Terpenes as possible drugs for the mitigation of arthritic symptoms - a systematic review.

Alexandra Carvalho, Luana Heimfarth, Klécia Anjos, Adriana Gibara, Laurent Picot, Jackson Roberto Guedes da Silva Almeida, Jullyana de Souza Siqueira Quintans, Lucindo José Quintans Junior

Terpenes as possible drugs for the mitigation of arthritic symptoms - a systematic review

Alexandra M.S. Carvalho[a,1], Luana Heimfarth[a,1], Klécia A. Santos[a], Adriana G. Guimarães[a], Laurent Picot[b], Jackson R.G.S. Almeida[c], Jullyana S.S. Quintans[a,*], Lucindo J. Quintans-Júnior[a,*]

[a] Department of Physiology, Federal University of Sergipe, São Cristóvão, SE, Brazil. E-mails: alexandrasantos22@hotmail.com, luhe@yahoo.com.br, klecias.anjos@gmail.com, adrianagibara@hotmail.com, jullyanaquintans@gmail.com, lucindojr@gmail.com

[b] UMRi CNRS 7266 LIENSs, University of La Rochelle, 17042 La Rochelle, France. E-mail: laurent.picot@univ-lr.fr

[c]Federal University of San Francisco Valley, 56304-205 Petrolina, PE, Brazil. E-mail: jackson.guedes@univasf.edu.br

*Corresponding authors at: Federal University of Sergipe. Department of Physiology, Laboratory of Neuroscience and Pharmacological Assays (LANEF). Av. Marechal Rondon, SN, Rosa Elze, São Cristóvão, Sergipe, CEP: 49.100-000, Brazil. E-mail: lucindojr@gmail.com (Prof. L.J. Quintans-Júnior) or jullyanaquintans@gmail.com (Prof J.S.S. Quintans).

Abstract

Background

Arthritis is a syndrome associated with exacerbated inflammation, joint destruction and chronic pain and disability. Chronic treatment of arthritis is associated with several side effects and high abandonment. Therefore, there has been an ongoing search for alternative treatments to overcome these problems.

Purpose

Natural products, which are already widely used for their biological, cosmetic and pharmacotechnic properties, are a possible source for new drugs. Terpenes, a large class of organic compounds produced mainly by plants and trees, are a promising natural product and have already been shown to be effective in treating chronic pain, particularly of an inflammatory origin.

Study Design and Methods

This review identifies the main terpenes with anti-arthritic activity reported in the last 10 years. A survey was conducted between December 2017 and June 2018 in the PUBMED,

SCOPUS and Science Direct databases using combinations of the descriptors terpenes, arthritis and inflammation.

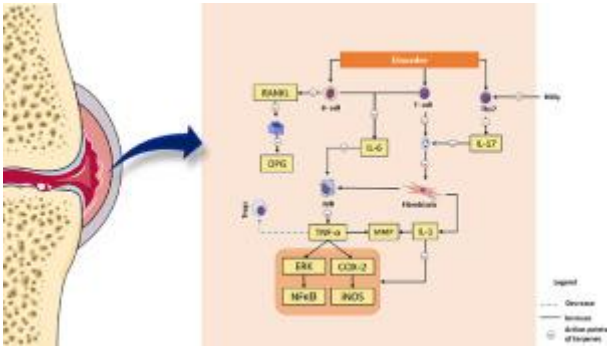
Results

The results showed that terpenes have promising biological effects in relation to the treatment of arthritis, with the 24 terpenes identified in our survey being effective in the modulation of inflammatory mediators important to the physiopathology of arthritis, such as IL-6, IL-17, TNF-α, NFκB, and COX-2, among others. It is important to note that most of the studies used animal models, which limits, at least in part, the direct translation to humans of the experimental evidence produced by the studies.

Conclusion

Together, our finds suggest that terpenes can modulate the immuno-regulatory and destructive tissue events that underlie the clinical presentation and the progression of arthritis and are worthy of further clinical investigation.

Graphical abstract



Keywords

Natural products
Rheumatic diseases
Chronic Disease
Inflammation
Pain
Cytokines

Abbreviations: AA, Autoimmune Arthritis
AIA – adjuvant induced-arthritis
CFA, Freund's complete adjuvant
CIA, collagen-induced arthritis
DMM, destabilization of the medial meniscus
Foxp3, Forkhead Box P3
GRO/KC, growth-regulated oncogene/ Keratinocyte chemoattractant
GR-α, glucocorticoid receptor alpha
KC, kaolin/carrageenan
MAPKAP2, Mitogen-Activated Protein Kinase-Activated Protein Kinase

MCP-1 – Monocyte chemoattractant protein-1
MMP13, matrix metalloproteinase-13
MMP3, matrix metalloproteinase-3
MMP9, Matrix Metalloproteinase-9
MPO – Myeloperoxidase
MSU- monosodium urate induced arthritis
MSUC, Monosodium urate crystal
NE, Neutrophil Elastase.
NFκB, Nuclear Factor-kappaB
OPG – Osteoprotegerin
(p)-MKK-3/6, phospho Mitogen-activated protein kinase kinase 3 or 6
p38MAPKs, p38 mitogen-activated protein kinases
PPARγ – Peroxisome proliferator-activated receptor γ
RANKL, Receptor activator of nuclear factor kappa-B ligand
RANTES, regulated upon activation normal T cell expressed and secreted
RORγ, Retinoic acid-related Orphan Receptor γ

Introduction

A common but little-understood disease, arthritis does not define a single disease, but rather a set of diseases that affect the joints and mainly target the synovial membrane, cartilage and bone. "*Arthron*" means joints (in Greek) and "*itis*" means inflammation (in Latin). The term arthritis is used to describe 100 to 150 types of rheumatic diseases or conditions that affect joints and tissues around them, as well as other diseases of connective tissue. It affects individuals in all age groups, sexes and races, being the leading cause of disability in America, where more than 50 million adults and 300,000 children (Hazes and Luime, 2011) have some form of arthritis. It is more common in females and tends to appear with advancing age.

Among the various diseases associated with joint damage is rheumatoid arthritis (RA), a chronic inflammatory disease that mainly affects the synovial membrane, cartilage and bone. Affecting around 1% of the population, RA is associated with significant morbidity, disability and increased mortality (Firestein, 2003). The pathophysiology involved in the inflammatory process involves the participation of several inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-17, NFκB, and COX-2, among others (McInnes and Schett, 2007).

The treatment is based on five drug classes: analgesics, non-steroidal anti-inflammatory drugs, corticosteroids, disease modifying anti-rheumatoid drugs (DMARD) and target therapy (Siebert et al., 2015, Singh et al., 2010). Biologic agents (DMARDS) are used in the treatment of moderate to severe active disease, acting as immunosuppressants; therefore, being able to reduce inflammation and prevent damage to the joints (Sullivan, 2008). This therapy is the basis of RA treatment, but its high cost may limit access to these effective therapies for may patients (Desai et al., 2014, Hopson et al., 2016) and the side effects associated with this treatment contribute to low adherence.

The problems associated with the use of this type of therapy in RA promotes a need to find new therapeutic options that provide relief from pain and reduce or block the tissue damage associated with chronic inflammation.. In this respect, natural products (NPs) are invaluable sources of new chemical entities with interesting biological activity profiles; among them, we highlight the terpenes and iridoids (a type of monoterpenoids in the general form of

cyclopentanopyran), secondary metabolites from plants, already known to be able to produce pharmacological effects in relation to the management of inflammation and pain in a number of clinical conditions (de Santana Souza et al., 2014, Gouveia et al., 2018, Guimarães et al., 2014, Sarmento-Neto et al., 2016). This family of compounds have several important biological properties including anti-inflammatory, antioxidant, antinociceptive, anti-tumor and other effects (Figueiredo et al., 2007). Additionally, the anti-inflammatory effects of terpene compounds are associated with changes in the production of pro- and anti-inflammatory mediators (Barreto et al., 2016, Lima et al., 2013, Pae et al., 2007).

Terpenes are the main constituents of essential oils, and the earliest recorded use was probably from the Egyptians who used them for a variety of purposes, including cosmetic, religious and medicinal purposes (Thompson, 2005). Recent studies have reported the efficacy of terpenes in the control and treatment of various diseases using animal models, presenting promising activity in the treatment of cancer (Huang et al., 2012), neuropathic pain (Lv et al., 2017, Piccinelli et al., 2015) and diseases of inflammatory origin (Dutra et al., 2012, Quintans Júnior et al., 2010, Rocha et al., 2011, Wang et al., 2011). Furthermore, there are several studies that address the low *in vivo* and *in vitro* toxicity of terpenes, thus demonstrating that these compounds are promising substances for pharmacotherapy, but the need for studies demonstrating their efficacy in humans is notorious.

Interestingly, there are few reviews of the possible use of these compounds as drugs to improve the symptoms of arthritis. Therefore, the purpose of this systematic review was to gather information about terpenes that possess an anti-arthritic profile when assessed in experimental models.

Methods

A systematic review was conducted through a bibliographic survey completed in July 2018 and includes articles published over approximately a 10-year period (December 2007 to June 2018). Three databases (PUBMED, SCOPUS and Science Direct) were consulted, using different combinations of the following keywords: terpenes, arthritis and inflammation. The central idea of this systematic review was to find articles that evaluated the therapeutic effect of terpenes in animal models of arthritis. Moreover, additional studies were included in our survey after a detailed analysis of all references of the selected articles. The selection of manuscripts was based on the following inclusion criteria: articles published in English with the keywords in the title, abstract or full text; studies of isolated terpenes; and in vivo studies. Studies performed with structurally modified terpenes were excluded. For the selection of the manuscripts, two independent investigators (AMSC and KAS) first selected the articles according to the title, then to the abstract and then through an analysis of the full-text of the publication. Any disagreement was resolved through a consensus between them or with the participation of an independent researcher, who was the final referee. The resulting articles were manually reviewed with the goal of identifying and excluding the works that did not fit the criteria described above.

Results and discussion

This review searched for terpenes that have anti-arthritic activity in in vivo experiments reported in the last 10 years. We found 604 articles, 203 in Science Direct, 145 in Scopus and 256 in PubMed. However, X number were duplicates and Y number did not meet the selection criteria and were therefore excluded, resulting in a total of 104 articles. After initial

screening of the abstracts and the full text of these 104 articles, 25 were selected as the others did not meet the inclusion criteria (n=79). A flow chart of the selection process is shown in Fig 2.

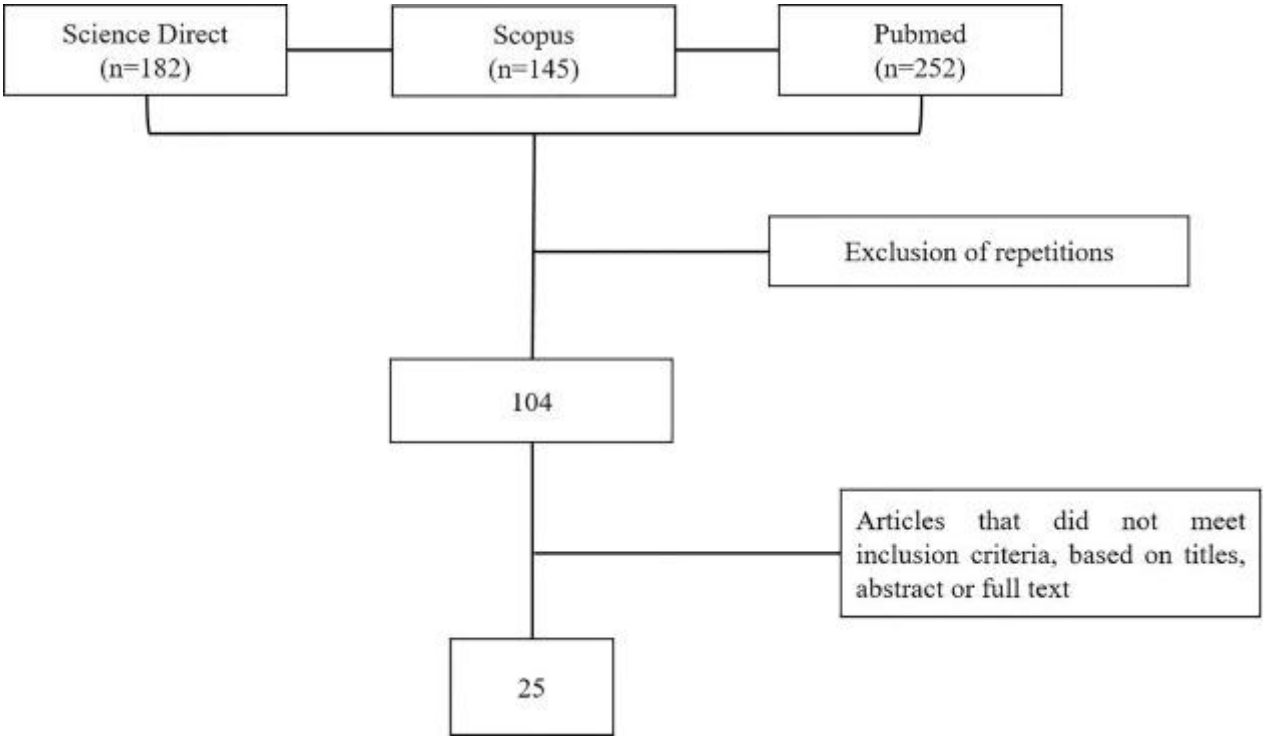


Fig. 2. Flowchart of included studies.

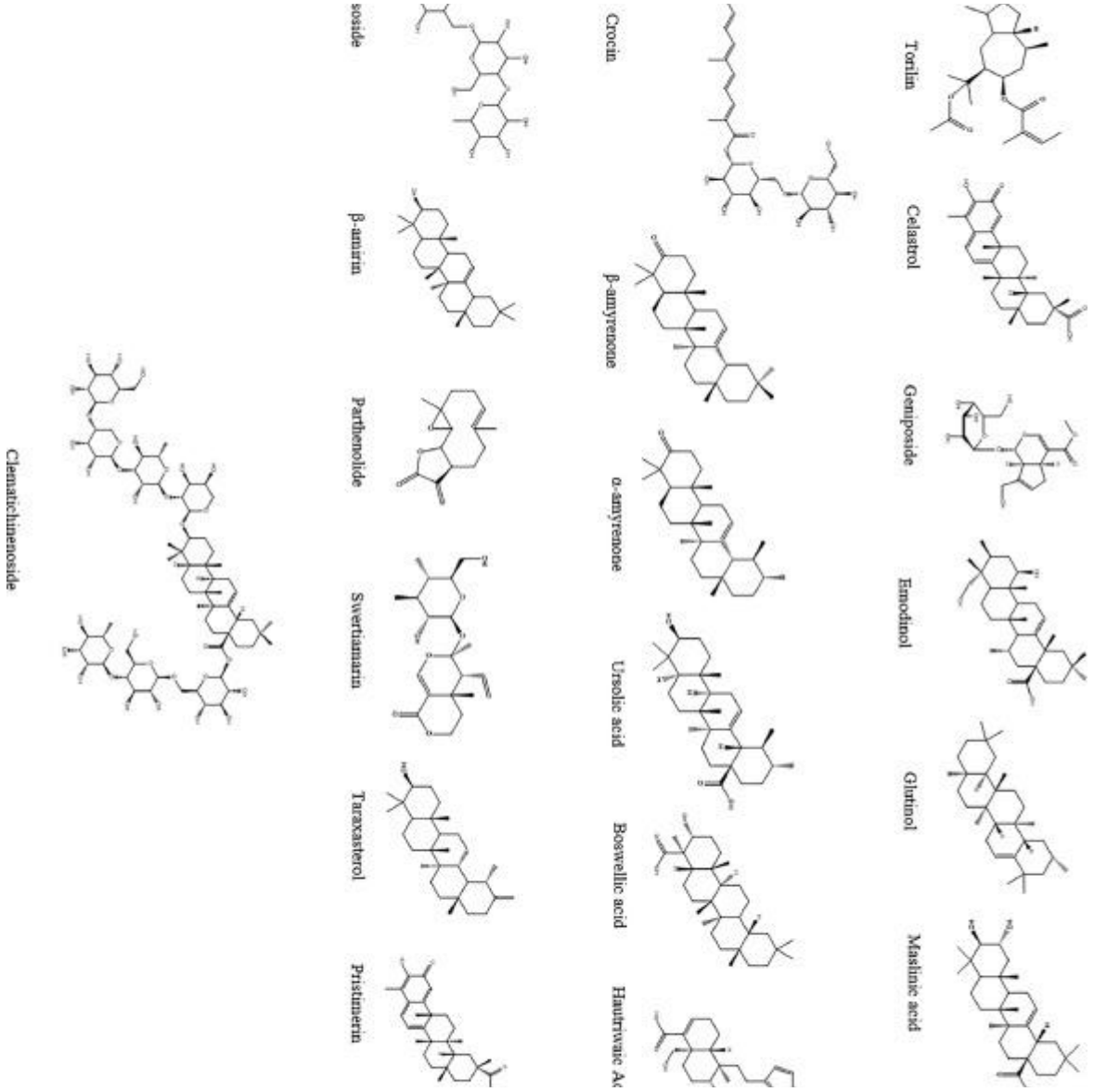


Fig. 3. Molecular struture of terpenes includig in the study.

Arthritis exhibits symptoms such as swelling, pain, stiffness and decreased or loss of function of the affected joint. The disease may result in chronic pain, inability to perform daily activities and hinder walking, this is mainly associated with permanent joint changes (American College of Rheumatology Pain Management Task Force 2010, Heiberg et al., 2005, Lee, 2013). Thus, the presence of these signs and symptoms, when possible, are extensively explored in experimental animal models of arthritis to try to create a correlation with the disease in humans and make these studies as translational as possible.

Anti-edematogenic effects

Edema is one of the five classic signs of the inflammatory process. Defined as swelling caused by excessive fluid retention in the soft tissues of the body, it is usually associated with the venous or lymphatic systems. This is not a classic sign of arthritis, but some medications used to treat arthritis, including non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, may decrease the formation of edema, reduce pain and some other arthritis symptoms (Trayes

et al., 2013). Experimental models of arthritis simulate the features found in human disease well, including joint edema. Animal models have been used for several decades to study arthritis and have contributed greatly to the unraveling of the mechanisms of pathogenesis and validating new targets for treatment (Vincent et al., 2012); however, there is no perfect model which brings together the complexity and all the symptoms of the disease.

In our research, 14 studies demonstrated anti-edematogenic effect of terpenes after initiation of treatment, both in the knee and paw of rodents. Li et al. reported that a reduction in edema may be associated with inhibition of iNOS in synovial capsule tissue (Li et al., 2017). This isoform produces a large amount of NO, causing increased capillary permeability (Bogdan, 2001). Additionally, other studies have associated reduced edema with decreased interleukins and cell infiltrate. The results shown by the original articles in this review corroborate the hypothesis that the reduction of cytokines, cellular infiltrates and iNOS may be associated with decreased joint edema.

Additionally, a study conducted by Cascão et al. (Cascão et al., 2012) using celastrol, a plant-derived triterpene known to improve autoimmune arthritis by suppressing Th17 differentiation, showed it to be more effective in reducing edema than digoxin (Lee et al., 2015). Celastrol was able to suppress arthritis scores in the early and late phase, while digoxin was only effective when administered in the early stage. Celastrol was effective against joint swelling induced by AIA (Adjuvant-Induced Arthritis), by reducing inflammatory infiltrate.

Molecular mechanisms involved in the attenuation of the symptoms of arthritis: terpenes and target molecules

Arthritis is a generic term for inflammatory joint disease, and there are various forms of arthritis, including osteoarthritis, rheumatoid arthritis and spondyloarthritis. Its pathophysiological mechanism is associated with the increase of inflammatory mediators in the joint. These appear the cardinal signs of inflammation: pain, heat, redness and edema. Its etiology involves genetic, immunological and environmental mechanisms. Recent advances in our understanding of the causes and progression of various forms of arthritis have created hopes for better management and possible remission of the disease. Pharmacotherapy has shifted from symptom management to the treatment of underlying disease processes (Casey, 2015). However, therapies that prevent or cure arthritis remain illusory, necessitating the search for new compounds that may fill the gaps in the treatment of this disease.

Several studies have shown that modulation of inflammation by controlling the inflammatory molecules in the synovial cavity (such as cytokines, chemokines, among others) (Leung et al., 2017, Röhner et al., 2012, Snelling et al., 2017) and the modulation of signaling pathways that perpetuate the inflammatory process (NFκB, COX-2, MAPK, among others) are important targets for the effective treatment of arthritis. In this sense, in this review we address the mechanisms by which terpenes act to relieve the symptoms of arthritis. We searched for evidence of the main target molecules reached from the treatment with terpenes in animal models. The union of these data may provide support for translational research, and may serve as an inspiration for the beginning of these studies.

Modulate inflammatory and anti-inflammatory cytokines

Cytokines are small proteins secreted by cells of the immune system such as macrophages and lymphocytes and have a specific effect on cell-cell communication, and can act in an

autocrine, paracrine or endocrine form (Zhang and An, 2007). The inflammatory response can be driven by the cytokine production and is certainly a major target in the management of inflammatory diseases, such as arthritis. The sustained overproduction of pro-inflammatory cytokines and the down-regulation of anti-inflammatory cytokines production are observed in the pathogenesis of arthritic diseases. They are expressed and functionally active in synovial tissues and contribute to chronic inflammation and progression of the disease (Dinarello, 2000, Feldmann, 2008).

Chen et al. (2013) demonstrated up-regulated IL-1β, IL-6, and TNF-α levels in serum of crystal-induced ankle arthritis in mice. In addition, the administration of collagen as an inductor agent of arthritis caused increased TNF-α, IL-17A, IL-6, IL1β, and IFN-γ levels, as well as decreased IL-4, IL-10, and TGF-β1 production in the synovial fluid (Lu et al., 2012; Z. M. Wang et al., 2011). Several studies report that arthritis induced by Freund's Complete Adjuvant (CFA) (Liu et al., 2014, Saravanan et al., 2014) or kaolin/carrageenan (Salinas-Sánchez et al., 2015) caused misregulation of pro-inflammatory or anti-inflammatory cytokines, such as IL-1β, IL-6, TNF-α and IL-10 in bone marrow or serum, respectively. Cytokines appear to play a key role in the development of arthritis and are a strategic target to mitigate arthritis symptoms. Moreover, the altered levels of these small molecules have been shown to contribute to bone loss, joint destruction and disease progression (Yue et al., 2018).

The use of substances able to induce anti-inflammatory or reduce proinflammatory cytokines can represent an important advance in the therapeutic treatment of a range of diseases. In this respect, terpenes stand out as an interesting option for the discovery of new bioactive molecules for arthritis injury, especially as an alternative to reduce the inflammatory process (Barreto et al., 2016, Brito et al., 2015, de Santana Souza et al., 2014, Lu et al., 2012, Salinas-Sánchez et al., 2015) . Our review highlighted 14 terpenes (Table 1) that are able to modulate the levels of cytokines in different models of arthritic diseases, and thereby contribute to improving the clinical profile by reducing the inflammatory process and pain.

Emodinol, a triterpene isolated from *Paeonia emodi* (Riaz et al., 2003), reduced the levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in the serum of MSU crystal-treated mice, contributing to a reduction in anti-gouty arthritis activity by improving inflammatory response (Chen et al., 2013). Geniposide, an iridoid glycoside purified from *Gardenia jasminoides* Ellis (Rubiaceae), decreased proinflammatory cytokines, such as IL-1β, IL-6, TNF-α, and increased the anti-inflammatory cytokine IL-10 in complete Freund's adjuvant (CFA) induced arthritis rats (Chen et al., 2015). In addition, Saravanan et al. (2014) evaluated the immunomodulatory activity of swertiamarin, an iridoid glycoside isolated from *Enicostema axillare,* and reported an important anti-inflammatory action for this terpene. Pretreatment with this terpene reduced levels of TNF-α and IL-1β and increased the release of IL-10 and IL-4 in the serum of animals, which appears to be critical in reducing arthritis.

Endale et al. (2013) and Lu et al. (2012), also demonstrated the modulation of IL-1β, TNF-α, IL-6, IL-10 and/or IL-4 levels induced by the sesquiterpene torilin in serum, and by the diterpenoid kirenol in synovial fluid, respectively. Moreover, both terpenes were able to decrease IL-17 release, which has been associated with arthritis disease severity (Kirkham et al., 2006). IL-17 enhances the activation of synoviocytes and the production of other cytokines, contributing to bone and cartilage destruction (Lubberts et al., 2004).

Recently, Fukumitsu et al. 2016 evaluated the anti-inflammatory and anti-arthritic activity of maslinic acid, a pentacyclic triterpene isolated from olive pomace. Treatment with maslinic

acid reduced the expression of IL-1β, TNF-α, and IFN-γ mRNA in the synovial membrane of knee joints caused by collagen antibody induced arthritis (CAIA). Moreover, a study has shown that the terpene clematichinenoside, a triterpenoid saponin, increased TGF-β1 release in the serum of CFA induced arthritis rats and that this effect was associated with inflammatory process attenuation (Xiong et al., 2014).

Accordingly, this review has shown that cytokines represent one of the most important targets for terpenoids and that this is an effective approach to in the treatment of arthritic diseases. Terpenes reduce proinflammatory levels and can increase the production of some anti-inflammatory cytokines, attenuating the inflammatory process and tissue destruction and disease progression. It is well-known that suppression of the anti-inflammatory cytokines IL-10 and IL-4 can cause cartilage degeneration (van Roon et al., 2003). Inflammation of the joint tissues is related to the accumulation of toxic substances in the synovium that lead to cartilage destruction (Darlington and Stone, 2001).

Moreover, TNF-α, IL-6 and IL1β were described as a molecular target of 13 terpenes (Table 1), thus highlighting the modulation of these cytokine levels as the main mechanism of action of terpenes, as anti-inflammatory agents and as antiarthritic substances. TNF-α, IL-1β and IL-6 promote synovial inflammation by up-regulating the expression of vascular growth factors, endothelial mitogenesis and activate matrix metalloproteinases (Pan et al., 2009). These cytokines facilitate the infiltration of inflammatory cells into the synovial tissues and oxygenation of mass cells which enhances the inflammatory response (Paleolog, 2002), contributing to development and progression of arthritic features.

The modulation of TNF-α, IL-6 and IL-1β release is evidence of the possible potent beneficial effect of terpenes against arthritis. Studies have reported that blocking TNF-α produced clinical benefits in inflammatory diseases (Gabay, 2002); and antagonize IL-6 receptor has also produced clinical improvement in patients with rheumatic arthritis (Genovese et al., 2008), showing the importance of TNF-α and IL-6 in the physiopathology of this disease.

Our results suggest that the terpenes analyzed are able to reduce pro-inflammatory cytokines (TNF-α and β, IL-1, IL-1β, IL-6, IL-17, IFN-γ) and increase anti-inflammatory cytokines (IL-4, IL-10, TGF-β1), reducing the response caused by the arthritic chemical agents. Such an effect may be associated with the regulation of the cells of the innate immune system. In addition, models using genetically modified animals could contribute, at least in part, to understanding the possible mechanisms of action of these terpenes and the real importance of modulating cytokines to produce the antiarthritic profile. The data presented by the original articles suggest that terpenes modulate cytokines, but do not clarify the mechanism of this modulation. Therefore, deeper studies are needed to understand how they act in these cells.

Modulation of signaling pathways associated with inflammatory diseases

Several studies have demonstrated that complex molecular targets and mechanisms are implicated in the pathology of arthritic diseases, contributing to damage of synovial membrane, cartilage and bone (Khalifé and Zafarullah, 2011, Klareskog et al., 2006, Miossec, 2003, Vincent et al., 2012). In this context, alterations in the inflammatory mediator's cascades play a pivotal role in the pathophysiological processes underlying inflammation and tissue destruction in arthritic diseases. Some studies indicate that the beneficial pharmacological properties of terpenes against arthritis phenomena are related to modulation of several intracellular signaling pathway proteins, such as RANKL (Wang et al., 2016),

NFκB (Z. M. Wang et al., 2011), the MAPK family (Chen et al., 2015), COX-2 (Lee et al., 2015), iNOS (Lee et al., 2015, Li et al., 2017), PGE-2 (Li et al., 2009), matrix metalloproteinases (Liu et al., 2015, Nanjundaiah et al., 2012), MPO (Zhang et al., 2017) and c-FOS (Kang et al., 2008). Terpenes can provoke the activation or inhibition of these molecules or pathways reducing the diseases progression. Our review highlighted 14 terpenes (Table 1) that modulate these inflammatory mediators in different models of arthritic diseases, differently modulating various pathways of the inflammatory process.

Wang et al. (2016a) reported that the triterpene taraxasterol alters the expression of RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) and OPG (osteoprotegerin) protein, an important signal regulating system of bone tissue metabolism that plays an essential role in osteoclastogenesis. RANKL and OPG are an essential mediator of bone resorption and osteoclast differentiation (Stolina et al., 2009, Van Campenhout and Golledge, 2009). In addition, the binding of RANKL to its receptor RANK in osteoclast precursor cells causes the activation of several intracellular signaling pathways associated with inflammatory response, including the mitogen-activated protein kinase (MAPK) pathways and the NF-kB signaling cascade (Darnay et al., 1999).

The MAPK family and NF-kB signaling cascade are two important targets of terpenoid molecules, altering the inflammatory process in several diseases, including arthritis (Feng et al., 2017, Kashyap et al., 2016, Sánchez-Fidalgo et al., 2015).

Wang et al. (2011) reported that kirenol, a terpene derived from *Herba siegesbeckia*, inhibited NF-κB activity and consequently the NF-κB binding to DNA and inflammatory molecules transcription. NF-κB is a transcription factor required for up-regulation of inflammatory and immune responses observed in arthritis pathology (Gilston et al., 1997, Han et al., 1998). Activated NF-κB has been found in synovial tissue in the early stage of joint inflammation (Gilston et al., 1997) and there is evidence suggesting that NF-κB activation plays a pivotal role in the initiation and perpetuation stages of the chronic inflammation characteristic of rheumatoid arthritis. The activation of this transcription factor also promotes cellular proliferation and inhibits cellular apoptosis, facilitating synovial hyperplasia and pannus formation (Makarov, 2001). All these characteristics contribute to the progression of inflammatory disease pathology, including that of arthritis. Terpenes, which suppress NF-κB activation, are a promising approach for arthritis treatment as they are also strong inhibitors of common pain processes in rheumatic disease (Gouveia et al., 2018, Guimarães et al., 2013).

MAPK is a conserved family of proteins that is involved in the control of several fundamental cellular processes that include cell survival, differentiation, apoptosis, proliferation, metabolism and inflammation (Chong et al., 2003, O'Neill and Kolch, 2004, Wellbrock et al., 2004) . One of the major roles of the MAPK family in arthritic diseases are regulation of the synthesis of TNF-α, IL-1 and IL-6, which contribute to joint inflammation and structural damage (Görtz et al., 2005, Lee et al., 1994). Studies have reported that terpenes are able to inhibit the activation of MAPK, causing a decrease in the inflammatory process (Alghasham and Rasheed, 2014, Ma et al., 2014) responsible for the tissue destruction in the arthritic condition. Chen et al. (2015) have shown that the geniposide, an iridoid glycoside, inhibits the expression of p38MAPK, decreasing the production of inflammatory mediators and tissue destruction in rats with adjuvant arthritis. These findings could be associated with improvements in the set of symptoms characteristic of the disease.

Evidence points to the up-regulation of COX-2 and iNOS expression as an important factor related to the inflammation process associated with the onset of arthritis (Fan et al., 2015). The expression of these proteins in synoviocytes leads to the production of active prostaglandin (PGE2) and NO, resulting in severe damage in bone and cartilage (Seibert et al., 1994).

Studies have reported the beneficial effect of terpenes in various inflammatory conditions by the attenuation of COX-2 and iNOS activation (Brinker et al., 2007). Lee et al. (2013) demonstrated that the sesquiterpenoid lemnalol, extracted from *Lemnalia tenuis* and *Lemnalia cervicorni* (Jean et al., 2008, Kikuchi et al., 1983), attenuated the MSU-induced up-regulation of iNOS and COX-2 expression in the ankle joint synovium. In this same study profile, Saravannan et al. (2014) described that the oral administration of swertiamarin, an iridoid glycoside, decreased the expression of the proangiogenic enzymes iNOS and COX-2 in a model of rheumatoid arthritis. In addition, swertiamarin downregulated PGE-2 production (Saravanan et al., 2014), leading to a lower inflammatory process and attenuating the bone and cartilage destruction in synovium tissue. PGE-2 are also inhibited by madecassoside, a triterpenoid, attenuating the CIA-induced arthritis (Li et al., 2009).

During inflammation, vascular permeability is increased by the activation of various inflammatory mediators (Loria et al., 2008, Phillipson and Kubes, 2011, Wilhelm, 1973), provoking migration of polymorphonuclear neutrophils to the inflammatory site and, consequently, the enhancement of myeloperoxidase (Butterfield et al., 2006, Selders et al., 2017). Elevated MPO levels have been found in inflamed synovial joints and the pannus in rheumatoid arthritis (Selders et al., 2017), being considered a new biomarker of inflammation in several diseases.

Studies have shown that terpenes play an appreciable role in reduced leukocyte migration and consequently MPO release in inflammatory diseases (Krishnan et al., 2014, Li et al., 2014, Wen et al., 2015). These molecules present an anti-inflammatory profile, reducing the degranulation of neutrophils and the MPO activity. In addition,Lazarević-Pašti, Leskovac and Vasić (2015) suggest that natural products are promising candidates for therapy, because many of them inhibit MPO activity without negative effects on the immune system and with additional benefits to the patient receiving the treatment (Lazarević-Pasti et al., 2015). Tanshinone IIA, a terpene extracted from *Salvia miltiorrhiza*, inhibits neutrophil activation, infiltration and apoptosis, leading to decreased MPO release. In agreement with these findings, another study found reduced tissue damage and joint inflammation in an adjuvant-induced arthritis model (Zhang et al., 2017).

Another class of protein associated to arthritis process that are target of terpenes are the matrix metalloproteinases (MMP). Liu et al (2016) described the inhibition of the expression of MMP3 and MMP13 by the sesquiterpene lactones in the collagen-induced arthritis (CIA). Moreover, Saravannan et al. (2014) reported the involvement of MMP9 in the beneficial effect of swertiamarin in an adjuvant induced arthritis model. These findings indicate that terpene treatment attenuates the arthritic inflammatory response by downregulating the production of proinflammatory factors in inflamed joints. Synovial inflammation and consequently bone destruction are directly related to the production of MMPs by synovial fibroblasts. These metalloproteinases potentiate inflammation and facilitate invasion of the articular cartilage (Itoh, 2015). Moreover, the synthesis and secretion of MMP are trigged by increased c-FOS expression, which provokes arthritic joint destruction (Aikawa et al., 2008, Cheung, 2006, Chu et al., 2004, McCarthy et al., 1998). c-FOS protein is routinely used as an

indicator for neuronal activation and is expressed in different conditions, including in inflammatory and pain conditions (Santos et al., 2017). Studies have reported that rheumatoid arthritis and osteoarthritis patients present up-regulated c-FOS protein expression in the synovial tissue (Cheung, 2006, McCarthy et al., 1998, Trabandt et al., 1992). Furthermore, Kang et al. 2008 observed an increased number of c-FOS positive neurons in the lumbar spinal cord of CFA-induced arthritis rats.

Features characteristic of joint destruction in rheumatic diseases, including synovial overgrowth and bone resorption, are experimentally produced by augmenting c-fos gene expression and its protein products, c-fos (Shiozawa et al., 1997). Several studies indicate that terpenes are able to suppress c-FOS expression in inflammatory and non-inflammatory diseases (Nascimento et al., 2014, Quintans-Júnior et al., 2016, Santos et al., 2017).

Lee et al. (2013) reported that the sesquiterpene lemnalol decreased c-FOS expression in the ankle synovium of MSU induced arthritis rats. In addition, the author suggests that lemnalol blocked the destruction of the joint by modulating the expression of c-fos protein. (Lee et al., 2013). Kang et al. (2008) demonstrated that oral administration of ursolic acid, a natural pentacyclic triterpenoid carboxylic acid, decreased the number of c-FOS positive neurons in the lumbar spinal cord, causing the inhibition of arthritic nociceptive input to the spinal cord. This finding is in agreement with other studies that reported that terpenes have effective action in inhibiting c-FOS protein expression; and it is also associated with the anti-nociceptive effect of this molecule (Quintans-Júnior et al., 2016, Santos et al., 2017). Ma and Jiang (Ma and Jiang, 2016), proposed that terpenes are among the most effective compound groups for the treatment of rheumatoid arthritis in traditional Chinese medicine.

Inhibit tissue destruction and bone changes

Morphological changes and tissue destruction appear with the progression of arthritis. The degree of progressive damage is related to the intensity and duration of inflammation, so suppression of inflammation in the early stages of the disease can result in substantial improvements in long-term outcomes for the joints and other components of the musculoskeletal system (National Institue for Health and Clinical Excellence Guideline, 2009).

In arthritis, changes are characterized by abnormal proliferation of synovium, neovascularization and formation of granulation tissue. During the development of rheumatoid arthritis, the exacerbated inflammatory process leads to destruction of the joints. In experimental models of arthritis, terpenes such as crocin (Li et al., 2017), torilin (Endale et al., 2013), celastrol (Cascão et al., 2012) and others reduced arthritic scores, resulting in reduced bone and cartilaginous degeneration. These results indicate a reduction in cellular infiltrate (Chen et al., 2015, Fukumitsu et al., 2016), inhibition of proliferation of fibroblasts and synovial cells as well as well as the suppression of the production of anti-collagen type II antibodies and a reduction in the formation of osteophytes (Wang et al., 2014).

Regulatory T cells (Tregs) are known for their important role in inducing and maintaining homeostasis of the immune system and in the process of peripheral tolerance. These cells are characterized by expression of the transcription factor Foxp3 that participates in the differentiation and regulation of its suppressor phenotype (Schlieer et al., 2012). It is well established that Foxp3 T cells are attracted to various chemokines and adhesion molecules

expressed in non-lymphoid tissues at inflammatory sites, and can suppress excessive inflammation (Kim, 2006).

Xiong et al (2014), studied the expression of Foxp3 in synovium, and found that expression was higher in rodents induced with AIA when compared to normal controls, suggesting that Foxp3 cells migrated to inflamed joint tissues, which may be necessary to suppress the activation of autoreactive lymphocytes. Animals treated with clematichinenoside, a triterpenoid saponin, decreased expression of Foxp3 and RORγ, which plays an important role for the differentiation of thymocytes in T helper cells 17 (Th17) (Sun et al., 2000).

Limitations of animal models in respect of translational research

Murine arthritis models have been developed with both rats and mice. They have contributed to a better understanding of the disease and its molecular mechanisms and enabled new substances for the treatment of arthritis to be studied. Other species have also been used over the years, however murine models are common because of the cost, and genetic homogeneity. Murine models are also widely used due to the ability to use genetically modified strains (Kannan et al., 2005).

Most arthritis models simulate some pathological features similar to those occurring in human diseases, but there are important differences such as rapid evolution, these models being characterized mainly by an acute inflammatory response (Bendele et al., 1999). Although several experimental models of arthritis have been developed in the last decades for mechanistic studies and validation of therapeutic targets, none of them reflect all the articular, systemic characteristics, immunological profiles and genetic factors typical of arthritis in human (Di Paola and Cuzzocrea, 2008). Thus, the models have been limited to producing localized lesions, or induction by chemical agents or by other types of stress, so proving specific symptoms and not the complex clinical state. Such characteristics limit the translation of the results obtained in these models, due to the lack of homogeneity when compared to the responses in human disease.

The pathology of RA is not confined to the joint and involves complex pathways and multiple tissues. Therefore it is imperative that any animal model chosen for investigation mimics enough of the human condition to be translatable (McNamee et al., 2015). In addition, in human disease protein citrullination and the appearance of rheumatoid factor are important features in the development of RA (Aho et al., 1991, Catrina et al., 2014). However, few models of RA demonstrate the emergence of these characteristics. Thus, investigating events that go beyond the inflammatory process, such as pain and associated comorbidities, reflects a challenge to translate the results of murine models for humans. There are some excellent reviews of the limitations imposed when studying arthritis in animal models, including those published by Bevaart et al., 2010, Moudgil et al., 2011, McNamee et al., 2015 and Choudhary et al. (2018).

Final Considerations

The treatment of arthritis remains a challenge for modern medicine and improving the quality of life of patients with the disease has been a challenge to be overcome by the new therapies. For decades, folk and traditional medicine has used medicinal plants rich in terpenes for the treatment of inflammatory conditions that affect the joints, cartilage and bone. Moreover, there has been a great deal of research studying the effects of different terpenes on modulating

the arthritis process, showing the beneficial effects of this family of molecules in the prevention of the symptoms of arthritis or mitigating inflammatory pathways that influence the establishment or evolution of this rheumatic disease.

In this review, we summarized the current knowledge on terpenes that present anti-arthritic profiles which are able to modulate the immune-regulatory and tissue-destructive events that underlie the clinical presentation and progression of arthritic diseases. Further, this review suggests which terpenoid molecules are most important in terms of an effective approach to treating this inflammatory disease.

This review described 23 terpenes (Fig. 3) that possess anti-arthritic profiles which modulate cytokine release or alter inflammatory mediators and signaling pathway, provoking suppression of bone or cartilage destruction. Several different inflammatory markers associated with arthritis pathology were evaluated as a target of terpenes across the studies included within the review. The proinflammatory and anti-inflammatory cytokines found were TNF (α and β), IL-1, IL-1β, IL-6, IL-17, IL-4, IL-10, TGF-β1, and IFN-γ. In addition, the most important inflammatory enzymes, inflammatory mediators or proteins found were RANKL, NFKB, MAPK family, COX-2, iNOS, PGE-2, MPP, MPO, c-FOS, Foxp3 and RORγ. The modulation of these molecules blocks morphological changes and tissue destruction, inhibiting progression of arthritis. Suppression of inflammation in the disease can result in substantial improvements in long-term outcomes for the joints and other components of the musculoskeletal system.

According to current the European League Against Rheumatism (EULAR) criteria, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) are used for RA diagnosis (Gavrilă et al., 2016). However, these biomarkers are relatively unexplored by animal studies. The experimental limitations of the animal models used in the studies in this review, and generally not described in the articles, need to be overcome in order to develop new drug proposals.

The common major pharmacological profile of these 23 terpenes is their ability to modulate inflammatory response in joints, attenuate tissue destruction and minimize arthritis symptoms, such as inflammation, swelling, pain and radiological changes. Despite the compelling evidence of the substantial anti-arthritic effects of terpenes, and their lack of potential toxicity, clinical studies are necessary to properly determine the use of these terpenes as new drugs in the treatment of arthritis.

Declaration of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Acknowledgements

This study was financed in part by the Conselho Conselho Nacional de Desenvolvimento Científico e Tecnológico – Brasil (CNPq), the Fundação de Apoio à Pesquisa e a Inovação Tecnológica do Estado de Sergipe (Fapitec/SE) - Brasil, the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES - Finance Code 001), and the Financiadora de Estudos e Projetos - Brasil (FINEP). The author A.M.S.C. is currently Master

student of the Post-Graduate Program in Health Science of the Federal University of Sergipe, Brazil.

References

Aho, K., Heliovaara, M., Maatela, J., Tuomi, T., Palosuo, T., 1991. Rheumatoid factors antedating clinical rheumatoid arthritis. J. Rheumatol.

Aikawa, Y., Morimoto, K., Yamamoto, T., Chaki, H., Hashiramoto, A., Narita, H., Hirono, S., Shiozawa, S., 2008. Treatment of arthritis with a selective inhibitor of c-Fos/activator protein-1. Nat. Biotechnol. 26, 817–823. https://doi.org/10.1038/nbt1412

Alghasham, A., Rasheed, Z., 2014. Therapeutic targets for rheumatoid arthritis: Progress and promises. Autoimmunity. https://doi.org/10.3109/08916934.2013.873413

American College of Rheumatology Pain Management Task Force, 2010. Report of the American College of Rheumatology Pain Management Task Force. Arthritis Care Res. (Hoboken). 62, 590–599. https://doi.org/10.1002/acr.20005

Barreto, R.S.S., Quintans, J.S.S., Amarante, R.S.R.K.L., Nascimento, T.S., Amarante, R.S.R.K.L., Barreto, A.S., Pereira, E.W.M., Duarte, M.C., Coutinho, H.D.M., Menezes, I.R.A., Zengin, G., Aktumsek, A., Quintans-Júnior, L.J., 2016. Evidence for the involvement of TNF-α and IL-1β in the antinociceptive and anti-inflammatory activity of Stachys lavandulifolia Vahl. (Lamiaceae) essential oil and (-)-α-bisabolol, its main compound, in mice. J. Ethnopharmacol. 191, 9–18. https://doi.org/10.1016/j.jep.2016.06.022

Bendele, A., McComb, J., Gould, T., McAbee, T., Sennello, G., Chlipala, E., Guy, M., 1999. Animal models of arthritis: relevance to human disease. Toxicol. Pathol. https://doi.org/10.1007/s11882-004-0018-0

Bevaart, L., Vervoordeldonk, M.J., Tak, P.P., 2010. Evaluation of therapeutic targets in animal models of arthritis: How does it relate to rheumatoid arthritis? Arthritis Rheum. https://doi.org/10.1002/art.27503

Bogdan, C., 2001. Nitric oxide and the immune response. Nat. Immunol. https://doi.org/10.1038/ni1001-907

Brinker, A.M., Ma, J., Lipsky, P.E., Raskin, I., 2007. Medicinal chemistry and pharmacology of genus Tripterygium (Celastraceae). Phytochemistry. https://doi.org/10.1016/j.phytochem.2006.11.029

Brito, R.G., Araújo, A.A., Quintans, J.S., Sluka, K.A., Quintans-Júnior, L.J., 2015. Enhanced analgesic activity by cyclodextrins – a systematic review and meta-analysis. Expert Opin. Drug Deliv. https://doi.org/10.1517/17425247.2015.1046835

Butterfield, T.A., Best, T.M., Merrick, M.A., 2006. The dual roles of neutrophils and macrophages in inflammation: A critical balance between tissue damage and repair. J. Athl. Train. https://doi.org/10.1016/S0162-0908(08)79217-1

Cascão, R., Vidal, B., Raquel, H., Neves-Costa, A., Figueiredo, N., Gupta, V., Fonseca, J.E., Moita, L.F., 2012. Effective treatment of rat adjuvant-induced arthritis by celastrol. Autoimmun. Rev. 11, 856–862. https://doi.org/10.1016/j.autrev.2012.02.022

Casey, G., 2015. Arthritis: joints inflamed. Nurs. N. Z. 21, 20–4.

Catrina, A.I., Jimmy Ytterberg, A., Reynisdottir, G., Malmström, V., Klareskog, L., 2014. Lungs, joints and immunity against citrullinated proteins in rheumatoid arthritis. Nat. Rev. Rheumatol. https://doi.org/10.1038/nrrheum.2014.115

Chen, J.Y., Wu, H., Li, H., Hu, S.L., Dai, M.M., Chen, J., 2015. Anti-inflammatory effects and pharmacokinetics study of geniposide on rats with adjuvant arthritis. Int. Immunopharmacol. 24, 102–109. https://doi.org/10.1016/j.intimp.2014.11.017

Chen, L., Lan, Z., Ma, S., Zhao, L., Yang, X., 2013. Attenuation of gouty arthritis by emodinol in monosodium urate crystal-treated mice. Planta Med. 79, 634–638. https://doi.org/10.1055/s-0032-1328430

Cheung, H.S., 2006. Crystal/cell interactions in osteoarthritis. Curr. Opin. Orthop. 17, 424–428. https://doi.org/10.1097/01.bco.0000244033.09671.38

Chong, H., Vikis, H.G., Guan, K.-L., 2003. Mechanisms of regulating the Raf kinase family. Cell. Signal. https://doi.org/10.1016/S0898-6568(02)00139-0

Choudhary, N., Bhatt, L.K., Prabhavalkar, K.S., 2018. Experimental animal models for rheumatoid arthritis. Immunopharmacol. Immunotoxicol. 40, 193–200. https://doi.org/10.1080/08923973.2018.1434793

Chu, S.-C., Yang, S.-F., Lue, K.-H., Hsieh, Y.-S., Hsiao, T.-Y., Lu, K.-H., 2004. The clinical significance of gelatinase B in gouty arthritis of the knee. Clin. Chim. Acta. 339, 77–83.

Darlington, L.G., Stone, T.W., 2001. Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. Br. J. Nutr. https://doi.org/10.1079/BJN2000239

Darnay, B.G., Ni, J., Moore, P.A., Aggarwal, B.B., 1999. Activation of NF-kappaB by RANK requires tumor necrosis factor receptor-associated factor (TRAF) 6 and NF-kappaB-inducing kinase. Identification of a novel TRAF6 interaction motif. J. Biol. Chem. 274, 7724–31.

de Santana Souza, M.T., Almeida, J.R.G. da S., de Souza Araujo, A.A., Duarte, M.C., Gelain, D.P., Moreira, J.C.F., dos Santos, M.R.V., Quintans-Júnior, L.J., 2014. Structure-Activity Relationship of Terpenes with Anti-Inflammatory Profile - A Systematic Review. Basic Clin. Pharmacol. Toxicol. 115, 244–256. https://doi.org/10.1111/bcpt.12221

Desai, R.J., Rao, J.K., Hansen, R.A., Fang, G., Maciejewski, M.L., Farley, J.F., 2014. Predictors of treatment initiation with tumor necrosis factor-α inhibitors in patients with rheumatoid arthritis. J. Manag. Care Pharm.

Di Paola, R., Cuzzocrea, S., 2008. Predictivity and sensitivity of animal models of arthritis. Autoimmun. Rev. https://doi.org/10.1016/j.autrev.2008.07.029

Dinarello, C.A., 2000. Proinflammatory cytokines. Chest. https://doi.org/10.1177/0149206309356804

Dutra, R.C., Simão Da Silva, K.A.B., Bento, A.F., Marcon, R., Paszcuk, A.F., Meotti, F.C., Pianowski, L.F., Calixto, J.B., 2012. Euphol, a tetracyclic triterpene produces antinociceptive effects in inflammatory and neuropathic pain: The involvement of cannabinoid system. Neuropharmacology 63, 593–605. https://doi.org/10.1016/j.neuropharm.2012.05.008

Endale, M., Lee, W.M., Kwak, Y.S., Kim, N.M., Kim, B.K., Kim, S.H., Cho, J., Kim, S., Park, S.C., Yun, B.S., Ko, D., Rhee, M., 2013. Torilin ameliorates type II collagen-induced arthritis in mouse model of rheumatoid arthritis. Int. Immunopharmacol. 16, 232–242. https://doi.org/10.1016/j.intimp.2013.04.012

Fan, H.W., Liu, G.Y., Zhao, C.F., Li, X.F., Yang, X.Y., 2015. Differential expression of COX-2 in osteoarthritis and rheumatoid arthritis. Genet. Mol. Res. https://doi.org/10.4238/2015.October.21.7

Feldmann, M., 2008. Many cytokines are very useful therapeutic targets in disease. J. Clin. Invest. https://doi.org/10.1172/JCI37346

Feng, Z., Li, X., Lin, J., Zheng, W., Hu, Z., Xuan, J., Ni, W., Pan, X., 2017. Oleuropein inhibits the IL-1β-induced expression of inflammatory mediators by suppressing the activation of NF-κB and MAPKs in human osteoarthritis chondrocytes. Food Funct. https://doi.org/10.1039/C7FO00823F

Figueiredo, C., Barroso, J., Pedro, L., Scheefeer, J., 2007. Factors affecting secondary metabolite production in plants: volatile components and essential oils. Flavour Fragr. J. https://doi.org/10.1002/ffj

Firestein, G.S., 2003. Evolving concepts of rheumatoid arthritis. Nature 423, 356–361. https://doi.org/10.1038/nature01661

Fukumitsu, S., Villareal, M.O., Fujitsuka, T., Aida, K., Isoda, H., 2016. Anti-inflammatory and anti-arthritic effects of pentacyclic triterpenoids maslinic acid through NF-κB inactivation. Mol. Nutr. Food Res. 60, 399–409. https://doi.org/10.1002/mnfr.201500465

Gabay, C., 2002. Cytokine inhibitors in the treatment of rheumatoid arthritis. Expert Opin. Biol. Ther. 2, 135–149. https://doi.org/10.1517/14712598.2.2.135

Gavrilă, B.I., Ciofu, C., Stoica, V., 2016. Biomarkers in Rheumatoid Arthritis, what is new? J. Med. Life.

Genovese, M.C., McKay, J.D., Nasonov, E.L., Mysler, E.F., Da Silva, N. a., Alecock, E., Woodworth, T., Gomez-Reino, J.J., 2008. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug the. Arthritis Rheum. https://doi.org/10.1002/art.23940

Gilston, V., Jones, H.W., Soo, C.C., Coumbe, A., Blades, S., Kaltschmidt, C., Baeuerle, P.A., Morris, C.J., Blake, D.R., Winyard, P.G., 1997. NF-kappa B activation in human knee-joint synovial tissue during the early stage of joint inflammation. Biochem. Soc. Trans. 25, 518S.

Görtz, B., Hayer, S., Tuerck, B., Zwerina, J., Smolen, J.S., Schett, G., 2005. Tumour necrosis factor activates the mitogen-activated protein kinases p38alpha and ERK in the synovial membrane in vivo. Arthritis Res. Ther. 7, R1140. https://doi.org/10.1186/ar1797

Gouveia, D.N., Pina, L.T.S., Rabelo, T.K., da Rocha Santos, W.B., Quintans, J.S.S., Guimaraes, A.G., 2018. Monoterpenes as Perspective to Chronic Pain Management: A Systematic Review. Curr. Drug Targets 19, 960–972. https://doi.org/10.2174/1389450118666170711145308

Guimarães, A.G., Quintans, J.S.S., Quintans-Júnior, L.J., 2013. Monoterpenes with analgesic

activity - A systematic review. Phyther. Res. https://doi.org/10.1002/ptr.4686

Guimarães, A.G., Serafini, M.R., Quintans-Júnior, L.J., 2014. Terpenes and derivatives as a new perspective for pain treatment: a patent review. Expert Opin. Ther. Pat. 24, 243–65. https://doi.org/10.1517/13543776.2014.870154

Han, Z., Boyle, D.L., Manning, a M., Firestein, G.S., 1998. AP-1 and NF-kappaB regulation in rheumatoid arthritis and murine collagen-induced arthritis. Autoimmunity. https://doi.org/10.3109/08916939808995367

Hazes, J.M.W., Luime, J.J., 2011. The epidemiology of early inflammatory arthritis. Nat. Rev. Rheumatol. 7, 381–390. https://doi.org/10.1038/nrrheum.2011.78

Heiberg, T., Finset, A., Uhlig, T., Kvien, T.K., 2005. Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. Ann. Rheum. Dis. https://doi.org/10.1136/ard.2004.022699

Hopson, S., Saverno, K., Liu, L.Z., AL-Sabbagh, A., Orazem, J., Costantino, M.E., Pasquale, M.K., 2016. Impact of Out-of-Pocket Costs on Prescription Fills Among New Initiators of Biologic Therapies for Rheumatoid Arthritis. J. Manag. Care Spec. Pharm. https://doi.org/10.18553/jmcp.2016.14261

Huang, M., Lu, J.-J., Huang, M.-Q., Bao, J.-L., Chen, X.-P., Wang, Y.-T., 2012. Terpenoids: natural products for cancer therapy. Expert Opin. Investig. Drugs. https://doi.org/10.1517/13543784.2012.727395

Itoh, Y., 2015. Metalloproteinases: potential therapeutic targets for rheumatoid arthritis. Endocr. Metab. Immune Disord. Drug Targets.

Jean, Y.H., Chen, W.F., Duh, C.Y., Huang, S.Y., Hsu, C.H., Lin, C.S., Sung, C.S., Chen, I.M., Wen, Z.H., 2008. Inducible nitric oxide synthase and cyclooxygenase-2 participate in anti-inflammatory and analgesic effects of the natural marine compound lemnalol from Formosan soft coral Lemnalia cervicorni. Eur. J. Pharmacol. https://doi.org/10.1016/j.ejphar.2007.08.048

Kang, S.-Y., Yoon, S.-Y., Roh, D.-H., Jeon, M.-J., Seo, H.-S., Uh, D.-K., Kwon, Y.-B., Kim, H.-W., Han, H.-J., Lee, H.-J., Lee, J.-H., 2008. The anti-arthritic effect of ursolic acid on zymosan-induced acute inflammation and adjuvant-induced chronic arthritis models. J. Pharm. Pharmacol. 60, 1347–1354. https://doi.org/10.1211/jpp/60.10.0011

Kannan, K., Ortmann, R.A., Kimpel, D., 2005. Animal models of rheumatoid arthritis and their relevance to human disease. Pathophysiology 12, 167–81. https://doi.org/10.1016/j.pathophys.2005.07.011

Kashyap, D., Sharma, A., Tuli, H.S., Punia, S., Sharma, A.K., 2016. Ursolic Acid and Oleanolic Acid: Pentacyclic Terpenoids with Promising Anti-Inflammatory Activities. Recent Pat. Inflamm. Allergy Drug Discov. https://doi.org/10.2174/1872213x10666160711143904

Khalifé, S., Zafarullah, M., 2011. Molecular targets of natural health products in arthritis. Arthritis Res. Ther. 13, 102. https://doi.org/10.1186/ar3222

Kikuchi, H., Manda, T., Kobayashi, K., Yamada, Y., Iguchi, K., 1983. Anti-tumor activity of lemnalol isolated from the soft coral Lemnalia tenuis Verseveldt. Chem. Pharm. Bull. (Tokyo). 31, 1086–8.

Kim, C.H., 2006. Migration and function of FoxP3+ regulatory T cells in the hematolymphoid system. Exp. Hematol. https://doi.org/10.1016/j.exphem.2006.03.014

Kirkham, B.W., Lassere, M.N., Edmonds, J.P., Juhasz, K.M., Bird, P.A., Lee, C.S., Shnier, R., Portek, I.J., 2006. Synovial membrane cytokine expression is predictive of joint damage progression in rheumatoid arthritis: a two-year prospective study (the DAMAGE study cohort). Arthritis Rheum. 54, 1122–31. https://doi.org/10.1002/art.21749

Klareskog, L., Padyukov, L., Lorentzen, J., Alfredsson, L., 2006. Mechanisms of disease: Genetic susceptibility and environmental triggers in the development of rheumatoid arthritis. Nat. Clin. Pract. Rheumatol. 2, 425–433. https://doi.org/10.1038/ncprheum0249

Krishnan, K., Mathew, L.E., Vijayalakshmi, N.R., Helen, A., 2014. Anti-inflammatory potential of β-amyrin, a triterpenoid isolated from Costus igneus. Inflammopharmacology. https://doi.org/10.1007/s10787-014-0218-8

Lazarević-Pasti, T., Leskovac, A., Vasić, V., 2015. Myeloperoxidase Inhibitors as Potential Drugs. Curr. Drug Metab. https://doi.org/10.2174/1389200216031508121206 40

Lee, H.P., Huang, S.Y., Lin, Y.Y., Wang, H.M., Jean, Y.H., Wu, S.F., Duh, C.Y., Wen, Z.H., 2013. Soft coral-derived lemnalol alleviates monosodium urate-induced gouty arthritis in rats by inhibiting leukocyte infiltration and iNOS, COX-2 and c-Fos protein expression. Mar. Drugs 11, 99–113. https://doi.org/10.3390/md11010099

Lee, J., Baek, S., Lee, J., Lee, J., Lee, D.G., Park, M.K., Cho, M. La, Park, S.H., Kwok, S.K., 2015. Digoxin ameliorates autoimmune arthritis via suppression of Th17 differentiation. Int. Immunopharmacol. 26, 103–111. https://doi.org/10.1016/j.intimp.2015.03.017

Lee, J.C., Laydon, J.T., McDonnell, P.C., Gallagher, T.F., Kumar, S., Green, D., McNulty, D., Blumenthal, M.J., Heys, J.R., Landvatter, S.W., 1994. A protein kinase involved in the regulation of inflammatory cytokine biosynthesis. Nature. https://doi.org/10.1038/372739a0

Lee, Y.C., 2013. Effect and treatment of chronic pain in inflammatory arthritis. Curr. Rheumatol. Rep. 15, 300. https://doi.org/10.1007/s11926-012-0300-4

Leung, Y.Y., Huebner, J.L., Haaland, B., Wong, S.B.S., Kraus, V.B., 2017. Synovial fluid pro-inflammatory profile differs according to the characteristics of knee pain. Osteoarthr. Cartil. https://doi.org/10.1016/j.joca.2017.04.001

Li, H., Gong, X., Zhang, L., Zhang, Z., Luo, F., Zhou, Q., Chen, J., Wan, J., 2009. Madecassoside attenuates inflammatory response on collagen-induced arthritis in DBA/1 mice. Phytomedicine 16, 538–546. https://doi.org/10.1016/j.phymed.2008.11.002

Li, J., Zhang, X., Huang, H., 2014. Protective effect of linalool against lipopolysaccharide/d-galactosamine-induced liver injury in mice. Int. Immunopharmacol. https://doi.org/10.1016/j.intimp.2014.10.001

Li, X., Jiang, C., Zhu, W., 2017. Crocin reduces the inflammation response in rheumatoid arthritis. Biosci. Biotechnol. Biochem. 81, 891–898. https://doi.org/10.1080/09168451.2016.1263145

Lima, M.D.S., Quintans-Júnior, L.J., De Santana, W.A., Martins Kaneto, C., Pereira Soares, M.B., Villarreal, C.F., 2013. Anti-inflammatory effects of carvacrol: Evidence for a key role of interleukin-10. Eur. J. Pharmacol. 699. https://doi.org/10.1016/j.ejphar.2012.11.040

Liu, L., Hua, Y., Wang, D., Shan, L., Zhang, Y., Zhu, J., Jin, H., Li, H., Hu, Z., Zhang, W., 2014. A Sesquiterpene Lactone from a Medicinal Herb Inhibits Proinflammatory Activity of TNF-α by Inhibiting Ubiquitin-Conjugating Enzyme UbcH5. Chem. Biol. 21, 1341–1350. https://doi.org/10.1016/j.chembiol.2014.07.021

Liu, Q., Zhao, J., Tan, R., Zhou, H., Lin, Z., Zheng, M., Romas, E., Xu, J., Sims, N.A., 2015. Parthenolide inhibits pro-inflammatory cytokine production and exhibits protective effects on progression of collagen-induced arthritis in a rat model. Scand. J. Rheumatol. 44, 182–191. https://doi.org/10.3109/03009742.2014.938113

Loria, V., Dato, I., Graziani, F., Biasucci, L.M., 2008. Myeloperoxidase: A new biomarker of inflammation in ischemic heart disease and acute coronary syndromes. Mediators Inflamm. https://doi.org/10.1155/2008/135625

Lu, Y., Xiao, J., Wu, Z.W., Wang, Z.M., Hu, J., Fu, H.Z., Chen, Y.Y., Qian, R.Q., 2012. Kirenol exerts a potent anti-arthritic effect in collagen-induced arthritis by modifying the T cells balance. Phytomedicine 19, 882–889. https://doi.org/10.1016/j.phymed.2012.04.010

Lubberts, E., Koenders, M.I., Oppers-Walgreen, B., Van Den Bersselaar, L., Coenen-De Roo, C.J.J., Joosten, L.A.B., Van Den Berg, W.B., 2004. Treatment with a Neutralizing Anti-Murine Interleukin-17 Antibody after the Onset of Collagen-Induced Arthritis Reduces Joint Inflammation, Cartilage Destruction, and Bone Erosion. Arthritis Rheum. https://doi.org/10.1002/art.20001

Lv, Y., Zhang, L., Li, N., Mai, N., Zhang, Y., Pan, S., 2017. Geraniol promotes functional recovery and attenuates neuropathic pain in rats with spinal cord injury. Can. J. Physiol. Pharmacol. 95, 1389–1395. https://doi.org/10.1139/cjpp-2016-0528

Ma, Q., Jiang, J.-G., 2016. Functional Components from Nature-Derived Drugs for the Treatment of Rheumatoid Arthritis. Curr. Drug Targets 17, 1673–1686. https://doi.org/10.2174/1389450117666616052712

Ma, X., Liu, Y., Zhang, Y., Yu, X., Wang, W., Zhao, D., 2014. Jolkinolide B inhibits RANKL-induced osteoclastogenesis by suppressing the activation NF-κB and MAPK signaling pathways. Biochem. Biophys. Res. Commun. https://doi.org/10.1016/j.bbrc.2014.01.145

Makarov, S.S., 2001. NF-??B in rheumatoid arthritis: A pivotal regulator of inflammation, hyperplasia, and tissue destruction. Arthritis Res. https://doi.org/10.1186/ar300

McCarthy, G.M., Augustine, J.A., Baldwin, A.S., Christopherson, P.A., Cheung, H.S., Westfall, P.R., Scheinman, R.I., 1998. Molecular mechanism of basic calcium phosphate crystal-induced activation of human fibroblasts. Role of nuclear factor kappab, activator protein 1, and protein kinase c. J. Biol. Chem. 273, 35161–9.

McInnes, I.B., Schett, G., 2007. Cytokines in the pathogenesis of rheumatoid arthritis. Nat. Rev. Immunol. https://doi.org/10.1038/nri2094

McNamee, K., Williams, R., Seed, M., 2015. Animal models of rheumatoid arthritis: How informative are they? Eur. J. Pharmacol. https://doi.org/10.1016/j.ejphar.2015.03.047

Miossec, P., 2003. Interleukin-17 in rheumatoid arthritis: If T cells were to contribute to inflammation and destruction through synergy. Arthritis Rheum. https://doi.org/10.1002/art.10816

Moudgil, K.D., Kim, P., Brahn, E., 2011. Advances in rheumatoid arthritis animal models. Curr. Rheumatol. Rep. 13, 456–463. https://doi.org/10.1007/s11926-011-0200-z

Nanjundaiah, S.M., Venkatesha, S.H., Yu, H., Tong, L., Stains, J.P., Moudgil, K.D., 2012. Celastrus and its bioactive celastrol protect against bone damage in autoimmune arthritis by modulating osteoimmune cross-talk. J. Biol. Chem. 287, 22216–22226. https://doi.org/10.1074/jbc.M112.356816

Nascimento, S.S., Camargo, E.A., Desantana, J.M., Araújo, A.A.S., Menezes, P.P., Lucca-Júnior, W., Albuquerque-Júnior, R.L.C., Bonjardim, L.R., Quintans-Júnior, L.J., 2014. Linalool and linalool complexed in β-cyclodextrin produce anti-hyperalgesic activity and increase Fos protein expression in animal model for fibromyalgia. Naunyn. Schmiedebergs. Arch. Pharmacol. 387, 935–942. https://doi.org/10.1007/s00210-014-1007-z

National Institue for Health and Clinical Excellence Guideline, 2009. No Title, Rheumatoid Arthritis: National Clinical Guideline for Management and Treatment in Adults.

O'Neill, E., Kolch, W., 2004. Conferring specificity on the ubiquitous Raf/MEK signalling pathway. Br. J. Cancer 90, 283–8. https://doi.org/10.1038/sj.bjc.6601488

Pae, H.-O., Jeong, G.-S., Kim, H.-S., Woo, W.H., Rhew, H.Y., Kim, H.S., Sohn, D.H., Kim, Y.-C., Chung, H.-T., 2007. Costunolide inhibits production of tumor necrosis factor-alpha and interleukin-6 by inducing heme oxygenase-1 in RAW264.7 macrophages. Inflamm. Res. https://doi.org/10.1007/s00011-007-7015-4

Paleolog, E.M., 2002. Angiogenesis in rheumatoid arthritis. Arthritis Res. 4, S81. https://doi.org/10.1186/ar575

Pan, R., Dai, Y., Gao, X., Xia, Y., 2009. Scopolin isolated from Erycibe obtusifolia Benth stems suppresses adjuvant-induced rat arthritis by inhibiting inflammation and angiogenesis. Int. Immunopharmacol. https://doi.org/10.1016/j.intimp.2009.02.019

Phillipson, M., Kubes, P., 2011. The neutrophil in vascular inflammation. Nat. Med. https://doi.org/10.1038/nm.2514

Piccinelli, A.C., Santos, J.A., Konkiewitz, E.C., Oesterreich, S.A., Formagio, A.S.N., Croda, J., Ziff, E.B., Kassuya, C.A.L., 2015. Antihyperalgesic and antidepressive actions of (R)-(+)-limonene, α-phellandrene, and essential oil from Schinus terebinthifolius fruits in a neuropathic pain model. Nutr. Neurosci. 18, 217–224. https://doi.org/10.1179/1476830514Y.0000000119

Quintans-Júnior, L.J., Araújo, A.A.S.S., Brito, R.G., Santos, P.L., Quintans, J.S.S.S., Menezes, P.P., Serafini, M.R., Silva, G.F., Carvalho, F.M.S.S., Brogden, N.K., Sluka, K.A., 2016. β-caryophyllene, a dietary cannabinoid, complexed with β-cyclodextrin produced anti-hyperalgesic effect involving the inhibition of Fos expression in superficial dorsal horn, Life Sciences. Elsevier B.V. https://doi.org/10.1016/j.lfs.2016.02.049

Quintans Júnior, L.J., Santana, M.T., Melo, M.S., de Sousa, D.P., Santos, I.S., Siqueira, R.S., Lima, T.C., Silveira, G.O., Antoniolli, A.R., Ribeiro, L. a a, Santos, M.R. V, 2010. Antinociceptive and anti-inflammatory effects of Costus spicatus in experimental animals. Pharm. Biol. 48, 1097–1102. https://doi.org/10.3109/13880200903501822

Riaz, N., Anis, I., Aziz-Ur-Rehman, Malik, A., Ahmed, Z., Muhammad, P., Shujaat, S., Atta-

Ur-Rahman, 2003. Emodinol, β-glucuronidase inhibiting triterpene from Paeonia emodi. Nat. Prod. Res. https://doi.org/10.1080/1057563021000060103

Rocha, N.F.M., Rios, E.R.V., Carvalho, A.M.R., Cerqueira, G.S., Lopes, A.D.A., Leal, L.K.A.M., Dias, M.L., De Sousa, D.P., De Sousa, F.C.F., 2011. Anti-nociceptive and anti-inflammatory activities of (-)-α-bisabolol in rodents. Naunyn. Schmiedebergs. Arch. Pharmacol. 384, 525–533. https://doi.org/10.1007/s00210-011-0679-x

Röhner, E., Matziolis, G., Perka, C., Füchtmeier, B., Gaber, T., Burmester, G.R., Buttgereit, F., Hoff, P., 2012. Inflammatory synovial fluid microenvironment drives primary human chondrocytes to actively take part in inflammatory joint diseases. Immunol. Res. https://doi.org/10.1007/s12026-011-8247-5

Salinas-Sánchez, D.O., Zamilpa, A., Pérez, S., Herrera-Ruiz, M., Tortoriello, J., González-Cortazar, M., Jiménez-Ferrer, E., 2015. Effect of Hautriwaic Acid Isolated from Dodonaea viscosa in a Model of Kaolin/Carrageenan-Induced Monoarthritis. Planta Med. 81, 1240–1247. https://doi.org/10.1055/s-0035-1546197

Sánchez-Fidalgo, S., Villegas, I., Rosillo, M.Á., Aparicio-Soto, M., de la Lastra, C.A., 2015. Dietary squalene supplementation improves DSS-induced acute colitis by downregulating p38 MAPK and NFkB signaling pathways. Mol. Nutr. Food Res. https://doi.org/10.1002/mnfr.201400518

Santos, P.L., Brito, R.G., Matos, J.P.S.C.F., Quintans, J.S.S., Quintans-Júnior, L.J., 2017. Fos Protein as a Marker of Neuronal Activity: a Useful Tool in the Study of the Mechanism of Action of Natural Products with Analgesic Activity. Mol. Neurobiol. https://doi.org/10.1007/s12035-017-0658-4

Saravanan, S., Hairul Islam, V.I.I., Prakash Babu, N., Pandikumar, P., Thirugnanasambantham, K., Chellappandian, M., Simon Durai Raj, C., Gabriel Paulraj, M., Ignacimuthu, S., 2014. Swertiamarin attenuates inflammation mediators via modulating NF-κB/I κb and JAK2/STAT3 transcription factors in adjuvant induced arthritis. Eur. J. Pharm. Sci. 56, 70–86. https://doi.org/10.1016/j.ejps.2014.02.005

Sarmento-Neto, J.F., Do Nascimento, L.G., Felipe, C.F.B., De Sousa, D.P., 2016. Analgesic potential of essential oils. Molecules. https://doi.org/10.3390/molecules21010020

Schlieer, U., Streitz, M., Sawitzki, B., 2012. Tregs. Curr. Opin. Organ Transplant. https://doi.org/10.1097/MOT.0b013e32834ee69f

Seibert, K., Zhang, Y., Leahy, K., Hauser, S., Masferrer, J., Perkins, W., Lee, L., Isakson, P., 1994. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.91.25.12013

Selders, G.S., Fetz, A.E., Radic, M.Z., Bowlin, G.L., 2017. An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration. Regen. Biomater. https://doi.org/10.1093/rb/rbw041

Shiozawa, S., Shimizu, K., Tanaka, K., Hino, K., 1997. Studies on the Contribution of c-fos/AP-1 to Arthritic Joint Destruction, J. Clin. Invest.

Siebert, S., Tsoukas, A., Robertson, J., McInnes, I., 2015. Cytokines as Therapeutic Targets in Rheumatoid Arthritis and Other Inflammatory Diseases. Pharmacol. Rev. 67, 280–309. https://doi.org/10.1124/pr.114.009639

Singh, J.A., Christensen, R., Wells, G.A., Suarez-Almazor, M.E., Buchbinder, R., Lopez-Olivo, M.A., Ghogomu, E.T., Tugwell, P., 2010. Biologics for rheumatoid arthritis: An overview of Cochrane reviews. Sao Paulo Med. J. https://doi.org/10.1590/S1516-31802010000500013

Snelling, S.J.B., Bas, S., Puskas, G.J., Dakin, S.G., Suva, D., Finckh, A., Gabay, C., Hoffmeyer, P., Carr, A.J., Lübbeke, A., 2017. Presence of IL-17 in synovial fluid identifies a potential inflammatory osteoarthritic phenotype. PLoS One. https://doi.org/10.1371/journal.pone.0175109

Stolina, M., Schett, G., Dwyer, D., Vonderfecht, S., Middleton, S., Duryea, D., Pacheco, E., Van, G., Bolon, B., Feige, U., Zack, D., Kostenuik, P., 2009. RANKL inhibition by osteoprotegerin prevents bone loss without affecting local or systemic inflammation parameters in two rat arthritis models: comparison with anti-TNFα or anti-IL-1 therapies. Arthritis Res. Ther. 11, R187. https://doi.org/10.1186/ar2879

Sullivan, S.D., 2008. The promise of specialty pharmaceuticals: are they worth the price? J. Manag. Care Pharm.

Sun, Z., Unutmaz, D., Zou, Y.R., Sunshine, M.J., Pierani, A., Brenner-Morton, S., Mebius, R.E., Littman, D.R., 2000. Requirement for RORγ in thymocyte survival and lymphoid organ development. Science (80-.). https://doi.org/10.1126/science.288.5475.2369

Thompson, R.Q., 2005. Encyclopedia of Analytical Science, Second Edition (Worsfold, Paul; Tonshend, Alan; Poole, Colin), in: Journal of Chemical Education. Division of Chemical Education, p. 1313. https://doi.org/10.1021/ed082p1313.2

Trabandt, A., Gay, R.E., Birkedal-Hansen, H., Gay, S., 1992. Expression of collagenase and potential transcriptional factors in the MRL/l mouse arthropathy. Semin. Arthritis Rheum. 21, 246–51.

Trayes, K.P., Studdiford, J.S., Pickle, S., Tully, A.S., 2013. Edema: Diagnosis and management. Am. Fam. Physician 88, 102–110.

Van Campenhout, A., Golledge, J., 2009. Osteoprotegerin, vascular calcification and atherosclerosis. Atherosclerosis 204, 321–329. https://doi.org/10.1016/j.atherosclerosis.2008.09.033

van Roon, J., Wijngaarden, S., Lafeber, F.P.J.G., Damen, C., van de Winkel, J., Bijlsma, J.W.J., 2003. Interleukin 10 treatment of patients with rheumatoid arthritis enhances Fc gamma receptor expression on monocytes and responsiveness to immune complex stimulation. J. Rheumatol.

Vincent, T.L., Williams, R.O., Maciewicz, R., Silman, A., Garside, P., Bevan, S., Chanalaris, A., Chapman, V., Cope, A., Cruwys, S., Dell'Accio, F., Gaskin, P., Gilroy, D., Glasson, S., Hegen, M., McDougall, J., Moore, A., du Sert, N.P., Perretti, M., Pitsillides, A., Robinson, V., Seed, M., Thompson, S., Walsh, D.A., Williams, N., 2012. Mapping pathogenesis of arthritis through small animal models. Rheumatol. (United Kingdom). https://doi.org/10.1093/rheumatology/kes035

Wang, J.P., Zhou, Y.M., Ye, Y.J., Shang, X.M., Cai, Y.L., Xiong, C.M., Wu, Y.X., Xu, H.X., 2011. Topical anti-inflammatory and analgesic activity of kirenol isolated from Siegesbeckia orientalis. J. Ethnopharmacol. 137, 1089–1094. https://doi.org/10.1016/j.jep.2011.07.016

Wang, Q., Pan, X., Wong, H.H., Wagner, C.A., Lahey, L.J., Robinson, W.H., Sokolove, J., 2014. Oral and topical boswellic acid attenuates mouse osteoarthritis. Osteoarthr. Cartil. 22, 128–132. https://doi.org/10.1016/j.joca.2013.10.012

Wang, S., Wang, Y., Liu, X., Guan, L., Yu, L., Zhang, X., 2016. Anti-inflammatory and anti-arthritic effects of taraxasterol on adjuvant-induced arthritis in rats. J. Ethnopharmacol. 187, 42–48. https://doi.org/10.1016/j.jep.2016.04.031

Wang, Z.M., Zhu, S.G., Wu, Z.W., Lu, Y., Fu, H.Z., Qian, R.Q., 2011. Kirenol upregulates nuclear Annexin-1 which interacts with NF-κB to attenuate synovial inflammation of collagen-induced arthritis in rats. J. Ethnopharmacol. 137, 774–782. https://doi.org/10.1016/j.jep.2011.06.037

Wellbrock, C., Karasarides, M., Marais, R., 2004. The RAF proteins take centre stage. Nat. Rev. Mol. Cell Biol. 5, 875–85. https://doi.org/10.1038/nrm1498

Wen, T., Xu, W., Liang, L., Li, J., Ding, X., Chen, X., Hu, J., Lv, A., Li, X., 2015. Clinical Efficacy of Andrographolide Sulfonate in the Treatment of Severe Hand, Foot, and Mouth Disease (HFMD) is Dependent upon Inhibition of Neutrophil Activation. Phyther. Res. https://doi.org/10.1002/ptr.5361

Wilhelm, D.L., 1973. Mechanisms responsible for increased vascular permeability in acute inflammation. Agents Actions 3, 297–306. https://doi.org/10.1007/BF01986484

Xiong, Y., Ma, Y., Han, W., Kodithuwakku, N.D., Liu, L.F., Li, F.W., Fang, W.R., Li, Y.M., 2014. Clematichinenoside AR induces immunosuppression involving Treg cells in Peyers patches of rats with adjuvant induced arthritis. J. Ethnopharmacol. 155, 1306–1314. https://doi.org/10.1016/j.jep.2014.07.028

Yue, J., Wu, D., Tam, L.-S., 2018. The role of imaging in early diagnosis and prevention of joint damage in inflammatory arthritis. Expert Rev. Clin. Immunol. 14, 499–511. https://doi.org/10.1080/1744666X.2018.1476849

Zhang, J.M., An, J., 2007. Cytokines, inflammation, and pain. Int. Anesthesiol. Clin. https://doi.org/10.1097/AIA.0b013e318034194e

Zhang, S., Huang, G., Yuan, K., Zhu, Q., Sheng, H., Yu, R., Luo, G., Xu, A., 2017. Tanshinone IIA ameliorates chronic arthritis in mice by modulating neutrophil activities. Clin. Exp. Immunol. 190, 29–39. https://doi.org/10.1111/cei.12993