IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 1, April 2023
Impact Factor: 7.301

A Review of Herbal Medicine for Rheumatoid Arthritis

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Abstract: *This review's goal is to assess Zingiber officinale's potential as a treatment for rheumatoid arthritis. Additionally, our goal is to provide an overview of the mechanism of action of certain Zingiber officinale phytochemicals that are reported to lessen pain in RA patients. Rheumatoid arthritis (RA) is an autoimmune illness that is chronic, inflammatory, and affects the synovial tissue in many joints. Even though RA patients often get symptom relief from traditional therapy, the high rate of adverse effects has prompted study into complementary and alternative medicine. We examined medical literature to verify the effectiveness of numerous medicinal herbs, which are historically utilized in Persian medicine to treat symptomatologies related to RA. Important conclusions According to scientific research, conventional medications help treat RA by downregulating pro-inflammatory cytokines like TNF-a, IL-6, and NF-jB; they also suppress oxidative stress; prevent cartilage degradation caused by destructive metalloproteinases; and improve antioxidant function. The medicinal plants have yielded a variety of active ingredients that fall into several chemical groups, such as flavonols, lignans, coumarins, terpenes, glycosyl flavonols, dihydroflavonols, phytoestrogens, sesquiterpene lactones, anthraquinones, alkaloids, and thymoquinones.*

Keywords: Herbal Remedies, Medicinal Plants, Phytotherapy, Joint Health

I. INTRODUCTION

RA is associated with early death, systemic comorbidities, increasing disability, and economical costs1. Data Monitor reports that 1.8 million Americans have RA, which has no identified etiology. No link exists between RA and aging. A malfunctioning immune system attacks healthy tissue and causes inflammation in RA. This causes joint discomfort and swelling and may cause irreparable joint damage and severe disability. Progressive immobility and morning stiffness are the main symptoms of RA, and long-term sufferers will always have joint deterioration. No therapy exists for RA. After diagnosis, treatment is advised to minimize symptoms and/or stop disease progression. RA causes enormous economic, health, and social costs. RA's progressive nature, which starts in early or middle life for many people, often impairs functioning for more than 30 years, which has a high social and economic cost2. Chronic pain and fatigue from RA often impede everyday life for many individuals. As a consequence, RA may prevent employment. One study found that one-third of RA patients must leave their employment after 10 years of diagnosis. Due to this, decreased production is a major illness consequence. Due to its severe health effects, RA is expensive and may reduce quality of life3. Thankfully, diagnosis and treatment have reduced the impact of RA on functioning and quality of life. It is important to realize that many RA studies were conducted before recent therapeutic advances, thus they do not account for the likelihood that the latest drugs will improve functionality. Many RA patients who could not work or care for themselves a few decades ago may today live happy lives because to new medicines.

Healthcare for RA sufferers is expensive. The American College of Rheumatology estimates that RA3 causes 9 million physician visits and 25,000 hospitalizations annually. The typical US RA patient spends $2500 on non-RA-related expenses and over $6,000 on direct RA-related expenses (excluding medication). Hospitalizations represent approximately 50% of RA health costs4. Healthcare costs rise with RA severity. In one research, individuals with a score of 3 on the Health Assessment Questionnaire, indicating a severe degree of impairment, paid three times more for health services than those with a score of 1. This statistic shows how important vigorous therapy is to prevent or delay RA's effects. Economic burden: RA may drastically impair work performance. It may force a person to work fewer

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hours or change careers to accommodate their disability. A person may have to leave their employment if their disease is bad. All these conditions cost money over time.One study found that RA patients had early work constraints and use disability payments more within two years of diagnosis. In another study on the financial burden of osteoarthritis and RA, RA patients spent more on home care, child care, medical equipment and gadgets, and housing alteration than non-RA patients. RA patients were three times as likely to lose family income and had more financial stress than osteoarthritis patients. RA patients were more likely to miss work and retire early than osteoarthritis patients. The investigation found that more RA patients than osteoarthritis patients or individuals without either ailment were unable to work.

Genetic factors

Family history accounts for 50% of RA risk.8. HLA-DR1 (HLA-DR beta *0101) also has this epitope and is risky in southern Europe. Approximately 60% of US RA patients contain a common epitope of the human leukocyte antigen (HLA)-DR4 cluster, which is one of the peptide-binding sites of specific HLA-DR molecules linked with RA. Other HLA-DR4 molecules, including beta 0402, lack this epitope, hence they are safe. Sequencing data from RA-affected families shows multiple resistance and susceptibility genes, including PTPN22 and TRAF59. Juvenile idiopathic arthritis (JIA), often known as juvenile rheumatoid arthritis, is a heterogeneous group of diseases that differs from adult RA. Its onset and symptoms are linked to numerous genes. Its characteristic is arthritis that occurs before 16, lasts longer than six weeks, and has no recognized cause. Both the VTCN1 and IL2RA/CD genes are JIA susceptibility loci. Future RA treatment and understanding may depend on imprinting and epigenetics, according to some researchers. Women are far more likely than men to get RA. It suggests parental genomic imprinting affects its expression15,16. The parent of origin's differential chromosomal methylation causes maternal genes to be expressed above paternal genes, defining imprinting. Epigenetics studies DNA expression changes caused by environmental methylation rather than structural alterations. We know that environmental factors and immune genetics will dominate future research.

Pathogenesis

RA causes systemic inflammation and local joint deterioration in small and medium-sized joints. RA has several periodically active inflammatory and autoimmune pathways, making it clinically and pathobiologically varied. Common RA subgroup features such inflammation and autoimmune disease must be considered.

Inflammation and Synovial Immunology Synovitis develops from leukocyte infiltration. Movement drives leukocyte accumulation, not local expansion. In synovial microvessels, endothelial activity produces adhesion molecules (integrins, selectins, and immunoglobulin superfamily members) and chemokines, promoting cell migration. Early and established synovitis is characterized by neoangiogenesis, caused by local hypoxic conditions and cytokines, and insufficient lymphangiogenesis, which hinders cellular egress.Due to extensive synovial architectural reconfiguration, local fibroblast activation, and microenvironmental changes, rheumatoid arthritis causes synovial inflammatory tissue buildup.

Adaptive Immune Pathways

Due to its genetics and autoantibodies, adaptive immunity drives early rheumatoid arthritis pathogenesis. Although T cells are abundant in the synovium, little is known regarding their function. T-cell-depleting treatments and cyclosporine targeting T cells are ineffective. This suggests that T-cell subsets should be studied and may imply "broad spectrum" depletion of regulatory and effector T cells. Rheumatoid arthritis synovium contains myeloid and plasmacytoid dendritic cells, which generate cytokines, HLA class II molecules, and costimulatory molecules for T-cell activation and antigen presentation. Abatacept, a fusion protein that unites the FC region of IgG1 with cytotoxic T-lymphocyte-associated antigen 4, also treats rheumatoid arthritis by inhibiting T-cell costimulation by CD28 interacting with CD80 or CD86. Autoreactive T cells recognize citrullinated self-proteins. Germinal-center responses, B-cell hypermutation, and synovial T-cell oligoclonality indicate local antigen-specific T-cell-mediated B-cell help. The role of type 17 helper T cells (Th17) in rheumatoid arthritis is increasingly being recognized, as they produce interleukin-17A, 17F, 21, and 22, as well as tumor necrosis factor α (TNF-α). TGF-β and interleukin-1β, produced by dendritic cells and macrophages, respectively, along with 6, 21, and 23, promote Th17 development and inhibit regulatory T cell

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differentiation, leading to an inflammatory T-cell homeostasis. Clinical research focus on interleukin-17A, which works with TNF-α to activate fibroblasts and chondrocytes. Forkhead box P3 [Foxp3+] regulatory T cells in rheumatoid arthritis tissues have limited function31. The imbalance between Th and regulatory T cells may be produced by local TNF-α, which decreases regulatory T cell activity. A non-specific activation of macrophages and fibroblasts by T-cell interaction and antigen is another pathogenic route. CD40, CD200, intracellular adhesion molecule 1, and leukocyte-function-associated antigen 118 interact to mediate these processes. Rheumatoid arthritis and humoral adaptive immunity are connected. Synovial B cells are mostly found in T-cell–B-cell aggregates, and some tissues have ectopic lymphoid follicles supported by APRIL, B-lymphocyte stimulator (BLyS), and CC and CXC chemokines.

Plasmablasts and plasma cells are more abundant in the synovium and juxta-articular bone marrow. Rituximab's efficacy in treating rheumatoid arthritis suggests CD20+ B cells cause arthritis. Clinical data indicate that B lymphocytes and their offspring have a role in rheumatoid arthritis pathogenesis beyond autoantibody formation, including autoantigen presentation and cytokine production (e.g., interleukin-6, TNF-α, and lymphotoxin-β). This is because anti-CD antibodies do not target plasma cells and autoantibody levels fluctuate following therapy.

Blood tests

Neither as a possible indicator of disease progression nor as a major aid in the diagnosis of RA in patients with early RA does routine viral screening by serologic testing. Three kinds of potentially helpful laboratory testing (immunologic parameters, hematologic parameters, and indicators of inflammation) include the following:

- CRP level and erythrocyte sedimentation rate (ESR) or CRP level Full blood count (CBC): Assay for rheumatoid factor (RF) Assay for antinuclear antibodies (ANA)
- The 2010 American College of Rheumatology [ACR]/European League against Rheumatism [EULAR] categorization criteria now employ the anti-mutated citrullinated vimentin (anti-MCV) and anti-cyclic citrullinated peptide (anti-CCP) tests.
- Antibodies against filaggrin (AFA) RNA molecules (miRNA) hematocrit measurements

Complete blood count (CBC)

A complete blood count (CBC) measures the concentrations of several blood components, such as red and white blood cells, platelets, kidney and liver function indicators, and uric acid. Individuals diagnosed with RA often present with anemia (lower hemoglobin or red blood cells) and thrombocytopenia (lower platelets) on their complete blood count (CBC).

II. IMMUNE-RELATED CHARACTERISTICS

Antibodies (e.g., RF), Anti-citrullinated protein antibodies (ACPA) (including anti-cyclic citrullinated peptide [anti-CCP] and anti-mutated citrullinated vimentin [MCV] antibody tests), Anti-filaggrin antibodies (AFA), and Micro RNA (miRNA) are examples of immunologic parameters.

Rheumatoid Factor (RF)

Less than 40% of individuals with early RA have rheumatoid factor, an immunoglobulin (Ig) M antibody that is directed against the Fc (crystallisable fraction) component of IgG. Rheumatoid factor is present in 60-80% of people with RA during the course of their illness (Steiner, 2007). Serum RF is present in 3% to 5% of healthy persons; in the elderly, this rises to 10% to 30%. As one of the American College of Rheumatology's (ACR) categorization criteria for RA, RF has been around longer than anti-CCP as a biomarker for RA38. The European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) states that RF is not a recommended diagnostic marker for RA, most likely due to its limited specificity. However, it is one of several prognostic markers used to identify patients with persistent and/or erosive disease. In addition to being frequent in infections, cancers, and other autoimmune illnesses, RF is a rather general sign of RA. The majority of nuclear antigen subsets have negative test results for antibodies, despite the fact that 40% of RA patients have ANAs.

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Treatment

Treatment should start as soon as RA has been identified and a preliminary assessment has been completed. The care of RA has been covered by recent recommendations, however patient choice is equally crucial. Because many drugs have negative effects on pregnancy, women of reproductive age need to take extra precautions. Reduction of joint discomfort and swelling, prevention of deformity and radiographic damage (e.g., erosions), preservation of quality of life (personal and occupational), and management of extra-articular symptoms are among the objectives of therapy.

Mortality

Compared to the general population, RA patients have higher mortality rates. There is a 3–10 year drop in life expectancy. Over the last two to three decades, the excess mortality linked to RA has not altered. Furthermore, the difference between the two has expanded as a result of new research demonstrating that RA patients have not witnessed the survival benefits seen in the general population. Cardiovascular, infectious, hematological, gastrointestinal, and pulmonary problems are the primary causes of mortality in people with RA. A better prognosis might be suggested by positive reactions to therapy. According to a 2005 Mayo Clinic research, people with RA had a twofold increased risk of heart disease, even after controlling for other risk factors including diabetes, alcoholism, high blood pressure, cholesterol, and body mass index. The existence of chronic inflammation has been suggested as a contributing factor, however the exact mechanism by which RA generates this elevated risk is yet understood. It is plausible that the utilization of novel biologic medication therapy might prolong the life expectancy of individuals with RA and mitigate the likelihood and advancement of atherosclerosis46. This is still speculative and is based on cohort and registry research. The question of whether biologics enhance vascular function in RA remains open. The atherogenic index did not improve, although the levels of total cholesterol and HDLc did rise.

Natural products from plants against Rheumatoid Arthritis

Traditional plant-based treatments have treated and prevented several diseases. Approximately 80% of people globally utilize traditional medicine, according to a WHO study. Over 90% of the 121 US drugs come from natural sources, largely plants51. Herbal remedies may relieve RA symptoms and overcome the limits of allopathic drug treatment. Zingiber officinale Roscoe (Zingiberaceae) reduces RA discomfort and inflammation, according to research. Ginger is made from Zingiber officinale rhizomes.From the Zingiberaceae family. Ancient peoples used it as a spice and medicine39. Due to its phytochemical makeup and medicinal characteristics, Zingiber officinale has been used to treat stroke, diabetes, constipation, and asthma. China produces 80% of the 100,000 tons of ginger produced annually. Benefits of Zingiber officinale for Arthritis Pain. Since ancient times, China and other countries have grown ginger as a spice and medicine. Ginger may alleviate rheumatoid arthritis joint pain, according to research. First to show ginger's anti-inflammatory capabilities was Kiuchi et al. in 1982. Ginger extracts included four new chemicals that blocked prostaglandin synthesis, the main cause of inflammation. A 1992 follow-up found that ginger blocked leukotriene and prostaglandin synthesis, making it anti-inflammatory. A catechol-group diarylheptanoid inhibited 5-lipoxygenase, suppressing leukotriene synthesis, which reduces inflammation. Another component, yakuchinone A, lowered prostaglandin production, which may lessen inflammation. Thomson and his colleagues examined Zingiber officinale's anti-inflammatory effects in rats. Experimental rats received an aqueous Zingiber officinale extract intraperitoneally or orally for four weeks. Ginger significantly lowered prostaglandin E2 at high doses but not at low levels. Ginger may reduce RA inflammation. Europe and India, especially the northwest Himalayas, grow aloe barbadensis. Aloe vera is a key traditional medicinal plant. Anthraquinone, anthracene, cinnamic acid, and anthranilic acid are aloe vera active components. Aloe vera treats eczema, poison ivy, mild wounds, bug stings, and bruising. It is antibacterial, antifungal, blood purifier, anti-inflammatory, diuretic, uterine tonic, spermatogenic, laxative, purgative, and fever reducer. Anti-arthritis benefits come from aloe vera's anthraquinone component. Aloe vera boosts immunity and reduces inflammation. Sprague Dawley rats with adjuvant-induced arthritis had less inflammation and arthritis after topical aloe vera extract. Ashwagandha, or Indian ginseng, is old. Indian Ayurvedic and Unani medicine uses ashwagandha roots. It grows in arid subtropical states like Madhya Pradesh, Rajasthan, Punjab, Haryana, Uttar Pradesh, Gujarat, and Maharashtra. Pharmaceutical effects come from the root's steroidal lactones and alkaloids. The most prevalent alkaloids are withanine, pseudo-withanine, tropine, pseudo-tropine, somniferine, and somnine. Roots provide sitoindosides-7

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and-8, acyl glucosides. Nowadays, the plant is used to treat senile dementia, asthma, ulcers, and sleepiness in addition to aphrodisiac and liver tonic. Clinical and animal studies support ashwagandha for neurological illnesses, inflammation, anxiety, and Parkinson's. Adding ashwagandha to the diet may reduce tumor growth. It improves aging, anemia, arthritis, tiredness, sports fitness, and stress with progressive, long-term results. Oral powdered Withenia somnifera Linn. root reduced arthritis in mice with adjuvant-induced arthritis94,95. South India is black pepper's homeland. Malaysia, Sri Lanka, Indonesia, and Brazil manufacture it. India grows the most of this substance. Pepper contains piperine, an alkaloid, volatile oil, aromatic resins, piperidine, and starch. It is carminative, stimulant, stomachic, and scented. This increases stomach fluid flow. It also improves drug bioavailability. Black pepper contains piperine. Carrageenan-induced acute paw arthritic symptoms improve with oral piperine at 20 and 100 mg/kg/day for eight days. Some plants bloom, like Cissampelos pareira Linn. A few flavonoids, alkaloids, and saponins are present. Its uses include antiseptic, aphrodisiac, analgesic, anti-hemorrhagic, cardiotonic, diaphoretic, expectorant, febrifuge, hepatoprotective stimulant, tonic, antibacterial, anti-inflammatory, antihistamine, antioxidant, antispasmodic, diuretic, hypotensive, muscle relaxant, uterine relaxant, Heart disease, asthma, dyspepsia, diarrhea, dropsy, coughing, and cystitis are treated with the roots. The leaves alleviate inflammation with antimicrobial qualities. The roots' ethanolic extract may relieve diarrhea, arthritis, and pain. The ethanolic extract of Cissampelos pareira Linn. roots protected against complete Freund's adjuvant-induced arthritis dose-dependently. Asteraceae: Lappa Arctium L. In traditional medicine, numerous Arctium species cure systemic and topical inflammatory conditions include chronic inflammatory bowel disease and rheumatoid arthritis. Arctium lappa seeds contain arctigenin, a lignan molecule. RA etiology inflammation releases NO and pro-inflammatory cytokines from macrophages. Experiments showed that arctigenin and its glycoside, arctiin, suppressed TNFa and several interleukins, including IL-1b, IL-6, IL-4, and IL-5. This chemical compound decreases NO levels by blocking iNOS synthesis and activity. Blocking MAPK phosphorylation and the nuclear signaling pathway (NF-jB) may explain arctigenin's anti-inflammatory and anti-arthritic effects. MAPK, which upregulates inflammatory mediators, is crucial to RA pathogenesis. The a-isoform controls intracellular signaling that generates TNFa or IL-1b. It also regulates COX-2, which regulates PGE2 in inflammation. MAPK inhibitors like arctigenin block arthritic mice's monocytes and synovial tissue from generating TNFa and IL-1b. Anti-inflammatory effects of A. minus (Hill) Bernh. leaf in carrageenan-induced paw oedema animal model.

III. CONCLUSION

In conclusion, ginger's different phytochemical components may have therapeutic functions in reducing RA symptoms and maybe even curing the disease itself. It is anticipated that additional research into the molecular mechanisms underlying these phytochemicals' actions will not only help find new medications to treat the symptoms of RA, such as pain and inflammation, but may also enable the reversal or prevention of the disease's damage. Numerous active phytochemical compounds obtained from the listed medicinal plants have the potential to be effective on RA, according to evaluated cellular and animal research. Flavonols (quercetin), lignans (arctigenin), coumarins (scopoletin and scoparone), oxyanthraquinones, terpenes (limonene), triterpene saponin, steroidal saponin (seiboldogenin), glycosylphenols, phytoestrogens (ferutinin), sesquiterpenes (umbelliprenin), sesquiterpenoid (ilicic acid and inuviscolide), sesquiterpene lactones (ergolide and granilin), dihydroflavonols (sakuranetin and 7-Omethylaromadendrin), anthraquinones (emodin), alkaloids (brucine and brucine N-oxide), and thymoquinone are some of the chemical groups that these phytoconstituents belong to. It is imperative that further study be done on the safety and bioefficacy of these phytochemical compounds in order to discover new natural medications.

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