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THERAPEUTIC POTENTIAL OF BIOCONSTITUENTS IN THE PREVENTION AND TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT
Background: Rheumatoid arthritis (RA), a joint disease characterized by inflammation and an autoimmune response, affects approximately 1% of the global population. The disruption of immunological tolerance causes the immune system to attack self-molecules, resulting in autoimmune disease. RA is characterized by synovial swelling, accompanied by morning stiffness and joint soreness. **Methodology:** Herbal pharmacotherapy is now a meaningful focus in the treatment of rheumatoid arthritis. Medicinal plants contain strong active components like flavonoids, alkaloids, stilbenoids, tannins, and sesquiterpene lactones. Their anti-inflammatory and antioxidant qualities make them a potential treatment option for RA. **Results and Discussion:** Standard medication aims to prevent further deterioration of the affected joint. This treatment includes several antirheumatic medications, such as methotrexate, biological agents, cytotoxic drugs, immunosuppressants, and NSAIDs. Urinary and respiratory tract infections have been reported in patients treated with certolizumab pegol. Several concerns regarding anti-rheumatoid medication arise during a woman's pregnancy. Therefore, rheumatoid arthritis is now being effectively treated with herbal pharmacotherapy. **Conclusion:** RA is a chronic autoimmune disorder that primarily affects joints through persistent inflammation. Conventional treatment regimens for RA can lead to the occurrence of adverse effects, such as urinary and respiratory tract infections. Given these challenges, herbal pharmacotherapy is emerging as a safer and more sustainable approach. This review highlights a variety of phytochemicals with anti-inflammatory and antiarthritic properties, including flavonoids, alkaloids, stilbenoids, tannins, and sesquiterpene lactones. It underscores the need for further research to elucidate their mechanisms of action, assess their long-term safety and clinical utility, and compare their efficacy.

INTRODUCTION

Autoimmune disorders are thought to be primarily caused by an immune response against the body's own molecules, resulting from a loss of immunological tolerance. A wide range of environmental and genetic factors influences the development of many autoimmune diseases. Rheumatoid arthritis, thyroiditis, insulin-dependent diabetes mellitus, and multiple sclerosis are a few examples. These conditions present numerous complex

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challenges and exhibit a range of symptoms, from systemic complications to organ-specific issues. Irritable bowel syndrome, schizophrenia, and arteriosclerosis are among the illnesses that are thought to be impacted by autoimmune processes [1,2].

It is, which means inflammation, and artho, which means joint, are the roots of the word arthritis. The immune system mistakenly targets the tissues around the joints, resulting in rheumatoid arthritis. This immune response causes the release of specific chemicals and enzymes, which gradually deteriorate the bones and cartilage, thereby aiding in the onset and progression of rheumatoid arthritis (RA), as shown in Figure 1 [3,4,5].

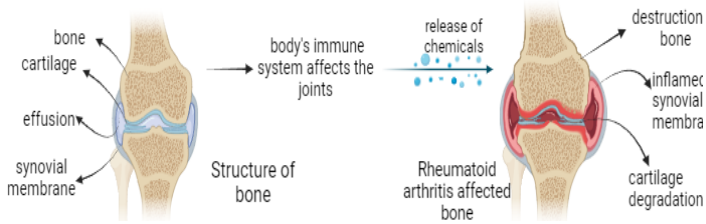

Figure 1: Visual representation of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a joint-related autoimmune inflammatory disease that affects about 1% of people worldwide. It's a degenerative disease that causes articular cartilage and bone to gradually deteriorate because of ongoing polyarticular inflammation in the synovial tissue, as shown in Figure 1 [6]. Joint deformities in the hips, knees, spine, and feet are caused by this condition, which makes daily tasks difficult and causes excruciating pain, decreased muscle strength, stiff joints, and limited mobility [7]. RA is characterized by peripheral nerve involvement, vasculitis, respiratory complications, lung fibrosis, rheumatoid nodules, and extensive systemic effects [7,8,9]. Fatigue, joint pain, inadvertent weight loss, and decreased appetite are typical symptoms. Sometimes RA can worsen and advance more quickly [5].

The onset of RA is thought to be primarily caused by an aberrant immune response, which results in synovial membrane inflammation and subsequent joint damage [6,9]. When T-cells are activated, they release interleukins (IL-1, IL-3, and IL-6) and cytokines, such as tumor necrosis factor-alpha (TNF-α), while also maintaining their cluster of differentiation markers. These inflammatory mediators stimulate the production of prostaglandins and other inflammatory chemicals, the release of chemokines, the expression of metalloproteinases, and the growth of synovial tissue. These processes, which are fueled by matrix metalloproteinase (MMP) remodeling & breakdown, lead to aberrant bone & cartilage degradation. Moreover, elevated adhesion molecule expression promotes excessive T-cell-synovial B-cell binding, which results in an excess of MMPs [4].

Elevated levels of biomarkers, such as IgM and IgA, are used to diagnose symmetric polyarthritis, a characteristic of rheumatoid arthritis that affects the synovial membrane, a specialized connective tissue [5,8]. It is well known that rheumatoid factors, such as IgA, IgG, and IgM autoantibodies, exacerbate the condition. The multifactorial nature of RA encompasses immune responses mediated by T-cells, B-cells, and macrophages, as well as angiogenesis, pannus formation, and synovial hyperplasia. Together, these elements cause bone loss and cartilage degradation [6].

The purpose of this review is to assess the potential therapeutic benefits of different bioactive components derived from plants in the management and prevention of rheumatoid arthritis. Phytochemicals such as flavonoids, alkaloids, stilbenoids, tannins, and sesquiterpene lactones are highlighted in the article for their anti-arthritic properties. Additionally, the pathological mechanisms of RA, the shortcomings of traditional therapies, and the potential of natural alternatives as treatment approaches are discussed.

METHODOLOGY

A comprehensive literature search was conducted using electronic databases, including PubMed, ScienceDirect, and Google Scholar, to identify relevant research on the use of phytoconstituents and traditional therapies in the treatment of rheumatoid arthritis. According to particular inclusion and exclusion criteria, studies were chosen. The inclusion criteria included peer-reviewed publications that examined the pharmacological processes or therapeutic effectiveness of phytoconstituents or traditional RA treatments, including in vitro, in vivo, and clinical trials.

Editorials, commentaries, non-English studies, and those unrelated to RA or focusing on other conditions, such as osteoarthritis, were excluded. Using a previously established format, data from the selected studies were systematically extracted, taking into account factors such as study type, treatment category, mechanisms of action, and therapeutic

outcomes. With a particular focus on anti-arthritic mechanisms, immune modulation, and control of disease progression, the extracted data were synthesized narratively, and the results were arranged thematically to compare the pharmacological effects, therapeutic relevance, and limitations of phytoconstituents and traditional treatments.

EPIDEMIOLOGY

The World Health Organization estimated that between 0.5 and 2% of adults worldwide suffer from rheumatoid arthritis. It is found to be more prevalent in Europe and North America than in Asia. In India, the prevalence of RA varies between 0.28 & 0.7%, & it disproportionately affects rural rather than urban populations. Compared to the general population, people with rheumatoid arthritis have a threefold higher overall death rate. According to the survey results, RA affects more women (3.6%) than men (1.7%) because oestrogen levels in women fall throughout menopause, thus making women more susceptible to RA than men. Depending on other genetic factors and the severity of the disease, the lifespan of RA patients is shortened by 5 to 10 years [3, 7, 11, 12].

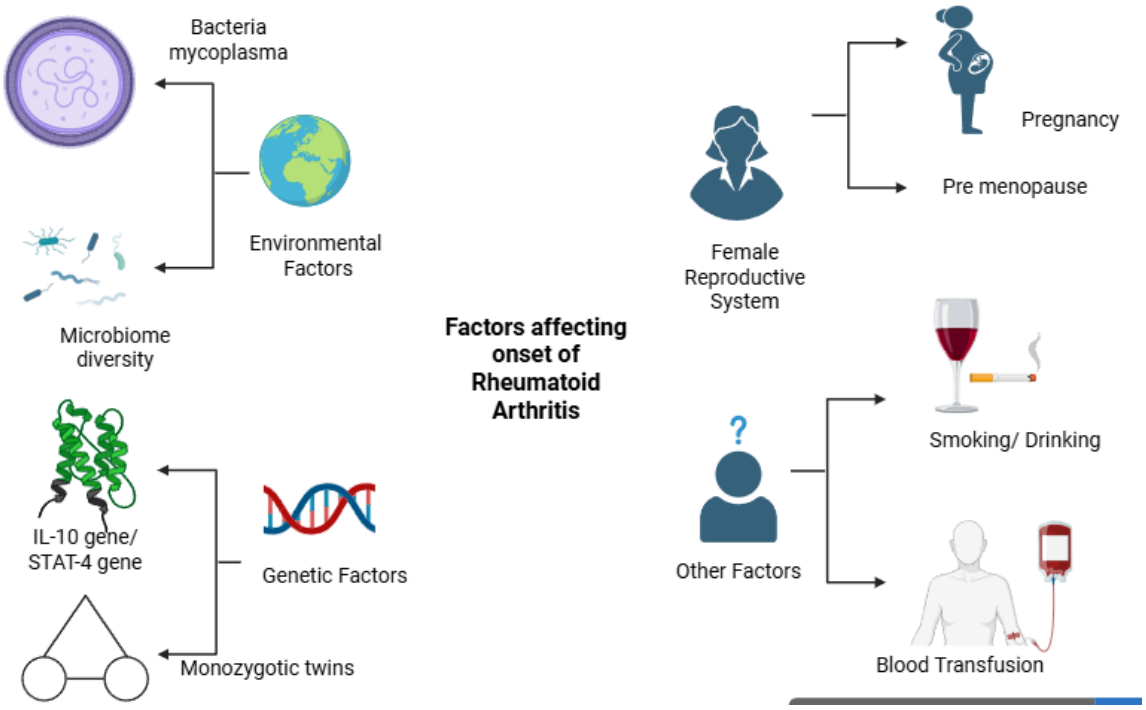

Figure 2: Factors influencing the onset of Rheumatoid arthritis

Aetiological factors

The immune response is triggered by a combination of climatic, sex hormone, and genetic factors [7]. Several factors contribute to the origin of rheumatoid arthritis, as depicted in Figure 2.

1. **Consequences of sex hormones:** Older women are three to four times more prone to develop rheumatoid arthritis than younger women. Oestrogen, possessing anti-inflammatory properties, inhibits the genes that produce inflammatory mediators by increasing the production of kB-Ras2 (an NF-κB inhibitor). It also reduces Tumor Necrosis Factor (TNF-α) and Interleukins (IL-6) levels, other factors associated with arthritis, and controls metabolism. The risk of arthritis increases as oestrogen levels drop during menopause. Hence, the pre-menopausal, postpartum, and pregnancy periods are when RA in women is most prevalent [7].
2. **Environmental factors:** Numerous bacteria present in the environment, like Salmonella and Campylobacter, have been linked to RA. Moreover, viruses such as Epstein-Barr virus (EBV) and rubella virus (RVV) may contribute to the development of rheumatoid arthritis [7].
3. **Hereditary factors:** Monozygotic twins have a 12- to 15% higher prevalence of RA than the overall population. This translates to a 2- to 5% increase in signal transducer polymorphism and STAT% in siblings [11]. Human leucocyte antigen (HLA) and interleukin (IL-4 and IL-10) genes can both be mutated, thereby increasing the chance of rheumatoid arthritis. Genetic factors contribute to roughly 40-65% of the heritability of rheumatoid arthritis [7,13].
4. **Other factors:** Cigarette smoking is one of the causes of the development of rheumatoid arthritis. With too much

increase in the consumption of salty foods and some mineral oils together with silica exposure and blood transfusion, rheumatoid arthritis has worsened as a condition to deal with [7,14].

TREATMENT

The goal of treatment for the condition is to prevent the afflicted joint from deteriorating. During the treatment, an attempt is made to control the harsh inflammatory response and its numerous mediators [7]. Traditionally, the use of pain-relieving drugs, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), has become common in recent decades. Our understanding of the causes of RA has evolved since its introduction into treatment. Their long-term use is restricted due to the numerous adverse effects that have a significant impact [16]. Gluco-corticoids are potent anti-inflammatory medications that may help manage the severity of osteoarthritis symptoms, either as a stand-alone medication or in combination with disease-modifying antirheumatic drugs (DMARDs) to slow the course of RA symptoms [10,15]. These days, combination therapy uses them. Another treatment option for RA is DMARD mono-therapy, which can also be used in combination with NSAIDs to reduce the likelihood of the disease remitting. The most commonly used DMARDs are sulfasalazine, chloroquine, penicillamine, and hydroxychloroquine [7, 12, 18].

Together with the second-line medications, Methotrexate (MTX), ciclosporin, cyclophosphamide, and azathioprine have also been used to treat RA. Methotrexate works as an effective DMARD [6,12]. MTX inhibits TNF-alpha and interleukins and can be used in combination with certolizumab pegol to treat rheumatoid arthritis; however, it has specific adverse effects, as mentioned in Table 1. The patients are at a prominent risk of clinically evident tuberculosis infection, respiratory infections, and severe teratogenic consequences [7,19,20]. Other antirheumatic medications like azathioprine and cyclophosphamide have been clinically reported to cause problems in conceiving in female patients. The teratogenic effects with DMARDs like high risk of abortion, foetal growth, retardation, or congenital abnormalities make treatment with these medications challenging for pregnant patients[7,12].

For the treatment of rheumatoid arthritis, biological agents may be considered an enhanced class of therapeutic modalities. Some of the drugs, such as infliximab, certolizumab pegol, tocilizumab, golimumab, abatacept, anakinra, and rituximab, are examples of these medications [6].

The use of these synthetic medications for a lifetime can have certain negative consequences on the various systems of our body. As mentioned in Table 2, FDA-approved anti-TNF drug Certolizumab pegol, used to decrease immune function in RA, was clinically reported to have hazardous effects.It raised the incidence of moderate-to-severe infections of the respiratory and urinary systems. Nasopharyngitis, sinusitis, and TB are among the severe side effects associated with doses of 200–400 mg [7].

As a result, the present therapy is probably focused on using herbal remedies that have little adverse effects, and as alternatives and complimentary treatments [7,21]. Table 2 enlists the active ingredients of many traditionally used herbal botanical medicines, including flavonoids, stilbenoids, terpenes, sesquiterpene lactones, berberines, and alkaloids with anti-inflammatory and antioxidant qualities which can be used to treat rheumatoid arthritis [7].

- **Flavonoids**

Plants are rich in flavonoids, which are phenolic chemicals that exist naturally. An orange extract that was initially presumed to belong to a novel class of vitamins during the 1930s was eventually identified as flavonoids [24]. Different plant organs contain flavonoids either internally or externally. Plants produce them as secondary metabolic products, and they have a variety of uses, including antimicrobial, antioxidant, photoreceptor, and feeding deterrent properties [25]. In terms of biological and pharmacological effects, flavonoids are believed to possess anti-inflammatory, cytotoxic, anticancer, hepatoprotective, anti-malarial, cardioprotective, neuroprotective, antileishmanial, and antiamoebic properties [24, 26, 27]. The variety of classes of flavonoids includes flavones, isoflavones, flavanones, flavonols, flavan-3-ols, aurones, anthocyanidins & chalcones. In plants, the primary flavonoids are glycosides and aglycones. Flavonoids function as anti-inflammatory agents by inhibiting the transcription factors and regulatory enzymes involved in the inflammatory process. A variety of kinases can mediate cell activation during inflammation, including phosphoinositol kinase, tyrosine kinase, and C-protein kinase, which are responsible for signal transduction through the phosphorylation of proteins or lipids [26]. Certain plants have a high flavonoid content, along with anti-inflammatory & antioxidant properties.

The flowering plant ***Paullinia pinnata L.***, which belongs to the Sapindaceae family, has antioxidant and anti-inflammatory qualities [28]. When administered orally to rats with inflammation induced by complete Freund's adjuvant (CFA), the aqueous and methanolic leaf extracts of P. pinnata L. demonstrated remarkable effects in reducing the production of NO, interleukin-1β, and tumor necrosis factor-α.This portrays that this plant has anti-arthritic and antioxidant effects [7,29].

The ***Ribes orientale***, also known as Ghonashatooh and a member of the Grossulariaceae family, is rich in flavonoids and polyphenols, two active phytoconstituents [30]. It has been demonstrated that oral administration of the aqueous ethanolic root extract in Sprague-Dawley rats is an effective treatment for arthritis, based on the Complete Freund's Adjuvant (CFA) model and the formaldehyde model for arthritis onset. Both the paw inflammation and the arthritic score were considerably decreased. Comparing these rats to CFA control rats also revealed reduced levels of COX-2, PGE2, NF-κB, IL-1β, IL-6, and TNF-α, as well as deregulated levels of IL-4 and IL-10. This suggests that the roots of R. orientale may be used to treat arthritis [7, 31, 32].

Swertiachirayita, a member of the Gentianaceae family, growing in the high Himalayas, is a significant source of flavonoids. According to a recent study, *Swertiachirayita's* hydroethanolic stem extract exhibits anti-inflammatory and antioxidant properties. In rats with rheumatism, oral administration of 200 mg/kg of *Swertiachirayita* leaf extract reduced paw oedema and the pro-inflammatory cytokines TNF-α and IL-1α. This plant also contains xanthones, iridoids, secoiridoid glycosides, and terpenoids among other biologically active phytochemicals [7,33].

Uncaria tomentosa can yield polyphenol active chemicals, which makes it a potent traditional medicine of the Rubiaceae family. Research has shown that certain polyphenol-active substances, including flavonoids, are anti-hormonal and have been linked to anti-inflammatory effects in the treatment of rheumatoid arthritis [34]. According to preclinical research, the extract from *Uncaria tomentosa* was successful in reducing the swollen, tense, and painful joints linked to RA. This is accomplished by blocking the selective and non-selective release of TNF cytokines and pro-inflammatory mediators, including interleukins (IL-1α, IL-1β, IL-4, and IL-17), as well as cytokines like TNF-α [35]. Although human studies have shown promising results, only about 53% of patients taking *U. tomentosa* supplements reported less joint pain, compared to 24% of patients receiving a placebo in addition to common medications like hydroxychloroquine and sulfasalazine [7].

Table 1. Conventional treatment of Rheumatoid arthritis

Drug (Therapy)	Mechanism of Action	Adverse Drug Reaction	Ref
Methotrexate, Penicillamine, Chloroquine (Disease Modifying Anti-rheumatic drugs)	Signals TNF-α, interleukin inhibitors	Respiratory infections, tuberculosis	[7,12]
Certolizumab pegol (Biological agent)	Inhibition of TNF	RTI & UTI, fever, headache, low appetite, low BP	[6,7]
Cyclophosphamide (Cytotoxic drugs)	Selective suppression of B-lymphocytes	Difficulty in conceiving in patients, teratogenic consequences	[6,7]
Azathioprine (Immunosuppressant)	Inhibition of purine synthesis	Hematologic toxicity, cirrhosis, immune reactions	[7]
Diclofenac, Paracetamol, Ketoprofen (NSAIDs)	Blocking cyclooxygenase enzyme-1	Ulcer, dizziness, headache, heartburn	[7]

- **Stilbenoids**

Stilbenoids are substances with considerable potential for use in medicine. The highest concentrations of phytoalexin, a class of polyphenols, are found in teas, grapes, berries, and nuts. Their primary role in plants is to act as a defense against fungi and diseases. Thus, heavy metals, fungi, and UV light can all be used to produce stilbenoid-rich grapes. The in vivo and in vitro activity of stilbenoids implies that these substances may stop the onset of inflammatory disorders [36].

Caragana pruinosa is a deciduous shrub belonging to the Leguminosae family that contains active phytochemicals such as

stilbenoids and flavonoids. The plant's roots, which are abundant in purinosanones D and E, as well as other analogues such as butin and scutellaprostin C, have been shown in recent studies to inhibit macrophages and reduce the production of nitric oxide [7,37].

- **Sesquiterpene lactones**

One of the main groups of secondary metabolites present in plants is sesquiterpene lactones (SL), which are extremely common in the Asteraceae family [38]. By cytokine-mediated activities, immune cell stimulation causes active inflammation. The tested SL inhibits neutrophil migration and prevents TNF-α release, producing anti-inflammatory effects. The suppression of macrophage LPS-induced nitric oxide generation and the decreased production of neutrophil IL-6, IL-8, and TNF-α are two known effects of SL on immunological regulation and inflammatory responses [39].

Active phytochemical components found in ***Inula helenium L***., a flowering plant in the Asteraceae family, include sesquiterpene lactones, particularly isoalantolactone and alantolactone, which have anti-arthritic qualities. Orally administered *I. helenium L.* root extract can reduce arthritis symptoms in rat models induced by collagen and adjuvant. Inflammatory mediators, such as TNF-α, which trigger the MAPK and NF-κB pathways, were also inhibited [7, 40].

In addition to its traditional uses as a laxative, anthelmintic, digestive tonic, and antipyretic, ***Xanthium strumarium Linn***, also known as burweed or burdock datura, is native to tropical India and has been generally used to improve complexion, voice, appetite, and memory. Both Ayurvedic and Chinese medicine systems have utilized plant infusions to treat rheumatism. Sesquiterpene lactones such as xanthin, xanthinin, and xanthatin; alkaloids; and sulphated glycosides are the active ingredients in *Xanthium strumarium* (XS) aerial portions.

The ethanolic extract from Xanthium strumarium Linn, when administered orally, exhibited anti-arthritic effects by inhibiting the release of inflammatory mediators. To summarize, XS exhibits potent anti-arthritic properties [21,41].

- **Berberines**

Berberine is one of the most intriguing and promising biological agents due to its physiological action, particularly in biochemical pathways implicated in metastasis, carcinogenesis, and apoptosis. For several clinical stages, including metabolic disorders and their associated symptoms, inflammation and its side effects, cancer prevention, and combination cancer treatments, berberine, a natural substance that does not harm healthy cells, is effective.

Berberine has been demonstrated to possess anti-inflammatory properties in both in vitro and in vivo studies. The transcription of genes that encode inflammatory proteins, including TNF-α, IL-1, and IL-6, is also suppressed. Both prostaglandin E2 and cyclooxygenase-2 expression are inhibited by berberine. Research has shown that berberine also prevents the increase of TNF-α [42].

The Berberidaceae family member ***Berberis lycium Royle,*** also known as barberry, contains active ingredients with anti-arthritic properties. This plant's bioactive phytochemical components include sindamine, umbellatine, baluchistanamine, punjabine, and berberine. When administered to mice for both acute and chronic inflammation, the crude extract of Berberis lycium inhibits the synthesis of prostaglandins in inflammation caused by carrageenan; however, phospholipase A2 has been demonstrated to inhibit inflammation caused by xylene [7].

A natural remedy for rheumatoid arthritis is the medicinal plant ***Berberis orthobotrys***, which belongs to the Berberidaceae family and contains beneficial phytochemicals such as beta-sitosterol, sesamin, and 10-eicosanol. Research indicates that rheumatoid arthritis is usually associated with the blocking of the transcriptional regulator NF-κB by the active phytoconstituent phytosterol beta-sitosterol. This is because NF-κB regulates genes that result in elevated levels of inflammatory mediators [7,43].

- **Alkaloids**

Out of all the plant secondary metabolites, alkaloids are the most numerous single class. They have an impressive range of pharmacological activity that is often spectacular but can also be hazardous to humans. Many alkaloids are employed as pharmacological and medicinal agents. Alkaloids have been found to have varied biological effects, including anti-inflammatory, antihypertensive, emetic, sympathomimetic, diuretic, antiviral, antidepressant, antimicrobial, and other actions. The detection of a signal that may be infectious or

inflammatory in origin, followed by the release of mediators—molecules from tissues and migrating cells—marks the start of the inflammatory response. Interferon (IFN-γ), Tumor Necrosis Factor-α, interleukin-1β, interleukin-12, and potentially interleukin-6 are pro-inflammatory cytokines that initiate this defense mechanism. Through the use of particular inhibitors and soluble cytokine receptors, immune-regulating molecules regulate the initial inflammatory response [44].

Bengal, the Deccan, Gujarat region, and western and southern India are home to the shrub ***Aristolochia bracteata Lam***. (AB), which is a member of the Aristolochiaceae family. It is occasionally referred to as worm killer or kidamari. Alkaloids, flavonoids, steroids, triterpenoids, and cardiac glycosides are the main chemical components of AB. In addition to preventing cytokine and leukotriene infiltration, *Aristolochia bracteata* preserves the synovial membrane and vascular permeability, which makes it effective against arthritis [21].

Boerhaavia diffusa Linn. (BD), a member of the Nyctagineae family, is found in India, and its root has important medicinal properties. BD has historical significance due to its diuretic, expectorant, laxative, diphoretic, and emetic properties. Gout and rheumatoid arthritis-related joint pain are treated with a root paste equal parts colchicum, tamarind stone, *Solanum nigrum*, stag's horn, and powdered ginger. In drachm doses, the root is used as a powder, decoction, or infusion to treat inflammatory conditions, such as arthritis. It was discovered that the air-dried plant had a very low concentration of the alkaloid panarnavine (0.01%) and high levels of potassium nitrate [21].

Ashwagandha, or ***Withania somnifera***, is a member of the Solanaceae family and is commonly referred to as the tropical winter cherry. It has been used extensively to treat rheumatoid arthritis. Activator protein-1 and other lipopolysaccharides were found to suppress RAW 264.7 macrophages. It was discovered that withanin, a key component of Withania somnifera, regulates the NF-κB transcription factor, pain mediators, and pro-inflammatory cytokines, such as TNF-α, while lowering RANKL levels, which are necessary for osteoclast differentiation [45].

Sinomenium acutum yields the alkaloid Sinomenine, which may be used to treat RA by focusing on various targets, and a possible medication therapy would involve combining it with anti-RA medications [16]. When administered intraperitoneally, it appears to be effective in treating RA. MMP-2, MMP-9, and IL-6 are inhibited in an animal model of arthritis [6].

- **Quercetin**

Quercetin, a flavonoid found in fruits and vegetables, possesses unique natural properties that enhance mental and physical functions, as well as reduce the risk of infections. The anti-inflammatory, psychostimulant, anticarcinogenic, antiviral, and antioxidant activities of quercetin may potentially benefit overall health and disease resistance. Additionally, it can promote mitochondrial biogenesis and suppress lipid peroxidation, capillary permeability, and platelet aggregation. Out of the six categories of flavonoid compounds, quercetin is classified as a flavonol. It is a naturally occurring regulator of polar auxin transport. According to reports, quercetin is a potent anti-inflammatory compound with long-lasting effects. Furthermore, it can regulate and modulate defense and inflammation in a biphasic manner. Additionally, the activity of dendritic cells is immunosuppressed by quercetin. Human dermal fibroblasts' matrix metalloproteinases are inhibited by quercetin. Biochemical pathways track the production of IL-1-stimulated IL-6 from human mast cells, as opposed to IgE-induced degranulation. Two critical signal transduction stages, as well as IL-6 secretion, can be interfered with by quercetin [46].

A flowering plant with 500 varieties, ***Ipomoea batatas*** (family Convolvulaceae) contains active phytoconstituents with anti-inflammatory qualities, including quercetin, gallic acid, rutin, catechin, and caffeic acid [47]. Methanolic and ethyl acetate extracts of Ipomoea batatas were made from the dry powdered tuber and roots. The administration of 300 mg/kg of this extract resulted in decreased paw oedema and arthritic symptoms in the rat model of Complete Freund's Adjuvant (CFA) induced by carrageenan and croton oil. By lowering nitric oxide and inflammatory biomarkers, such as interleukins (IL-1β and IL-6), this extract also exhibits a potent anti-arthritic effect [7,47].

For centuries, ***Rutagraveolens Linn*** (RG), an herbaceous annual plant, has been used as an anti-rheumatic, expectorant, anthelmintic, and antiseptic. Rutin, quercetin, rutacridone, and rutacridone epoxide are the principal chemicals extracted from the RG. The anti-inflammatory, anti-rheumatic, analgesic, antihyperlipidemic, antiandrogenic, antihyperglycemic, and anticancer properties of RG have been documented. By

suppressing the synthesis of prostaglandins, lowering CRP, ceruloplasmin, lipid peroxidation, and releasing additional inflammatory mediators, the polyphenolic fraction demonstrated its biological activity. To sum up, RG exhibits antiarthritic properties [21].

Pomegranate or ***Punica granatum Linn.*** (PG) is a member of the Lythraceae family. Pomegranate seed oil and fermented pomegranate juice extract can inhibit the enzymes lipoxygenase and cyclooxygenase (COX), which initiate inflammatory cascades [48]. Pomegranates are rich in antioxidants, so consuming their fruit may help lower the composite disease activity index in rheumatic patients. Eating pomegranates could be a helpful supplementary tactic to lessen the clinical symptoms of RA. PG contains a variety of phytochemicals, including fatty acids, flavones, quercetin, and rutin. PG is effective against rheumatoid arthritis at doses of 13.6-34 mg/kg. By blocking the signal transduction pathway spectrum, male Wistar rats can exhibit anti-arthritic activity. Therefore, PG has strong anti-arthritic properties [21].

- **Anthraquinones**

With a wide range of applications, anthraquinones are a significant class of synthetic and natural compounds. Anthraquinone derivatives have been utilized in medicine for a long time as antibiotics, laxatives, and anti-inflammatory agents, in addition to serving as colorants. Currently under treatment are conditions like cancer, gout, multiple sclerosis, and constipation [49].

As a member of the Asphodelaceae family, ***Aloe barbadensis*** (aloe vera) possesses strong anti-inflammatory and anti-arthritic qualities. A variety of other compounds, including anthraquinones, tannins, mono and polysaccharides, and sterols, are also found in aloe vera [50]. Although aloe vera is typically used as a cosmetic, its biological component, aloe emodin, is an anthraquinone alkaloid that exhibits anti-inflammatory properties by inhibiting prostaglandin E2 and inducible nitric oxide synthase [51]. Aloe vera can therefore be used to treat allergies, rheumatoid fever, and arthritis [52,53]. NF-κB and p38 kinases, which mediate inflammatory signaling cascades, are prevented from translocating. Consequently, pro-inflammatory mediators, such as cytokines (IL-8, TNF-α, IL-6, and IL-1), are reduced, and PGE2 production is suppressed, according to preclinical animal data [7,54].

- **Tannins**

The roots, leaves, bark, wood, fruits, and seeds are among the plant parts that can contain high levels of tannins, which are generally polyphenols. Understanding how tannins function biologically and their potential applications as food additives, anticancer medications, and antioxidants has gained popularity over the past 20 years [55]. Depending on their chemical structures, tannins can be categorised as hydrolysable tannins, phenol derivatives, condensed tannins, and complex tannins [56]. The antioxidant and anti-inflammatory effects of tannic acid were tested in the murine macrophage cell line RAW264.7 using a nanogel-based delivery system. By using tannic acid, the inflammatory stimulant phorbol 12-myristate 13-acetate (PMA) caused a significant decrease in intracellular ROS, TNF-α, and IL-6 [57,58].

Terminalia chebula, sometimes referred to as chebulic myrobalan, is a member of the Combretaceae family of plants. Numerous chemical components with potent antirheumatoid effects were found in *T. chebula*, including tannins, flavonoids, resins, and fixed oil, according to the phytochemical screening. In a preclinical investigation, the hydroalcoholic fruit extract of *T. chebula* was tested against animal models of rheumatoid arthritis, specifically those caused by formaldehyde and CFA. Joint puffiness decreased, and inflammatory mediators (TNF-α, IL-6, and IL-1β) that are linked to the pathophysiology of rheumatoid arthritis showed a significant decrease in activity[7]. When applied to models of induced arthritis, *T. chebula* reduces serum levels and inhibits joint swelling. It may be possible to treat rheumatoid arthritis with a hydroalcoholic extract of *T. chebula* (TCHE). Additionally, TCHE treatment decreased serum TNF-α levels and the synovial expression of IL-6, TNF-R1, and IL-1β [59].

Red sage or lava are other names for ***Lantana camara Linn.***(LC), a plant in the Verbinaceae family [45]. Historically, LC was used to treat fever, colds, sores, rheumatism, ulcers, chicken pox, measles, and high blood pressure. In Asian countries like India, rheumatism was traditionally treated with a decoction made from the leaves of *Lantana camara*. In Ghana, people with arthritis are treated with infusions of the entire plant[21]. The injected hind paw edema, body weight changes, arthritic index, hematological changes, biochemical changes, and maximal inhibition were all significantly inhibited in the Freund's Adjuvant Arthritic rat model when 400 mg/kg of L.

camara ethanolic and aqueous extract was administered. According to the study, L. camara's ethanolic extract exhibits exceptional antiarthritic activity [60].

The devil's tree, or saptaparni, is the common name for ***Alstonia scholaris Linn.*** (AS), a member of the Apocynaceae family. Rheumatism, leprosy, malarial fevers, asthma, pruritus, gastrointestinal problems, bronchitis, and chronic ulcers are all conditions that are traditionally treated using AS bark [58]. Oil and milky juice were combined, then applied to relieve rheumatic discomfort. Amino acids, tannins, cardiac glycosides, phenols, saponins, and steroids are also present in AS flowers. The anti-arthritic efficacy was primarily achieved by inhibiting the movement of lymphocytes, monocytes, and macrophages, as well as total leukocyte migration [21].

- **Terpenoids**

Terpenoids, also known as isoprenoids, are naturally occurring substances derived from isoprene that play crucial roles in the metabolism of all living organisms. In plants, the diversity of terpenoid chemical species is particularly significant. Terpenoids mediate numerous plant-animal ecological interactions. The recruitment of primary metabolism genes promoted the development of terpenoid secondary metabolism in plants.

The terpene synthase and cytochrome P450 gene families, which are widely distributed in plant genomes, further accelerated this process. Medical discoveries have mainly been derived from the terpenoid family of natural compounds, and many plant terpenoids have found unexpected medical applications[62]. Tropical regions of Asia and Africa are home to the medium-sized deciduous tree known as Boswellia serrata (BS), which belongs to the Family Burseraceae. Boswellic acid is a terpene that is initially found in oleo gum resins [21]. The resin of BS oleo gum is utilized in several Unani and Ayurvedic medications.

Boswellia serrata, a rich source of terpenoids, is used to treat rheumatoid arthritis by reducing inflammation [7]. They are also used to treat lung disorders, gas, cough, diarrhea, and intestinal issues. In addition to being an internal and external stimulant, it also has stomachic, diuretic, and expectorant properties [21,61]. In BS essential oil, β-pinene is the main monoterpene that is predominant [45]. The n-hexane extract of BS gum resin, when mixed with a methanolic extract of Glycyrrhiza glabra rhizome, effectively prevents arthritis in male Vistar rats. It helps prevent rheumatoid arthritis by preventing leucocyte migration [7].

Chinese traditional medicine uses ***Centella asiatica*** herbs for treating RA. Several triterpenoid substances, including asiaticoside, madecassoside, centelloside, and asiatic acid, are present in it [6]. Mice with collagen-induced arthritis (CIA) exhibited a dose-dependent decrease in paw inflammatory swelling and erythema when administered madecassoside orally; however, this treatment did not affect the weight loss associated with the disease. Additionally, it significantly reduced pathological markers, including the formation of pannus, synovial hyperplasia, inflammatory cell infiltration into the joint cavity, and bone and cartilage erosion. Madecassoside was thought to downregulate aberrant humoral and cellular immunity, including excessive auto-antibody production, excessive T-cell activation, and joint destruction [62]. Rich in phytochemical constituents such as triterpenoids, alkaloids, saponins, and cardiac glycosides, ***Aristolochia bracteata Lam.*** (AB) has been used for a long time to treat inflammation, ulcers, dermal disorders, amenorrhea, leprosy, and jaundice.

The Deccan, Gujarat, Bihar, Bengal, and parts of Sindh are home to this shrub, which is commonly referred to as worm killer or kidamari. AB has anti-arthritic properties because it inhibits the infiltration of cytokines and leukotrienes while preserving the synovial membrane and vascular permeability [21].

DISCUSSION

A progressive autoimmune disease that affects synovial joints, rheumatoid arthritis (RA), frequently results in irreversible disability if treatment is not received. Preventing joint damage, reducing inflammation, and enhancing functional status are the main objectives of RA treatment. In RA therapy, traditional methods have included corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic medications (DMARDs) like leflunomide and methotrexate. Despite their effectiveness, these medications frequently have serious side effects like hepatotoxicity, immunosuppression, bone marrow suppression, gastrointestinal irritation, infertility in women, and an elevated risk of infections when taken for an extended period. Finding safer but equally effective substitutes or supplements to these treatments is therefore necessary.

Table 2. Herbal pharmacotherapy for the treatment of Rheumatoid arthritis

Chemical Constituent	Herbal Plant (Family)	Common Name	Mechanism of Action	Ref
Flavonoids	*Paulliniapinnata L.* (Sapindaceae family)	Twiantin	Production of Interleukins (IL-1b), Tumor Necrosis Factor (TNF-α) was decreased	[29]
	Ribesorientale (Grossulariaceae family)	Ghonashatooh	Deregulation of IL-4 & IL-10 Suppression of TNF-α, COX-2, IL-1b, levels.	[7,31, 32]
	Swertiachirayita (Gentinaceae family)	Chirayita	Lowering of TNF-α, IL-1α	[7,33]
	Uncariatomentosa (Rubiaceae family)	Cat's claw	Suppresses the release of interleukins and cytokines (TNF-α)	[7,35]
Stilbenoids	*Caragana pruinosa* (Leguminosae family)	–	Limits macrophage activity and lowers nitric oxide synthesis	[7]
Berberines	*Berberis lyceum Royle* (Berberidaceae family)	Barberry	Impedes the formation of prostaglandins during inflammation	[7]
	Berberis orthobotrys (Berberidaceae family)	Zereshk	Blocks the transcriptional regulator NF-κB	[7,43]
Alkaloids	*Aristolchiabractaeta Lam.* (Aristolchiaceae family)	Worm killer	Inhibiting cytokines and leukotriene infiltration	[21]
	Withaniasomnifera (Solanaceae family)	Ashwagandha	It regulates the NF-kB transcriptor factor, pain mediators, pro-inflammatory cytokines, TNF-α	[45]
	Boerhaaviadiffusa Linn. (Nyctaginae family)	–	Immune-regulating molecules and soluble cytokine receptors, regulate the first inflammatory response	[21]
	Sinomeniumacutum	–	Suppresses MMP-2, MMP-9, IL-6 in arithmetic animal model	[6,16]
Quercetin	*Ipomoea batatas* (Convolvulaceae family)	–	Reduce IL-1b and IL-6 levels, two indicators of inflammation	[7,47]
	Punicagranatum Linn (Lythraceae family)	Pomegranate	Decrease the composite disease activity index of RA patients	[21,48]
	Rutagraveolens (Rutaceae family)	Rue	Prostaglandin production inhibition, a drop in CRP. The limited release of inflammatory mediators.	[21]
Anthraqui-nones	*Aloe barbadensis* (Asphodelaceae family)	Aloe vera	Blocks prostaglandin E2 production. Inhibition of NF-κBSuppressionof TNF-α,IL-1, IL-6, IL-8 levels.	[7,54]
Tannins	*Alstoniascholaris* (Apocynaceae family)	Saptaparni	Prevention of lymphocyte, macrophage, and overall leukocyte migration	[21]
	Lantana camara Linn (Verbinaceae family)	Red sage	Inhibiting the lipoxygenase and cyclooxygenase	[21,60]
	Terminalia chebula (Combrataceae family)	Kaddukai	Drop in IL-6, IL-1b,TNF-α levels	[7,59]
Terpenoids	*Aristolchiabractaeta Lam.*	Worm killer	Preventing cytokine and leukotriene infiltration	[21]
	Bosswellia serrata (Burseraceae family)	Salai	Suppression of COX-2,NF-κB and LOX-5	[21]
	Centellaasiatica	Asiatic pennywort or jalbrahmi	Controlling aberrant humoral and cellular immunity and providing combined protection	[6,62]

Phytotherapy is a promising option in this regard. In preclinical research, several medicinal plants and their bioactive components have demonstrated anti-arthritic properties, particularly in experimental models such as collagen-induced arthritis and Freund's adjuvant-induced arthritis. These natural remedies have antioxidant, immunomodulatory, and anti-inflammatory qualities. They work on the same pathways as prescription medications, but frequently through more balanced, multi-targeted processes with fewer adverse effects.

The mechanisms and preclinical efficacy of several of the phytoconstituents examined in this review make them particularly promising for the treatment of rheumatoid arthritis (RA). Similar to traditional DMARDs, flavonoids, such as those found in *Paullinia pinnata* and *Swertia chirayita*, exhibit strong anti-inflammatory activity by inhibiting TNF-α, IL-1β, and COX-2. These mechanisms also have additional antioxidant benefits. The consistent inhibition of the 5-LOX pathway by Boswellia serrata, which is rich in terpenoids such as boswellic acid, suggests that it may serve as a natural alternative to NSAIDs with fewer gastrointestinal side effects.

Ashwagandha (*Withania somnifera*) exhibits multitargeted actions, including immune modulation and NF-κB suppression, which suggests that it can be used as an adjuvant therapy in conjunction with traditional treatments. Plants containing alkaloids, such as *Sinomenium acutum* and *Boerhaevis diffusa*, also exhibit potent anti-arthritic effects by inhibiting cytokines and leukotrienes. Boswellic acid and withaferin A are the most promising compounds based on available experimental data due to their well-established mechanisms and favorable safety profiles.

Phytoconstituents may have broader biological effects by modulating oxidative stress, immune balance, and cytokine suppression, in addition to sharing mechanistic similarities with traditional RA medications, according to the combined evidence from multiple studies. Herbal pills are uniquely positioned as possible supplements or substitutes for existing pharmaceutical treatments due to their polypharmacological profile and reduced toxicity burden.

There are still several restrictions, despite the promising outcomes of experimental research. Only small-scale human studies or animal models have been used to assess many of the herbal agents. Problems such as inconsistent plant composition, low oral bioavailability, and non-standard dosages must be addressed. Furthermore, to validate these findings in RA patients, high-quality clinical trials are required.

Phytochemicals such as flavonoids, alkaloids, stilbenoids, tannins, and sesquiterpene lactones are utilized in the treatment of Rheumatoid arthritis due to their anti-inflammatory, immunomodulatory, antioxidant, and analgesic properties.

As a result of their established effectiveness and regulatory approval, traditional medications continue to be the first choice for treating RA; however, herbal pharmacotherapy presents a promising alternative. Particularly for patients looking for alternative therapies or those who encounter intolerable side effects from traditional medications, phytoconstituents may be incorporated into mainstream RA management with additional clinical validation.

CONCLUSION

This review highlights the drawbacks of traditional rheumatoid arthritis (RA) treatments, such as their high expense, long-term toxicity, and side effects like immunosuppression, gastrointestinal problems, and hepatotoxicity. These treatments are still essential for managing RA, but because of their drawbacks, interest in herbal pharmacotherapy is rising. *Boswellia serrata*, *Uncaria tomentosa*, *Withania somnifera*, *Aristolochia bracteata*, *Ipomoea batatas*, and others are among the medicinal plants and their phytoconstituents that have shown encouraging anti-inflammatory, immunomodulatory, and antioxidant effects in a variety of experimental arthritis models. With fewer documented adverse effects, these natural substances offer therapeutic effects comparable to those of prescription medications by targeting key inflammatory pathways.The combination of phytotherapy and traditional medicine may be the way of the future for treating RA. The bioavailability of important phytochemicals can be significantly increased by utilizing advanced formulation techniques, such as nano-delivery systems or bioenhancers.

Ultimately, RA management may benefit from a multi-targeted, individualized treatment strategy that combines conventional pharmacology with evidence-based herbal therapy to enhance therapeutic outcomes and improve patient quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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NIL

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AUTHOR CONTRIBUTION

Yashashvi Srivastava and Kartikey Kumar collected data and literature and wrote the first draft of the manuscript. Vikash Jakhmola and Srishti Morris edited the first draft of the manuscript. Srishti Morris supervised and guided. the whole work. All the authors contributed to revising the manuscript and approved the final draft.

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