



Rheumatoid Arthritis: Herbal Medicines as Alternative Source to Alleviate its Symptoms and Current Animal Models

SAWSAN MOHAMED ALI EL-SHEIKH¹, ABD EL-ALIM FOUAD ABD EL-ALIM¹, AZZA AHMED ABD EL-GHAFFAR GALAL^{1*}, REHAB GAMAL EL-SAYED², NAIF AHMED AL-GABRI³

¹Department of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, Egypt; ²Faculty of Pharmacy, Zagazig University, Zagazig 44511, Egypt; ³Veterinary Department, Faculty of Agriculture and Veterinary Medicine, Tamar University, Dhamar 2153, Yemen.

Abstract | Rheumatoid arthritis (RA) is a chronic debilitating autoimmune disease that affects all the body systems in human and animals. Animal models have proven to be indispensable for the unraveling of pathophysiological mechanisms of inflammatory arthritis and for the analysis of therapeutic agents. Current therapy has a goal of complete and long-lasting remission but, typically, only partial remission is achieved and frequent relapses or even non-response are common. Both immune-modulating and anti-rheumatic medications have severe side effects, some of which could be dangerous or even life-threatening. Herbal medicines are an alternative source for relieving symptoms in patients with RA as well as for overcoming the disadvantages associated with current therapy techniques. Interestingly, a wide range of medicinal plants provides a huge resource for such anti-arthritic active principles. This review will throw the light on the current animal models and various active principles derived from plants that have shown promise as anti-arthritic agents in latest years and will outline their prospective action mechanism.

Keywords | Rheumatoid arthritis, Medicinal plants, Alternatives, Management

Received | September 19, 2019; **Accepted** | October 26, 2019; **Published** | December 12, 2019

***Correspondence** | Azza Ahmed Abd El-Ghaffar Galal, Department of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, Egypt; **Email:** azzapharma@yahoo.com, azzagalal@zu.edu.eg

Citation | El-Sheikh SMA, El-Alim AAFA, Galal AAAG, El-Sayed RG, Al-Gabri NA (2019). Rheumatoid arthritis: Herbal medicines as alternative source to alleviate its symptoms and current animal models. *Vet. Sci.* 7(s2): 71-78.

DOI | <http://dx.doi.org/10.17582/journal.aavs/2019/7.s2.71.78>

ISSN (Online) | 2307-8316; **ISSN (Print)** | 2309-3331

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune systemic illness that impacts joints and other tissue. RA is defined as a progressive and permanent harm to the synovial-lined joints triggering loss of joint space, bone, and function as well as deformity in the vast majority of patients. It can affect any joint, but it generally occurs in metacarpophalangeal, metatarsophalangeal and proximal interphalangeal joints, as well as knees and wrists (Grassi *et al.*, 1998). RA affects articular and extra-articular structures that lead to pain, disability and death (Birch and Bhattacharya, 2010). Extracellular matrix destruction is a characteristic feature of RA that accountable for the typical breakdown of cartilage, bone, ligaments, and tendons. Chronic inflammation results in erosive joint

damage and disabilities (El Miedany *et al.*, 2008; Combe, 2009). RA affects up to 1–3% of the population (Grassi *et al.*, 1998). Its prevalence is two to three times higher in women than in men (Thakur *et al.*, 2018) and increases with age (Chalan *et al.*, 2015). RA in dogs is an uncommon chronic and systemic inflammatory disorder, occurring in approximately 2 per 25,000 dogs. This disorder occurs mainly in small or toy breeds aged 8 months to 8 years (Kimura, 2017).

RA develops from people who are genetically sensitive to abnormal immune responses and have been subjected to particular environmental factors. There are more than 100 genetic sites linked to RA. The heritability of RA indicates that a significant percentage of the disease may be caused by environmental risk factors (Yarwood *et al.*, 2016).

Multiple environmental, dietary and lifestyle factors have been associated with RA such as female sex, smoking or exposure to tobacco smoke, occupational dust (silica), air pollution, high sodium, red meat, and iron consumption, obesity, microbes, Low vitamin D intake and levels, alcohol intake, birth weight, breastfeeding, socioeconomic status and region of birth have also been demonstrated to contribute to risk (Liao et al., 2009; Deane et al., 2017). Only certain cases of RA are associated with pet contact as pets might serve as a reservoir of environmental agents that trigger RA after a period of latency (Bond and Cleland, 1996; Gottlieb et al., 1974).

PATHOGENESIS OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis pathogenesis is complex, with numerous genetic, environmental, immunological and other factors contributing to the development and manifestation of the disease. The significance of different underlying factors changes constantly with the progression of an individual's disease and may differ between patients and patient groups. The initiation of RA results from a combination of genetic and random events. Susceptibility to RA depends on the pattern of inherited genes, especially those in the human leukocyte antigen (HLA) major histocompatibility complex (MHC). In addition, hundreds of minor genes, including cytokine promoters, T-cell-signaling genes, and many others, lead to disease. But, other factors, particularly environmental stimuli, are also important, as the concordance rate for identical twins is only 12 to 15%. Of the environmental stimuli that contribute, smoking is best defined, which can increase susceptibility up to 20- to 40-fold in combination with specific genetic factors (Lundstrom et al., 2009). Epigenetic influences, such as abnormal DNA, dysregulated histone marks, or expression of microRNAs, can also contribute to disease by increasing pro-inflammatory gene expression (Bottini and Firestein, 2013). Repeated activation of innate immunity, particularly on mucosal surfaces, is a probable mechanism for the environmental portion. This process may take several years, with autoimmunity proof gradually increasing until some mysterious mechanism tips the balance towards clinically evident disease. Cigarette smoking, for example, is strongly associated with RA and induces expression of peptidyl arginine deiminase (PAD) in alveolar macrophages. Instead, these enzymes transform arginine into citrulline in the airway, producing neoantigens that the adaptive immune system may recognize (Makrygiannakis et al., 2008).

In the initial disease stage there are qualitative and quantitative disturbances of peptide citrullination as well as other protein modifications, followed by antigen presenting cell (APC) (macrophages and dendritic cells) and fibroblast like synoviocytes (FLS) activation.

Some microbes foster this processes by APC and FLS direct and indirect activation. In the second phase, APC produces a particular humoral B cell reaction resulting in the production of specific antibodies and autoreactivity of T cells. Inherited and acquired defects in B and T cell responses resulting from repeated activation of innate immunity as well as the loss of tolerance, resulting in chronic autoimmune inflammation, mainly from synovial membranes, and cellular pannus development. Pathological stimulations of the osteoclasts and release of the effector molecules of the immune system and proteolytic enzymes harm the composition and structure of the cartilage, bone, and tendons. Persistent inflammation through its complicated mechanisms outcomes in many systemic and extra-articular RA manifestations of nearly all organ systems, resulting in serious complications and comorbidities including rheumatoid lung, vasculitis, carditis, anemia, cachexia, myocardial and cerebrovascular vascular disease, accelerated atherosclerosis, lymphoma, depression and osteoporosis. Lastly, cumulative complications and comorbidities lead in disability, social dysfunction and premature death (Branimir and Miroslav, 2014).

CLINICAL MANIFESTATIONS OF RHEUMATOID ARTHRITIS

The clinical manifestations of RA differ, but the most common finding is an insidious beginning of pain with symmetrical swelling of tiny joints. In approximately 25% of patients with RA, the onset is acute or subacute, but its manifestations also include palindromic onset, monoarticular presentation, extra-articular synovitis, polymyalgic-like onset, and general signs (exhaustion, malaise, fever and weight loss). The clinical features of synovitis are particularly apparent in the morning. Morning stiffness in and around the joints, is lasting at least 1 h before maximal improvement is a typical sign of RA. Hand involvement is the typical early manifestation of RA (Grassi et al., 1998).

DIAGNOSIS OF RHEUMATOID ARTHRITIS

Early diagnosis and treatment may affect disease outcomes even to a remission state. Rheumatoid factor (RF) is the popular RA autoantibody for several years. It can be detected in many other rheumatological and non-rheumatological illnesses and also in the healthy individuals. Currently, anti-cyclic citrullinated peptide (Anti-CCP) is the most specific autoantibody in RA with a specificity of more than 95%. Elevated titer of Anti-CCP or RF and positivity of Anti-CCP and RF are RA serological hallmarks. It's well documented that the serum levels of Anti-CCP and RF can be detected up to 10 years before clinical disease onset (Smolen et al., 2018). The concurrent existence of Anti-CCP and RF in the serum of the individual was also extremely specific to the development of future RA (Whiting et al., 2010). Negative

Anti-CCP or RF can be detected in 20%-30% of cases with RA and negative Anti-CCP and RF can be detected in the initial presentation up to 50% and in the course of RA up to 20% (Nishimura et al., 2007). Conventional radiography is the most commonly used imaging method for assessing damage of joint structure in RA. In relation to its diagnostic usefulness, conventional radiography plays a significant role in tracking disease progression, provided that it is done at periodic intervals (Guidelines, 2002). Magnetic resonance imaging (MRI) is the most sensitive technique for detection of changes in the early phases of RA. It helps the evaluation of soft tissue, bone and cartilage structural changes in addition to erosions than conventional radiography (Forslind et al., 2003; Duer-Jensen et al., 2008). The existence of anti-CCP antibodies and MRI erosions in patients with highly clinical suspicion of RA but high RF serology and radiography are extremely specific for RA diagnosis (Narváez et al., 2008).

CURRENT ANIMAL MODELS OF ARTHRITIS PAIN

Animal models have proven to be indispensable for the unraveling of pathophysiological mechanisms of inflammatory arthritis and for the analysis of therapeutic agents (Fischer et al., 2017). Rat adjuvant-induced (AIA), collagen-induced (CIA) and streptococcal wall-induced (SCW) are recommended models of joint pathology that occurs in human RA. Arthritis may be induced in susceptible strains of rats (e.g., Lewis or DA rats) by intradermal injection of adjuvants, including complete or incomplete Freund's adjuvant (CFA, IFA), pristane and squalene, or intraarticular administration of SCW products or antigens in presensitized rats or mice (Bolon et al., 2011; Holmdahl et al., 2001). CIA is the most commonly used experimental model of arthritis. Inflammatory arthritis is induced via immunization of genetically susceptible rats, mice, rabbits and other species with type II collagen, typically of bovine origin (Brand et al., 2003). Collagen-antibody-induced arthritis (CAIA) may be induced in either rats or mice by intravenous injection of a mixture of anti-collagen II monoclonal antibodies, most often followed by intraperitoneal injection of lipopolysaccharides (LPS) to intensify the impact (Fischer et al., 2017).

MANAGEMENT OF RHEUMATOID ARTHRITIS

The management of RA takes place by disease-modifying antirheumatic drugs (DMARDs) (Smolen et al., 2018). The goal of therapy is remission or a state of at least low disease activity that should be achieved within 6 months. Methotrexate (MTX) is first-line treatment and should be prescribed at an ideal oral dose of 25 mg weekly and co-administered with glucocorticoids; with this regimen, 40%-50% of patients achieve the treatment goal (Aletaha and Smolen, 2018). If this therapy fails, the sequential use of targeted therapies, such as biological agents (newer

DMARDs) generated by genetic engineering, inhibits the development of inflammatory cytokines that are over synthesized in diseased joints (Burmester et al., 2014). Different biologics used for RA management are anti-IL-6 receptor antibody (Tocilizumab), IL-1 receptor antagonist (Anakinra), T cell signaling inhibitor (Abatacept), B cell depleting anti CD20 antibody (rituximab), TNF α -receptor fusion protein (etanercept), anti-TNF- α monoclonal antibodies (adalimumab, infliximab, and golimumab) and anti-TNF α PEGylated antigen-binding fragment (certolizumab pegol) (Keystone et al., 2004; Mertens and Singh, 2009; Emery et al., 2008; Caporali et al., 2010).

Corticosteroids, specifically glucocorticoids, are widely used for the treatment of RA (Hench et al., 1950). They act by interacting with cytosolic glucocorticoid receptors and by inhibiting of inflammatory genes transcription, which causes a decreased production of cell adhesion molecules, pro-inflammatory cytokines and chemokines, and other key mediators of inflammation (Singh et al., 2004; Smoak and Cidlowski, 2004).

SIDE EFFECTS OF CURRENTLY USED ANTIRHEUMATIC DRUGS

Even though the MTX response rate in RA patients is about 50% (Lopez-Olivo et al., 2014), the prolonged MTX administration can cause liver fibrosis, some instances may require liver transplantation (Carneiro et al., 2008; Conway and Carey, 2017; Cheng and Rademaker, 2018). Anti-TNF- α is presently the standard treatment for RA patients and is commonly used either alone or in combination with other medications like MTX (Weinblatt et al., 2003; Monaco et al., 2015). About 10%-30% of patients do not respond to initial therapy with anti-TNF- α and 23%-46% of patients lose response over time (Roda et al., 2016). In addition, owing to the immunosuppressive impact of TNF- α blocking, RA patients have an increased risk of repeated infections (Goh et al., 2013). Anti-IL-6 has been shown to be effective in suppressing RA (Oldfield et al., 2009; Kim et al., 2015) and it may be useful in patients who do not respond to other treatment (Navarro-Millan et al., 2012). However, anti-IL-6 has comparable adverse-effects as anti-TNF- α (Smolen et al., 2013).

Furthermore, long-term corticosteroids administration is associated with several side effects such as impaired wound healing, cushingoid habitus, mild hirsutism, linear growth inhibition, myopathy, osteoporosis, osteonecrosis, candidiasis, peptic ulcers, and pancreatitis (Anstead, 1998; Stanbury and Graham, 1998).

HERBAL MEDICINES AS AN ALTERNATIVE SOURCE TO RELIEVE SYMPTOMS OF RHEUMATOID ARTHRITIS

Current therapy has a goal of complete and long-lasting remission, but typically, only partial remission is

achieved and frequent relapses or even non-response are common. Both immune-modulating and anti-rheumatic medications have severe side effects, some of which could be dangerous or even life-threatening (Turner and Muller-Ladner, 2008). Herbal medicines are an alternative source for relieving symptoms in patients with RA as well as for overcoming the disadvantages associated with current therapy techniques (Gupta, 2017). Interestingly, a wide range of medicinal plants provide a huge resource for such anti-arthritis active principles (Dudics et al., 2018).

Thymoquinone (TQ), *Nigella sativa*'s most significant active principle, is well known to have anti-inflammatory, antioxidant, analgesic, and antimicrobial characteristics. Intraperitoneal administration of TQ in adjuvant-induced arthritic (AIA) rats had the same therapeutic significance as MTX (Tekeoglu et al., 2007). Another study revealed that TQ oral administration at 5mg/kg/day leads to inhibition of the serum interleukin (IL)-1 β and TNF- α concentrations in RA (Ahmad et al., 2013). TQ's anti-inflammatory and disease modifying properties significantly lower both paw volume and histological parameters of inflamed joints (Faisal et al., 2018). Moreover, TQ administration reduced the synovial inflammation, arthritic score; C-reactive protein (CRP) levels bone erosion, and pannus formation. TQ has got the potential to alleviate RA by downregulating of toll-like receptor2 (TLR2), toll-like receptor 4 (TLR4), IL-1, nuclear factor-kappa B (NF κ B) and TNF- α expression levels (Arjumand et al., 2019).

β -Caryophyllene (BCP), is an anti-inflammatory sesquiterpene, presents in very large quantities in plants e.g. cinnamon leaves, clove oil, and copaiba balsam. It is a main component of Cannabis, which is a natural selective agonist to the CB2 receptors. BCP's anti-inflammatory characteristics may be useful for management and prevention of inflammation-related diseases (Dahham et al., 2015). The joint inflammation and destruction in AIA rats was suppressed by BCP. It is an efficient experimental anti-arthritis agent and has prospects for future therapy of RA (Vijayalaxmi et al., 2015). Monotherapy with BCP considerably decreased paw thickness and arthritic index; recovered the histopathological alterations in hind paw joints; and reduced oxidative stress and TNF- α concentration in arthritic rats. Furthermore, Co-administering BCP, MTX and/or leflunomide (LEF) considerably enhanced the therapeutic efficacy of MTX and/or LEF and considerably lowered the myelosuppressive and hepatotoxic impacts of MTX and/or LEF (El-Sheikh et al., 2019).

Curcumin is the main natural polyphenol derived from *Curcuma longa* (Aggarwal et al., 2003). It has a wide variety of anti-inflammatory activities (Edrees et al., 2018)

that make it an effective anti-arthritis bioactive molecule (Dudics et al., 2018). Intravenous administration of curcumin in AIA rats had an anti-arthritis effect similar to MTX. Its anti-arthritis effect is induced through lowering of NF- κ B expression and inhibition of IL-1 β and TNF- α release (Zheng et al., 2015). Curcumin inhibited the CIA-induced Mammalian target of rapamycin (mTOR) pathway and the RA-induced infiltration of inflammatory cells into the synovium. It inhibited the increased levels of IL-1 β , TNF- α , Matrix metalloproteinase (MMP)-1, and 3 in CIA rats (Dai et al., 2018).

Quercetin (QCT) is a natural flavonoid found abundantly in almost all edible vegetables and fruits. There is increasing evidence that QCT has excellent therapeutic benefits in the prevention and therapy of various chronic illnesses, including neurodegenerative and cardiovascular diseases, as well as cancer (Lesjak et al., 2018). It has anti-nociceptive and anti-inflammatory activities. Five hundred milligrams per day QCT supplementation for 8 weeks resulted in significant improvements in clinical symptoms (early morning stiffness, morning and after-activity pain), disease activity and high-sensitivity of TNF- α plasma levels in women with RA (Javadi et al., 2017). QCT is a promising agent for arthritis treatment as it has analgesic, anti-inflammatory, and antioxidant effects on induced arthritis. Furthermore, its administration ameliorated zymosan-induced reduction of reduced glutathione (GSH) concentrations, IL-1 β and TNF α production, and prepro-endothelin-1 (preproET-1), gp91phox, and cyclooxygenase-2 mRNA expression. These molecular effects of QCT were linked to NF κ B inhibition and Nuclear factor erythroid 2-related factor (Nrf2)/heme oxygenase (HO-1) pathway induction (Guazelli et al., 2018). QCT is a widely used phytoconstituent with comparable activity to NSAIDs. Owing to low skin permeability, it has restricted applicability via the topical route. The QCT-nanoemulsion gel improved physicochemical stability, mechanical characteristics and improved skin permeability, thus improving its antiarthritic activity (Gokhale et al., 2019).

Resveratrol (RSV) is a natural polyphenolic compound that exists in skin of red grapes, peanuts and in many other natural sources (Walle, 2011). It has potent anti-inflammatory, antioxidant, and anticancer properties. RSV has been identified as a new possible agent to alleviate CIA inflammation in the mouse by reducing serum and joint tissue concentrations of IL-1 β , IL-6, TNF- α , and the soluble receptor activator of NF- κ B ligand, monocyte chemoattractant protein 1 as well as NF- κ B expression (Cheon et al., 2015). In a randomized controlled clinical trial, a daily RSV capsule of 1 g with the DMARDs for 3 months considerably reduced the clinical markers (tenderness and swelling) and the disease activity score in administered patients. Moreover, serum

levels of CRP, erythrocyte sedimentation rate, MMP-3, undercarboxylated osteocalcin, IL-6 and TNF- α were also significantly decreased in RSV-treated group (Khojah et al., 2018). RSV can reduce periodontal destruction and Anti-CCP local levels and it induced ameliorative effect on the RF and IL-4 levels in arthritic rats and reduced the inflammatory manifestations of arthritis and articular damage (Correa et al., 2018).

Carvacrol (CV) is a monoterpene phenol obtained from number of aromatic plants like *Thymus vulgaris* and *Origanum vulgare*. It has a wide range of biological pharmacological activities, such as anti-inflammatory, hepatoprotective, analgesic, antioxidant, and antitumor activities (Suntres et al., 2015). It was recorded that the treatment with CV suppresses autoimmune arthritis (Spiering et al., 2012). In addition, it alleviates LPS-induced cell proliferation and migration of RA-Fibroblast-like synoviocytes (FLSs). It reduced the release of inflammatory cytokines (such as TNF- α , IL-8 and IL-6), inhibited MMPs (including MMP-1, MMP-3, and MMP-13) in LPS-induced RA-FLSs. Furthermore, CV prevented LPS-induced activation of the NF- κ B, TLR4, p38, myeloid differentiation primary response 88 (MyD88), and ERK1/2 pathways in RA-FLSs (Li et al., 2019).

CONCLUSION

Animal models have proved invaluable in providing key insights into the inflammatory pathophysiology of arthritis, leading to a revolution in the RA therapy. Any practical alternatives to control the rheumatoid arthritis are of great importance. Application of the same preclinical approaches and further studies on plants and their derivatives can lead to the development of powerful anti-arthritic agents.

ACKNOWLEDGEMENTS

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHORS CONTRIBUTION

Rehab Gamal El-Sayed and Naif Ahmed Al-Gabri: Drafting of the manuscript.

Sawsan Mohamed Ali El-Sheikh, Abd El-Alim Fouad Abd El-Alim, Azza Ahmed Abd El-Ghaffar Galal: Critical revision of the manuscript

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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