EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 4
376-386
Year: 2024

HERBAL REMEDIES FOR AUTO IMMUNE DISORDER SPECIALLY IN RHEUMETOID ARTHRITIS

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Article Received on 26/02/2024 **Article Revised on 17/03/2024** **Article Accepted on 07/04/2024**

ABSTRACT
The most prevalent type of inflammatory joint disease, rheumatoid arthritis (RA), is thought to have an unknown etiology. It affects around 1% of the global population and, in contrast to osteoarthritis (OA), typically affects many joints due to its systemic nature. Reports indicate that between 60 and 90 percent of patients with arthritis who are not satisfied with their treatment plan will probably consider CAM. Rheumatoid arthritis is a debilitating inflammatory illness that progresses over time and causes systemic inflammation of the joints, causing damage to the surrounding bone and cartilage. Being a systemic condition, it can impact the internal organs, including the heart, lungs, and eyes, as well as the entire body. Even though many synthetic medications are employed as the normal course of treatment for rheumatoid arthritis, they have side effects that can jeopardise the effectiveness of the therapeutic intervention. Regretfully, current medication can only treat the disease's symptoms, which include relieving joint pain and inflammation, leaving no proven effective treatment for rheumatoid arthritis. There exist diverse applications for herbs and plants that might be employed to alleviate joint discomfort and inflammation.

KEYWORDS: Rheumatoid arthritis, Joint pain, Inflammation, Disease's, Symptoms.

Arthritis
The word "arthritis" covers about 100 conditions that affect the joints and/or the surrounding tissues, including the muscles, tendons, and bones. These illnesses are the leading cause of impairment among the elderly, affecting about 36 million Americans. While these diseases usually contribute more to morbidity than to mortality, growing evidence suggests that rheumatoid arthritis as well as systemic lupus erythematosus contribute to premature mortality. With few exceptions, these diseases cannot be prevented or cured by either medical or behavioral interventions Like other chronic disease, most forms of arthritis must be managed over a long period of time.[1]

The goal of management is to minimize pain, disability, deformity, and the social/ psychological dysfunction which often accompany long-term, painful illnesses. While the use of medical and surgical interventions has increased, these have a major impact on a relatively small percent of people with arthritis. For this reason, arthritis patient education is of major importance as a therapeutic intervention to help people live successfully with the disease. The aims of arthritis patient education are somewhat different from those of other chronic conditions. Unlike hypertension and diabetes, compliance is not always of prime importance. Arthritis waxes and wanes on an almost daily basis.

Therefore, the patient must be taught to adjust his or her exercise, rest and sometimes even medication to the daily disease symptoms. Rather than prescribing a treatment program which must be followed rigidly, the arthritis patient must be helped to Arthritic diseases are characterized by inflammation and loss of in the joints and connective tissue, associated with significant morbidity and mortality.1−3 Currently, there are more than 100 varieties of arthritic diseases, and they collectively become a major health and financial burden for societies. The most common arthritic diseases include rheumatoid arthritis (RA), osteoarthritis (OA), ankylosing spondylitis (AS), gout, lupus, and psoriatic arthritis.[2]

Types of arthritis
There are different type of arthritis some are given below.
1. Osteoarthritis arthritis
2. Rheumatoid arthritis
3. Psoriatic arthritis
4. Septic arthritis
5. Reactive arthritis

1. Osteoarthritis

Osteoarthritis (OA) is a common chronic condition resulting in pain, fatigue, functional limitations, increased healthcare utilization and high economic costs to society. The burden of OA is projected to increase, due in part to obesity and population aging. While the prevalence of OA increases with age, there is a growing recognition that OA affects people at younger ages. Quadriceps strength deficits have been reported in 20%–70% of patients with knee OA. Any improvement in muscle strength or peak power of the lower extremities with decreased levels of particular pain may be important and is a strong predictor of functional ability. As lower limb musculature is the natural brace for the knee joint, potentially important muscle dysfunction may arise from either quadriceps weakness or relative weakness of the hamstrings in comparison to the quadriceps, usually assessed as the hamstrings Osteoarthritis (OA), also known as degenerative joint disease, primary OA, wear and-tear arthritis, or age-related arthritis, is a leading cause of disability in the US and worldwide Inpublic health sectors, arthritis is a blanket term used to refer to more than 100 rheumatic diseases and conditions that affect the joints, the tissues surrounding the joints, and other connective tissue OA is the most common joint disorder in the US.[3]

2. Rheumatoid arthritis (RA)

Rheumatoid Arthritis is defined as a systemic autoimmune pathology associated with a chronic inflammatory process, which can damage both joints and extra-articular organs, including the heart, kidney, lung, digestive system, eye, skin and nervous system. The study of illness distribution and its causes in human communities is known as epidemiology. The foundation of this definition is the belief that human disease is not random and that there are preventive and causative factors that can be found by conducting systematic research on various populations or subgroups of individuals within a population in various locations or at various times. Therefore, basic descriptions of how a disease manifests in a population (i.e., disease frequency, incidence, and prevalence, mortality, trends over time, geographic distributions, and clinical characteristics) and descriptions of the potential contribution of risk factors to the occurrence of disease are included in epidemiologic studies.[4]

3. Psoriatic arthritis

As opposed to being the result of two common diseases occurring coincidentally, the idea of psoriatic arthritis as a distinct disease entity is relatively new. The evidence supporting this notion has come from a variety of sources, the most prominent of which are clinical, serologic, and radiologic studies; epidemiologic surveys have also significantly improved our understanding of the condition. The following discussion will focus on these areas of research and their role in securing the current status of psoriatic arthritis as disease suigeneris. Psoriatic arthritis still lacks a fully adequate definition.[5]

4. Septic arthritis

Septic arthritis is a rare emergency that has the potential to be lethal. To prevent irreversible joint deterioration or even death, early diagnosis and timely, efficient therapy are crucial. Different clinical characteristics of this illness apply to adults, children, and neonates. A positive culture of the pathogen or direct detection of bacteria in synovial fluid are necessary for the final diagnosis of septic arthritis. The cornerstone of a successful course of treatment is the combination of antibiotics and the expeditious evacuation of purulent material from the afflicted joint. Furthermore included in this article are gonococcal arthritis and prosthetic joint infections.[6]

5. Reactive arthritis

The development of sterile inflammatory arthritis following a distant infection, frequently in the gastrointestinal or urogenital tract, is known as reactive arthritis (ReA). The diagnosis is primarily clinical and is predicated on acute oligoarticular arthritis of bigger joints occurring 2-4 weeks after the previous infection, despite the lack of widely accepted diagnostic criteria. Studies on populations have shown that the yearly incidence of ReA is 0.6–27/100,000. The diagnosis of the triggering infection is necessary for the diagnosis of ReA in addition to the standard clinical picture.[7]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects around 5 out of every 1000 persons globally. The illness can strike at any age and affects women two to three times more frequently than men. The sixth decade is the peak incidence. In the past, RA caused increased mortality, disability, and incapacity to work. Better outcome metrics and medicines have been developed, together with a deeper understanding of the pathophysiology of RA, to produce recent improvements in outcomes[8]. The definition of rheumatoid arthritis (RA) is a systemic autoimmune illness linked to a persistent inflammatory process that can harm extra-articular organs such as the kidney, lung, heart, digestive tract, eyes, skin, and nervous system in addition to joints. To categorize arthritis into non-inflammatory (Osteoarthritis) and inflammatory (Pseudogout, basic calcium phosphate disease, gout) types, as well as bacterial and viral infections (Staphylococcus aureus, Neisseria gonorrhea, complications of Lyme disease, Parvovirus, Enterovirus), or autoimmune processes, a great deal of research and description has been done on arthritis. Systemic lupus erythematosus (SLE), Sjögren's syndrome, adult-onset scleroderma, spondylarthritis (SpA), psoriatic arthritis (PsA), polymyositis (PM), and other conditions are included in the diverse group of autoimmune rheumatic illnesses. Differential diagnosis is crucial because their indications and symptoms may be identical. The etiology of RA is still unknown, despite the fact that several biomolecular pathways have been postulated. One recent theory holds that dysregulated citrullination causes the

generation of anti-citrullinated protein antibodies (ACPAs).[2]

Sympathetic polyarticular arthritis, or rheumatoid arthritis (RA), mainly affects the tiny diarthrodial joints in the hands and feet. Local articular structures are invaded and destroyed by the aggressive front of tissue known as pannus, in addition to inflammation in the synovium, the lining of the joint. Normally, the synovium is a structure that is mostly acellular and has a thin intimal lining.[2]

In the industrialized world, 0.5–1% of people suffer from rheumatoid arthritis (RA), a chronic inflammatory and degenerative joint disease that frequently results in severe disability and a corresponding decline in quality of life. It can begin at any age and is two to three times more common in women than in men. It peaks in incidence between the fourth and sixth decades of life. In addition to being expensive, RA can shorten life expectancy if treatment is not received.[8]

Epidemiological overview

Relevant and relevant findings were obtained from epidemiological studies that measured the prevalence of RA in a few European, Asian, North American, and South American countries between 1990 and 2005. Serbia (0.18%), China (0.28%), France (0.31%), Italy (0.33%), and the US (0.41%) all had low prevalence ratios, whilst Japan (1.7%) and Argentina (1.97%) showed greater prevalence ratios. It is important to note that because the types of studies conducted were so different, there may have been methodological biases in earlier research that led to variations in the prevalence of RA. These studies included cross-sectional studies, random selection, telephone surveys, postal questionnaires, initial cohorts, outpatient, and hospitalization medical records. Additionally, it was noted that there are gender variations in the prevalence of RA. According to all the research, women are three to five times more likely than men to have RA. The closest numbers were obtained in Serbia (women 0.29%, males 0.09%), but the most significant difference was reported by the Argentine study (women 3.2%, men 0.6%).[9]

Pathophysiology

In RA, memory and naïve B cells accumulate in synovial tissue, where certain B cell clones with a high migratory capacity seem to be continuously activated. According to flow cytometry studies, peripheral B cells from RA patients express important molecules differently, with low levels of the inhibitory receptor for IgG immune complexes (FcgRIIb) and high amounts of the costimulatory protein CD86. TNF inhibition caused expression to rise and decrease, respectively, indicating that inflammation may dysregulate CD86 and FcgRIIb, possibly causing tolerance to break down and humoral autoimmunity to emerge. A transcription factor called FOXO3a is involved in the control and survival of the cell cycle. In RA patient blood, FOXO3a mRNA was elevated in microarray tests, mostly in polymorphonuclear cells. T lymphocytes in inflammatory aggregation in the RA synovial tissue sublining confirmed this observation. This shows that FOXO3a overexpression may contribute to chronic inflammation in RA by extending the survival of these cell types. Others found that the sera of RA patients had elevated amounts of sH4 (soluble B7–H4). The B7–H4 molecule is known to block the B7–CD28 signaling pathway on the cell surface. According to mice models, sH4 may exacerbate arthritis by competing with the cell-surface molecule.[10,12]

Other routes and mediators, such myeloid DAP12-associating lectin (MDL)-1, are still being thoroughly investigated. MDL-1 can induce osteoclast activation, bone erosion, and synovial inflammation in vitro by attracting a significant number of bone marrow-derived inflammatory macrophages and neutrophils. Finally, it has been shown that certain RA patients' sera contain auto-antibodies to BRAF (v raf murine sarcoma viral oncogene homologous B1). BRAF is a serine–threonine kinase that is upstre am of the generation of pro-inflammatory cytokines in the mitogen-activated protein kinase (MAPK) signaling pathway. Because of this, auto-antibodies connected to this pathway might contribute to the development of the pro-inflammatory environment in RA.[13]

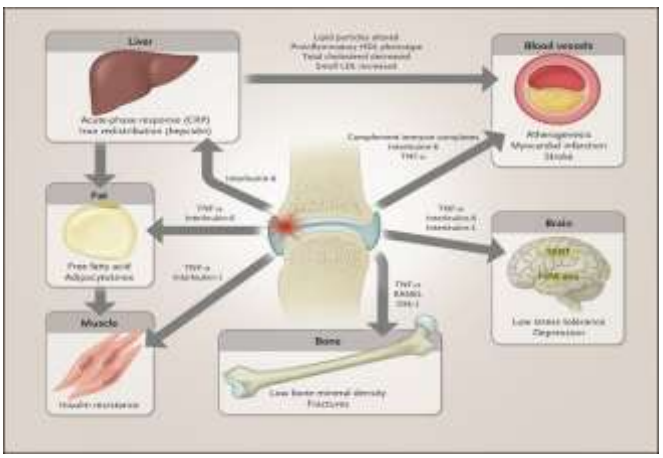

Figure 1: Pathophysiology of RA.

Pathogenesis

Chronic inflammation of the synovial membrane, which can lead to the destruction of articular cartilage and juxtaarticular bone, is a pathogenesis of RA. New insights into the biological pathways involved have contributed to a better understanding of the phenomena and outcomes related to rheumatoid inflammation. Therapeutic intervention can target newly found substances and cells inside the biologic route.[7] The inflammatory and immune systems are closely related to the degeneration of bone and cartilage in RA. Numerous pathways implicated in the development of the disease have been found, and some of these have been categorically designated as significant by therapeutic proof-of-principle studies, despite the fact that the penultimate link connecting the two systems is still elusive and the etiology of RA is unknown. Though there is currently little evidence to support the long-held theory, infectious organisms may be the cause of RA. It's interesting to note that, in this regard, medications with antibiotic activity or derived from antibiotics tend to be more beneficial for RA patients. However, this benefit is typically attributed to non-antibacterial modes of action.[8]

Conventional and genome-wide methods have been used to investigate the genetics of RA, and the genetic architecture of the illness is well understood. More than 100 loci are linked to the development and risk of disease, and most of these involve immunological effector or regulatory gene products. The MHC class II locus, particularly HLA DR01/04, which is linked to T cells recognizing autoreactive peptide, co-stimulatory pathways, such as CD28, CD40, chemokines, and cytokine receptors (e.g., IL-6R), post translational modification enzymes, such as PADI, and intracellular regulatory pathways, such as PTPN22, TNFAIP3, and STAT3, are prominent examples of these. These pathways have the potential to modify the threshold for immune activation or failed regulation. Nonetheless, it is acknowledged that strong epidemiologic consequences leverage this genetic foundation to fuel illness. Numerous studies have demonstrated the potential role of smoking (particularly in HLADR01/04+ persons), other lung exposures such as silica dust, plus other factors like vitamin D deficiency and obesity as pro-disease causing factors.[9]

The majority of the T cells invading the synovial membrane are CD4+ memory cells, which are pre-activated or further activated by antigen-presenting cells (APCs) in conjunction with arthritogenic (auto)antigen(s) and appropriate major histocompatibility complex (MHC) class II molecules, co-stimulation (primarily through CD80/81 and CD28), and specific cytokines (IL-1, IL-15, IL18). Additionally, these cells produce IL-2 and IFN-γ to a similar extent as antigen-triggered T cells. These T cells activate monocytes, macrophages, and synovial fibroblasts by cell-cell interaction (e.g., through CD11- and CD69-mediated processes) and various cytokines (e.g., IFN-γ, TNF-α, and IL-17). Subsequently, the overproduction of pro-inflammatory cytokines, primarily TNF-α, IL-1, and IL-6, appears to be the key factor contributing to chronic inflammation. These cytokines trigger a range of genes linked to inflammatory responses, such as those encoding other cytokines and matrix metalloproteinases (MMPs) that break down tissue, through intricate signal transduction cascades. Additionally, TNF-α and IL-1 cause macrophages to produce RANK. These macrophages then develop into osteoclasts, which resorb and destroy bone, when they interfere with RANKL on stromal cells or T cells. Furthermore, chondrocytes are stimulated, which results in the release of MMPs. Prior to T-cell engagement, early events may also involve APC activation via Toll-like receptors (TLRs). TCR stands for T-cell receptor; RANK, receptor activator of nuclear factor-κB; RANKL, RANK ligand; RF, rheumatoid factor.[8]

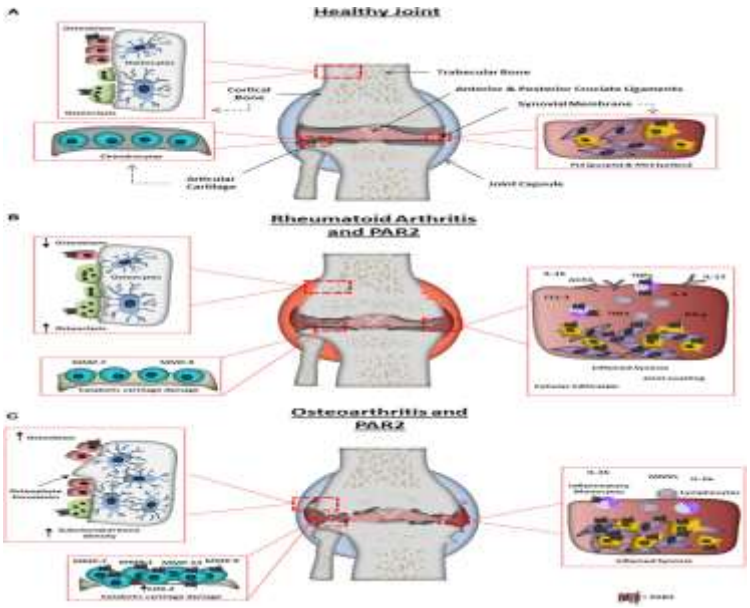

Figure 2: Schematic representation of events occurring in rheumatoid arthritis.

Relevant and relevant findings were obtained from epidemiological studies that measured the prevalence of RA in a few European, Asian, North American, and South American countries between 1990 and 2005. Serbia (0.18%), China (0.28%), France (0.31%), Italy (0.33%), and the US (0.41%) all had low prevalence ratios, whilst Japan (1.7%) and Argentina (1.97%) showed greater prevalence ratios. It is important to note that because the types of studies conducted were so different, there may have been methodological biases in earlier research that led to variations in the prevalence of RA. These studies included cross-sectional studies, random selection, telephone surveys, postal questionnaires, initial cohorts, outpatient, and hospitalization medical records. Additionally, it was noted that there are gender variations in the prevalence of RA. According to all the research, women are three to five times more likely than men to have RA. The closest numbers were obtained in Serbia (women 0.29%, males 0.09%), but the most significant difference was reported by the Argentine study (women 3.2%, men 0.6%).[7]

Risk factor of ra

Hormonal:- It has been suggested that a hormonal or reproductive influence on onset may be responsible for the increased incidence of RA in women. The recent Nurses' Health Study found that these characteristics had a minimal impact. Nonetheless, a recurring conclusion across multiple studies suggests that the oral contraceptive pill (OCP) might offer some protection. More than eighteen research have looked at this concept, and the majority—though not all—of them have discovered that use, whether recent or past, does have a protective impact. There are doubts about the biological plausibility of these data because oestrogens are known to promote inflammation. Moreover, the growth in OC use may account for the recent decline in incidence among women over the last 50 years. Because OC use is associated with both high socioeconomic status and avoiding pregnancy, this apparent link may be complicated. The Royal College of General Practitioners came to the conclusion that OC use delayed rather than prevented the start of RA in one of the few large-scale follow-up studies.[14]

Environmental influences: - The descriptive epidemiology of RA raises the possibility of environmental influences as well. There seems to be a larger prevalence of the disease in urban than rural areas. There has been a noticeable recent fall in incidence among high incidence populations, including the Pima Indians. This observation has also been made in other populations. The influence of birth cohort is a more compelling indicator of an environmental effect, as those who were born more recently have a lower age-adjusted incidence. These kinds of data strongly imply changes in environmental exposure over time.[15]

Cigarette smoking: - One of the most extensively researched potential lifestyle risk factors is cigarette smoking. Therefore, if a man smokes, his risk of developing RA is about three times higher. For both sexes, the effect of heavy smoking (41–50 pack years) can raise this risk to above 13. Most importantly, a population-based case-control study's findings show that quitting smoking can lower the chance of getting seropositive RA. The risk still doubles for people who quit smoking during the last 1–9 years, but it only hovers around 1.5 for those who have quit smoking for 10–19 years. Similarly, compared to present or more recent smokers, there was an approximately twofold decrease in risk for seropositive RA in Ex smokers who had stopped smoking for at least ten years in the Iowa Women's Health Study.[16]

Diet: - It is an often reported experience that nutrition may have an impact on the development and maintenance of RA, and there is mounting evidence in the scientific literature to support this theory. However, there are a number of issues with studying diet: first, prospective studies are necessary to make sure that any dietary variability predates the disease rather than being a result of arthritis; second, accurate diet intake analysis is challenging and time-consuming, and popular methods like the food frequency questionnaire can mask real associations; and third, there is a high level of diet confounding, making it challenging to determine which food or nutrient is truly biologically important. A common recommendation is that eating a Mediterranean diet can lower your chance of developing inflammatory arthritis. This has been put to the test in an intervention meant to enhance RA's results. It was possible to improve quality of life and reduce important components of disease activity, such as the Disease Activity Score and the Health Assessment Questionnaire, by making dietary changes. An important component of a Mediterranean diet is its high oily fish content, which is based on the theory that high Omega 3 fatty acid levels may provide inflammatory protection.[17]

Caffeine:- Numerous investigations have discussed the impact of coffee on the onset of RA; nevertheless, the ensuing discrepancy suggests that a true effect is improbable. The Iowa Women's Health Study found no correlation between the amount of caffeinated coffee consumed or daily caffeine intake; however, consuming more than four cups of decaffeinated coffee per day was linked to a two and a half-fold increase in risk. They also discovered that consuming three cups of tea a day provided some protection. Those with seropositive illness showed greater relationships with these factors. In contrast, there was no correlation between the amount of caffeine consumed overall, in tea, coffee, or both decaffeinated and caffeinated, according to a recently published analysis of the Nurse's Health research, a prospective cohort research.[18]

Occupation:- Potentially hazardous environmental exposures can be concentrated in occupational settings, yet there aren't many high-risk jobs that have been found.

A postal questionnaire was employed in a large study comprising more than 2000 population referents and over 700 cases to examine the relationship between RA development and lifetime employment history. It is hardly surprising that a number of favorable connections arose given the abundance of possible careers, even though most of them lack a compelling biological explanation. Male employees in the agricultural, paper, and transportation industries thus had a five-fold higher chance of acquiring RA. Postal workers and printers were identified as having a higher risk of contracting the disease in female employees. A detailed investigation into one theory pertaining to pesticide use among female farm workers was conducted, but no such link was discovered.[19]

Clinical aspects of ra

The early signs and symptoms of RA, which are often articular, typically manifest in one of two ways: slowly and subtly at first, or suddenly and explosively. 55–65% of cases start slowly over the course of weeks or months. Eight to fifteen percent of individuals experience acute onset symptoms that peak in a few days. Some people may experience generalized musculoskeletal symptoms, weariness, malaise, puffy hands, or stiffness in the mornings before developing synovitis. Asymmetrical presentations, in which symmetry appears later in the illness, are not uncommon. RA patients have symmetric joint involvement. While the distal interphalangeal (DIP) joints and the lumbosacral spine are spared, the most frequently affected joints are the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, wrists, elbow, knee, metatarsophalangeal (MTP) joints and toe PIPs, and cervical spine. Usually, smaller joints develop symptoms before larger joints do. The 1987 updated American Rheumatism Association (ARA) criteria are the ones that are now used to classify RA.[20]

Table 1: To receive the classification of having RA, a patient must have four of the following seven criteria.[20]

Criterion	Definition
Morning stiffness	Morning stiffness in the joints and surrounding tissues that lasts for at least an hour before it fully improves
Arthritis of three or more joint areas	A clinician must witness at least three joint regions at the same time that have soft-tissue swelling or fluid (rather than just bony overgrowth). The 14 potential joint areas are the PIP, MCP, wrist, elbow, knee, ankle, and MTP joints (either right or left).
Arthritis of hand joints	At least one of the wrist, MCP, or PIP joints' swollen areas is seen above.
Symmetric arthritis	Simultaneous involvement of PIP, MCP, or MTP joints is allowed without perfect symmetry. Simultaneous involvement of the same joint areas (as in criteria 2) on both sides of the body
Rheumatoid nodules	Subcutaneous nodules that a doctor observes over bony prominences, extensor surfaces, or in juxtaarticular regions
Serum rheumatoid factor	Any technique that has shown evidence of elevated serum levels of "rheumatoid factor" and produced a positive result in fewer than 5% of healthy control participants
Radiographic changes	Osteoarthritis changes alone do not qualify as typical RA alterations on PA hand and wrist radiographs; these must include erosions or clear-cut bone decalcification localized to or most markedly adjacent to the affected joints.

Treatment

The idea that disease-modifying therapy should start as soon as feasible after diagnosis and be continued until the disease reaches low activity or full remission is a key paradigm in the management of RA. Among nonpharmacologic management is RA education for patients. Long-standing nonprofit advocacy group The Arthritis Foundation (www.arthritis.org) offers patients educational materials, connections to neighbourhood services, and community programs. Referrals to physical therapy and occupational therapy for joint-protection techniques, strengthening, assistive technology, and supplementary pain management can also have a significant influence on pain and functioning.[21]

Disease-modifying antirheumatic drug therapy

Starting treatment with a DMARD monotherapy is the initial step. Given its outstanding efficacy in reaching remission or low disease activity in 30 to 40% of patients, its well-established safety and toxicity profile, and its relative affordability, methotrexate is the most frequently chosen DMARD as a first-line treatment. Although its exact mode of action in RA is unknown, this structural counterpart of folic acid inhibits DNA synthesis and increases adenosine release by acting on numerous enzymes, which lowers inflammatory responses and cell proliferation[22] To avoid potential side effects (mucosal ulcers, anemia) linked to its folate antagonist, it is taken as a weekly oral or subcutaneous dose, with typical therapeutic doses ranging from 15 to 20 mg weekly. It is also given in conjunction with daily folic acid or weekly folinic acid. Due to creatinine's renal clearance, periodic laboratory work is necessary for regular monitoring for cytopenias, hepatotoxicity, and other related conditions. An further first-line DMARD that suppresses dihydroorotate dehydrogenase, a crucial

enzyme for DNA synthesis and lymphocyte proliferation, is leflunomide. It is taken orally once a day, and it has comparable side effects and monitoring needs as methotrexate. Women of reproductive age who take methotrexate or leflunomide need to use adequate birth control because these drugs are both teratogenic. Leflunomide needs to be washed out with cholestyramine in the event of toxicity or pregnancy because of its extended enterohepatic circulation.[23]

Biologic therapy

Currently, six classes of biological agents are authorized for use in RA. These are more powerful immunosuppressive drugs than traditional DMARDs, and rheumatology experts should be the ones to initiate and oversee their use. Primary care physicians, however, should be knowledgeable about screening and monitoring techniques as well as the general and class-specific effects of biologic therapy. When a patient does not respond fully to conventional DMARDs or experiences an adverse reaction, TNF inhibitors are the first-line biologic treatments that are employed. Although the five medications in this class have different chemical compositions, half-lives, and modes of administration, they all function by preventing TNF-alpha from binding to its receptors. Injection/infusion reactions are possible side effects; these are usually moderate and tolerable. An increased risk of infections is one of the more dangerous side effects, especially with larger treatment dosages.[21]

Herbal drugs used in the treatment of ra

Herbal medicine is one of the many components of the natural approach to treating people with rheumatoid arthritis (RA), and it will be the focus of this article. Other components include lifestyle adjustments. Botanical remedies are typically utilized in conjunction with other therapy procedures to address underlying causes of RA symptoms rather than being employed as a stand-alone treatment.[24]

The symptoms of RA are typical of a complex illness, for which there is no single cause that has been found to be entirely responsible. Uncertain genetic susceptibilities enable the disease to be triggered by a range of environmental variables. A vegetarian diet, probiotic supplements, an increase in the consumption of fermented foods, periodic fasting, stopping smoking when appropriate, and/or an elimination/challenge diet to identify and eliminate potential food triggers are all important lifestyle modifications that can address these environmental factors that may precipitate the disease.[25]

Man relied entirely on medicinal plants to treat illnesses prior to the development of synthetic medications. Every member of this civilization is aware of the healing properties of plants. Folk remedies were mostly made from natural product extracts in the nineteenth and preceding centuries, especially those made from botanical species. But biologically-active organic compounds started to be separated in relatively pure form for application in medicine in the later half of the nineteenth century. For instance, in 1874, salicylic acid—the forerunner to aspirin—was extracted from willow bark. There are a ton of further instances. Many synthetic medications are used as the conventional treatment for rheumatoid arthritis, but these treatments have side effects that might hinder the therapeutic treatment. Because of these side effects, there is a greater likelihood of using herbal plants to treat rheumatoid arthritis. The focus of this review is on medicinal herbs that are used to treat rheumatoid arthritis.[26]

List of medicinal plants used in the rheumatoid arthritis treatment: The plants possess the anti-rheumatoid arthritis properties are given below:

Aloe vera linn.

Biological Name: *Aloe Barbadensis*
Common Name: Curacao aloe, Lily of the desert
Family: Liliaceae

Figure 3:- *Aloe barbadensis.*

Aloe barbadensis is grown throughout Europe and most of India, particularly the northwest Himalayan region. One of the most significant plants in traditional medicine has long been aloe vera. The active ingredients in aloe vera plants are anthraquinone, anthracene, cinnamic acid, and anthranilic acid. Aloe vera is used to treat a range of skin conditions, including eczema, poison ivy, bruises, small wounds, and insect stings. Along with being a blood purifier, anti-inflammatory, diuretic, uterine tonic, spermatogenic, laxative, purgative, and fever reducer, it also possesses antibacterial and antifungal qualities.[27]

The anthraquinone molecule in aloe vera is responsible for its anti-arthritic properties. Aloe vera is an effective anti-inflammatory and immune system stimulant. When aloe vera extract is applied topically to Sprague Dawley rats with adjuvant-induced arthritis, it reduces inflammation and arthritis.[28]

Ashwagandha biological

Name: *Withania somnifera Linn.*
Family: Solanaceae

Figure *4: Withania somnifera linn.*

Indian ginseng, or ashwagandha, is a significant ancient plant. Ayurveda and Unani, two historic medical systems in India, have used ashwagandha roots. It grows in arid areas of subtropical states like Gujarat, Maharashtra, Madhya Pradesh, Uttar Pradesh, Haryana, Rajasthan, and Punjab. The root's pharmacological properties are ascribed to its alkaloids and steroidal lactones. Withanine, withanine, pseudo-withanine, tropine, pseudo-tropine, somniferine, and somnine are the most common alkaloids. From roots, two acyl glucosidessitoindosides-7 and 8—have been identified. The herb has been used for thousands of years as an anti-inflammatory, liver tonic, aphrodisiac, and, more recently, as a treatment for senile dementia, asthma, ulcers, and sleeplessness.

Ashwagandha has been shown to be effective in treating inflammation, anxiety, neurological conditions, and Parkinson's disease in clinical trials and animal. Including ashwagandha in the diet can stop or slow the formation of malignancies in people. It assists in delivering gradual, long-lasting outcomes for a range of health issues, including stress disorders, aging, anemia, arthritis, exhaustion, and sports fitness. In rats with adjuvant-induced arthritis, oral treatment of Withenia somnifera Linn. root powder demonstrated the anti-arthritic activity.[24]

Shallaki
Biological Name: *Boswellia serrata Linn.*
Family: Burseraceae

Figure 5:- *Boswellia serrata linn.*

India, Northern Africa, and the Middle East are home to the moderate-to-large branching tree known as Boswellia serrata Linn. It can be found in Gujarat, Madhya Pradesh, and Bihar, India. Peeling away the boswellia bark strips reveals gummy-oleo resins. The resin part of it contains β-boswellic acid, which has been proven to have anti-inflammatory, anti-atherosclerotic, and anti-arthritic properties. Astringent, stimulant, expectorant, anti-septic, juvenomimetic, anti-atherosclerotic, analgesic, and sedative properties have also been applied to this gummy oleo resin extract. It is also known to restore the integrity of the vessel that has been damaged or spasmed in the joints. Terpenoids, carbohydrates, and volatile oil are the primary ingredients of boswellia. Boswellia serrata extract naturally reduces inflammation by inhibiting pro-inflammatory cytokines and mediators at the sites of chronic inflammation. When used in conjunction with non-steroidal anti-inflammatory medicines, the breakdown of glycosaminoglycan production might hasten the deterioration of joints in arthritic diseases. Conversely, *Boswellia serrata* Linn. inhibits this process.[27]

Black pepper
Biological Name: Piper nigrum Linn.
Family: Piperaceae

Figure 6:- Black pepper.

The native land of black pepper is planted in South India. Additionally, Malaysia, Sri Lanka, Indonesia, and Brazil cultivate it. India is the country that cultivates this substance the most. The ingredients of pepper include starch, volatile oil, spicy resins, piperidine, and the alkaloid piperine. It has carminative, stimulating, stomachic, and fragrant properties. It causes the stomach fluids to flow more. It also makes some medications more bioavailable. Black pepper is the source of piperine. When carrageenan-induced acute paw arthritis is treated with piperine orally at doses of 20 and 100 mg/kg/day for eight days, the symptoms of arthritis reduce.[26]

Ginger
Biological Name: *Zingiber officinale*
Family: Zingiberaceae

Figure 7:- Ginger rhizome.

One of the most beneficial herbal supplements is ginger. Although it is native to Southeast Asia, it is grown in the Caribbean, Africa, Australia, Mauritius, Taiwan, and India. almost 30% of the output is in India. Ginger is made up of inorganic matter, carbohydrates, fat, fiber, volatile oil, and leftover moisture. Monoterpine, sesquiterpine hydrocarbons, oxygenated mono, and sesquiterpines are all present in ginger oil. Ginger has several uses, including carminative, aromatic, stomachic, stimulant, and flavoring. It is applied to alleviate diarrhea, vomiting, and nausea. Moreover, it has anti-inflammatory, antiseptic, anticarcinogenic, antifungal, and antimicrobial properties. One of the best treatments for arthritis joint pain that doctors offer is ginger extract. The primary components are sesquiterpenoids, which include (-) zingiberene. Natural substances called sesquiterpene lactones (SLs) are in charge of their anti-inflammatory properties.[29]

Milkweed
Biological Name: *Calotropis Procera* Linn.
Family: Asclepiadaceae

Figure 8:- *Calotropis procera* linn.

Calotropis procera Linn. is a species of flowering plant native to North Africa, Tropical Africa, Western Asia, South Asia, and Indochina. It belongs to the dogbane family, Apocynaceae. There have been reports of anti-inflammatory, analgesic, antioxidant, and antifungal properties in various portions of this plant. In a variety of animal models, this plant's latex exhibits strong anti-inflammatory properties. The petroleum extract from latex exhibits strong antibacterial properties. It has been demonstrated that latex and its methanolic extract both prevent the infiltration of inflammatory cells and the development of edema brought on by different inflammagens. Additionally, it enhances locomotor abilities in rats with experimentally induced monoarthritis. In the granuloma-induced cotton pellet model and the paw edema model caused by carrageenan, roots of Calotropis Procera Linn. were administered at doses of 180 mg/kg (methanol extract) and 200 mg/kg.[26]

Turmeric
Biological name*: Curcuma longa Linn*.
Family: Zingiberaceae

Figure 9:- Turmeric rhizome.

For its rhizome, turmeric is grown in Jamaica, Peru, China, India, and Sri Lanka. In addition to starch grains, volatile oil, and compounds with a yellow hue called curcuminoids are found in turmeric. Curcumin is the main ingredient of curcuminoids. Curcumin, a naturally occurring substance found in the rhizomes of the Curcuma longa plant, has been shown to have anti-inflammatory properties. utilized in the treatment of wounds, hepatoprotection, neuroprotection, etc.

Its properties include antimutagenic, antispasmodic, antibacterial, and anticancer effects. In the acute and chronic phases of arthritis, daily intraperitoneal (i.p.) injection of a low dose of pure curcuminoids (4 mg total curcuminoids/kg/d) decreased joint inflammation.[27]

Green tea
Biological Name: *Camellia sinensis Linn.*
Family: Theaceae

Figure 10:- *Camellia sinensis* Linn.

The *Camellia sinensis* Linn. is a tiny tree or evergreen shrub. Although *Camellia sinensis* Linn. is native to

mainland China, South and Southeast Asia, it is currently grown in tropical and subtropical climates all over the world.

Polyphenols (catechins and flavonols) are Camellia sinensis Linn.'s active ingredients. Essential oils and caffeine are additional ingredients. Strong antioxidant (-) epigallocatechin is the most significant catechin in green tea. In the arthritic joints of mice fed green tea, there was a noticeable suppression of the inflammatory mediators COX-2, IFNγ, and TNFα, which was indicative of a decreased incidence and severity of collagen-induced arthritis. The serum and arthritic joints of mice given green tea had reduced levels of total immunoglobulin (IgG) and type II collagen-specific IgG.[30]

REFERENCE

1. Singh S, Singh TG, Mahajan K, Dhiman S. Medicinal plants used against various inflammatory biomarkers for the management of rheumatoid arthritis. Journal of Pharmacy and Pharmacology, 2020; 72(10): 1306-27.
2. Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. Cells, 2021; 23, 10(11): 2857.
3. Lindler BN, Long KE, Taylor NA, Lei W. Use of herbal medications for treatment of osteoarthritis and rheumatoid arthritis. Medicines, 2020; 28, 7(11): 67.
4. Rajguru N, Rajput N, Sonawane M, Agrawal S. Use of Herbal Medications for Treatment of Osteoarthritis and Rheumatoid Arthritis. Use of Herbal Medications for Treatment of Osteoarthritis and Rheumatoid Arthritis, 2023; 12, 1(12): 1.
5. Sailaja AK, Rani EV, Swetha V. Herbal medicine for the treatment of rheumatoid arthritis. Journal of Physics & Optics Sciences, 2020; 25, 114: 3.
6. García-Arias M, Balsa A, Mola EM. Septic arthritis. Best practice & research Clinical rheumatology, 2011; 1, 25(3): 407-21.
7. Hannu T. Reactive arthritis. Best Practice & Research Clinical Rheumatology, 2011; 1, 25(3): 347-57.
8. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. Jama, 2018; 2, 320(13): 1360-72.
9. Abdel-Nasser AM, Rasker JJ, Vaikenburg HA. Epidemiological and clinical aspects relating to the variability of rheumatoid arthritis. InSeminars in arthritis and rheumatism, 1997; 1, 27, 2: 123-140. WB Saunders.
10. Azuma T, Zhu G, Xu H, Rietz AC, Drake CG, Matteson EL, Chen L. Potential role of decoy B7-H4 in the pathogenesis of rheumatoid arthritis: a mouse model informed by clinical data. PLoS medicine, 2009; 20, 6(10): e1000166.
11. Zanin-Zhorov A, Ding Y, Kumari S, Attur M, Hippen KL, Brown M, Blazar BR, Abramson SB, Lafaille JJ, Dustin ML. Protein kinase C-θ mediates negative feedback on regulatory T cell function. Science, 2010; 16, 328(5976): 372-6.
12. Whalley D, Mckenna SP, De Jong Z, Van der Heijde D. Quality of life in rheumatoid arthritis. British journal of rheumatology, 1997; 1, 36(8): 884-8.
13. Kvien TK, Uhlig T. Quality of life in rheumatoid arthritis. Scandinavian journal of rheumatology, 2005; 1, 34(5): 333-41.
14. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, Scott D, Silman A. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology, 2002; 1, 41(7): 793-800.
15. Kaipiainen-Seppänen O, Aho K, Isomäki H, Laakso M. Incidence of rheumatoid arthritis in Finland during 1980-1990. Annals of the Rheumatic Diseases, 1996; 55(9): 608.
16. Ragan C, Farrington E. The clinical features of rheumatoid arthritis: prognostic indices. Jama, 1962; 25, 181(8): 663-7.
17. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. European journal of radiology, 1998; 1, 27: S18-24.
18. Karlson EW, Mandl LA, Aweh GN, Grodstein F. Coffee consumption and risk of rheumatoid arthritis. Arthritis & Rheumatism, 2003; 48(11): 3055-60.
19. De Roos AJ, Cooper GS, Alavanja MC, Sandler DP. Rheumatoid arthritis among women in the Agricultural Health Study: risk associated with farming activities and exposures. Annals of epidemiology, 2005; 1, 15(10): 762-70.
20. Khurana R, Berney SM. Clinical aspects of rheumatoid arthritis. Pathophysiology, 2005; 1, 12(3): 153-65.
21. Steultjens EE, Dekker JJ, Bouter LM, Schaardenburg DD, Kuyk MA, Van den Ende EC. Occupational therapy for rheumatoid arthritis. Cochrane database of systematic reviews, 2004; (1).
22. Borchers AT, Keen CL, Cheema GS, Gershwin ME. The use of methotrexate in rheumatoid arthritis. In Seminars in arthritis and rheumatism, 2004; 1, 34, 1: 465-483. WB Saunders.
23. Behrens F, Koehm M, Burkhardt H. Update 2011: leflunomide in rheumatoid arthritis–strengths and weaknesses. Current opinion in rheumatology, 2011; 1, 23(3): 282-7.
24. Yarnell E. Herbs for rheumatoid arthritis. Alternative and Complementary Therapies, 2017; 1, 23(4): 149-56.
25. Wang Y, Chen S, Du K, Liang C, Wang S, Boadi EO, Li J, Pang X, He J, Chang YX. Traditional herbal medicine: Therapeutic potential in rheumatoid arthritis. Journal of ethnopharmacology, 2021; 28, 279: 114368.
26. Kaur A, Nain P, Nain J. Herbal plants used in treatment of rheumatoid arthritis: a review. Int J Pharm Pharm Sci, 2012; 4(4): 44-57.
27. Joseph B, Raj SJ. Pharmacognostic and phytochemical properties of Aloe vera linn an overview. Int J Pharm Sci Rev Res, 2010; 1, 4(2): 106-10.

28. Davis RH, Agnew PS, Shapiro E. Antiarthritic activity of anthraquinones found in aloe vera for podiatric medicine. J Am Podiatr Med Assoc, 1986; 76(2): 1-8.
29. Feng T, Su J, Ding ZH, Zheng YT, Li Y, Leng Y, Liu JK. Chemical constituents and their bioactivities of "Tongling White Ginger"(Zingiber officinale). Journal of agricultural and food chemistry, 2011; 9, 59(21): 11690-5.
30. Chopade V, Phatak A, Upaganlawar A, Tankar A. Green tea (Camellia sinensis): Chemistry, traditional, medicinal uses and its pharmacological activities-a review. Pharmacognosy Reviews, 2008; 2(3): 157.