CHAPTER 11

Botanical Solution for Arthritis: Harnessing Nature's Remedies

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SUMMARY

Rheumatoid arthritis (RA) is a 0.5% of the population inflammatory illness that is chronic and has an unknown etiology. It can cause joint damage and disability due to inflammation of the synovium in the joints, as well as progressive degradation of the cartilage and bone that leads to eventual immobility. The most significant drawback of the powerful synthetic medications that are now on the market is their toxicity and recurrence of side effects after stopping use. Patients with RA are becoming more interested in herbal medications due to the limitations of current pharmacological compounds. herbs with naturally occurring active components that are used to treat illness or lessen arthritic symptoms are known as medicinal herbs. This chapter also discusses the medicinal plants that are used to treat rheumatoid arthritis (RA) and interact with the mediators of inflammation.

INTRODUCTION

A systemic autoimmune illness linked to a persistent inflammatory process, rheumatoid arthritis (RA) can harm extra-articular organs such as the heart, kidney, lungs, digestive tract, skin, nervous system and eyes in addition to joints. To categorize arthritis into inflammatory (pseudogout, gout and basic calcium phosphate disorder) types and non-inflammatory (osteoarthritis) as well as viral and bacterial infections (Neisseria gonorrhea, Enterovirus, Parvovirus, problems of Lyme disease, Staphylococcus aureus), and autoimmune activities, a great deal of research and description has been done on arthritis (Radu & Bangua, 2021). One of the most common long-term inflammatory illnesses is RA.

Three instances per 10,000 people worldwide and 1% are the yearly incidence and prevalence rates of RA, respectively (Prasad et al., 2023). It has become clear in recent years that both epigenetic and genetic factors contribute to the development of RA; nevertheless, environmental factors, such as dust exposure, cigarette smoke and as well as the microbiome, which also serves as an "internal" environment, must also be taken into consideration (Scherer et al., 2020). The treatment plan is intricate, involving not only nonpharmacologic therapies but also many pharmacological classes with various modes of administration. The most crucial aspects are occupational and physical therapy, exercise, and patient education. There is a higher chance of developing coronary atherosclerosis, so lowering risk factors like obesity, smoking, hyperlipidemia, and high blood pressure is important. When an acute illness develops, glucocorticoids (GC) are frequently used intra-articularly or orally to reduce pain and swelling quickly and manage inflammation. Only short-term (3-4 months) use is recommended for oral GC, and it should be discontinued as quickly as feasible to avoid negative effects. Disease Modification Anti-Rheumatic Drugs (DMARD) to leave GC are required for long-term inflammatory control. There are a lot of options, challenges, and chances available these days (Kohler et al., 2019). T peripheral helper cells are among the primary pathogenic cell states that have been found in inflammatory RA synovial tissue recently (Weinand et al., 2023).

Establishing an early diagnosis with good accuracy is crucial to the current management of RA. This 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) established criteria for the traditional diagnosis of the RA. These guidelines suggest multiple parameters for assessment, including the total number and kind of affected joints, quantitative and qualitative analysis of ACPA, RF, CRP, and erythrocyte sedimentation speed. For differential diagnosis, a biopsy is necessary for several medical disorders that are identical. To improve the specificity of diagnostic and prognostic biomarkers (such as 14-3-3 eta protein, antibodies against mutated citrullinated vimentin, cartilage oligomeric matrix protein, calprotectin, survivin and antibodies against carbamylated proteins,), it may be necessary to identify, quantify, and comprehend the interaction within the biomolecular level of these biomarkers. International guidelines state that the following imaging modalities are used: ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), conventional radiography (X-ray), and computed tomography (CT). Each of these modalities has a specific drawback, such as low sensitivity for early detection of signs of degradation

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and erosion or radiation exposure that may damage cellular DNA or inadequate soft tissue in contrast (Radu et al., 2023).

DEVELOPMENT OF RHEUMATOID ARTHRITIS

There is no known cause for RA, yet research has indicated that environmental and genetic variables have a role in the disease's development. Like other autoimmune disorders, it is possible that two distinct events are needed for RA to initially develop: the patient's genetic predisposition, which produces autoreactive T and B cells, and an external trigger, like viral or bacterial infection or tissue damage, which results in the generation of autoreactive lymphocytes that are then initiated by activated antigen-presenting cells (APCs), which compromises tolerance and leads to the destruction of tissue or parts. Therefore, in genetically susceptible people, the development of RA is likely to come from an interaction of genetic variation, environmental factor or epigenetic alteration triggered by stochastic event e.g., an accident and infection. Causes of RA have been observed to involve infections, periodontitis, overweight or obese status, Ultraviolet light exposure, drugs, sex hormones, alterations in the microbiota of mouth, gut, lung or periodontal disease (Littlejohn et al., 2018). Between these, the link in between periodontal disease and the start of Rheumatoid Arthritis is one of more remarkable ones. Recent investigations have shown that infection caused by *Porphyromonas gingivalis*, common periodontal bacteria may trigger autoimmune reactions by citrullinating host peptides, despite the long-standing link between periodontitis and the onset of RA. The procedure involves the transformation of positively charged arginine residues in "self" proteins to neutral citrulline residues and is carried out by the enzyme protein arginine deiminase (PAD). This process onset a net decline in surface charge, enhance the vulnerability of citrullinated "self" proteins to protein degradation, and produces neoepitopes (McGraw et al., 1999).

By enabling the transformation by arginine into citrulline, *P. gingivalis* displaying PADi4 breaches local tolerance, which in turn triggers autoimmune reactions and the subsequent production of anti-citrullinated protein antibodies (ACPAs). Furthermore, it has been proposed that additional viral and bacterial infections, such as the Epstein-Barr virus and Proteus mirabilis or Escherichia coli, may initiate the development of RA through molecular mimicry mechanisms resulting from sequence similarities among specific bacterial along with viral proteins and sequences of amino acids of the "self" antigens. In addition to citrullination, carbamylation of residues of lysine plays a role in the production of neoepitopes from a variety of "self" proteins (such as vimentin, fibrinogen, or collagen) and the consequent disruption of immune "self" tolerance (Aletaha et al., 2018).

We must presume that genetic variables also play a role in the development of RA as concord risk rates for twins who are identical are higher than in non-identical twins and non-related control collectives, and there are more chances of developing RA in those individuals who have a family history of RA three to five times. Single nucleotide polymorphisms (SNPs) have been used in genome large association research, which has shown over 100 loci linked to the development of RA (Smolen et al., 2016). Many of those loci have links in various chronic inflammatory illnesses and play a role in the induction, modulation, and maintenance of immune responses, as would be expected. The existence of specific HLA alleles, modifications to co-stimulatory pathways (such as through changes in CD28 or CD40 expression), variations in the innate immune cell activation, activation of lymphocytes thresholds (such as PTPN22), and cytokines signaling are a few of the risk factors associated with RA. Of the genes involved in the development of RA, HLA-DRB1 alleles (DRB1*01 and DRB1*04; DQ8) are responsible for around half of the hereditary vulnerability that has been reported. According to studies, those HLA alleles have the capacity to present certain peptide epitopes that are generated by crucial RA auto antigens preferentially because they share sequences of amino acids inside its peptide binding groove. Furthermore, a higher mortality rate and more aggressive bone degradation are linked to certain HLA-DRB1 alleles. When combined, these data point to a significant T cell-dependent component in RA, and the majority of cells in the inflammatory synovial tissue are Th17 and Th1 T cell types (Lin et al., 2020).

HOW PATIENTS AND RHEUMATOLOGISTS VIEW MIND-BODY PRACTICES

More than 30% of adults in a 2012 study of the general public in America reported having attempted alternative and integrated therapies, frequently for the treatment of chronic pain. Research on these methods for treating inflammatory arthritis revealed that patients desire more control over their treatment. Although nutritional therapies are the most popular, patients are becoming more interested in mind-body techniques, partly due to their current "in" status.

Few research has been done on the integration of complementary techniques by rheumatologists. It mostly depends on the current care culture and the training that these professionals receive. In Germany, for instance, medical students receive extensive early instruction in complementary practices along with national standards for knowledge and skills that all physicians are required to fulfill. In Germany, at least one of the supplementary therapies with German Medical Association registration is taught to around 70% of the general practitioners. There are integrated medical centers both inside and outside of colleges in France. In order to balance open-mindedness with university-level rigor, French CUMIC (University College of Integrative and Complementary Medicine) seeks to promote the training and teaching regarding these methods that are taught in many universities, including Strasbourg.

Because the degree of data from science supporting mind-body therapies is not strong enough, rheumatologists frequently show little interest in them. This can be the result of a lack of theoretical and applied understanding of these procedures. It seems sense that practitioners are more receptive to those techniques when they draw on personal experience and practice (Sibilia et al., 2024).

Arthritis pain in older adults

One of the more problematic symptoms that millions of older persons with rheumatoid arthritis and osteoarthritis

experience is chronic pain. Of adults with arthritis, 29.7% reported having pain. Rheumatoid arthritis and osteoarthritis account for about 70% of persistent pain cases in older persons. Compared to older persons without arthritic pain, those who reported having anxiety and sadness were more common. Reduced physical function, a greater incidence of impairment, and a lowered quality of life have all been linked to arthritis pain. There may be a connection between long-term pain and psychological problems, physical impairment, or both, which could make it more difficult for people with arthritis to manage their mental and physical health.

The primary goal of treating arthritis should be pain management since it can enhance or preserve the quality of life. It has been shown that managing oneself education program for osteoarthritis efficiently improves the lives of persons with the condition; however, the education programs do not significantly enhance the management of arthritic pain. Healthcare professionals, patients, or caregivers in the US, UK, EU, and WHO are all very interested in learning how to better manage pain in persons with arthritis. Elucidating older individuals' viewpoints and personal experiences of living via pain is essential to developing an arthritic treatment solution (Chen et al., 2020).

People suffer in arthritis

Eight qualitative publications including 212 RA patients, 69% of whom were female and ranged in age from 20 to 83, were included. The general idea that emerged from the synthesis was "A deadly circle caused by an unexpected symptom." Four more subthemes emerged from the synthesis: "managing fatigue"; "time being a challenge"; "being alone via fatigue"; and "language being a tool to increased understanding." For those with RA, fatigue has an impact on every aspect of daily life. They make an effort to schedule, prioritize, pace, unwind, and rest. In addition, they attempt to employ a range of terminology and similes to clarify to others how they perceive the distinction between normal weariness and fatigue associated with RA. In spite of this, individuals who suffer from fatigue associated with RA may feel isolated from their condition and create unique coping mechanisms for it in their daily lives (Primdahl et al., 2019).

HERBAL TREATMENTS FOR ARTHRITIS

In the last three decades, global interest in herbal medicine has been observed. Because they are believed to be effective, safe, and have been beneficial for patients, for thousands of years in many different cultures (Yang, 2013). Botanical medicines are used as alternative therapies for treating many kinds of diseases. There are remedies for RA pain and symptom alleviation with current medicine. Allopathic remedies do have some negative effects, nevertheless, which could limit their application (Lee, 2004). Interest in alternative therapies for arthritis has increased due to worries about the price and safety of traditional treatment.

Arthritis patients frequently use alternative and complementary therapies (Fung, 2015). Massage therapy employing the Swedish technique is a secure and effective means of lowering pain and improving function in individuals suffering from symptomatic osteoarthritis of the knee. In addition, massage therapies have long been performed historically using many different kinds of oils. Numerous studies have demonstrated that massage reduces pain. In fact, massage is one of the most popular complementary therapies and has been a part of the nursing profession's toolkit for years. Interestingly, though, nurses barely give massages in a time when the general public is utilizing them in increasing numbers (Perlman, 2006). The use of heat or cold therapy is another common alternative medicine technique. A large number of arthritis patients in one study reported utilizing both externally and locally applied cold and heat therapy. There was a statistically significant rise in knee strength, function, and range of motion after receiving an ice massage as opposed to a control group.

Conventional therapy

Non-steroidal anti-inflammatory drugs (NSAIDs) or, more recently, a related family of medications known as COX-2 inhibitors are typically the conventional treatment for arthritis. Glucocorticoids or so-called “disease-modifying drugs” (such methotrexate or gold) might be prescribed in more extreme situations (Akram, 2021). Pharmacotherapy now offers options for RA pain and symptom alleviation. The use of these drugs, however, may be limited due to their adverse reactions. NSAIDs are not recommended for the long-term therapy of arthritis due to the potential for gastrointestinal, cardiovascular, and nephrotoxic adverse reactions (Smolen et al., 2018). Hepatotoxicity may be triggered by paracetamol. The central nervous system and digestive system can be affected by tramadol (Vazzana et al., 2015). Intra-articular corticosteroids may worsen joint and tissue damage and have uncertain efficiency in treating RA (Weick et al., 2016). The early stages of Rheumatoid Arthritis can be effectively treated with non-biologic DMARDs with little disease activity; nevertheless, these drugs have a risk of blood disorders, hepatotoxicity, digestive concerns and nephrotoxicity (Gilani et al., 2012). Although biologics have a low tolerance rate and raise the possibility of major diseases, cancers or heart failure, these are useful for managing RA that is mild to severe. Finally, there is an opportunity of infection and blood issues while using Janus kinase inhibitors for the management of RA that is mild to severe (Yamaoka, 2016). In the end, both doctors and patients have to consider the benefits and drawbacks of adopting pharmaceutical therapy.

Herbal drugs for the management of RA

Herbs could offer an additional or alternative approach to safe, effective therapy. This chapter offers a summary of the current pharmacological therapy for RA in addition to new research on the use of herbs to control the disease. Give a detailed explanation of the functions, safety, and efficacy (as well as any effects on pain and inflammation) of several herbal remedies for RA. As of right now, it is known that 25% of recently utilized crude medications come from herbal remedies, and 25% come from naturally occurring materials that have undergone chemical alteration. Complex phytochemicals, including alkaloids, resins, glycosides,

tannins, flavonoids and several other components, are responsible for the herbs' effectiveness. These constituents have also been shown to have a variety of pharmacological actions. Persian medicine has long employed a wide variety of medicinal plants to treat RA. The effectiveness and pharmacological aspects of this natural medicine were described, along with a compilation of several experimental research on these medicinal herbs.

Zingiber officinale

The main components of ginger consist of volatile oils, linoleic acid, oleoresin (gingerol) or trace elements like magnesium, potassium and phosphorus. A strong phenolic component of the ginger, [6]-gingerol, inhibited LPS-caused iNOS expression and manufacturing of the NO and other RNS species in macrophages and disabled peroxynitrite-induced oxidation and nitration responses in vitro (Ippoushi et al., 2003). These results propose that [6]-gingerol is a strong NO synthesis inhibitor while a potent shield against harm caused by peroxynitrite. In accordance with another in vitro investigation by controlling the activation of NF-κB or decomposition of its inhibitor IκB, ginger extract was found to be effective in suppressing the synthesis of PGE2, TNF-α, and COX-2 in human synoviocytes (Thomoson et al., 2002). Anti-inflammatory actions of ginger fractions from silica gel chromatography were also tested by utilizing a PGE2 test in vitro. According to the result, the majority of portions that include gingerols or metabolites of gingerol had highly effective at inhibiting the generation of PGE2 triggered by LPS (Jolad et al., 2004). PGE2 levels in rats were significantly reduced by ginger extract either by mouth or intraperitoneally once a day for four weeks (Thomoson et al., 2002).

Althaea officinalis

One of the primary components of A. officinalis leaves is scopoletin, which has a potential to mitigate RA symptoms by combating the phrase of COX-2 and decreasing the release of proinflammatory cytokines like PGE2, IL-6, TNF-α and IL-1b. It also controls hyperplasic cell in the synovial tissues and limits angiogenesis in tissues. It also protects against cells eroding and reduces the osteoclast activity in cartilage and bone. Increased amount of vascular endothelial growth factor is due to stimulation of macrophages of synovial tissue by Scopletin, into joint cavity that attaches to certain receptors on local endothelium that cause the enhancement of migration and angiogenesis (paola, 2008).

Arctium lappa

There are several species of arctium, and almost all of them are used in conventional medicine to treat inflammatory diseases like RA and chronic bowel inflammation. The primary components of Arctium lappa seeds that are accountable for activity are secondary metabolites that plants own, especially arctigenin (lignan compound). Increased VEGF expression and the generation of inflammatory cytokines and nitric oxide by macrophages increase the inflammatory response in RA (Zhang, 2014). In the same manner, A. minus Bernh leaf demonstrates anti-inflammatory activity in an animal model of paw edema caused by carrageenan (Pashikanti, 2014). Arctigenin, getting a substrate of the MAPK, inhibits production and activity of IL-1b or TNF-α in synovial tissue and monocytes of the arthritic animals.

Artemisia absinthium

Persian medicine has long understood the medicinal uses of Artemisia absinthium's aerial part for treating autoimmune disorders, rheumatic diseases, and neuralgia. As the main secondary metabolite of A. capillaris Thunb, scoparone has been found to significantly suppress a variety of inflammatory cascades that macrophages develop in response to LPS and IFN-c activation of RAW 264.7 cells. This mechanism comprises direct decrease in the amount released of proinflammatory compounds PGE-2 and NO (Mamatha, 2013). In rheumatoid conditions, the nuclear communication system regulates the cellular release of the COX-2 and formation in numerous cytokines and inflammatory mediators, notably TNF-α, IL-6, IL-1b, and IL-8. This process is additionally impacted greatly by the active component of the plant (Yamaoka, 2016).

Cassia angustifolia

One of the major conventional therapies for RA clinical symptoms is cassia angustifolia. Sennosides A and B (rhein dianthrones), sennosides C and D (rhein aloeemodin heterodianthrones), and dianthrone glycosides are few of the anthraquinones which make up senna. The successful use of this species in curing rheumatoid conditions has not been proven by scientific research (Nair, 2012). Nonetheless, the leaf of *C. alata L.* reduces swelling and cartilage deterioration associated with RA and reduces leucocyte infiltration in the synovial fluids of rat knees joint.

Citrus medica L.

This herbal remedy has been suggested in traditional medical practice to treat hepatitis, arthritis and rheumatism. The fruits' antioxidant and anti-inflammatory qualities have been verified. In rheumatoid arthritis, the outer layers of the *C. medica* and fruits of the *C. unshiu marcow* suppresses the agitating responses (Kim, 2013). By decreasing inflammatory cytokine such as TNF-a, IL-6, PGE2 and IL-1b, which control various intercellular and vascular cell adhesion molecules and draw leucocytes to inflammatory regions, these natural remedies have anti-inflammatory properties. Supercritical carbon dioxide extraction produces citropten, while hydro distillation and cold pressing (CP) yield substantial phytoconstituents like limonene and γ-terpinene (Menichini, 2011).

Colchicum autumnale

This medicinal plant effectively reduces the symptoms of rat paw edema, involving the suppression of TNF-α, IL-1b and IL-6, three inflammatory cytokines in sensitive tissues, which causes the development of granulomas. Important phytochemical component of *C. luteum,* colchicine, has been

demonstrated to interact with S. Saleem et al. 113 cellular tubulin protein and reduce pro-inflammatory cells like macrophages (Nair, 2012). Hepatitis, rheumatoid arthritis, hemorrhoids, gout, and maize of Colchicum autumnal are only a few of the inflammatory diseases for which it has been utilized for centuries as an anti-inflammatory agent. It is one of the most significant and efficient natural medications.

Cuscuta epithymum

One of traditionally utilized medicinal plant, *Cuscuta epithymum*, have been used to treat a variety of illnesses by Persian doctors. When tested in vitro, methanolic extract from *C. campestris* seeds was shown to reduce the process by which active macrophages produce nitrite. Among the major compounds found in *C. campestris* seeds is quercetin. It could promote this plant's anti-inflammatory effects. In their research, Lee et al. found that processed seeds of *C. campestris* have more quercetin, that in turn increase inhibition in the inflammatory response in RAW264.7 cell (Lee, 2011).

***Ferula asafoetida* L.**

One of the key medications in traditional Persian medicine, oleo-gum resin made from the *F. persica* and the *F. asafoetida*, has been used for a variety of diseases, particularly inflammatory ones. Ferutinin and teferdin, two active phytoconstituents, play a vital role in reducing inflammatory response, according to research (Geroushi, 2010). Ferunitinin, compound containing phytoestrogen, is found in significant amounts in the genus Ferula. It has powerful osteoprotective properties. The treatment of osteoporosis caused by an estrogen deficit in rats with ovariectomized hearts for two consecutive months with ferutinin on a daily basis has been discovered.

Nigella sativa

Various individuals refer to nigella sativa seeds as cumin or black caraway. Its native region is south and southwest Asia, where the seeds have long been utilized for a range of medicinal uses by traditional healers. Giving patients *N. sativa* oil decreased their disease activity score and joint inflammation, among other signs of RA (Gheitha, 2012). Furthermore, it has been noticed in studies that N. sativa seed extracts enhance animal model ear and paw edema. *Nigella sativa* shows the main ability to recover cellular impairment caused by antioxidants. This is got by improving activity of the antioxidant enzymes and limiting the byproducts of lipid peroxidation and NO (Ghannadi, 2005).

***Rheum palmatum* L.**

Multiple studies done on animals have shown potent anti-inflammatory effects of *R. palmatum* roots. Emodin (1,3,8-trihydroxy-6-methylanthraquinone), a derived of the anthraquinone gained from rhizomes or roots of the *R. palmatum*, have the significantly vital ability to prevent overexpression of the inflammatory factor, including NF-κB, p65, TNF-α, and iNOS. Emodin has an ability to inhibit HIF-1 and VEGF overexpression, potentially lessening the impact of hypoxia-induced RA. In addition, it decreases the availability of proinflammatory cytokines, including PGE2, TNF-a, IL-6, and IL-8. In the case of rheumatoid arthritis, this effect is neutralized by blocking COX-2 activity (Ha et al., 2011). These results offer strong proof of the compound's therapeutic effect on the RA advancement.

***Smilax china* L. and *S. glabra* Roxb**

Roots of *S. china* and *S. glabra* are widely recognized in Persian medicine for their anti-inflammatory effects. They are also useful as a gastrointestinal tonic and can be prescribed for joint problems, gout, and hemorrhoids (Xu, 2003). This plant was additionally demonstrated in several pharmacological tests to have the anti-inflammatory, anti-cancer, and anti-nociceptive impacts. Chinese medicine suggests that these plants have been used for centuries as a treatment for a variety of therapeutic benefits, including persistent pelvic inflammation. The anti-inflammatory effect of this natural medicine was demonstrated and confirmed in inflammatory models by the animals employed. It works by reducing the profuse manifestation of the pro-inflammatory mediator like TNF-α, IL-2 and NO. Furthermore, one potential mechanism for its antiarthritic action has been discovered linked to the modulation of nuclear signaling (NF-κB). In the immunological events of the pathogenic processes involved in RA, T lymphocytes play a distinctive position. Studies conducted in vitro have demonstrated that this medication can considerably reduce T lymphocyte proliferation.

***Strychnos nux-vomica* L.**

S. nux-vomica is one of herbal products that have long been used to treat inflammatory conditions, comprising rheumatoid arthritis. This herb is believed to have a palliative effect on rheumatic pain in traditional medicine (Chaurasia, 2009). In accordance with experimental research, S. nux-vomica seeds exhibit anti-inflammatory effects that include reducing vascular permeability and lowering PGE2. Two naturally occurring alkaloids, brucine or the brucine N-oxide, are obtained from the S. nux-vomica seed.

Camellia sinensis

Multiple studies have demonstrated that the polyphenol EGCG, a component of the extract of green tea, mimics the majority of its health advantages (Curtis et al., 2004; Siddiqui et al., 2004;). Subsequently, further studies with this compound were conducted and it has been noticed that EGCG suppressed the activity of the transcription factor nuclear factor kappa-B (NF-κB) in human chondrocytes eliminated by the Osteoarthritis cartilage in conjunction with IL-1β-inducible nitric oxide synthase (iNOS) or COX-2, leading to a decrease in nitric oxide (NO) or prostaglandin E2, also known as PGE2 (Ahmed et al., 2004). EGCG has also been shown to selectively inhibit IL-1β-induced phosphorylation of the c-Jun N-terminal kinase (JNK) isoform p46, leading to lower level of phospho-c-Jun and DNA-binding activity of activator protein-1 (AP- 1), a transcription factor involved in inflammatory response in human OA chondrocytes (Singh et al., 2003). This is important since degenerative and inflammatory disorders are mostly triggered by JNK kinase.

***Tripterygium wilfordii* Hook F.**

One of the therapeutically active ingredients of TwHF, triptolide, is believed to mediate the anti-inflammatory and immunosuppressive actions (Qui et al., 2003). In animal studies, triploids significantly inhibited the synthesis of proMMP-3 and proMMP-1 in the cultured synovial fibroblasts and murine macrophages, as well as CIA in mice induced by IL-1 (Lin et al., 2001). According to recent studies, Triptolide suppressed the expression of the iNOS gene via decreasing the JNK pathway and NF-κB DNA-binding activity (Wang et al., 2003). In other studies, it has been demonstrated that the TwHF extract and its active component Triptolide reduces the production of COX-2, MMP-13 and MMP-3 in particular chondrocytes that is caused by LPS and cytokines (Sylvester et al., 2001). Recently, triptolide has been demonstrated to inhibit IL-1, IL-17 or TNF-α-encouraged aggrecans gene expression in the human chondrocytes (Liacini et al., 2005). Another mechanism of its anti-inflammatory effect may be the suppression of adhesion molecules E-selectin, ICAM-1 and VCAM1. Although molecular mechanism by which triptolide or TwHF extracts decrease the severity of RA disease is still unidentified these and other research offer compelling proof regarding the scientific basis for the well-established beneficial impacts seen in the RA patients. According to the previous in vitro research as well as further studies, triptolide, the physiologically active component of TwHF extract, is useful in treating RA (Lin et al., 2001; Liacini et al., 2005).

Curcuma longa

Turmeric includes a non-toxic food pigment termed curcumin, which effectively inhibits the ubiquitous transcription factor NF-κB in a wide range of cell types (Ranjan et al., 2004; Schulze-Tanzil et al., 2004). Further investigation has demonstrated that curcumin inhibits catalytic activity of phospholipases A2, D and Cy1 in a variety of cell line, hence inhibiting/modulating the initial phase pathway of arachidonic acid cascade (COX-2 and LOX) (Hong et al., 2004; Frondoza et al., 2004). Curcumin inhibited the JNK, NF-κB and AP-1 pathways, thereby dramatically suppressing the production of the MMP-3 or MMP-13 genes in human chondrocytes. According to other research, curcumin inhibits NF-κB and AP-1 activation, which prevents NO and TNF-α from being produced in vitro in response to LPS and interferon-γ. Additionally, curcumin prevented the synthesis of leukotriene B4 and C4, the generation of PGE2, the integration of arachidonic acid into membrane lipids, and the secretion of collagenase, hyaluronidase and elastase by macrophages (Wallace et al., 2002). In addition, IL-1β-caused MMP-3 upregulation was inhibited by curcumin in the time-dependent manner. Moreover, the treatment with curcumin additionally avoided the reduction in type II collagen manufacturing caused by IL-1β. The information gathered led to an understanding that curcumin opposes the crucial catabolic effects of IL-1β signaling, which play a role in the pathophysiology of RA. Although not conclusive, the results presented unequivocally show that more research must determine and employ optimal dosages in assigned, placebo-controlled medical studies in order to support or contradict the suggested efficiency of using curcumin for RA.

Withania somnifera

Ashwagandha and Withania somnifera is an Ayurvedic herb recognized for its anti-inflammatory and analgesic effects. It has been found that W. somnifera extract inhibits activation of NF-κB or activator protein 1 (AP-1) activation pathway, which inhibits the production of TNF-α, IL-12 and IL-1β (Ganesan et al., 2011). W. somnifera extract lowered the pace at which type I collagen in the bovine Achilles tendon broke down by blocking collagenase activity. The administration of W. somnifera decreased edema, ankylosis, redness and deformity in the rat model of collagen-induced arthritis (Gupta, 2013). W. somnifera's ability to lower the ROS, IL-1B, TNF-α, MMP-8, IL-6, NF-κB activation and raise IL-10 secretion may be important for anti-arthritic effects (Khan et al., 2019). Additionally, a significant decline in the VAS values for stiffness, pain and impairment was noted. In comparison to low dose and placebo, the larger dose shows efficacy earlier (at 4 weeks), superior physician global assessments and decreased need for rescue medicine with paracetamol (Aryaeian et al., 2019).

Paeonia lactiflora

Chinese medicines have long used to dried up root of *P. lactiflora Pallas* and Radix *Paeonia. Radix Paeoniae* decoction has been used to treat RA and other inflammatory diseases. Totally glucosides in paeony (TGP), primarily paeoniflorin, are present in water/ethanol extract of *Radix Paeoniae Alba* (Xu et al., 2018). Previous research has shown that *paeoniflorin* and TGP decrease the synthesis of PGE2, leukotriene B4, nitrogen oxides, reactive oxygen species, and various other mediators that promote inflammation. Additionally, paeonia has demonstrated anti-inflammatory activity by reducing microvascular permeability and inflammatory cell infiltration. The paeoniflorin component of TGP may also inhibit osteoclast differentiation and TNF-α-induced apoptotic (Lai et al., 2018). There is insufficient evidence from science for some of the medicinal herbs that have been generally used to treat RA, such as *Astragalus arbusculinus Bornm.* and *Gauba (Fabaceae), Convolvulus arvensis L. (Convolvulaceae), Opopanax chironium W.D.J. Koch (Apiaceae), Dolichos lablab L. (Fabaceae), Peganum harmala L. (Nitrariaceae), ammoniacum D. Don. (Apiaceae), Narcissus tazzeta L. (Amaryllidaceae) and Nepeta menthoides Boiss. and Buhse (Lamiaceae).* Preclinical and cellular research in a randomized clinical trial, the hepatotoxicity of leflunomide (LEF), methotrexate (MTX), and TGP was compared to that of just LEF and MTX. By the halfway and end of the study, the combination containing TGP was shown to be equally effective with significantly less hepatotoxicity. TGP may have hepatoprotective effects due to its anti-inflammatory qualities, which include reducing TNF-α, IL-6, and C-Reactive Protein (CRP) (Xu et al., 2018).

Biochemical pathways/mechanism in the pathogenesis of RA

Research has demonstrated that conventiIFN-c, onal medications help reduce the symptoms of RA by acting on multiple molecular and cellular levels. These mechanisms include suppressing the production of cytokines that are pro-

inflammatory like IL-12, IL-1a, IL-2, IFN-c, IL-8, TNF-a, IFNc, and IL-6 as well as preventing the start of a response of inflammation. Certain conventional natural medicines that target these cytokines may also function as anti-TNF inhibitors and anti-IL-1 receptor antagonists. A growing body of research has demonstrated the connection between excessive production of free radical or oxidants in joints that are arthritic and oxidative damage in the pathological stages of the inflammatory arthritis as well as rheumatoid diseases (Gheita & Kenawy, 2012). Thus, one of anti-arthritic mechanism of natural medicines used in conventional Persian medicine is the repression of the oxidative-associated destruction of arthritis tissue mediated by the reducing free radicals or NO in addition to downregulating the expression of iNOS. Similarly, another way that natural medicines work is by boosting the production and activity of antioxidant enzymes like catalase, GPx and SOD, which improve anti-oxidative capacity (Fig 1). Over 20 different proteinases make up matrix metalloproteinases (MMPs), which are highly expressed in synovial cells and chondrocytes in arthritis-related joints and play a major part in the matrix degradation associated with RA (Turner, 2015).

Research has shown that conventional natural remedies prevent cartilage deterioration by suppressing the activity of damaging metalloproteinases, such as MMP-9 and MMP-3. The result of present review paper demonstrates that a key factor in the potential for natural therapies to be therapeutic for the pathological conditions of the RA is modulation of transduction and transcriptional signaling pathways, such as NF-κB or MAPK with upward regulatory functions regarding inflammatory and oxidative stress cascade. Although the outcomes of the in vitro and preclinical research are initial,

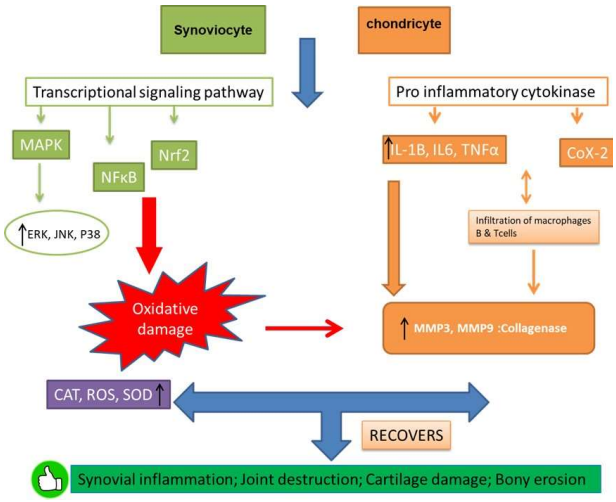

Fig 1. Potential biochemical routes and mechanisms where medicinal plants may be effective in the pathophysiology of rheumatoid arthritis. TNF-a, tumor necrosis factor-alpha; Nrf2, nuclear factor E2-related factor 2; MAPK, IL-1b, interleukin-1b; nitogen-activated protein kinase; NF-κB, nuclear factor κB; The terms COX1, JNK, cyclooxygenase-2, MMP, CAT, matrix metalloproteinases, catalase, superoxide dismutase, SOD, and ROS stand for extracellular signal-regulated kinase, reactive oxidative species and catalase.

they point to the promising potential of the natural medications indicated in terms of reducing the related RA symptoms. Furthermore, it was shown that the majority of herbal medicines have a good tolerance and have been used for a long time in traditional medicine. Nonetheless, in order to ascertain the toxicity profiles of nearly all commonly used medicinal herbs for the treatment of RA, nonclinical research is required.

Numerous active phytochemical compounds obtained from the listed medicinal plants have the potential to be effective on RA, according to evaluated cellular and animal research. Flavonols (quercetin), coumarins (scopoletin and scoparone), (arctigenin), oxyanthraquinones, triterpene saponin,terpenes (the chemical), steroidal saponin (seiboldogenin), glycosylphenols, phytoestrogens (ferutinin), phytoestrogens (ferutinin), sesquiterpenoid (ilicic acid and inuviscolide), sesquiterpenes (umbelliprenin), sesquiterpene lactones (ergolide and granilin),7-Omethylaromadendrin), dihydroflavonols (saturating and anthraquinones (emodin), thymoquinone and alkaloids (brucine N-oxide and brucine). In order to discover new natural medications, further research has to concentrate on the phytochemical agents' safety and bio efficacy.

CONCLUSION

The current recommendations for pharmaceutical therapy for RA are linked to varying degrees of safety and efficacy, particularly when it comes to treating inflammation and chronic pain. Some herbal remedies can be used in conjunction with pharmaceutical medications or as a supplemental therapy to lessen their necessity. Herbal medicine therapy may possibly provide a safer option with comparable or even higher efficacy. Herbs' anti-arthritic properties include blocking pro-catabolic and pro-inflammatory mediators through signaling pathways (NF-κB, PI3K/Akt and RANKL), including cytokines, MMPs, PGE2, ROS, and apoptotic proteins. With few side effects, these exercises may help reduce RA joint discomfort, inflammation, edema, function and structure. Further trial is required to ascertain medical safety and efficaciousness of the plant medicine in treating chronic pain diseases such as arthritis. More research on herbal chemical components or isolates could potentially lead to the development of more specialized treatment alternatives. Finally, to optimize treatment, herbal formulations with optimal bioavailability and kinetic will need to be developed.

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