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Review Paper

Herbal Therapeutics in Rheumatoid Arthritis: A Comprehensive Review

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovitis, progressive cartilage degradation, and bone erosion, resulting in irreversible joint damage and multisystem involvement. Its pathogenesis involves a complex interplay of genetic susceptibility, environmental triggers, and immune dysregulation, resulting in the production of autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies, along with elevated pro-inflammatory cytokines including TNF- α and IL-6. NSAIDs, glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs) are some of the current treatments that help with symptoms and control the disease, but they have side effects and can be toxic in the long term. Phytotherapeutic agents like *Curcuma longa*, *Boswellia serrata*, and *Withania somnifera* have strong anti-inflammatory and immunomodulatory effects by changing the way cytokines signal and the way oxidative stress pathways work. More clinical validation is needed

INTRODUCTION

The crippling autoimmune disease known as rheumatoid arthritis (RA) is characterised by persistent inflammation of the synovial joints, which causes pain, swelling, and stiff joint deformities. It can also harm extra-articular organs such as the heart, lung, digestive system, eye, skin, and nervous system. Rheumatoid arthritis (RA) is a chronic inflammatory, systemic, progressive autoimmune disease in which the body's immune

system, which is primarily responsible for defending against foreign bacteria and viruses, unintentionally targets the joints, causing thickened synovium, the formation of pannus, and the destruction of bone and cartilage (1). If left untreated, it can lead to a number of complications, including rheumatoid vasculitis, Ely's syndrome, permanent joint damage that necessitates an arthroplasty, and splenectomy. The precise cause of this illness is still unknown to scientists. Age, gender, genetics, and environmental exposure—

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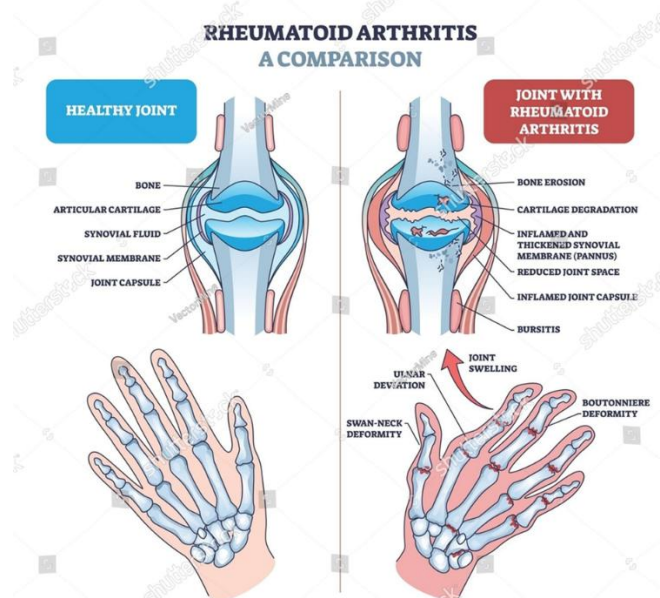
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such as cigarette smoking, air pollution, and occupational exposure—are thought to contribute to the development of RA. Since there is no known cure for RA, the main objectives of treatment are to lessen pain and prevent or slow further damage. In the developed world, RA affects 0.5 to 1% of adults, with 5 to 50 new cases per 100,000 people annually. The immune system typically exhibits self-tolerance in autoimmune diseases and does not target the body's own constituents. An autoimmune disorder results from HL's self-tolerance breaking down. Articular cartilage and juxta-articular bone can be destroyed by chronic inflammation of the synovial membrane, which is part of the pathophysiology of RA. Arthritis is a very common health issue that causes functional disability related to activities of daily living (ADLs) and instrumental activities of daily living

(IADLs), limits social and occupational participation, and makes it difficult for people to fulfil their roles in life. Rheumatoid arthritis, osteoarthritis, gout, tuberculosis, and other infections are among the more than 200 conditions that can result in arthritis (2). Ankylosing spondylitis, gout, osteoarthritis, psoriatic arthritis, rheumatoid arthritis, septic arthritis, calcium pyrophosphate deposition disease, crystal arthritis, bacterial infections, systemic lupus erythematosus (SLE), fibromyalgia, lupus, scleroderma, post-traumatic arthritis, hemochromatosis arthritis, enteropathy arthritis, giant cell arthritis, Bechet's disease, relapsing polychondritis, gonococcal arthritis, Pseudo-gout, and Relapsing polychondritis are the most common types of arthritis (3)

(4)



ETIOLOGY:-

The etiology of rheumatoid arthritis (RA), a chronic autoimmune disease, is multifactorial and involves a complex interplay of immune system dysregulation, environmental triggers, and genetic susceptibility. Genetic factors are important, especially differences in the HLA-DRB1 gene (shared epitope alleles), which make joint tissues more vulnerable to autoimmune reactions. In

people who are genetically predisposed to the disease, environmental factors like cigarette smoking, infections, and exposure to specific pollutants can cause aberrant immune activation and the production of autoantibodies like anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF). These antibodies cause synovial hyperplasia, cartilage degradation, and bone erosion by starting a chronic inflammatory

reaction in the synovial membrane of joints. It has also been proposed that changes in the gut microbiome and hormonal effects play a role in the development and progression of disease. Current research suggests that RA develops through the interaction of genetic predisposition with environmental and immunological mechanisms, which ultimately result in chronic joint inflammation and systemic manifestations, even though the precise cause is still unknown. (5,6,7).

PATHOPHYSIOLOGY:-

The chronic autoimmune disease known as rheumatoid arthritis (RA) is caused by a complex interplay between immune system dysregulation, environmental triggers, and genetic susceptibility. The human leukocyte antigen (HLA) system and other loci that affect immune signalling and lymphocyte activation, such as CD28, CD40, and PTPN22, are genetically strongly linked to the disease. Histone alterations and DNA methylation are examples of epigenetic modifications that further contribute to the development of disease. Through mechanisms like molecular mimicry, environmental factors like smoking, infections, and socioeconomic conditions act as triggers, causing the immune system to mistakenly attack self-antigens.

The development of autoantibodies, specifically rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), which can be identified years before clinical symptoms manifest, is the defining feature of RA pathophysiology. These antibodies create immune complexes that trigger tissue damage by activating the complement system and inflammatory cells like macrophages and osteoclasts. Chronic inflammation of the synovial membrane caused by both innate and adaptive immune responses is the hallmark of the illness. Leukocyte infiltration and pro-inflammatory cytokines, particularly tumour necrosis factor-alpha (TNF- α), interleukin-6 (IL-

6), and, to a lesser extent, interleukin-1 (IL-1), are involved in this inflammation.

By encouraging the expression of receptor activator of nuclear factor kappa-B ligand (RANKL), which stimulates osteoclast formation and bone resorption, synovial fibroblasts become activated as the inflammatory process advances and contribute to joint destruction. Concurrently, chondrocytes are affected by cytokines, which causes the release of matrix metalloproteinases that break down cartilage. Joint deterioration, deformity, and loss of function follow from this. Furthermore, although the precise mechanisms are still unknown, changes in the microbiome have been noted in RA patients and may contribute to the development and course of the disease. In general, the pathophysiology of RA involves an ongoing cycle of inflammation and autoimmunity that, if left untreated, eventually results in irreversible joint destruction. (8)

TYPES OF RHEUMATOID ARTHRITIS:-

• SERO-POSITIVE RHEUMATOID:-

The arthritis Patients who have positive blood tests for anti-cyclic citrullinated peptide (anti-CCP) and/or rheumatoid factor (RF) are referred to as having seropositive RA. It is the most prevalent and serious type of rheumatoid arthritis. Patients usually exhibit extra-articular symptoms, more aggressive joint destruction, and quicker disease progression. Anti-CCP antibodies can show up years before clinical symptoms manifest, making them extremely specific indicators for RA. Compared to seronegative patients, people with seropositive RA frequently exhibit higher levels of inflammatory activity and more radiographic joint damage. Important markers of diagnosis Factor rheumatoid (RF) Anti-CCP, or anti-cyclic citrullinated peptide antibodies.

• SERO-NEGATIVE RHEUMATOID: -



Seronegative Patients who exhibit clinical symptoms consistent with rheumatoid arthritis but do not exhibit detectable RF or anti-CCP antibodies in laboratory tests are referred to as having seronegative RA. In contrast to seropositive RA, the disease course is frequently milder and less damaging. Clinical symptoms, imaging results, and inflammatory markers like ESR and CRP are the primary factors used in diagnosis. As antibodies start to show up over time, some seronegative patients may eventually develop seropositive RA. Because conditions like psoriatic arthritis or spondyloarthritis can initially mimic seronegative RA, differential diagnosis is crucial. (9,10,11)

MECHANISM OF RHEMATOID ARTHRITIS:-

- Environmental Trigger and Genetic Predisposition Rheumatoid arthritis is more common in people with specific genetic markers, such as HLA-DRB1 alleles (shared epitope). In people who are genetically predisposed, environmental factors like smoking, infections, or changes in the microbiome can activate the immune system. These triggers cause the immune system to recognize citrullinated proteins abnormally, which starts autoimmunity.
- Development of Autoantibodies Autoantibodies are produced by the immune system in response to self-antigens. The key antibodies that are involved are: An antibody called rheumatoid factor (RF) targets the Fc

region of IgG. Antibodies against Citrullinated Proteins (ACPAs). By depositing in the synovial membrane and triggering the complement system, these antibodies create immune complexes that increase inflammation.

- Immunological Cell Activation B-cells, macrophages, and synovial fibroblasts are stimulated by CD4⁺ T-cells activated by antigen-presenting cells. Inflammatory mediators are released by activated immune cells, such as: TNF- α (tumor necrosis factor alpha) and IL-1 (interleukin 1) Interleukin 6 (IL-6). These cytokines are responsible for the joint's persistent inflammation.
- The Development of Pannus and Synovial Inflammation Synovial hyperplasia, increased vascularization, and inflammatory cell infiltration are all brought on by chronic inflammation. A proliferative tissue called Pannus (rheumatoid arthritis) is formed by the inflamed synovium and grows over bone and cartilage.
- Destruction of Bone and Cartilage Osteoclasts are activated by the pannus, which releases matrix metalloproteinases (MMPs), resulting in: Damage to cartilage Erosion of the bone Joint deformity and loss of function that progresses The symmetrical joint damage that characterizes rheumatoid arthritis can be explained by this destructive process.(10,11,12)

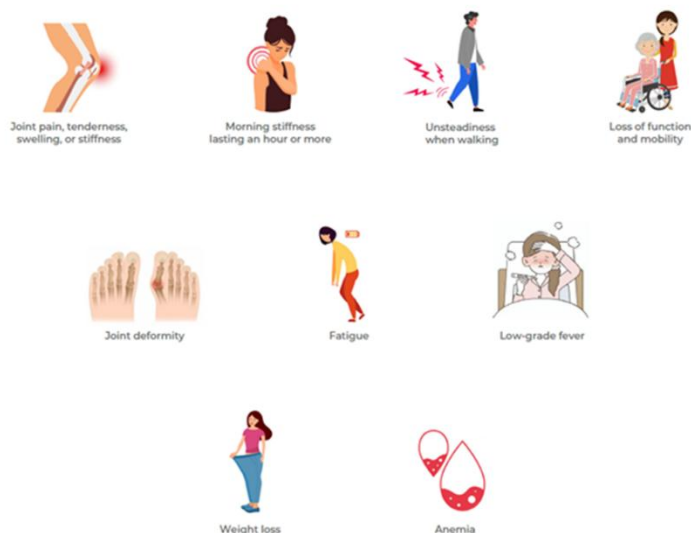
SYMPTOMS OF RHEUMATOID ARTHRITIS:-

Category	Symptom	Description	Citation
Articular	Joint pain (Arthralgia)	Persistent pain in multiple joints, commonly small joints (hands, wrists, feet)	[13]
	Joint swelling	Synovial inflammation leading to soft tissue swelling	[13]
	Morning stiffness	Stiffness lasting >30–60 minutes, especially in early morning	[14]



	Reduced range of motion	Limited joint mobility due to inflammation and pain	[14]
	Symmetrical joint involvement	Bilateral involvement of MCP, PIP, wrist, knee joints	[14]
Systemic	Fatigue	Most common systemic complaint due to chronic inflammation	[15]
	Low-grade fever	Mild fever associated with inflammatory activity	[15]
	Malaise	General feeling of discomfort and illness	[15]
Extra-articular	Rheumatoid nodules	Firm subcutaneous nodules on extensor surfaces	[16]
	Dry eyes (Keratoconjunctivitis sicca)	Autoimmune involvement of lacrimal glands	[16]
	Dry mouth (Xerostomia)	Salivary gland involvement	[16]
	Pulmonary involvement	Interstitial lung disease, shortness of breath	[16]
	Neurological symptoms	Nerve compression causing numbness/tingling	[16]
Early/Preclinical	Arthralgia (without swelling)	Early symptom before clinical RA develops	[17]
	Palindromic rheumatism	Intermittent episodes of joint inflammation	[17]
General Clinical Feature	Chronic progressive inflammatory disorder	RA is a systemic autoimmune disease affecting synovial joints with progressive damage	[18]

Symptoms



(19)

DIAGNOSIS:-

- Medical history: - A doctor will ask about your symptoms, any other medical conditions you or your family have, and any medications you are taking.

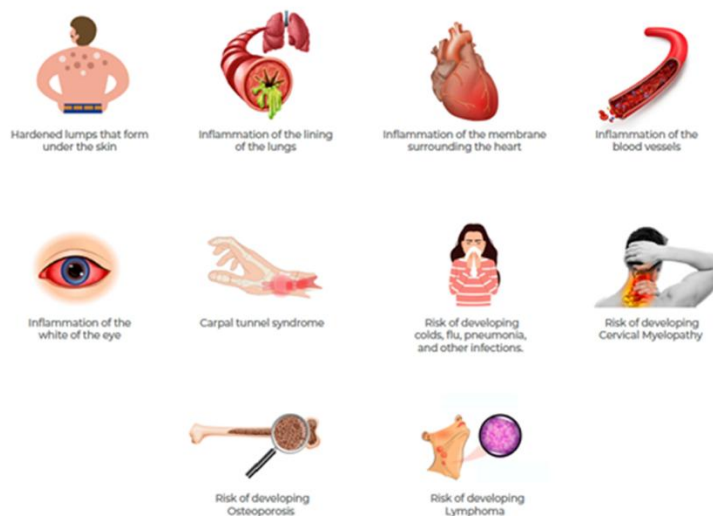
- Physical exam: A doctor will check your general health, reflexes, and problem joints.
- Imaging tests
- X-rays
- Ultrasound
- Magnetic resonance imaging (MRI)
- Computed tomography (CT)
- Blood tests
- Antinuclear antibody (ANA) test
- Complete blood count (CBC)
- Creatinine
- Sedimentation rate
- Rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibody tests
- White blood cell count
- Uric acid
- Surgery: Synovectomy is a procedure that removes damaged connective tissue lining a joint cavity.
- Disease-modifying anti-rheumatic drugs (DMARDs) can help with symptom remission if started early.(20)

COMPLICATION OF RHEUMATOID ARTHRITIS:-

SERIAL N.O.	SYSTEM/CATEGORY	COMPLICATION	DESCRIPTION
1.	ARTICULAR	Joint destruction & deformity	Chronic synovial inflammation → cartilage erosion, bone destruction, deformities (e.g., ulnar deviation)
		Functional disability	
			Progressive loss of joint mobility and function
2.	SKELETAL	Osteoporosis	Reduced bone density due to inflammation and corticosteroid use → ↑ fracture risk
3.	HEMATOLOGIC	Anemia of chronic disease	Decreased RBC production due to chronic inflammation
		Felty's syndrome	Triad: RA + splenomegaly + neutropenia
4.	CRDIOVASCULAR	Atherosclerosis	Chronic inflammation accelerates plaque formation → ↑ MI and stroke risk
		Pericarditis / Myocarditis	
5.	PULMONARY	Pleural effusion	Fluid accumulation in pleural cavity
		Pulmonary hypertension	Increased pulmonary arterial pressure
6.	NEUROLOGICAL	Peripheral neuropathy	Nerve compression or vasculitis-related nerve damage
		Cervical myelopathy	Atlantoaxial subluxation leading to spinal cord compression
7.	OCULAR	Sjögren's syndrome	Dry eyes due to autoimmune gland destruction
		Scleritis / Episcleritis	

8.	CUTANEOUS	Rheumatoid nodules	Subcutaneous nodules, commonly over pressure points
		Vasculitis	Inflammation of blood vessels → ulcers, ischemia
9.	RENAL	Amyloidosis	Protein deposition in kidneys → renal dysfunction
10.	INFECTIOUS	Increased infection risk	Due to immunosuppression (disease + therapy)C
11.	PSYCHOLOGICAL	Depression / anxiety	Chronic pain and disability affecting mental health
12.	METABOLIC/SYSTEMIC	Cachexia	Muscle wasting due to chronic inflammation. (21-23)

Complications



(24)

CONVENTIONAL DRUGS OF RHEUMATOID ARTHRITIS WITH LIMITATIONS:-

Category	Drug/Class	Mechanism of Action	Key Effects in RA	Major ADRs / Limitations	Refs
NSAIDs	Non-selective (Ibuprofen, Diclofenac, Naproxen)	COX-1 & COX-2 inhibition → ↓ Prostaglandins	Symptomatic relief only	GI ulcer, bleeding, renal & CV risk	[25-27]
	COX-2 inhibitors (Celecoxib, Etoricoxib)	Selective COX-2 inhibition	Reduced GI toxicity vs NSAIDs	↑ Cardiovascular risk	[26-28]
Glucocorticoids	Prednisolone	↓ Cytokines (IL-1, TNF-α), immunosuppression	Rapid relief, slows joint damage	Osteoporosis, diabetes, infection, adrenal suppression	[29-31]

Conventional DMARDs	Methotrexate	↑ Adenosine, ↓ T-cell activation	First-line, slows progression	Hepatotoxicity, myelosuppression, GI toxicity	[32-34]
	Hydroxychloroquine	Inhibits lysosomal activity & cytokines	Mild RA, combination therapy	Retinopathy, GI upset	[35-36]
	Sulfasalazine	↓ NF-κB, TNF-α	Anti-inflammatory	GI upset, hypersensitivity	[37]
	Leflunomide	Inhibits pyrimidine synthesis	↓ Lymphocyte proliferation	Hepatotoxicity, teratogenicity	[38]
	Azathioprine	Inhibits purine synthesis	Immunosuppressive	Bone marrow suppression, hepatotoxicity	[39]
	Cyclosporine	Calcineurin inhibitor → ↓ IL-2	Reduces immune activation	Nephrotoxicity, hypertension	[40]
Biologic DMARDs	TNF inhibitors (Etanercept, Infliximab, Adalimumab)	Block TNF-α	Strong disease control	Serious infections (TB), malignancy risk	[41-43]
	Abatacept	Inhibits T-cell activation (CD80/86)	Reduces immune response	Infection risk	[44]
	Tocilizumab	IL-6 receptor blocker	Effective in resistant RA	Infection, liver enzyme elevation	[45]
	Rituximab	Anti-CD20 → B-cell depletion	Severe RA	Infusion reactions, infection	[46]
Targeted Synthetic DMARD	Tofacitinib	JAK inhibitor	Oral alternative	Infection, thrombosis risk	[47]

MANAGEMENT OF RHEUMATOID ARTHRITIS:-

- A better patient outcome depends on early symptom recognition and diagnosis. Early review makes it possible to start treatment and reduce inflammation more quickly.
- Analyses have unequivocally shown that the length of symptoms prior to diagnosis influences the response to DMARD therapy.
- Rheumatoid arthritis can be diagnosed using inflammatory markers and normal autoantibodies. If rheumatoid arthritis is suspected, primary care doctors shouldn't wait for test results before making a referral. Better outcomes have been linked to early referral to a specialist rheumatology clinic.
- Primary healthcare:-Analgesia should be the first line of treatment for primary care patients who exhibit joint symptoms suggestive of inflammatory arthritis. Compound analgesics, codeine, and paracetamol are examples of this. In primary care, standard NSAIDs and selective COX2 inhibitors are further options. Corticosteroids ought to be started in secondary care only after review.
- Interdisciplinary Care:-Occupational therapy, physical therapy, psychology, patient support, and patient education are all part of the multidisciplinary approach used in a

rheumatology clinic to manage rheumatoid arthritis.

- As members of the multidisciplinary team, patients with rheumatoid arthritis may receive care from the following specialists:
- ✓ Occupational therapist: Splints, wrist supports, and pacing guidance to assist with daily tasks
- ✓ Physiotherapist: Particular joint and muscle function, eccentric and concentric exercise regimens

- ✓ GP: Comorbidity assessment and management, including cardiovascular risk and bone health consideration
- ✓ Podiatrist: Take care of your feet and wear the right shoes.
- ✓ Practical guidance and assistance from a rheumatology nurse specialist
- ✓ Orthopaedic surgeons perform joint replacements.(48)

MEDICINAL PLANTS WITH ANTI-ARTHRITIC ACTIVITY:-

S. No.	Plant	Family	Active Constituents	Mechanism of Anti-RA Action	Ref.
1	Aloe barbadensis	Liliaceae	Aloe-emodin	↓ PGE2, NO, IL-6, TNF- α , NF- κ B inhibition	[49-51]
2	Abrus precatorius	Fabaceae	Abrusosides	Anti-inflammatory	[52,53]
3	Alstonia scholaris	Apocynaceae	Alkaloids	↓ COX, LOX, NO, leukocyte migration	[54,55]
4	Andrographis paniculata	Acanthaceae	Andrographolide	NF- κ B inhibition	[56-59]
5	Arctium lappa	Asteraceae	Arctigenin	↓ NO, iNOS, cytokines	[60,61]
6	Artemisia capillaris	Asteraceae	Scoparone	↓ NO, PGE2, NF- κ B	[62,63]
7	Berberis lyceum	Berberidaceae	Alkaloids	↓ prostaglandins	[64,65]
8	Boswellia serrata	Burseraceae	Boswellic acids	↓ NF- κ B, COX-2, LOX	[66-68]
9	Cannabis sativa	Cannabaceae	Cannabidiol	↓ TNF- α , IL-6	[69,70]
10	Curcuma longa	Zingiberaceae	Curcumin	↓ NF- κ B, LOX	[71-75]
11	Glycyrrhiza glabra	Leguminosae	Glycyrrhizin	↓ IL-6, TNF- α	[76,77]
12	Moringa oleifera	Moringaceae	Polyphenols	↓ COX-2, cytokines	[78,79]
13	Nigella sativa	Ranunculaceae	Thymoquinone	↓ IL-1 β , TNF- α	[80-85]
14	Piper nigrum	Piperaceae	Piperine	↓ prostaglandins	[86]
15	Rheum palmatum	Polygonaceae	Emodin	↓ NF- κ B, cytokines	[87,88]

16	Terminalia chebula	Combretaceae	Tannins	↓ TNF- α , IL-6	[89]
17	Withania somnifera	Solanaceae	Withanolides	NF- κ B inhibition	[90]
18	Zingiber officinale	Zingiberaceae	Gingerol	↓ PGE, NO	[91,92]
19	Vitis vinifera	Vitaceae	Resveratrol	↓ Th17, IL-17	[93-95]

MECHANISM OF ANTI-RHEUMATOID ARTHRITIS ACTIVITY:-

- **Cytokine Suppression (Core Mechanism):-** The majority of these plants work by reducing pro-inflammatory cytokines, which are key factors in the pathophysiology of RA. TNF- α , IL-1 β , and IL-6 are examples of cytokines that encourage pannus formation, synovial inflammation, and joint degradation. Herbal remedies such as Terminalia chebula, Aloe barbadensis, Nigella sativa, and Moringa oleifera dramatically lower these mediators, reducing inflammation and slowing the progression of disease.
- **NF- κ B Pathway Inhibition (Master Switch Control):-** NF- κ B is an important transcription factor that controls the expression of genes related to inflammation. Numerous plants inhibit NF- κ B activation, such as Andrographis paniculata, Curcuma longa, Boswellia serrata, and Withania somnifera. As a result, downstream mediators like adhesion molecules, COX-2, and cytokines are suppressed, effectively stopping the inflammatory cascade at its source.
- **Inhibition of Prostaglandins and COX/LOX Pathways:-** Prostaglandins, particularly PGE₂, are important mediators of inflammation and pain. Zingiber officinale, Piper nigrum, Berberis lyceum, and Alstonia scholaris are among the plants that reduce prostaglandin and leukotriene synthesis by inhibiting the COX and LOX enzymes.
- **Nitric Oxide (NO) and iNOS Suppression:-** Nitric oxide overproduction is linked to inflammation and cartilage damage in RA. Joint tissues are shielded from oxidative damage by extracts from Arctium lappa, Citrus medica, and Moringa oleifera that inhibit iNOS expression and NO production.
- **Antioxidant and Oxidative Stress Modulation:-** Oxidative stress hastens the deterioration of joints. By lowering ROS and boosting endogenous antioxidant enzymes, plants such as Nigella sativa, Citrus limon, and Vitis vinifera have antioxidant effects. This stops cellular damage and delays the course of illness.
- **Inhibition of Matrix Metalloproteinases (MMPs):-** Extracellular matrix and cartilage are broken down by MMPs. Ferula asafetida and Clematis ochroleuca are two plants that inhibit MMP-2 and MMP-9, preventing structural damage and joint destruction.
- **Immunomodulatory Effects (Advanced Mechanism):-** Some plants regulate immune responses in addition to reducing inflammation. For instance, Vitis vinifera specifically targets autoimmune mechanisms in RA by lowering Th17 cell populations and IL-17 levels. In a similar vein, Tripterygium wilfordii suppresses adhesion molecules that are necessary for leukocyte migration.(41-95)

LIMITATIONS OF CONVENTIONAL ANTI-RHEUMATOID ARTHRITIS:-

- GI haemorrhage (NSAIDs)
- Infection risk plus osteoporosis (glucocorticoids)
- Methotrexate-induced hepatotoxicity plus bone marrow suppression
- TB and other severe infections (Biologic DMARDs)
- Risk of thrombosis (Tofacitinib)

RECENT ADVANCEMENT AND FUTURE PROSPECTS OF ANTI-RHEUMATOID ARTHRITIS THERAPY:-

Targeted, disease-modifying strategies have replaced symptomatic relief in the treatment of rheumatoid arthritis (RA) due to recent developments. The first-line treatment is still methotrexate, but by focusing on particular immune pathways, biologic DMARDs like TNF- α inhibitors, interleukin inhibitors, rituximab, and abatacept have greatly improved disease control. Targeted synthetic DMARDs act on intracellular signaling pathways and are administered orally, especially JAK inhibitors such as tofacitinib and baricitinib. While the treat-to-target strategy emphasizes early diagnosis and ongoing monitoring to achieve remission, the introduction of biosimilars has improved treatment accessibility. Personalized medicine, pharmacogenetics, epigenetic treatments, and stem cell-based strategies for accurate and long-term management are some of the future prospects. However, there are still a lot of obstacles to overcome, including high costs, safety issues, and inconsistent patient response. (96-98)

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