REVIEW ARTICLE

Rheumatoid arthritis: Pathophysiology, treatment and improved efficacy of targeted treatment using novel herbal therapeutics formulations

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Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease that leads to synovial inflammation, destruction of articular cartilage, bone erosion, deformities, accompanied by pain, swelling, and stiffness, most commonly in limbs. The pathophysiology elaborates on the role of T-helper (Th1) cells secreted in response to interleukin-1 (IL-1) and 12, thus producing pro-inflammatory ILs whereas Th2 cells activated by IL-4 secretes anti-inflammatory cytokines (IL-4, 5, 10 and 13). A neutralization of endogenous anti-inflammatory cytokines mainly IL-10 by the production of anti-IL-10 monoclonal antibodies, results in the downregulation of anti-inflammatory cytokines which lead to more severe collagen-induced arthritis. Conventional treatment for RA includes non-steroidal anti-inflammatory drugs, glucocorticoids, non-biologics, and biological disease-modifying anti-rheumatic drugs, a conjugate of the humanized monoclonal antibody, dendritic cells, etc. Although, conventional therapy and newer treatments are effective but suffer from several limitations like serious adverse effects, high cost, and invasive intervention. The information regarding disease, pathophysiology, treatment, and novel interventions was collected through vigorous literature search from authentic search engines, books and journals using relevant keywords. Novel herbal therapies using phytochemicals of *Curcuma longa*, *Zingiber officinale*, *Glycyrrhiza glabra*, *Withania somnifera*, *Tripterygium wilfordii*, *Boswellia serrata*, *Camellia sinensis*, *Tanacetum parthenium*, *Commiphora wightii*, *Mukul*, *Plumbago zeylanica* through their promising novel drug delivery systems like microspheres, transdermal patches, ethosomes, liposomes, and phytosomes. have shown promising response and efficacy via well-defined immune mechanism along with their easy accessibility, mild or negligible adverse effects, thus gaining the edge over conventional and invasive therapies for RA. This review indicates that there is a need to study these novel formulations, extensively on preclinical and clinical levels and develop these herbal therapies as a promising alternative to conventional therapies for the treatment of RA.

Key words: Rheumatoid arthritis, cytokines, interleukins, herbal therapies, novel formulations, autoimmune mechanism

INTRODUCTION

The term "Arthritis" is a Greek word that is obtained from two words: arthron, meaning a joint and it is meaning inflammation. Rheumatoid arthritis (RA) has been known as an autoimmune and chronic disease which involves inflammatory conditions characterized by persistent and symmetrical synovitis and destructive arthritis. Inflammation typically involves redness, heat, swelling, and tenderness.[1] If the joints are red, hot, swollen, and tender, this is often described as inflammatory arthritis. Arthritis is a condition in which joints are painful, and stiff.[2] RA makes it more difficult for people to be physically active. So, not being physically active is a risk factor for many chronic diseases. More than half of adults with diabetes or heart disease also have arthritis.[3] A related term which is now less

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often used by the doctors, is rheumatism. This term refers to the conditions of stiffness, pain, and inflammation related to joints, tendons, ligaments (which are small 'cushions' that lie under a tendon to protect it from injury).[4]

In the Global Burden of Disease 2010 survey, the estimated global prevalence of RA was 0.24% and was 2-fold higher in women.[5] A key metric, years lived with disability, was found to have increased from 48 to 55 per 100,000 population between 1990 and 2010 and was higher among females than males.[6,7] When the cumulative lifetime prevalence was considered in Olmsted County, Minnesota, the risk for RA was appreciated as relatively higher, approaching 4% in women compared with 2% in men.[8] The prevalence of RA in India is higher than that reported from China, Indonesia, and the Philippines. Arthritis and related conditions are the third-largest contributors, behind cardiovascular disease and neurological disorders, to the direct expenditure on health in the western world, and the USA.[9]

India is continuing to use herbal drugs in the official recognized alternate system of health which is safe. Herbal drugs are the oldest sort of health care. There are some main reasons for the uses of herbal formulations as there is a growing concern over the dependence, the safety of drugs, surgery, and conventional medicine is failing to completely treat many of the most common health conditions. Also, the most of the natural drugs are being shown to produce better results than drugs or surgery without side effects.[8]

Knowledge and use of plants as herbal medicines have occurred in various populations throughout human evolution.[10] The World Health Organization has characterized natural medications as finished, labelled therapeutic products which contains active pharmaceutical ingredients, underground pieces of the plant, other material, and combinations.[11,12]

In the past few years, Researchers and scientists focused on the development of novel drug delivery systems for herbal drugs.[13] The novel carriers should ideally fulfill two needs. Firstly, it should deliver the drug at a rate directed by the requirements of the body, throughout treatment. And secondly, it should channel the active part of the herbal drug to the site of action.[14] Traditional dosage forms are not able to achieve these points. Within the formulation of plant research, developing nano-dosage structures like polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles, phytosomes, and nanoemulsions have some favourable circumstances for herbal medicines which including increment bioavailability, pharmacological activity, solubility, bioavailability, stability, protection from toxicity, improving tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation.[15,16] Thus, the nanosized novel drug delivery systems of herbal drugs have a possible future for improving the movement and defeating issues identified with plant medicines.[17]

MATERIALS AND METHODS

An extensive literature survey was conducted using the relevant keywords like "RA", "cytokines and interleukins (ILs)", "herbal therapies", "novel formulations", "autoimmune mechanism" using authentic search engines (PubMed, Science Direct and Google Scholar) and electronic databases/indexed journals (Web of Science, Scopus, Direct, Google scholar, Springer etc.) and traditional, Ayurvedic and curriculum books covering important and relevant information till date.

RA: CAUSES, PATHOPHYSIOLOGY AND SIGN AND SYMPTOMS

Causes

RA is a chronic inflammatory disease characterized by a heterogeneous clinical response to the different treatments. RA begins slowly, starting in a few joints and then spreading to other joints over a few weeks to a few months.[18] As time goes on, RA involves more joints on both sides of the body in a symmetrical pattern. This means if joints in your right hand are swollen, then joints in your left hand would probably be swollen.[19] The symptoms of RA different from person to person. Some people have only a few joints involved with mild inflammation, whereas others have many joints involved with severe inflammation. The symptoms of RA also vary from times when the joints feel good to other times when the joints become more stiff, sore, and swollen.[20]

RA mostly affects the synovial joints, which are lined with a tissue called synovium and is characterized by chronic, progressive inflammation joint destruction. Activated macrophages are responsible for the production of inflammatory cytokines that result in progressive inflammation, joint swelling, bone erosion, and cartilage damage.[21,22] These results in chronic pain, swelling, stiffness, inflammation, and functional impairment.[23,24] RA is usually symmetrical and typically affects the joints of the hands, the feet, and can affect the whole body, including the heart, lungs, and eyes.[25] The main aim of drug therapy in RA is to reduce pain associated with inflammation and to slow down the disease progression by further prevention of joint destruction.[26]

The most well-known joints affected by rheumatoid joint inflammation are:

a. Between the fingers and the palms of the hand
b. Between the vertebrae
c. In the hips, knees, wrists.

Pathophysiology

The pathophysiology of RA remains unknown but appears to involve a complex series of events involving T-lymphocytes, B-lymphocytes, macrophages and many cytokines and enzymes leading to the destruction of bone, cartilage and also for inflammations in joints.[27] Tumour Necrosis Factor-α (TNF-α) and IL-1 appear to be intimately involved in this process, but numerous other cytokines, inflammatory mediators, and enzymes also seem to play an important role [Table 1]. The co-stimulation-dependent interactions among T cells, B cells, and dendritic cells are shown as occurring primarily in the lymph node. These events generate an autoimmune response to citrulline which contains self-proteins. In the bone marrow and synovial membrane, adaptive and innate immune pathways combine to promote tissue remodelling and damage.[28] Positive feedback intervened by the interactions among chondrocytes, osteoclasts, leukocyte and synovial fibroblasts along with the molecular products of damage, drive the chronic phase in the pathogenesis of RA.[29]

Infiltration of the synovial membrane with plasma cells, dendritic cells, lymphocytes, macrophages, CD4+ T lymphocytes, including T-helper 1 (Th1) cells and Th17 cells play a central role by interacting with other cells in the synovium.[30] Regulatory T (T_{reg}) cells have important functions in peripheral immune tolerance. Dysfunction of T_{reg} is considered as a pivotal cause of RA. T_{reg} cells are a distinct set of thymical produced T cells responsible for suppressing autoreactive deleterious activities of effector T cells like Th1 and Th17 by activation of IL-10.[31] However, the action of T_{reg} cell is inhibited by inhibitors ILs like IL-6, IL-15, IL-18, IL-32 and chemokines which are activated by macrophages.[32,38] Lymphoid follicles structure inside the synovial membrane in which T cell–B cell associations lead B cells to produce cytokines and autoantibodies, including Rheumatoid factor (RF) and anti-citrullinated protein antibody.[33] Synovial macrophages - activated by immune complexes produce pro-inflammatory cytokines, including TNF, IL-1, IL-6 and IL-15.[34,35] Inflammatory cytokines also act on synovial fibroblasts, to enhance swelling of the synovial membrane and damage to soft tissues and cartilage [Figure 1].

Damage-associated molecular pattern, Pathogen-associated molecular pattern and proteases are the molecules release by stressed cells and act as endogenous danger signals to promote and exacerbate the inflammatory response throughout the cycle from macrophages to fibroblast-like synoviocyte.[40]

Activation of chondrocytes and osteoclasts is responsible for the destruction of bone and cartilage. The RA joint is hypoxic and this promotes new blood vessel formation (neo-angiogenesis). The inflammatory granulation

Table 1: Actions of Immunologic Mediators in RA

Substance	Source	Stimulates (Inhibits)
IL-1, TNF	Macrophages	Major Histocompatibility Complex (MHC-I) Expression, Chemotaxis Release of PGE_2, IL-6, GM-CSF, Collagenase, Metalloprotease[25,26]
IL-1	Macrophages	Lymphocyte Proliferation and Activation Growth Factor Release[29,32]
IL-6	Fibroblasts, T-Lymphocytes	T-Cell and B-Cell Function, GM-CSF Release[36]
IL-10	Synovial Cells, B -Cells, Memory CD4+T-Cells	IgM And IgG Release, (Inhibits TNF-A Action), (Inhibits Activation of Antigen-Processing Cells And T-Cells)[37-39]
IL-13	Synovial, Endothelial Cells	T-cell migration and activation, TNF Production By T-Cells and Macrophages[30,28]
IFN-Γ (Interferon)	T-Lymphocytes	MHC-I and MHC-II Expression (Inhibits Collagenase and PGE_2 Release)[30,32]
GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor)	Macrophages, Lymphocytes	Bone Marrow Cell Formation, IL-1 Production, PMN Activation, Monocyte Attraction[28,29]
PGE_2	Fibroblasts	Growth Factor Release, Cartilage Degradation, Inflammation, Pain[28,29]
Collagenase	Fibroblasts	Cartilage Degradation[28,29]
Growth Factors		Synovial Tissue Proliferation[40]
Transforming Growth factor		Synovial Tissue Proliferation, IL-1 Production, Monocyte Chemotaxis (Inhibits Lymphokine and Protease Secretion, Synoviocyte growth)[40]

TNF-a: Tumour Necrosis Factor-α, RA: Rheumatoid arthritis, IL: Interleukin

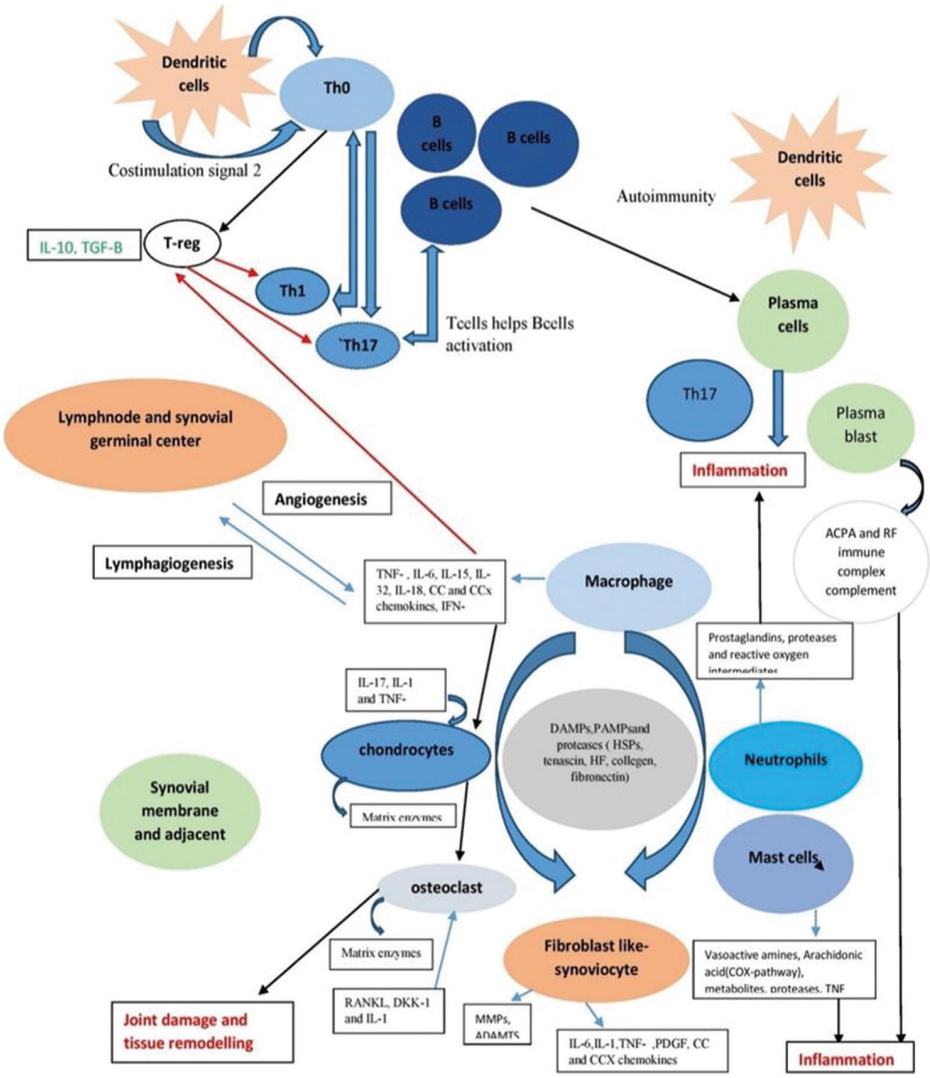

Figure 1: Adaptive and natural immune processes within the joint in rheumatoid arthritis from co-stimulation of dendritic cells to inflammation, joint damage and tissue remodelling: ADAMTS: A disintegrin and metalloprotease with thrombospondin-1–like domains; DAMP: Damage-associated molecular pattern; Dkk-1: Dickkopf-1; FcR: Fc receptor; FGF: Fibroblast growth factor; GM-CSF: Granulocyte–macrophage colony-stimulating factor; HA: Hyaluronan, HSP: Heat-shock protein; IFN: α/β-interferon-α/β; MMP: Matrix metalloproteinase; NLR: Nucleotide-binding oligomerization domain–like receptor; PAMP: Pathogen-associated molecular pattern; PAR2: Protease-activated receptor 2; PDGF: Platelet-derived growth factor; RANKL: Receptor activator of nuclear factor κB ligand; TGF-β: Transforming growth factor β; Th0: Type 0 helper T cell; Th1: Type 1 helper T cell; Th17: Type 17 helper T cell; TLR: Toll-like receptor; TNF-α: Tumour necrosis factor α;VEGF: Vascular endothelial growth factor; Red arrow indicates inhibitory response; blue arrow indicates the stimulatory response to enzymes for the activation of other inflammatory cells; black arrow indicated the progression of the events

tissue (pannus) shaped by the above sequence of events spreads over and under the articular cartilage, which is progressively disintegrated and destroyed. Muscles adjacent to inflame tissue show atrophy and maybe infiltrated with lymphocytes.[30]

Signs and Symptoms

The signs and symptoms of RA includes-

a. Pain and stiffness lasting for more than 30 min in the morning time or after a long rest
b. Rheumatoid nodules
c. Tender, warm, swollen joints[41]
d. Joint inflammation affecting the wrist and finger joints closest to the hand; other affected joints can include those of the neck, shoulders, elbows, hips, knees, ankles, and feet[36,33]
e. Symmetrical pattern. For example, if one knee is affected by RA, the other one is also
f. Fatigue, fever and a general sense of not feeling well (malaise)
g. Positive serum RF
h. Radiographic evidence of erosions or per articular osteopenia in hand or wrist joints.[37]

TREATMENTS FOR RA

Conventional Treatment

The treatment of RA involves lifestyle changes and medications. Many drugs are used for managing the pain, inflammation and slowing the progression of RA, but none completely cure the disease.[42,43] The goal of the drugs treatment for RA is to reduce disease activity and achieve remission. All medications used for the treatment of RA along with their molecule target have risks and show complications [Table 2].

Alternative Treatments

Some alternative treatments are used to show appropriate effect for the treatment of RA:

a. Physical therapy
b. Counselling- individual motivational counselling sessions with a health professional and text messages aiming at improving motivation for light intensity physical activity is effective for RA patients[63]
c. Fish oil and Mediterranean diet include whole grains, legumes, fruit, vegetables, extra-virgin olive oil, and low in red meat consumption, might have the potential to reduce the risk of RA[64]
d. Acupuncture alone or joined with other treatment modalities is gainful to the clinical states of RA and can improve capacity and personal satisfaction and merits attempting[65]
e. Stress Reduction Techniques like meditation, prayer, yoga, and hypnosis can be useful to treat RA.[66]

Herbal Medicines and Their Improved Formulations Used for RA

Herbal medicines have been widely used as effective medicines for the prevention and treatment of most kind of health conditions.[67] Plants play a vital role in the treatment of a various disorder of human and herbal formulations are increasing patient compliance due to the reduction of side effects allopathic drugs. RA is one of the most common inflammatory conditions in developing countries.[68] Now a day's scientists have a focus on developing a novel drug delivery system for the treatment of RA using herbal medicines.[69] Novel systems of herbal drugs not only reduce the side effects, but also help to increase the therapeutic value by reducing toxicity and increasing bioavailability.[70-72] Some following herbal medicines are described [Table 3].

The consumption of these herbal medicines is increasing steadily throughout the world as alternative treatment for RA. In India use of herbal drugs is much more because of easy accessibility. Use of herbal medicines has some more following benefits as lower cost, Effective with chronic conditions, More Potency and efficiency, Widespread availability, more protective, Reduce the risk of side effects, Complete accessibility.[91]

Table 2: Conventional therapies used in RA and their complications

Chemical Class	Drugs	Mechanism of action	Complications
Non-Biological Disease Modifying Anti-Rheumatic Drugs (DMARDS)	Cyclosporine (Alaren), Azathioprine (Azasan), Chloroquine (Neural), Methotrexate	Suppress the function Of Natural Killer Cells And T-Cells, Inhibit IL-1 And B-Lymphocytes	Nausea, Paresthesias, Tremor, Headaches, Gingival Hypertrophy, Lymphoma[44-47]
Biological DMARDS	Anakinra (Orencia), Abatacept (Kineret), Etanercept, Infliximab, Adalimumab	TNF-α Inhibitors and IL-1 Antagonist	Infections and Decreased Neutrophil Counts, Dizziness, Nausea, Hypersensitivity[48-52]
Corticosteroids	Prednisolone (Prelone) And Cortisone (Cortone Acetate)	Immuno-Suppressants and Anti-Inflammatory Effects	Exacerbation, Organ- Threatening Disease, Vasculitis[53,54]
Non-Steroidal Anti-Inflammatory Drugs	Aspirin (Ecitrin), Ibuprofen (Motrin)	Inhibit Prostaglandins, Migration Along with Other Monocyte and Polymorph nuclear Leukocyte Functions	Serious Effect on Gastrointestinal[42,55]
Cox-2 Inhibitors	Celecoxib (Celebrax), Etoricoxib (Arcoxia)	Inhibit Cyclooxygenase-2	Heart Attack and Stokes[56-59]
Surgical treatment			Psychological disadvantages, post-operative site-specific infections[60-62]

TNF-α: Tumour Necrosis Factor-α, RA: Rheumatoid arthritis, IL: Interleukin

Table 3: Herbal alternatives

Common Name	Biological Source (Family)	Chemicals	Mechanism of Action	Improved Formulations
Turmeric	*Curcuma longa* (Zingiberaceae)	Curcuminoids	Inhibit Pro-inflammatory Cytokines and Chemokines and Change the Expression of various Transcription Factors, Cell Cycle Proteins	Nano Carriers, Micro Particles (Biodegradable Starch, Transfersome)[73-75]
Thunder God Vine	*Tripterygium wilfordii* (Celastraceae)	Diterpenoids	Inhibit T-Cells and-Kappa B (κb) -Regulated Gene Products	Liposomes[76-79]
Salai Guggul	*Boswellia serrata* (Burseraceae)	Mono, Di, Tri and Tetraterpenes, Tetracyclic Triterpenic Acids	Inhibits 5-Lipoxygenase	Phytosomes, Liposomes, Niosomes[80]
Ginger	*Zingiber officinale* (Zingiberaceae)	Sesquiterpenewith (-) Zingiberene	Inhibit Pg Synthesis (Cyclooxygenase-1 and Cyclooxygenase-2 Inhibitors), 5- Lipoxygenase	Transdermal Patches[81,82]
Feverfew	*Tanacetum parthenium* (Asteraceae)	Sesquiterpene Lactones, Parthenolide	Inhibit 5- Lox, Phosphodiesterase-3 and Phosphordiesterase-4, Release of Nitric Oxide, Pg, E2 and TNF- From Macrophages	Enteric Coated Tablets Containing the Spray-Dried Extract[83]
Green Tea	*Camellia sinensis* (Theaceae)	Epigallocatechin-3- Gallate	Inhibits DCs (Dendritic Cells) And, T-cell-Mediated Immune Responses	Phytosomes[84-85]
Guggul lipid	*Commiphora mukul* (Burseraceae)	E, Z-Guggulsterone (4,17 (20)-Pregnadiene-3, 16-Dione)	It downregulates Cox-2 and Mmp-9	Liposomes, Vesicles, Micelles[86]
Liquorice	*Glycyrrhiza glabra* (Fabaceae)	Glycyrrhizin, Glycyhrritinic Acid	Anti-Inflammatory Effects	Ethosomal, Macrophages[87]
Grape Seed	*Vitis vinifera* (Vitaceae)	Pro-anthocyanidins, Resveratrol	Inhibit Transcript Factors Like Nf-Kappa B or Activator Protein-1	Nano-sponges[88-90]

CONCLUSION

Herbal medicines are a promising alternative to conventional therapy for arthritis because of their fewer side effects and low cost. Formulation into new drug delivery technologies would further enhance the effectiveness of plant actives/extracts as a result of increased bioavailability and/or drug targeting.

Thorough studies are needed to gain knowledge about the exact mechanism of action of these actives to make the correct choice of a drug delivery system to achieve maximum efficacy. Herbal medicines formulated into a novel drug delivery system thus can prove to be a therapy of choice for arthritis patients due to its safety, efficacy, and affordability.

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