn, diarrhea, constipation, gas, Headache.	[46] [47] [48] [49] [50] [51] [52] [53]
2.	Ibuprofen	Nanosuspensions Microemulsions Microspheres	Decrease side-effects Good stability Effective therapy	Heartburn and indigestion	[54] [55] [56]
3.	Indomethacin	Capsules Pellets Liposome Microballoons Microspheres Nanoemulsions Suppositories Dendrimers	Better safety Faster release of drug Minimum side effects Good floating ability Prolonged delivery Transdermal delivery More therapeutic efficacy	Upset stomach, heartburn, headache, drowsiness, or dizziness	[57] [58] [59] [60] [61] [62] [63] [64]

			Improve bioavailability		
4.	Naproxen	Tablets Nanoparticles	Better safety Implantable sustains release.	Upset stomach, nausea, heartburn, headache	[65] [66]
5.	Ketoprofen	Tablets Microspheres Microcapsules Microsponges Nanoemulsions Transdermal patch Suppository Floating microparticles	Improve bioavailability Increase in-vitro release High drug loading Usage in dermatology Modify drug release More skin permeation Good efficacy profile Good flow property	Upset stomach, constipation, diarrhea, dizziness, lightheadedness	[67] [68] [69] [70] [71] [72] [73]
DMARDS (Disease modifying Anti-Rheumatic Drugs)					
1.	Methotrexate	Microspheres Sustain release tablets Injections	Better targeting Good efficacy Improve safety	Stomatitis, rash, hepatotoxicity, rare but potentially life- threatening pulmonary toxicity	[74] [75] [76]
2.	Sulfasalazine	Delayed release tablets	Improved efficacy	Stomach upset, headache	[77]
3.	Azathioprine	Sustain release tablets	Better safety	<ul style="list-style-type: none"> • Hair loss, • skin rashes, • Sensitivity to sunlight. 	[78]
4.	Tacrolimus	Solid dispersion	Potent suppressive activity	Upset stomach, nausea, heartburn, headache	[79]
5.	Leflunomide	Sustain release Tablets Microcapsules Microspheres	More safety profile Better sustain action Rapid action of drug	Nausea, heartburn, headache Hair loss	[80] [81] [82]
6.	Auranofin	Sustain release Tablets Injectables	More efficacy Produce high drug concentration at target site	Pale skin, easy bruising or bleeding	[83] [84]
Corticosteroids					

1.	Prednisolone	Liposomes Microspheres Nanoparticles	Better targeting Fast release of drug Prolonged release	Insomnia. Leg swelling. • weight gain, ncreased blood sugar,high blood pressure	[85]
2.	Blood plasma- or serumderived	Immunosuppressive Exosomes	Safe therapeutic approach for arthritis	Nausea, heartburn, headache Hair loss.	[86]

Herbal medicine for Rheumatoid Arthritis

Prolonged use of the present allopathic drugs produces many side effects in a patient. Hence there is a need for an alternative therapeutic approach. Herbal therapy is very effective against the disease. It provides a safe and effective approach toward the treatment of the disease. Nowadays many herbal medicines are used for the treatment of the disease. Many plants are under scientific observation

to develop a natural herbal drug. The management of rheumatoid arthritis is a multidisciplinary approach to lessen the pain, reduction of inflammation, and restoration of joints function. In practical terms suppression of inflammation is the target intensive therapy. Herbal medicines have become popular for the treatment of rheumatoid arthritis worldwide recently. [87]

Table 2: Herbal plants used for the treatment of Rheumatoid Arthritis [88-106]

S. No.	Common name	Botanical name	Family	Plant part used
1	Aloe vera	Aloe vera	Liliaceae	Leaves
2	Mountain soursop	Annona montana.	Annonaceae	Leaves, fruit, seeds, bark, roots
3	Shatawari	Asparagus racemosus	Liliaceae	Roots, Leaves, flowers and fruits
4	Punarnava	Boerhavia diffusa	Nyctaginaceae	Root
5	Salai guggul	Boswellia serrata	Burseraceae	Olegum, resin
6	Ginger	Curcuma longa	Zinziberaceae	rhizome
7	Marijuana	Cannabis sativa	Cannabinaceae	Fruit, flower
8	Coriander	Coriander sativum	Umbelliferae	Fruits
9	Sodom apple	Calotropis procera	Asclepiadaceae	Latex, Root
10	Fringed spider flower	Cleome rutidosperma	Capparidaceae	Aerial parts
11	Dhatura	Datura alba	Solanaceae	Seed
12	Lemon scented gum	Eucalyptus citriodora	Myrtaceae	Leaves
13	Fire lily	Gloriosa superba	Liliaceae	Root
14	Besharam	Ipomoea carnea Jacquin	Convolvulaceae	leaf
15	Barbados nut	Jatropha curcas	Euphorbiaceae	seeds
16	Gu Phool	Lantana camara	Verbenaceae	Leaves
17	Moringa	Moringa oleifera	Moringaceae	Flowers, leaves

18	Bitter gourd	Momordica charantia	Cucurbitaceae	fruit
19	Chinaberry tree	Melia azedarach	Meliaceae	seeds
20	Tobacco	Nicotiana tabacum	Solanaceae	Leaves
21	Parijata	Nyctanthes arbortristis	Oleaceae	Leaves, stems
22	Long Pepper	Piper longum	Piperaceae	Seeds
23	Pomegranate	Punica granatum	Lythraceae	Seeds and juice
24	Peach	Prunus persica	Rosaceae	The oil of seeds
25	Caster bean	Ricinus communis	Euphorbiaceae	Root, seed
26	Multiflora rose	Rosa multiflora Thunb	Rosaceae	Hips
27	Marking nut	Semecarpus anacardium	Anacardiaceae	Fruits
28	Heart-leaved moonseed	Tinospora cordifolia	Menispermaceae	Leaves, stem
29	Chinese chaste tree	Vitex negundo	Verbenaceae	Root
30	Kala jira	Vernonia anthelmintica	Asteraceae	Seeds, dried seeds, leaves and Roots
31	Fire flame bush	Woodfordia fruticosa	Lythraceae	Root
32	Cocklebur	Xanthium strumarium	Compositae	Whole plant
33	Ginger	Zinziber officinalis	Zinziberaceae	Rhizome

III. CONCLUSION

Available literature has described the use of the plants in the traditional system of medicine as antirheumatic agents ensuring their clinical efficacy and safety. The present review is a survey of literature demonstrates the importance of natural herbal products in the treatment of Rheumatoid Arthritis. Nowadays, Due to fewer side effects of herbal drugs medicines, the significance of herbal drugs in medicine has increased broadly. Therefore, the demand for herbal formulation is increasing day by day. This review will help researchers who are working in arthritis and provide information regarding the synthetic and herbal approach for the treatment of arthritis.

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