Advancements in the Management of Rheumatoid Arthritis: A Comprehensive Overview

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Abstract:

Systemic inflammation is a hallmark of rheumatoid arthritis (RA), a chronic, multisystemic inflammatory disease that mostly affects the joints. It is recognized as the most prevalent systemic inflammatory rheumatic illness, leading to significant morbidity, disability, and mortality. Over recent decades, advancements in the understanding of RA's pathogenesis have resulted in improved prognosis due to the introduction of effective treatment options. If left untreated, RA can lead to severe joint damage, disability, decreased quality of life, and increased comorbidities, with a global prevalence estimated at 0.5% to 1%, varying by geographical location and associated with a complex interaction of genetic and environmental risk factors. The epidemiology of RA reveals that the condition poses a substantial burden on both individuals and society due to associated physical disabilities and reduced quality of life. The disorder's prevalence is higher in urban areas compared to rural ones and appears to vary between regions, potentially influenced by genetic predispositions, smoking, and socioeconomic factors. Studies suggest a significant hereditary component, with familial history increasing RA risk considerably. This complexity underlines the importance of understanding both genetic and lifestyle factors in managing and diagnosing the disease. Current management strategies for RA emphasize early detection and treatment, with a focus on minimizing joint inflammation and preventing long-term damage. Disease-modifying antirheumatic medications (DMARDs) are essential, and patients who don't react to conventional treatments might choose from biologic alternatives. Better patient outcomes are also a result of complementary therapies like physical therapy and lifestyle changes. Herbal remedies, which have been used historically in many cultures, are gaining popularity because they may provide further anti-inflammatory advantages without the negative side effects that are sometimes linked to prescription drugs.

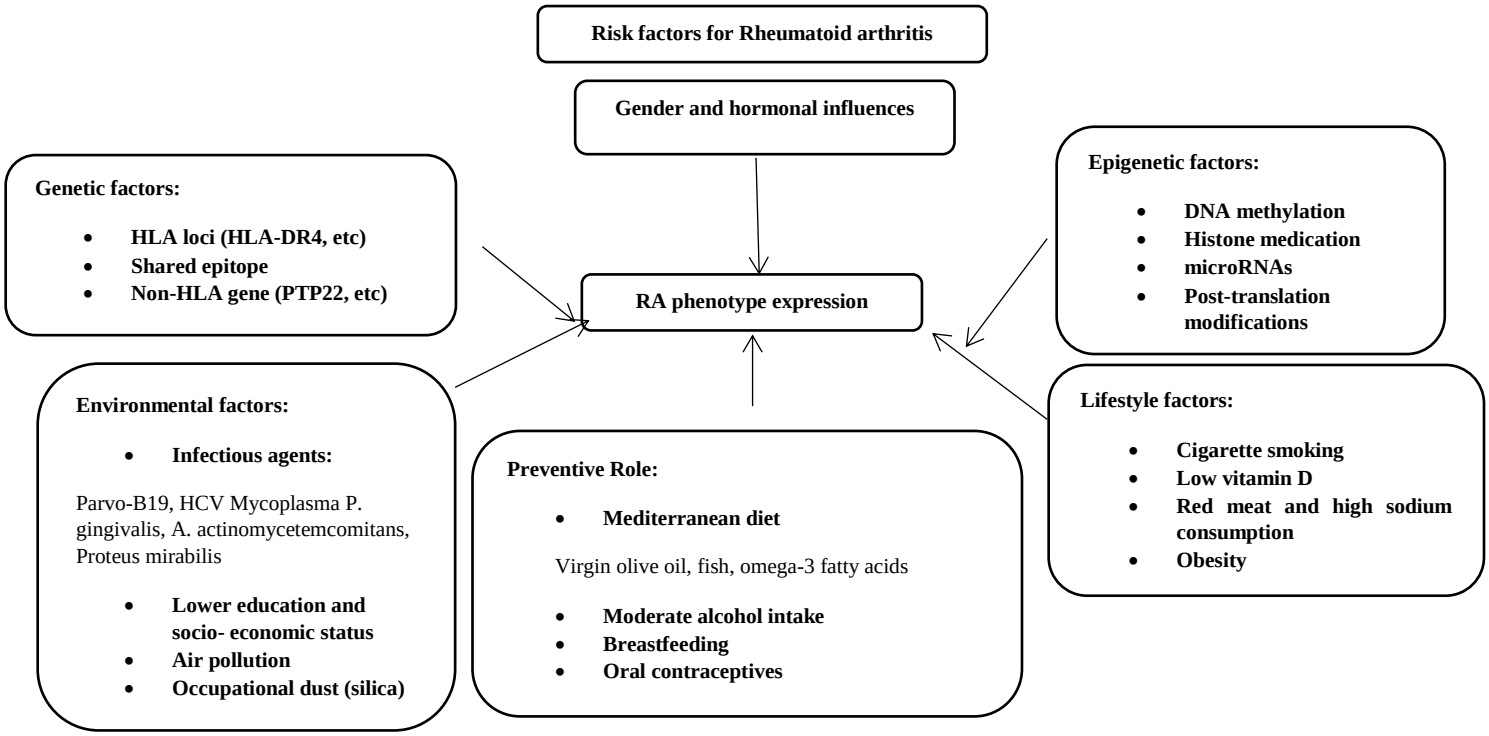
Keywords: Rheumatoid Arthritis, DMARDs, Conventional medications, Multisystemic, Herbal remedies.

INTRODUCTION:

A chronic, multisystemic immune-mediated illness that mostly affects the joints is called rheumatoid arthritis (RA). It is the most common type of inflammatory rheumatism in the body [1, 2] and is linked to a high rate of morbidity, disability, and death [3]. The last few decades have observed a notable improvement in RA patients' prognosis as a result of the expanding amount of information about the etiology and pathophysiology of the condition, which has enabled the development of a number of currently available, highly effective drugs [4]. If untreated RA is associated with joint degradation, severe disability, reduced quality of life, comorbidities, and early death, among other consequences [5].An autoimmune condition known as rheumatoid arthritis (RA) affects 0.5% to 1% of persons globally [6]. RA researchers have observed that North America and Europe may have higher prevalence rates than Asia [7]. It is unknown if genetic, environmental, or study design variables are to blame for this geographic variability [8]. The last ten years have seen a therapeutic revolution in the treatment of RA, which includes the introduction of new therapeutics, earlier therapy initiation, and the use of successful treatment techniques. The results have changed in such a way that systemic features have decreased and long-term damage and functional decline have been greatly reduced [9-10]. According to clinical standards, the symptoms of RA in its early stages differ greatly from those in its later stages, which are not sufficiently addressed. Early-stage RA is characterized by a variety of symptoms, such as fatigue, a flu-like feeling, swollen and aching joints, and stiffness in the morning. It is also linked to increased levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [11]. Interstitial lung disease and lung nodules, lymphomas, vasculitis in small or medium-sized arteries, keratoconjunctivitis, atherosclerosis, pleural effusions, joint malalignment, loss of range of motion, bone erosion, cartilage destruction, rheumatic nodules, and hematologic abnormalities (e.g., anemia, leukopenia, neutropenia, eosinophilia, thrombocytopenia, or thrombocytosis) are among the significant systemic manifestations of poorly managed RA, however, that make up its complex clinical picture [12–14].

RHEUMATOID ARTHRITIS RISK FACTORS:

Over the past few decades, a great deal of research has been done on the risk factors for RA. In addition to genetic considerations, a number of environmental factors also play a role in the disease's development. Certain risk factors are genetically inherited and passed down from parent to child. Tobacco use is one of many other factors linked to environmental and lifestyle choices that people seem to have control over. It also supports the preventative role of other factors, like specific foods in the diet. However, we cannot predict RA, and a better knowledge of the risk variables and their interactions is essential for RA diagnosis and treatment [15–16].



EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS:

RA places a significant strain on the individual as well as society [18–20]. A person's load, which comprises a decline in physical function and quality of life as well as an increase in co-morbid risk, is directly caused by musculoskeletal impairments [21-23].Aside from significant direct medical expenses, the socioeconomic burden results from functional disability and the resulting decreased ability to work and participate in society[24]. The frequency of RA ranges from 0.5% to 1%, and it appears to be declining from urban to rural and from the north to the south [25-27].Together with varying genetic backgrounds, smoking and a lower socioeconomic position are consistently mentioned risk factors for RA development and higher disease severity [28-31]. These factors may help to explain the aforementioned findings. A positive family history raises the risk of RA by approximately three to five times; twin concordance rates are high, suggesting a role for genetic variables in the pathophysiology [26-30]. There is disagreement over the heredity of RA; it is presently thought to be between 40 and 65 percent for seropositive illness and 20 percent for seronegative RA [32-33].

PATHOGENESIS:

In certain people, an environmental component in a genetically susceptible host causes RA. A tobacco-using patient with the HLA-DRB1 "shared epitope" gene developing ACPA-positive RA is the greatest example [34]. The most well-known autoantibodies in RA are RF and ACPA antibodies, while there are a number of additional autoantibodies that are fairly unique to RA. "Seropositive RA" is the term used to describe rheumatoid arthritis with antibodies. Any antibody isotype that binds to the Fc region of IgG is known as an RF antibody. Antibodies that target citrullinated proteins are frequently found in RA patients. Numerous tests have shown these antibodies in RA patients since 1964, when the antiperinuclear factor

was identified [35]. Anti-keratin antibodies were identified in 1979 [36]. In the 1990s, the remarkable specificity of these antibodies for RA was discovered [37]. According to further research, the antibodies were specifically directed against the citrullinated peptide filaggrin [38–39]. The epitopes of these antibodies are citrullinated peptides. In clinical practice, an ELISA test was developed to detect these antibodies in patients using cyclic citrullinated peptide (CCP) [39]. We refer to these antibodies as anti-cyclic citrullinated peptide antibodies (ACPA).Peptidyl arginine deiminase (PAD) enzymatically converts arginine to citrulline after transcription. This change occurs in regions characterized by inflammation and tissue damage, such as the lungs of smokers. The common epitope of HLA-DRB1 primarily displays epitopes that include citrulline. ACPA can be found in IgG, IgM, or IgA isotypes. They can bind citrullinated residues on self-proteins, including vimentin, fibronectin, fibrinogen, histones, and type 2 collagen [40].RA patients also have anti-carbamylated protein, or anti-CarP, antibodies. Cyanate is produced from thiocyanate by myeloperoxidase. Despite the same chemical structure of citrulline and homocitrulline, anti-CarP antibodies are different antibodies that have been linked to RA in both ACPA-positive and non-ACPA-positive patients [40]. In RA patients, many autoantibodies have been found, including those against fibrinogen, enolase, and vimentin [41].Far from the synovial joints, the immune response in RA starts in the gastrointestinal tract, lung, and gums. These tissues undergo biochemical processes such as citrullination, which alter proteins. It is thought that the mechanism underlying environment-triggered RA involves the repeated stimulation of innate immunity. Smoking cigarettes, for example, causes peptidyl arginine deiminase (PAD) to be expressed by alveolar macrophages, which in turn causes arginine to be converted to citrulline in the airway [42]. This process results in the production of a "neoantigen" that generates an immune response and the production of anti-citrullinated protein antibodies (ACPAs) [42].Through their interactions with B cells, T cells stimulate antigen-specific B cells to develop into plasma cells that generate ACPA and RF. By binding to their antigens, these autoantibodies create immune complexes that can activate the complement system and exacerbate the inflammatory response [43]. Certain T cells that have been stimulated develop into type 1 (Th1) and type 17 (Th17) helper T cells. The proinflammatory cytokine IL-17, which is produced by Th17 cells, draws in neutrophils and other T cells [44, 45].The synovium produces a lot of cytokines, which are crucial in causing a severe inflammatory reaction that erodes bone and destroys cartilage [46]. Additionally, chronic inflammation contributes to related comorbidities such an elevated risk of cardiovascular disease. The most significant cytokine implicated in the pathophysiology of RA is included in the following table.

TREATMENT AND MANAGEMENT OF RHEUMATOID ARTHRITIS:

After RA is diagnosed and a first evaluation is finished, treatment should begin. Although new guidelines have addressed the management of RA [47–48] patient preference is just as important. Special monitoring is necessary for women of reproductive age because of the adverse effects of certain medications on pregnancy. Treatment goals include treating extra-articular symptoms, preventing deformity (such as ulnar deviation) and radiographic damage (such as erosions), reducing joint pain and swelling, and maintaining one's personal and

professional quality of life. DMARDs, or disease-modifying antirheumatic drugs, are the mainstay of RA treatment.

DMARDs: Biologic and nonbiologic DMARDs are both possible [49]. Monoclonal antibodies and recombinant receptors are examples of biologic medicines that inhibit cytokines that fuel the inflammatory cascade that causes RA symptoms. Unless it is contraindicated or not tolerated, methotrexate is advised as the initial course of treatment for individuals with active RA [47] although gastrointestinal side effects are more frequent, leflunomide (Arava) might be used in place of methotrexate. Patients with mild disease activity or those without unfavorable prognostic characteristics (such as seronegative, nonerosive RA) are advised to use hydroxychloroquine (Plaquenil) or sulfasalazine (Azulfidine) as monotherapy [47-48].Compared to monotherapy, combination therapy including two or more DMARDs is more effective; nonetheless, there may be more side effects [50]. A biologic DMARD should be started if a nonbiologic DMARD is not effectively controlling RA [47-48].

GLUCOCORTICOIDS AND NSAIDS: NSAIDs and oral, injectable, or intra-articular corticosteroids may be used as part of RA medication therapy to manage inflammation and discomfort. It is best to limit the use of corticosteroids and NSAIDs to temporary relief. The recommended course of treatment is DMARDs [49-50].

PHYSICAL AND MEDICAL THERAPY: Exercise has been demonstrated in randomized controlled trials to improve RA patients' quality of life and muscle strength [51–52]. Pain ratings, RA disease activity, and radiographic joint damage have not been shown to be adversely affected by exercise training regimens [53]. Despite the paucity of randomized trials, tai chi has been shown to improve ankle range of motion in individuals with RA [54]. Randomized controlled trials are currently being conducted to investigate Iyengar yoga for young adults with RA [55].

JOINT REPLACEMENT: Joint replacement is advised when medications are unable to alleviate the symptoms of severe joint degeneration. It is a sign of favourable long-term outcomes since only 4 to 13 percent of major joint replacements require revision within 10 years [56].The two joints that are replaced the most often are the hip and knee.

HERBAL PLANTS FOR RHEUMATOID ARTHRITIS TREATMENT:

Herbal medicines have been used to cure a variety of ailments from ancient times, and it is not hyperbole to say that the use of herbal remedies predates humanity [66]. Generations of physicians with hundreds of years of experience in the traditional medical system use their therapeutic knowledge to manufacture herbal treatments [67]. Because the current pharmaceuticals on the market are either extremely expensive or have certain side effects, researchers are now particularly interested in pharmacological molecules derived from plants [68].

A gift from nature, herbal plants are found all over the world and offer medicinal ingredients for the prevention and treatment of a variety of ailments [69]. The WHO estimates that 80 percent of individuals use herbal medicines for their basic medical requirements. Herbal treatments have been used by human culture to combat illness since the dawn of civilization [70]. The chemical components of these herbal plants that have medicinal significance are what provide the body with the desired physiological impact [71].Throughout India's officially acknowledged alternative health systems, such as Ayurveda, Unani, Sidha, Homeopathy, and Naturopathy, herbal therapies have been utilized since ancient times [72]. In India, around 2500 plant species are currently used as herbal remedies. For about 3,000 years, herbal medicines have been used, either directly as traditional medicine or indirectly in the production of contemporary pharmaceuticals [73]. Therefore, one may be able to find novel, more affordable, and effective medications by using the knowledge of traditional botanicals [74]. We have attempted to address every ayurvedic remedy for RA that is used without any potential negative effects in this review post. More effective alleviation from RA should be possible in the future [70].

Table 1: Herbal remedies used to treat rheumatoid arthritis

S.no.	Biological name	Common name	Family	Chemical constituent	Refrences
1.	*Barbadensis aloe*	Aloevera	Asphodelaceae	Cinnamic acid, anthranilic acid, anthraquinone, and anthracene	56
2.	*Scholarisa Alstonia*	Saptaparni	Apocynaceae	Picrinine, echitamidine, tubotaiwine, and ecgitamine	57
3.	*Royle's Berberis lycium*	Barberry	Berberidaceae	Berbrine, umbellatine	58
4.	*Boswellia serrate linn.*	Salai	Burseraceae	Verbenol, borneol, verbenone, pinocarveol	59
5.	*Cannabis sativum*	Marijuana	Urticaceae	Cannabidiol	60
6.	*Curcuma longa*	Turmeric	Zingiberaceace	Demethoxycurcumin, turmerone, atlantone, cineole	61
7.	*Glyccirhyza glabra*	Liquorice	Fabaceae	Glycyrrhizin, resins, fats	62
8.	*Hmidesmus indicus*	Indian sarsaparilla	Asclepdiaceae	Terpenoids, Cumarin	63

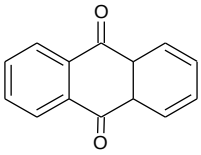
9.	*Zingiber officinale*	Ginger	Zingiberaceae	Zingiberene, sesquiphellandrene, gingerol, paradols	64
10.	*Salix*	Willow Bark	Salicaceae	Salici, saligenol, salicylic acid	65

Aloe barbadensis:

Common name: Aloe vera

Family: Asphodelaceae

Chemical constituents: Anthranilic acid, cinnamic acid, anthraquinone, and anthracene.



Anthraquinone

Aloe barbadensis, often known as aloe vera, has been studied for its possible medicinal benefits in the management of rheumatoid arthritis and other inflammatory conditions. Aloe vera has several bioactive properties that may help lessen joint pain and inflammation associated with rheumatoid arthritis, according to studies [(75)].

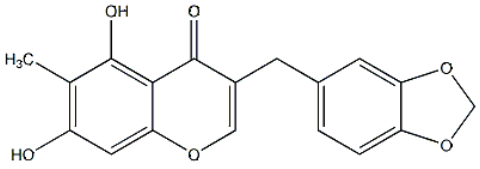
Rheumatoid arthritis-related inflammation can be lessened by aloe vera gel's well-known anti-inflammatory qualities. TNF-α and IL-1β are two examples of pro-inflammatory cytokines that it has been shown to prevent human immune cells from producing. Because of its anti-inflammatory properties, topical application of Aloe vera gel to swollen and painful joints also increases mobility and reduces discomfort [(76)].

Alstonia scholarisa:

Common name: Saptaparni

Family: Apocynaceae

Chemical constituents: Tubotaiwine, ecgitamine, echitamidine, and picrinine.



Tubotaiwine

Rheumatoid arthritis has been researched in relation to *Alstonia scholaris*, which is well-known for its many therapeutic benefits. With a primary focus on the latex and leaves of Alstonia scholaris, this study summarizes the research findings about the plant's anti-inflammatory and anti-arthritic properties [(77)].

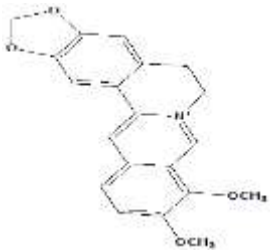
Since ancient times, the tropical tree *Alstonia scholaris* has been used in traditional medicine. The plant's leaves, bark, roots, and latex are among its elements that have long been used to treat a variety of illnesses, including inflammation, discomfort, and swelling. This plant is gaining popularity because of its strong bioactive chemicals, which may help treat diseases like rheumatoid arthritis [(78-79)].

Berberis lycium Royle:

Common name: Barberry

Family: Berberidaceae

Chemical constituents: Berbrine, Umbellatine.



Berbrine

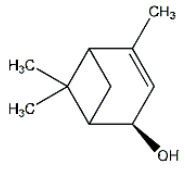
The Indian barberry, or Lycium, is another name for the medicinal plant Berberis lycium Royle, which is widely known for its therapeutic properties. It has been used for a long time in many medical systems, especially to treat inflammatory disorders like rheumatism. The use of Berberis lycium Royle in rheumatoid arthritis (RA) has garnered attention due to its potential mechanisms of action and efficacy [(80)].In traditional medicine, particularly in Ayurvedic and Unani systems, Berberis lycium has long been utilized for its analgesic and anti-inflammatory qualities. Alkaloids like berberine are among the many bioactive components of the plant that are believed to provide therapeutic benefits. Given their ability to modify immune responses, these compounds may help reduce the joint inflammation linked to rheumatoid arthritis [(79–80)].

Boswellia serrate linn. :

Common name: Salai

Family: Burseraceae

Chemical constituents: Verbenol, Borneol, Verbenone, Pinocarveol.



Verbenol

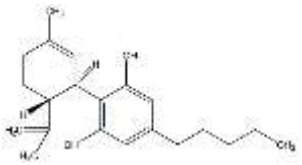
Boswellia serrata, sometimes known as Indian frankincense, has attracted attention because of its potential medical applications, particularly in the treatment of rheumatoid arthritis (RA). Studies have demonstrated the analgesic and anti-inflammatory properties of its extracts to be beneficial in the treatment of RA symptoms [(81)]. Extracts of Boswellia serrata contain significant concentrations of boswellic acids, which are the active components. These ingredients are necessary to provide the resin's health benefits. Boswellia acids are widely known for their potent anti-inflammatory properties, which aid in reducing pain and swelling in inflammatory tissues. Given that inflammation is a primary characteristic of rheumatoid arthritis, these attributes are particularly beneficial for those seeking to reduce their symptoms [(82)].

Cannabis sativum:

Common name: Marijuana

Family: Urticaceae

Chemical constituents: Cannabidiol.



Cannabidiol

A lot of attention has been paid to the potential medicinal benefits of Cannabis sativum, especially its non-psychoactive component cannabidiol (CBD), in the management of RA. Numerous biological processes linked to inflammation and joint health may be impacted by CBD, according to research, which could provide new information about how to manage RA pain and how the disease progresses [(83)]. *Cannabis sativa* may be able to alleviate the chronic pain that comes with rheumatoid arthritis, according to several studies. Both THC and CBD

have been shown to interact with the body's endocannabinoid system to help reduce both acute and chronic pain.

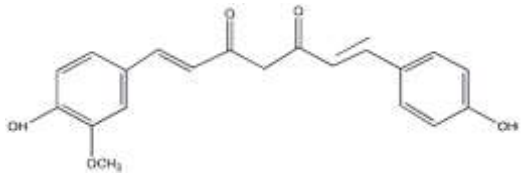
For example, it has been shown that CBD suppresses the production of pro-inflammatory cytokines like TNF-alpha and IL-6, which are linked to the inflammatory response that defines RA, and raises intracellular calcium levels. Furthermore, it has been demonstrated that treating RA patients with cannabis enhances their sleep, which in turn improves their general quality of life [84].

Curcuma longa:

Common name: Turmeric

Family: Zingiberaceace

Chemical constituents: Demethoxycurcumin, Turmerone, Atlantone, Cineole.



Demethoxycurcumin

Turmeric, or *Curcuma longa*, has gained popularity recently because of its possible use in the treatment of rheumatoid arthritis (RA). Research has focused on curcumin, its main constituent, because of its anti-inflammatory and antioxidant qualities, which may help to reduce the symptoms of an autoimmune disease [85].

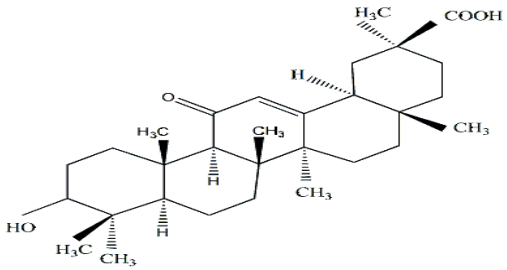
Curcumin, the primary bioactive component of turmeric, has several pharmacological effects that could be beneficial in the treatment of RA. Studies have shown that curcumin reduces inflammation and joint pain associated with RA by blocking inflammatory pathways. Clinical studies have demonstrated improvements in key laboratory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in people who take curcumin supplements, which may suggest an anti-inflammatory effect [86].

Glyccirhyza glabra:

Common name: Liquorice

Family: Fabaceae

Chemical constituents: Glycyrrhizin, Resins, Fats.



Glycyrrhizin

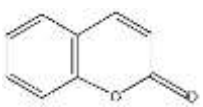
Glycyrrhiza glabra is a perennial herb or subshrub that can reach heights of 3 to 7 feet. Its long, cylindrical, branched, flexible rootstock has a runner that enables it to burrow. In the fall, the roots and dried runners are collected and used as components. Licorice root's primary active component is glycyrrhizin, also known as glycyrrhizic acid or glycyrrhizinic acid. This triterpenoid saponin is usually found in concentrations ranging from 6% to 10%. It is believed that glycyrrhizin is hydrolyzed by intestinal flora to yield a sugar moiety and the aglycone molecule (glycyrrhetinic acid), which are subsequently absorbed [(87)]. Despite the fact that both glycyrrhizin and glycyrrhetinic acid bind to glucocorticoid receptors and that the majority of the plant's anti-inflammatory activity has been ascribed to its cortisol-like effects [(88-89)], glycyrrhiza has strong anti-allergic and anti-inflammatory properties [(90)]. Actually, a lot of the plant's health benefits work against or in opposition to cortisol. Thymus atrophy inhibition, hepatic glycogen buildup, hepatic cholesterol synthesis stimulation, tryptophan oxygenase activation, and reduction of adrenocorticotropic hormone synthesis and secretion are some of the antagonistic effects of cortisol. However, glycyrrhizin amplifies the suppression of inflammation, stress response, and antibody formation by cortisol [(91)]. Glycyrrhiza's primary impact on glucocorticoid metabolism, similar to its mineralocorticoid action, is most likely associated with its suppression of 5-β-reductase activity, which extends the half-life of cortisol. The conversion of cortisol to the more potent cortisone can also be accelerated by glycyrrhetinic acid [(92)].

Hmidesmus indicus:

Common name: Indian sarsaparilla

Family: Asclepdiaceae

Chemical constituents: Cumarin, Terpenoids.



Cumarin

The medicinal qualities of the traditional plant *Hemidesmus indicus* have drawn attention to

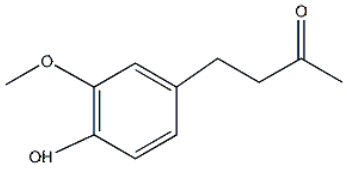
its potential in the treatment of rheumatoid arthritis. Numerous investigations have examined its effectiveness and modes of action, indicating positive impacts on the symptoms of arthritis [93].*Hemidesmus indicus* has long been used to treat inflammation and joint discomfort in a variety of traditional medical systems, such as Ayurveda and Unani. Its medicinal properties are thought to be facilitated by bioactive chemicals found in its roots. It may help reduce joint stiffness and swelling, which are signs of rheumatic disorders, according to indigenous knowledge about its use [94].Alkaloids, flavonoids, and coumarins are among the phytochemicals known to be present in *Hemidesmus indicus* roots. These substances have potent anti-inflammatory and antioxidant qualities. According to research, these active ingredients may aid in preventing the synthesis of inflammatory mediators, which would alleviate persistent inflammation, a defining feature of diseases like rheumatoid arthritis [93-94].

Zingiber officinale:

Common name: Ginger

Family: Zingiberaceae

Chemical constituents: Zingiberene, Sesquiphellandrene, Gingerol, Paradols.



Zingiberene

Ginger, or *Zingiber officinale*, has anti-inflammatory and bioactive qualities that make it a promising supplemental treatment for rheumatoid arthritis (RA) [94].

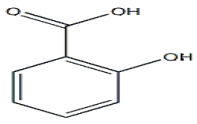
For thousands of years, people have grown *Zingiber officinale* for its culinary and therapeutic uses. Numerous phenolic chemicals found in its rhizome, such as zingerone, shogaols, and gingerols, have been demonstrated to have a range of pharmacological effects. These substances provide ginger its analgesic and anti-inflammatory qualities, which make it a potential treatment for rheumatoid arthritis symptoms [95].

Salix:

Common name: Willow Bark

Family: Salicaceae

Chemical constituents: Salicylic acid, Salici, Saligenol.



Salicylic acid

It has been acknowledged that willow bark (Salix spp.) may help reduce pain in the treatment of arthritis, particularly in the management of its symptoms. Its applicability, effectiveness, and safety in this context are highlighted by recent studies.

According to research, willow bark may have a moderate impact on rheumatoid arthritis pain relief. Participants who took willow bark reported a 15% decrease in pain in a randomized controlled experiment, while the placebo group only showed a 4% decrease. The authors did point out that this discrepancy could simply be the result of coincidence. This implies that although there might be some advantage, there is insufficient data to make firm judgments regarding its efficacy [96-97].

DIAGNOSIS:

Because its symptoms and indicators sometimes mimic those of other illnesses, rheumatoid arthritis (RA) can be difficult to diagnose, especially in its early stages. Therefore, a thorough strategy involving a range of diagnostic instruments and techniques is necessary for precise identification [98].

Evaluation of Symptoms:

Laboratory Tests: In order to diagnose RA, laboratory testing is essential. Important tests consist of:

Rheumatoid Factor (RF): Although not all patients test positive, this blood test finds the presence of rheumatoid factor, an antibody frequently seen in RA patients [98–99].

Anti-Cyclic Citrullinated Peptide (anti-CCP): This test assists in early identification by looking for antibodies that may show up years before RA symptoms develop [99].

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are tests that measure the body's level of inflammation, which may indicate RA [99–100].

These tests can help clarify the inflammatory mechanisms at work and show how severe the sickness is [100].

Imaging methods: In order to diagnose and evaluate rheumatoid arthritis, imaging investigations are very crucial. X-rays are frequently used to track the disease's course over

time and can show joint deterioration. However, X-rays may show no abnormalities in the early stages of RA [98]. As a result, other imaging methods like MRI and ultrasound can be applied. These techniques are very useful for determining inflammation and spotting early alterations in joint structure [99].

RECENT ADVANCEMENTS IN RHEUMATOID ARTHRITIS: Recent advances in the diagnosis and treatment of rheumatoid arthritis (RA) have led to new therapies and improved patient outcomes. Significant progress is being made in biological therapeutics, customized medicine, and new pharmaceutical discoveries [100–103].

Novel Approaches to the Treatment of RA:A number of novel treatment approaches have been developed recently with the goal of efficiently controlling the symptoms of rheumatoid arthritis. The most well-known are Janus kinase (JAK) inhibitors, which have FDA approval for the treatment of RA and include Olumiant (baricitinib) and Rinvoq (upadacitinib). The way these drugs reduce joint damage and enhance patient outcomes is by blocking immune system pathways that lead to inflammation. Researchers are also looking at the efficacy of novel biologics that target particular inflammatory pathways and Bruton's tyrosine kinase (BTK) inhibitors [104].

Developments in Personalized Medicine and Gene Therapy: The use of genetically engineered cells to activate regulatory T cells in rheumatoid arthritis-affected joints has sparked a renewed interest in gene therapy. This strategy seeks to lower inflammation and rewire the immune system [105].

Conclusion:

People's quality of life is severely impacted by rheumatoid arthritis (RA), a chronic inflammatory illness, because of its complicated nature and related comorbidities. Due to its particular impact on joint performance, the condition cause Because the condition has a particular influence on joint performance, it causes substantial physical harm and places a long-term strain on healthcare systems. Disease-modifying antirheumatic medications (DMARDs) should be used early to prevent long-term damage, according to recent developments in our understanding of the biology of RA. Dietary decisions, environmental variables like smoking, and genetic predispositions are some of the complicated risk factors for RA. Furthermore, a complicated interplay between genetic and environmental factors is revealed by the regional variations in RA prevalence, with certain populations possibly being more affected than others. The pathophysiology of RA is characterized by autoantibodies, especially anti-citrullinated protein antibodies (ACPAs), which are crucial to the disease's progression. Recent research shows the substantial benefits of both traditional and novel therapies, like herbal remedies, which have long been used to reduce inflammation and alleviate the symptoms of RA. In order to improve patient outcomes for rheumatoid arthritis, a comprehensive treatment strategy that incorporates lifestyle changes, complementary therapies, and successful pharmaceutical interventions is necessary. With continued research

into more specialized treatments that can offer more relief with fewer side effects, improving the quality of life for individuals afflicted, the future of managing RA is bright.

Declaration:

Conflicts of interest: The authors declare that they have no conflict of interest regarding the publication of this paper.

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REFRENCES:

1. Silman AJ, Hochberg MC. *Epidemiology of the Rheumatic Diseases*. 2nd ed. Oxford: Oxford University Press; (2001).
2. . Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther*. (2009) 11:229. 10.1186/ar2669.
3. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al.. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Jt Bone Spine*. (2013) 80:29–33. 10.1016/j.jbspin.2012.02.005.
4. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. *Nat Rev Dis Prim*. (2018) 4:18001. 10.1038/nrdp.2018.1.
5. ScottDL, Wolfe F, Huizinga TW (2010) Rheumatoid arthritis. *Lancet* **376** (9746), 1094–108.
6. Carmona L, Cross M, Williams B, Lassere M, March L (2010) Rheumatoid arthritis. *Best Pract Res Clin Rheumatol* **24**, 733–45.
7. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D (2008) Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* **59**, 1690–7.
8. Fatima F, Rao U, Moots R, Goodson N (2009) Raised traditional cardiovascular risk factors in Indians with rheumatoid arthritis. *Arthritis Rheum* **60** (S10), 948.
9. Nam JL, Ramiro S, Gaujoux-Viala C, Takase K, Leon-Garcia M, and Emery P et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis2014; 73(3):516-528.
10. Gaujoux-Viala C, Nam J, Ramiro S, Landewe R, Buch MH, and Smolen JS et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013

update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis2014; 73(3):510-515.

11. *Brzustewicz E., Henc I., Daca A., Szarecka M., Sochocka-Bykowska M., Witkowski J., Bryl E. Autoantibodies, C-reactive protein, erythrocyte sedimentation rate and serum cytokine profiling in monitoring of early treatment. Cent. Eur. J. Immunol. 2017; 42:259–268. doi: 10.5114/ceji.2017.70968.*
12. Smolen J.S., Aletaha D., McInnes I.B. Rheumatoid arthritis. Lancet Lond. Engl. 2016; 388:2023–2038. Doi: 10.1016/S0140-6736(16)30173-8.
13. Littlejohn E.A., Monrad S. Early Diagnosis and Treatment of Rheumatoid Arthritis. Prim. Care: Clin. Off. Pr. 2018; 45:237–255. Doi: 10.1016/j.pop.2018.02.010.
14. *Aletaha D., Ramiro S. Diagnosis and Management of Rheumatoid Arthritis. JAMA. 2018; 320:1360–1372. Doi: 10.1001/jama.2018.13103.*
15. Molina E, Del Rincon I, Restrepo JF, Battafarano DF, and Escalante A. Mortality in Rheumatoid Arthritis (RA): factors associated with recording RA on death certificates. BMC Musculoskelet Disord 2015; 16:277.
16. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K,et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum 2000; 43(1):30-7.
17. Venetsanopoulou, A. I., Alamanos, Y., Voulgari, P. V., & Drosos, A. A. (2023). Epidemiology and Risk Factors for Rheumatoid Arthritis Development.
18. Lundkvist J, Kastang F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ2008; 8 (Suppl 2):S49-S60.
19. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet2012; 380(9859):2197-2223.
20. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H et al. A comparative risk assessment of burden of disease andinjury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet2012; 380(9859):2224-2260.
21. Stoffer MA, Smolen JS, Woolf A, Ambrozic A, Bosworth A, Carmona L et al. Development of patient-centred standards of care for rheumatoid arthritis in Europe: the eumusc.net project. Ann Rheum Dis2014; 73:902-905.
22. Puolakka K, Kautiainen H, Pekurinen M, Mottonen T, Hannonen P, Korpela M et al. Monetary value of lost productivity over a 5-year follow up in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo Trial. Ann Rheum Dis2005; Nov 16; [Epub ahead of print].
23. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis2014; 73(7):1316-1322.
24. Sokka T, Kautiainen H, Pincus T, Verstappen SM, Aggarwal A, Alten R et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-RA study. Arthritis Res Ther2010; 12(2):R42.

25. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am2001; 27:269-281.
26. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res2002; 4 (Suppl 3):S265-S272.
27. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum2006; 36(3):182-188.
28. Uhlig T, Hagen KB, Kvien TK. Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. J Rheumatol1999; 26(1):47-54.
29. Michaud K, Messer J, Choi HK, Wolfe F. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum2003; 48(10):2750-2762.
30. Millar K, Lloyd SM, McLean JS, Batty GD, Burns H, Cavanagh J et al. Personality, socio-economic status and inflammation: cross-sectional, population-based study. PLoS One2013; 8(3):e58256.
31. Callahan LF, Pincus T. Education, self-care, and outcomes of rheumatic diseases: further challenges to the "biomedical model" paradigm. Arthritis Care Res1997; 10(5):283-288.
32. Jiang X, Frisell T, Askling J, Karlson EW, Klareskog L, Alfredsson L et al. To what extent is the familial risk of rheumatoid arthritis explained by established rheumatoid arthritis risk factors? Arthritis Rheumatol2015; 67(2):352-362.
33. Frisell T, Hellgren K, Alfredsson L, Raychaudhuri S, Klareskog L, Askling J. Familial aggregation of arthritis-related diseases in seropositive and seronegative rheumatoid arthritis: a register-based case-control study in Sweden. Ann Rheum Dis2016; 75(1):183-189.
34. Klareskog L, Ronnelid J, Saevarsdottir S, Padyukov L, Alfredsson L. The importance of differences; on environment and its interactions with genes and immunity in the causation of rheumatoid arthritis. J Intern Med. 2020 May; 287(5):514-533.
35. NIENHUIS RL, MANDEMA E. A NEW SERUM FACTOR IN PATIENTS WITH RHEUMATOID ARTHRITIS; THE ANTIPERINUCLEAR FACTOR. Ann Rheum Dis. 1964 Jul; 23(4):302-5.
36. Young BJ, Mallya RK, Leslie RD, Clark CJ, Hamblin TJ. Anti-keratin antibodies in rheumatoid arthritis. Br Med J. 1979 Jul 14; 2(6182):97-9.
37. Sebbag M, Simon M, Vincent C, Masson-Bessiere C, Girbal E, Durieux JJ, Serre G. The antiperinuclear factor and the so-called antikeratin antibodies are the same rheumatoid arthritis-specific autoantibodies. J Clin Invest. 1995 Jun; 95(6):2672-9.
38. Hoet RM, Boerbooms AM, Arends M, Ruiter DJ, van Venrooij WJ. Antiperinuclear factor, a marker autoantibody for rheumatoid arthritis: colocalisation of the perinuclear factor and profilaggrin. Ann Rheum Dis. 1991 Sep; 50(9):611-8.
39. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, van Venrooij WJ. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000 Jan; 43(1):155-63.

40. Derksen VFAM, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol. 2017 Jun; 39(4):437-446.
41. Van Delft MAM, Huizinga TWJ. An overview of autoantibodies in rheumatoid arthritis. J Autoimmun. 2020 Jun; 110:102392.
42. Makrygiannakis D, Hermansson M, Ulfgren AK, Nicholas AP, Zendman AJ, Eklund A, Grunewald J, Skold CM, Klareskog L, Catrina AI. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis. 2008 Oct; 67(10):1488-92.
43. Fang Q, Zhou C, Nandakumar KS. Molecular and Cellular Pathways Contributing to Joint Damage in Rheumatoid Arthritis. Mediators Inflamm. 2020; 2020:3830212.
44. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011 Dec 08; 365(23):2205-19.
45. Lin YJ, Anzaghe M, Schulke S. Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells. 2020 Apr 03;9(4)
46. Kondo N, Kuroda T, Kobayashi D. Cytokine Networks in the Pathogenesis of Rheumatoid Arthritis. Int J Mol Sci. 2021 Oct 10;22(20)
47. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008; 59(6):762-784.
48. Deighton C, O'Mahony R, Tosh J, et al.; Guideline Development Group. Management of rheumatoid arthritis: summary of NICE guidance. *BMJ.* 2009; 338:b702.
49. AHRQ. Choosing medications for rheumatoid arthritis. April 9, 2008. Accessed June 23, 2011.
50. Choy EH, Smith C, Dore CJ, et al. A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. *Rheumatology (Oxford).* 2005; 44(11):1414-1421.
51. Brodin N, Eurenius E, Jensen I, et al. Coaching patients with early rheumatoid arthritis to healthy physical activity. *Arthritis Rheum.* 2008; 59(3):325-331.
52. Baillet A, Payraud E, Niderprim VA, et al. A dynamic exercise programme to improve patients' disability in rheumatoid arthritis: a prospective randomized controlled trial. *Rheumatology (Oxford).* 2009; 48(4):410-415.
53. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, et al. Dynamic Exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst Rev.* 2009(4):CD006853.
54. Han A, Robinson V, Judd M, et al. Tai chi for treating rheumatoid arthritis. *Cochrane Database Syst Rev.* 2004; 3:CD004849.
55. Evans S, Cousins L, Tsao JC, et al. A randomized controlled trial examining Iyengar yoga for young adults with rheumatoid arthritis. *Trials.* 2011; 12:19.
56. Wolfe F, Zwillich SH. The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis Rheum.* 1998; 41(6):1072-1082.

57. Arulmozhi S, Mazumder PM, Sathiyanarayanan L, Ashok P. Anti-arthritic and antioxidant activity of leaves of Alstonia scholaris Linn R Br. Eur J Integr Med. 2011;3:e83–90.
58. Nadkarni KM. I. Bombay, India: Poupular Pakashan Pvt. Ltd; 2009. Indian Materia Medica.
59. *Mishra NK, Bstia S, Mishra G, Chowdary AK, Patra S. Anti-arthritic activity of Glycyrrhiza glabra, Boswellia serrata and their synergistic activity in combined formulation studied in Freund's adjuvant induced arthritic rats. J Pharm Educ Res. 2011; 2:92–8.*
60. *Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A. 2000; 97:9561–6. Doi: 10.1073/pnas.160105897.*
61. *Herbal Remedies, Supplements & Acupuncture for Arthritis*. (2024). rheumatology.org.
62. Huang, Q.-C., Wang, M.-J., Chen, X.-M., Yu, W.-L., Chu, Y.-L., He, X.-H., & Huang, R.-Y. (2015). Can active components of licorice, glycyrrhizin and glycyrrhetinic acid, lick rheumatoid arthritis? *Oncotarget*.
63. Nandy, S., Mukherjee, A., Pandey, D. K., Ray, P., & Dey, A. (2020). Indian Sarsaparilla (Hemidesmus indicus): Recent progress in research on ethnobotany, phytochemistry and pharmacology. *Journal of Ethnopharmacology*.
64. Tracy Stickler, Chief Content Officer. (2020). *Natural Supplements for Rheumatoid Arthritis: Herbs and More*. Healthline Media.
65. *Herbal Remedies, Supplements & Acupuncture for Arthritis*. (2024). rheumatology.org.
66. *Tandon V, Gupta RK. Histomorphological changes induced by Vitex negundo in albino rats. Indian J Pharmacol. 2004; 36:176–7.*
67. *Vispute S, Khopade A. Glycyrrhiza glabra Linn.-"Klitaka": A review. Int J Pharm Bio Sci. 2011; 2:42–51.*
68. *Badami S, Moorkoth S, Suresh B. Caesalpinia sappan a medicinal and dye yielding plant. Nat Prod Rad. 2004; 3:75–82.*
69. *Kalaria P, Gheewala P, Chakraborty M, Kamath J. A phytopharmacological review of Alstonia scholaris: A panoramic herbal medicine. IJRAP. 2012; 3:367–371.*
70. *Sudha K, Mathanghi SK. Traditional underutilized green leafy vegetables and its curative properties. Int J Pharm. 2012; 2:786–93.*
71. *Singh V, Patel H, Suvagiya V, Singh K. Some traditionally used anti-arthritic herbs a review. Int Res J Pharm. 2011; 2:43–5.*
72. *Kiran D, Rohilla A, Rohilla S, Khan MU. Phyllanthus amarus: An ample therapeutic potential herb. Int J Res Ayur Pharm. 2011; 2:1096–9.*
73. *Thirumal M, Vadivelan R, Kishore G, Brahmaji VS. Aristolochia bracteolata: An overview on pharmacognostical, phytochemical and pharmacological properties. Earth J. 2012; 1:66–78.*
74. Kalita S, Kumar G, Karthik L, Rao BV. A review on medicinal properties of Lantana camara Linn. Res J Pharm Technol. 2012; 5:711–5.

75. Kamal, R. M., Sabry, M. M., Aly, Z. Y., & Hifnawy, M. S. (2021). Phytochemical and In-Vivo Anti-Arthritic Significance of Aloe thraskii Baker in Combined Therapy with Methotrexate in Adjuvant-Induced Arthritis in Rats. *Molecules*.
76. Bałan, B. J., Niemcewicz, M., Kocik, J., Jung, L., Skopinska-Rozewska, E., & Skopinski, P. (2014). Experimental immunology Oral administration of Aloe vera gel, anti-microbial and anti-inflammatory herbal remedy, stimulates cell-mediated immunity and antibody production in a mouse model. *Central European Journal of Immunology*.
77. Arulmozhi, S., Mazumder, P. M., Sathiyanarayanan, L., & Ashok, P. (2011). Anti-arthritic and antioxidant activity of leaves of Alstonia scholaris Linn. R.Br. *European Journal of Integrative Medicine*.
78. Choudhary, M., Kumar, V., Malhotra, H., & Singh, S. (2015). Medicinal plants with potential anti-arthritic activity: *Journal of Intercultural Ethnopharmacology*.
79. Bapan Banik. (2024). *Anti-arthritic potential of latex of Alstonia scholaris (L.) R. Br.: an in silico and in vivo approach | Semantic Scholar*. Semanticscholar.
80. Sharma, A., Tirpude, N. V., Bhardwaj, N., Kumar, D., & Padwad, Y. (2022). Berberis lycium fruit extract and its phytoconstituents berberine and rutin mitigate collagen–CFA-induced arthritis (CIA) via improving GSK3β/STAT/Akt/MAPKs/NF-κB signaling axis mediated oxi-inflammation and joint articular damage in murine model. *Inflammopharmacology*.
81. *BOSWELLIA SERRATA: Overview, Uses, Side Effects, Precautions, Interactions, Dosing and Reviews*. (2024).
82. Kumar, R., Kumar, R., Singh, S., Saksena, A., Pal, R., & Jaiswal, R. (2019). Effect of Boswellia serrata extract on acute inflammatory parameters and tumor necrosis factor-α in complete Freund's adjuvant-induced animal model of rheumatoid arthritis. *International Journal of Applied and Basic Medical Research*.
83. Gonen, T., & Amital, H. (2020). Cannabis and Cannabinoids in the Treatment of Rheumatic Diseases. *Rambam Maimonides Medical Journal*.
84. Paland, N., Hamza, H., Pechkovsky, A., Aswad, M., Shagidov, D., & Louria-Hayon, I. (2023). Cannabis and Rheumatoid Arthritis: A Scoping Review Evaluating the Benefits, Risks, and Future Research Directions. *Rambam Maimonides Medical Journal*.
85. Kou, H., Huang, L., Jin, M., He, Q., Zhang, R., & Ma, J. (2023). Effect of curcumin on rheumatoid arthritis: a systematic review and meta-analysis. *Frontiers in Immunology*.
86. Zeng, L., Yang, T., Yang, K., Yu, G., Li, J., Xiang, W., & Chen, H. (2022). Efficacy and Safety of Curcumin and Curcuma longa Extract in the Treatment of Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trial. *Frontiers in Immunology*.
87. Hattori M., Sakamoto T., Kobashi K., et al. Metabolism of glycyrrhizin by human intestinal flora. Planta Med. 1983; 48:38–42. Doi: 10.1055/s-2007-969875.
88. *Kuroyanagi T., Saito M. Effect of prednisolone and glycyrrhizin on passive transfer of experimental allergic encephalomyelitis. Arerugi. 1966; 15:67–74.*

89. *Cyong J., Otsuka Y. A pharmacological study of the anti-inflammatory activity of Chinese herbs. A review. Acupunct Electrother Res. 1982; 7:173–202. Doi: 10.3727/036012982816952116.*
90. *Kumagai A., Nanaboshi M., Asanuma Y., et al. Effects of glycyrrhizin on thymolytic and immunosuppressive action of cortisone. Endocrinol Jpn. 1967; 14:39–42. Doi: 10.1507/endocrj1954.14.39.*
91. *Van Uum S.H., Walker B.R., Hermus A.R., et al. Effect of glycyrrhetinic acid on 11 beta-hydroxysteroid dehydrogenase activity in normotensive and hypertensive subjects. Clin Sci (Colch) 2002; 102:203–211. Doi: 10.1042/cs20010194.*
92. Subramaniyan, V. (2019). Hemidesmus indicus and Usage for Arthritic Conditions. *Bioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases*.
93. Mehta, A., Sethiya, N. K., Mehta, C., & Shah, G. (2012). Anti–arthritis activity of roots of Hemidesmus indicus R.Br. (Anantmul) in rats. *Asian Pacific Journal of Tropical Medicine*.
94. Szymczak, J., Grygiel-Gorniak, B., & Cielecka-Piontek, J. (2024). Zingiber Officinale Roscoe: The Antiarthritic Potential of a Popular Spice—Preclinical and Clinical Evidence. *Nutrients*.
95. Al-Nahain, A., Jahan, R., & Rahmatullah, M. (2014). *Zingiber officinale*: A Potential Plant against Rheumatoid Arthritis. *Arthritis*.
96. *Willow bark*. (2024). Versus Arthritis. https://versusarthritis.org/about-arthritis/complementary-and-alternative-treatments/types-of-complementary-treatments/willow-bark/
97. Lin, C.-R., Tsai, S. H. L., Wang, C., Lee, C.-L., Hung, S.-W., Ting, Y.-T., & Hung, Y. C. (2023). Willow Bark (Salix spp.) Used for Pain Relief in Arthritis: A Meta-Analysis of Randomized Controlled Trials. *Life*.
98. *Rheumatoid Arthritis: Symptoms, Diagnosis, and Treatment | Arthritis Foundation*.(2024).arthritis.org.
99. *Rheumatoid arthritis - Diagnosis and treatment - Mayo Clinic*. (2024). mayoclinic.org.
100. NHS website. (2023). *Rheumatoid arthritis - Diagnosis*. nhs.uk. https://www.nhs.uk/conditions/rheumatoid-arthritis/diagnosis/
101. Alexandra Benisek. (2024). *Conditions That Can Look Like RA*. WebMD. https://www.webmd.com/rheumatoid-arthritis/conditions-look-like-ra
102. Carol Eustice. (2024). *Other Diseases To Consider Before Diagnosing Rheumatoid Arthritis*. Verywell Health. https://www.verywellhealth.com/diseases-that-mimic-rheumatoid-arthritis-190335
103. Mack Mazeski. (2022). *4 Diseases that Mimic Rheumatoid Arthritis | Conditions Mistaken With RA*. Illinois Pain & Spine Institute. https://illinoispain.com/blog/4-diseases-mimic-rheumatoid-arthritis/
104. Julie Marks. (2024). *New Therapies for Rheumatoid Arthritis Pain*. Verywell Health. https://www.verywellhealth.com/new-rheumatoid-arthritis-treatment-5221441

105. Emerson Dameron. (2023). *New hope for treating rheumatoid arthritis*.UniversityofCalifornia.https://www.universityofcalifornia.edu/news/new-hope-treating-rheumatoid-arthritis