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Herbal medicinal products target defined biochemical and molecular mediators of inflammatory autoimmune arthritis

Shivaprasad H. Venkatesha[1], **Brian M. Berman**[2], and **Kamal D. Moudgil**[1,3]

[1] Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, MD 21201

[2] Center for Integrative Medicine, University of Maryland School of Medicine, Baltimore, MD 21201

[3] Division of Rheumatology, Department of Medicine, University of Maryland School of Medicine, Baltimore, MD 21201

Abstract

Rheumatoid arthritis (RA) is a chronic debilitating disease characterized by synovial inflammation, damage to cartilage and bone, and deformities of the joints. Several drugs possessing anti-inflammatory and immunomodulatory properties are being used in the conventional (allopathic) system of medicine to treat RA. However, the long-term use of these drugs is associated with harmful side effects. Therefore, newer drugs with low or no toxicity for the treatment of RA are actively being sought. Interestingly, several herbs demonstrate anti-inflammatory and anti-arthritic activity. In this review, we describe the role of the major biochemical and molecular mediators in the pathogenesis of RA, and highlight the sites of action of herbal medicinal products that have anti-arthritic activity. With the rapidly increasing use of CAM products by patients with RA and other inflammation-related disorders, our review presents timely information validating the scientific rationale for the use of natural therapeutic products.

Keywords

Complementary and alternative medicine (CAM); Herbal products; Inflammatory mediators; Rheumatoid arthritis (RA)

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that mainly targets the joints [1]. Both genetic and environmental factors are involved in the initiation and progression of the disease. Initiation of RA involves the activation of autoreactive T cells and the recruitment of these T cells along with other leukocytes into the joints. These leukocytes produce a variety of mediators of inflammation that induce synovial inflammation and eventually cause tissue damage in the joints (Fig. 1). Consequently, these mediators serve as potential

Corresponding author's address: Kamal D. Moudgil, Department of Microbiology and Immunology, University of Maryland School of Medicine, 685 W. Baltimore Street, HSF-1, Suite-380, Baltimore, MD 21201; Tel: +1-410-706-7804; Fax: +1-410-706-2129; kmoud001@umaryland.edu.

targets for therapeutic agents for arthritis. The suppression of arthritis in experimental animal models using well-defined biochemical/pharmacological inhibitors has been reported [2, 3]. Interestingly, many of these mediators also can be targeted by natural products, including herbal mixtures belonging to traditional or complementary and alternative medicine (CAM). In this review, we describe the role of various biochemical and molecular mediators of inflammation in the pathogenesis of RA (Table 1 and 2), as well as provide examples of plant medicinal products that target these mediators leading to the downmodulation of arthritis (Table 3–5).

The natural plant products discussed in this article have been examined for their anti-inflammatory and anti-arthritic activity. The in vivo testing was performed using well-established experimental models of human RA (e.g., adjuvant-induced arthritis (AA) [4–7], collagen-induced arthritis (CIA) [8, 9] and streptococcal cell wall-induced arthritis [10–12]), whereas the in vitro testing was based on cultures of defined cell types (e.g., macrophages, chondrocytes and fibroblasts) [13–16]. For the in vivo studies, the plant products were tested either as an extract (e.g., water-extract and alcoholic extract) [5, 17–19] or as a purified bioactive compound (e.g., triptolide, curcumin, epigallocatechin-3-gallate (EGCG) and acetyl-11-keto-beta-boswellic acid (AKBA) [12, 13, 15, 20]) (Fig. 2). Oral feeding and intraperitoneal injection represent the two major routes of administration employed for the in vivo testing. The readout for the efficacy of plant products in the arthritis models included assessment of the severity of arthritis using clinical criteria for grading or objective parameters such as paw volume, histopathological evaluation of tissue damage in the joints and bone mineral density [7, 9–12]. For the in vitro models, specific compounds purified from the natural product were added to the cell culture in the presence of an inflammatory stimuli (e.g., interleukin-1 beta (IL-1β) and lipopolysaccharide; LPS) [15, 16]. The cells tested were derived either from mice/rats (naïve or treated with the plant products) or from cell lines. The readouts of these cellular assays are comprised of various biochemical and molecular mediators of inflammation as discussed below in detail.

2. Biochemical mediators of inflammation and arthritis

Inflammation is physiological response of the organism to different stimuli such as trauma, infection or immune reactions [21]. A variety of biochemical mediators act in concert to initiate and perpetuate the inflammatory reaction. We discuss below in detail the characteristics of these major biochemical mediators and also report the targeting of these mediators by synthetic and natural products leading to suppression of arthritis. The major biochemical mediators include phospholipase A_2 (PLA_2), cyclooxygenase (COX), lipoxgenase (LOX), matrix metalloproteases (MMPs), nitric oxide synthases (NOS), indoleamine 2,3-dioxygenase (IDO), tissue inhibitors of metalloproteases (TIMPs), prostaglandins (PG), leukotrienes (LT) and nitric oxide (NO). These mediators act via different interconnected pathways resulting in arthritic inflammation (Fig. 1). The functions of PLA_2, COX, LOX, MMPs, NOS and IDO are summarized in Table 1.

2.1 Phospholipase A_2 (PLA_2)

PLA_2 hydrolyzes the fatty acid from the sn-2 position of membrane phospholipids. Free fatty acids thus released can be metabolized to various lipid mediators of biological importance [22]. The remaining lysophospholipids also serve important roles in biological processes [23, 24]. There are more than 14 distinct groups of PLA_2 enzymes [25, 26]. Among the four main types of PLA_2 are the secreted PLA_2 ($sPLA_2$), cytosolic PLA_2 ($cPLA_2$), calcium-independent PLA_2 ($iPLA_2$) and platelet activating factor (PAF) acetyl hydrolase/oxidized lipid lipoprotein-associated PLA_2 ($LpPLA_2$). $cPLA_2$ is the predominant type synthesized at the site of inflammation [27] and it is the only PLA_2 with a preference for arachidonic acid in the sn-2 position of phospholipids [28, 29]. As arachidonic acid is the precursor of eicosanoids,

$cPLA_2$ represents the central enzyme involved in the generation of eicosanoids and hence, is the mediator of many inflammatory processes, including RA [30–33]. In addition, $cPLA_2$ upregulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in neutrophils and monocytes, releasing superoxides during the inflammatory process [27, 34]. $sPLA_2$ can hydrolyze different fatty acids at the sn-2 position of the substrate phospholipid [35]. Further, the role of the mammalian $sPLA_2$ in eicosanoid generation is not clear. Different studies on this subject have yielded inconclusive results, and clinical trials of the efficacy of $sPLA_2$ against arthritis and allergies revealed no significant therapeutic effects [36, 37].

2.2 Cyclooxygenase (COX) and prostaglandins (PG)

COX converts arachidonic acid into prostaglandin H_2 (PGH_2), which is further catalyzed by distinct synthases to 5 major bioactive prostaglandins (PGE_2, PGI_2, PGF_2, PGD_2, and thromboxane A_2 (TXA_2)) 38. There are two isoforms of COX that are designated as COX-1 and COX-2. COX-1 is constitutively expressed in most tissues, whereas COX-2 is induced by a range of mitogenic and inflammatory stimuli. Prostaglandin synthesis in inflammatory conditions is attributable largely to COX-2. However, COX-1 also is associated with the generation of proinflammatory prostaglandins [39]. PGE_2 and TXA_2 are potent inflammatory mediators that contribute to the pathogenesis of RA [40–42]. PGE_2 causes vasodilatation and recruits neutrophils to the affected joints in RA. The latter effect is attributable both to the production of IL-23-induced IL-17 and the impaired production of IL-12 and IFN-γ production [43]. Moreover, PGE_2 mediates matrix degradation and cartilage destruction [44]. PGE_2 also plays a role in angiogenesis evoked by inflammation by stimulating the production of vascular endothelial growth factor (VEGF) [45]. Moreover, PGE_2 contributes to inflammatory pain by sensitizing to bradykinin as well as histamine-induced nociceptive stimuli, and to edema via plasma extravasation. In addition, the effects of IL-1, IL-6 and TNF-α on bone resorption have been shown to be PGE_2 dependent [46]. TXA_2, the other product of COX, induces rapid irreversible aggregation of human platelets and it is a potent inducer of smooth muscle contraction [47]. TXA_2 also is a mediator of endothelial cell migration as well as angiogenesis [48]. The role of inhibition of COX in inhibiting inflammation and arthritis is discussed below.

2.3 Lipoxgenase (LOX) and leukotrienes (LT)

LOX constitutes a group of non-heme iron-containing dioxygenases. So far, 5-LOX, 12-LOX, and 15-LOX have been identified, which stereospecifically integrate oxygen at carbon atom 5, 12 or 15, respectively of the substrate fatty acid [49]. 5-LO catalyzes the synthesis of leukotriene B4 (LTB_4) from arachidonic acid, and it is known to play an important role in the pathogenesis of RA [50]. In contrast, 12- and 15-LOX represent major anti-inflammatory enzymes operative during the course of inflammatory joint disease [51]. LTB_4 is a chemoattractant and mediates the infiltration of leukocytes into the RA joint [50]. There, these cells proliferate and form an invasive pannus, which leads to cartilage and bone destruction [52]. Recent reports suggest that LTB_4 increases the production of pathogenic TNF-α and IL-1β at both the mRNA and the protein level [53] LTB_4 not only serves as a chemoattractant, but also activates neutrophils to release superoxides and proteolytic enzymes, which in turn cause matrix destruction [54]. The release of inflammatory lipid mediators, particularly PGE_2, TXA_2 and LTB_4 is regulated by a cascade of reactions starting from PLA_2. Table 1 depicts the functions of PLA_2, COX and LOX.

Selective inhibitors of LOX or COX display suppressive effect against inflammation in the joint [55, 56]. However, dual inhibitors of LOX and COX are more effective than selective single-enzyme inhibitors in preventing arthritis in experimental models [57, 58]. In comparison, the inhibition of over-expressed $cPLA_2$ should simultaneously diminish the

activity of multiple lipid mediators that facilitate the recruitment of neutrophils to the site of inflammation and the release of superoxides [27, 59].

Plant extracts and purified compounds derived from them can selectively inhibit COX, LOX or PLA_2 and suppress arthritis (Table 3). For example, *Bidens pilosa* extract inhibits IL-1β-induced COX-2 expression and PGE_2 production, and this effect is attributable to inhibition of mitogen activated protein kinase (MAPK), particularly p38 [16]. Similarly, total flavonoids derived from *Turpinia Arguta* reduce the production of IL-1β and PGE_2 by peritoneal macrophages, and this effect correlates with their anti-arthritic activity observed in rats [7]. A curcuminoid-containing turmeric extract that inhibits experimental arthritis in rats also inhibits the expression of COX-2 and reduces PGE_2 levels in the joints in part via preventing the activation of nuclear factor-kB (NF-kB) [10]. Another study highlights the anti-inflammatory activity of an extract of *Gentiana macrophylla* (Gentianaceae) in an experimental arthritis model, and that activity is associated with reduced PGE_2 levels in the inflamed tissues [19]. Ursolic acid inhibits sPLA2 [60] and downregulates lipooxygenase and COX-2 owing to the inhibition of NF-kB activity [61]. Resveratol, a phytoalexin, is a potent inhibitor of COX-2 production [62] as are Celastrol (from plants of *Celastraceae* family) [63] and Withanolides from *Withania somnifera* (Ashwagandha) [64]. Similarly, phenolic gingerols from *Zinziber officinale* suppress COX-1 and COX-2 activity [11]. A mechanism common to several of the herbal products described above involves inhibition of NF-kB activity, which in turn suppresses the activity of COX and other inflammation-related biomolecules.

2.4 Matrix metalloproteases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs)

In arthritic conditions, inflammatory cytokines such as IL-1β and TNF-α stimulate the production of MMPs, enzymes that can irreversibly degrade components of extracellular matrix (ECM), including the articular cartilage and bone [65–67]. Cartilage is made up of proteoglycans and type II collagen, while bone is composed primarily of type I collagen. The degradation of collagen by MMPs is the rate-limiting step in cartilage and bone damage. MMP-1 is produced primarily by the synovial cells that line the joints, while MMP-13 is a product of the chondrocytes that reside in the cartilage. MMP-13 degrades collagen as well as the proteoglycan molecule, aggrecan. The expression of other MMPs such as MMP-2, MMP-3, MMP-9, MMP-12, and MMP-14 is also elevated in arthritis [68]. These enzymes degrade non-collagenous protein components of the matrix resulting in complete joint destruction. In addition, they play a critical role in angiogenesis [69, 70], which is one of the vital components of the pathogenic process in inflammatory arthritis. Summary of the functions of MMPs are given in Table 1. Inhibiting the activities of pathogenic MMPs can prevent or significantly reduce joint destruction, thereby benefiting arthritis patients with an improved quality of life. TIMPS 1–4 are the natural inhibitors of MMPs, and they also inhibit proinflammatory cytokines and tissue damage in the joint [71, 72]. Significant effort has been invested in designing effective inhibitors of MMP activity and/or synthesis [73] that display anti-arthritic activity in experimental animal models [74]. Moreover, a number of MMP inhibitors derived from herbal products have been shown to suppress arthritis (Table 3). For example, the anti-arthritic activity of total glucosides of paeony (TGP), a TCM product, in rats is attributable in part to the inhibition of the production of IL-1β and TNF-α by macrophage-like synoviocytes, and that of MMP-1 and MMP-3 by the fibroblast-like synoviocytes [9]. Furthermore, this concurrent inhibition of different mediators of inflammation can be explained by the fact that IL-1β and TNF-α regulate the expression of MMP-1 and MMP-3. Similarly, in another study, *Triphala guggulu*, an Ayurvedic medicine, is shown to inhibit certain key enzymes involved in tissue damage in arthritis, including hyaluronidase, collagenase and MMPs [75]. Ursolic acid suppresses the expression of MMP-9 [61], one of the NF-kB-regulated genes. Celastrol (from *Celastraceae* family plants) [63], Ikarisoside (from *Epimedium koreanum*) [14], and AKBA (from *Boswellia serrata*, an

Ayurvedic medicine) [20] inhibit the activity of MMP9, whereas green tea inhibits MMP1 and 13 [13].

2.5 Free radicals

Free radicals are continually generated within metabolically active cells of aerobic organisms and they utilize molecular oxygen (dioxygen or O_2). The major reactive oxygen species (ROS) generated are the superoxide anion radical (dioxide or O_2^-), the hydroxyl radical (OH) and the peroxynitrite anion ($ONOO^-$). Free radicals are highly reactive [76] and they can be quite toxic and cause cellular dysfunction and even cell death [77]. The harmful effects of free radicals are owing to their tendency to interact with and to damage macromolecules such as DNA, proteins, carbohydrates and lipids [77]. Oxygen radical generation is relatively high in the RA joint [78, 79]. In regard to RA pathogenesis, the effects of free radicals on connective tissue macromolecules (collagen, hyaluronic acid (HA), proteoglcans), intact tissues and immunoglobulins are of high relevance [80]. The free radicals generated by polymorphonuclear cells (PMNs) alter IgG, which could in turn activate PMNs to generate additional superoxides [81]. Free radicals themselves also activate PMNs [82]. ROS might also perpetuate inflammation by facilitating the generation of chemotactic factors at the local site. Superoxide dismutase (SOD) is a ubiquitously distributed anti-oxidative enzyme that affords protection against free radical damage. In addition, anti-oxidants can scavenge the free radicals and limit damage. NO is a free radical that serves as an important messenger molecule in inflammatory conditions [83]. The role of NO in the pathogenesis of RA is discussed below.

NO is synthesized from the guanidino group of L-arginine by a family of enzymes termed NO synthases (NOS), and this process involves the incorporation of molecular oxygen into L-arginine. Inducible macrophage type NOS (iNOS), endothelial cell NOS (ecNOS) and brain NOS (bNOS), represent different isoforms of NOS [84–86]. A variety of immunological stimuli including pro-inflammatory cytokines induce the expression of iNOS in a number of non-hematopoietic cells, including fibroblasts [87]. The induction of iNOS may have either a toxic or a protective effect [88–91]. In arthritis, NO induces the production of pathogenic cytokines such as TNF-α, IL-1β and IFN-γ, as well as collagenase [92–96]. NO also induces certain chemokines that contribute to the disease progression in arthritis. The functions of NOS are summarized in Table 1. Decreased production of NO via suppressing or inhibiting NOS reduces arthritic symptoms and affords protection against the loss of body weight [17, 97]. Anti-oxidants that are present in a number of plant extracts scavenge NO and other free radicals. Plant-derived compounds also can suppress iNOS and increase SOD activity. Examples of herbal preparations and compounds isolated from them that can scavenge NO, suppress iNOS or increase SOD are given in Table 3. For example, oral feeding to rats of Quercetin, a flavonoid, ameliorates adjuvant arthritis (AA), and this effect is associated with reduced production of various mediators of inflammation, including NO by macrophages [6]. In another study based on the AA model, treatment with *Trewia polycarpa*, an Ayurvedic medicine, revealed its free radical-scavenging property [5]. The treatment led to an increase in the activity of SOD and glutathione peroxidase but a reduction in the level of lipid peroxide. *Celastrus aculeatus* Merr. (Celastrus) has anti-inflammatory and anti-arthritic activity as tested in the AA model [18]. Celastrus-treated rats show a significant reduction in the levels of NO both in serum as well as in culture supernate of antigen-stimulated draining lymph node cells (LNC) [18]. In another study, Celastrol, an active component of Celastrus and other *Celastraceae* family of plants, has been shown to modulate the expression of iNOS [63].

2.6 Indoleamine 2,3-dioxygenase (IDO)

Tryptophan is an essential amino acid that is critical for cell survival and proliferation[98, 99]. It can be catabolized by IDO yielding kynurenine, which can induce apoptosis of T cells.

Furthermore, IDO-mediated deprivation of tryptophan inhibits T cell proliferation. IDO is expressed in dendritic cells (DC) and activated macrophages but not in T cells. IDO-positive DC play an important role in the induction and maintenance of peripheral tolerance via the depletion of self-reactive T cells [100] and the generation/activation of regulatory T cells [101, 102]. It has been shown in the CIA model that the induction of IDO significantly reduces both the accumulation of pathogenic Th1 and Th17 cells in the arthritic joints [103] and the severity of the disease [104]. However, it has also been reported that inhibiting IDO activity might attenuate rather than aggravate arthritis [105]. The activity of IDO can be modulated by IFN-γ [106] as well as $CD4^+CD25^+$ regulatory T cells (Treg) [101]. Furthermore, the cytoplasmic enzyme tryptophanyl-tRNA-synthetase (TTS) mediates the association of tryptophan with its specific tRNA [107], and this accumulation of tryptophan can antagonize the IDO-mediated deprivation of tryptophan [108, 109]. It has been reported that autoreactive T cells in the rheumatoid joints resist IDO-mediated inhibition and persist during disease progression [110]. This effect might be because of the enhanced expression of TTS in T cells by inflammatory cytokines such as IFN-γ and TNF-α [110]. The role of IDO in the pathogenesis of RA is illustrated in Fig. 1. As of now, herbal preparations have not been studied much for their ability to modulate arthritis via altering IDO activity.

3. Molecular mediators of inflammation and arthritis

The initiation and progression of arthritic inflammation requires transduction of signals from the arthritogenic stimuli. Defined ligands bind to the appropriate receptors on the target cells, initiating a chain of reactions, including the activation of transcription factors. The generation of a variety of mediators (e.g., cytokines, chemokines, MMPs and other enzymes) of inflammation and tissue damage in RA are controlled at the transcriptional level [111]. Hence, cell signaling pathways and transcription factors are important components of the effector pathways leading to arthritis. The roles of major signaling molecules and transcription factors are summarized in Table 2 and discussed below.

3.1 Cell signaling pathways

Mitogen-activated protein (MAP) kinases are central components of signal transduction pathways leading to the enhanced expression of mediators of inflammation that play a key role in the pathophysiology of RA and other inflammatory diseases [112, 113]. Consequently, members of the MAP kinase pathways are potential therapeutic targets in RA. MAP kinases are proline-directed serine/threonine protein kinases. Nuclear translocation of activated MAP kinases facilitates the modulation of gene transcription via the induction and/or transactivation of transcription factors [114, 115]. The 3 major mammalian MAP kinase pathways include the ERK pathway, the JNK/SAPK pathway, and the p38 pathway. The kinases in each pathway have multiple isoforms that may be differentially expressed in various tissues and play different roles. Summary of the functions of these pathways are given in Table 2 and discussed below.

3.1.1 Extracellular-signal-regulated kinase (ERK) pathway—The ERK pathway is activated by the MAP kinase kinases (also known as MAP kinase/ERK kinases (MEKs)). MEKs phosphorylate critical tyrosine and threonine residues of ERK [116]. MEK/ERK pathway plays an important role in lymphocyte activation and differentiation [117–119], in the production of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6 [120–123], in the production of MMPs [124, 125], and in the development of synovitis, pain, and tissue destruction in RA. Accordingly, MEK inhibitors are being exploited to inhibit diverse inflammatory pathways. For example, a selective MEK inhibitor demonstrates anti-arthritic activity [126]. In this regard, medicinal plants being used in CAM might be an invaluable

resource for novel MEK/ERK inhibitors. Examples of the herbs that target ERK are shown in Table 4.

3.1.2 P38 MAP kinase pathway—The p38 MAP kinase has many isoforms (p38α, β, γ and δ), and p38α is believed to be a critical regulator of the inflammatory response, including the release of cytokines by immune competent cells and the functional response of neutrophils to inflammatory stimuli [127, 128]. p38 MAP kinase phosphorylates several transcription factors, including signal transducer and activator of transcription (STAT), nuclear factor of activated T cells (NFAT), and downstream kinases [129]. In addition, it regulates a variety of genes involved in inflammation, such as TNF-α, IL-1β, IL-6, IL-8, COX-2, and MMPs [128]. The p38 pathway also mediates cellular functions, including cell migration, cell survival and cell death [130–132]. Inhibition of p38 MAPK suppresses paw swelling, joint damage and the production of inflammatory cytokines [133, 134]. The herbal extracts that target p38 MAP kinase in experimental models of arthritis are shown in Table 4. For example, *Bidens pilosa* (BP) extract has been shown to possess anti-inflammatory activity [16]. One of the molecular mediators targeted here is MAPK. The phoshorylation of MAPK is inhibited by BP, with a predominant effect on p38.

3.1.3 c-Jun N-terminal kinase (JNK) pathway—JNKs phosphorylate and activate transcription factors and other cellular factors which regulate the expression of many genes encoding cytokines (TNF-α, IL-2), growth factors, cell surface receptors, cell adhesion molecules (E-selectin) and degradative enzymes (MMPs) [135]. Activated JNK can be detected in synovial fibroblasts and chondrocytes from the joints of arthritic patients but not from normal controls, and it has been implicated in chondrocyte injury and cartilage degeneration [136, 137]. Furthermore, the disease-suppressive effect of a JNK inhibitor in an animal model of arthritis has been reported [138]. Inhibitors of JNK can be found in a certain Chinese herbs that are used in CAM for the treatment of several inflammatory disorders including RA [139] (Table 4). For example, Ikarisoside, a purified compound from *Epimedium koreanum*, has inhibitory effects on JNK and Akt (besides NF-kB) when tested for its effects on osteoclastogenesis using monocyte/macrophage RAW 267.7 cells [14]. The molecules targeted here are involved in abnormal bone lysis in RA. In another study, 6-dehydrogingerdione, a compound purified from ginger, was shown to enhance the activity of JNK without much effect on ERK and p38, resulting in the induction of apoptosis in the target cells [140].

3.2 Transcription factors

3.2.1 Nuclear factor-kB (NF-kB)—The transcription factor NF-kB regulates the expression of a wide variety of genes. RelA, RelB, c-Rel, NF-kB1 and NF-kB2 are members of NF-kB family. These members activate characteristic sets of genes in a cell-type and stimulus-type manner, thus regulating the transcription of genes [141–145]. NF-kB remains in an inactive form by binding to the inhibitor of NF-kB proteins (IkB), but cellular stimuli including cytokines, mitogens and stress activate IkB via activating NF-kB kinase (IkB kinase (IKK) complex) and subsequent degradation of IkB [146, 147]. The activated NF-kB translocates to the nucleus and stimulates the transcription of genes containing the consensus kB sequence 5′-GGGPuNNPyPyCC-3′ (where Pu denotes a purine and Py denotes a pyrimidine). Such genes include those encoding certain cytokines and chemokines, adhesion molecules, MMPs, VEGF, iNOS, COX-2, etc. Most of these genes have been reported to have important role in the pathogenesis of RA [141]. VEGF as well as a few other molecules involved in angiogenesis are attractive targets for therapeutic agents against RA [148].

3.2.2 Activator protein-1 (AP-1)—AP-1 is another transcription factor that transduces extracellular signals in immune cells. AP-1 gets activated in response to a variety of

inflammatory stimuli. Activated AP-1 interacts with the binding site(s) in their promoter/enhancer regions resulting in the expression of specific target genes enciding MMPs and pro-inflammatory cytokines [149–151]. AP-1-mediated cytokine production is in cooperation with transcription factors of the nuclear factor of activated T cells (NFAT) family [152], wherein AP-1 and NFAT form stable ternary complexes on DNA-binding sites. AP-1-mediated activation of NFAT and integration of the signals via the receptor activator for nuclear factor kB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) are required for osteoclast differentiation [153]. AP-1 also regulates the differentiation of naïve T cells into T helper 1 (Th1) or T helper 2 cells (Th2), and it interacts with and trans-represses the glucocorticoid receptor [154, 155]. All these mechanisms affect the severity of arthritic inflammation.

3.2.3 Other transcription factors—Signal transducer and activator of transcription (STAT) family of proteins, interferon regulatory factors (IRFs), forkhead (Fox) family proteins, T-box transcription factor 21 (TBX21)/T-box expressed in T cells (T-bet), the (cytidine-cytidine-adenosine-adenosine-thymidine) CCAAT-enhancer binding protein family and the E-twenty six (Ets) transcription factor family represent other transcription factors implicated in the pathogenesis of RA [156]. Furthermore, single nucleotide polymorphisms in the Runt-related transcription factor 1 (Runx1)-binding site of the SLC22A4 gene, the major histocompatibility complex class II transactivator (CIITA) gene, and the STAT4 gene are associated with RA [157–160]. Modulation of the synthesis and/activity of transcription factors represents an alternative therapeutic strategy for RA. Specific inhibitors for NF-kB and NFAT have already been reported [161–163]. However, the inhibition of such transcription factors that regulate a variety of pathways might induce unexpected side effects in vivo.

Numerous examples of herbs that target NF-kB and other transcription factors are shown in Table 4. For example, the anti-arthritic activity of a turmeric extract containing curcuminoid as an active ingredient, was associated with a reduction in the local activation of NF-kB and thereby modulation of the expression of various inflammation-related genes controlled by NF-kB [10]. Similarly, a component of *Epimedium koreanum*, Ikarisoside, has an inhibitory effect on NF-kB signaling pathways, which in turn influences the osteoclastogenic activity associated with arthritis [14]. Using an in vitro model of inflammation, triptolide, a bioactive compound isolated from *Tripterygium wilfordii*, was shown to inhibit NF-kB-regulated reporter transcription in LPS-stimulated macrophages [15]. Celastrol has been shown to modulate both inducible as well as constitutive NF-kB activity [63]. Specifically, Celastrol inhibits the TNF-α-induced activation, phosphorylation and degradation of IkBα; nuclear transport and phosphorylation of p65; and TAK-1-induced NF-kB activation [63]. Similar effects on NF-kB were observed with withanolides isolated from *Withania somnifera*, an Ayurvedic medicine [64]. Ursolic acid inhibits both the DNA binding of NF-kB and the IkBα kinase activity, as well as phosphorylation and nuclear transport of p65 [61]. Resveratol is a potent inhibitor of NF-kB activation [62], and AKBA was shown to inhibit NF-kB-regulated gene expression induced by IL-1β, TNF-α or LPS, but the binding of NF-kB to DNA was unaffected [20]. However, AKBA inhibits the activation of IkBα kinase (IKK) and the phosphorylation, ubiquitination and degradation of IkBα, as well as phosphorylation and nuclear transport of p65 [20]. The effect of AKBA on IkBα is mediated through inhibition of Akt. EGCG showed a dose-dependent inhibition of NF-kB and AP-1, providing insights into the anti-inflammatory effects of this flavonoid [13].

4. Concluding remarks

It is clear from the above description that herbal medicinal products target specific defined mediators of inflammation and arthritis. The major benefit of using herbs and other natural

products lies in their limited or no undesirable side effects. Therefore, the interdisciplinary efforts of researchers aimed at identifying new herbal products and defining their mechanisms of action should be reinforced. This would facilitate the discovery and development of safe and effective natural products for the treatment of RA and other immune-mediated disorders.

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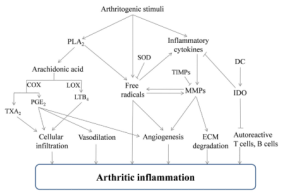

Figure 1. Schematic representation of the initiation and propagation of autoimmune arthritis

An arthritogenic stimulus (e.g., heat-killed M. tuberculosis H37Ra in adjuvant arthritis and Type II collagen in collagen-induced arthritis) initiates a series of pathogenic events that involve a variety of mediators of inflammation. Prominent among these mediators are arachidonic acid metabolites, pro-inflammatory cytokines, free radicals and matrix-degrading enzymes. These mediators modulate the processes relating to cellular migration into the joints as well as angiogenesis and degradation of the extracellular matrix within the joints leading to the arthritic inflammation. These mediators also are the targets of a variety of natural products. (COX- cyclooxygenase, LOX- lipooxygenase, TXA_2- thromboxane A_2, PGE_2- prostaglandin E_2, leukotriene B_4 (LTB_4), SOD- superoxide dismutase, MMP- matrix metalloprotease, TIMPS-tissue inhibitors of metalloproteases, ECM- extracellular matrix, DC- dendritic cells, and indoleamine 2,3-dioxygenase (IDO).)

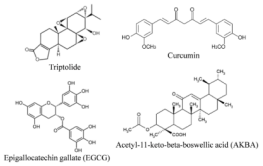

Figure 2. Chemical structures of four representative bioactive compounds isolated from natural plant extracts are shown

Triptolide: a diterpene isolated from *Tripterygium wilfordii*, Curcumin: a polyphenol isolated from *Curcuma longa*, epigallocatechin-3-gallate (EGCG): a flavonoid from *Camellia sinensis*, and acetyl-11-keto-beta-boswellic acid (AKBA): an organic acid from *Boswellia serrata*. These natural compounds possess anti-inflammatory activity that can suppress autoimmune arthritis.

Table 1

Characteristics of the biochemical mediators of immune pathology in RA

Enzyme	Isoforms	Substrate/Target	Product released/formed	Function	Reference
PLA_2	**cPLA$_2$,** iPLA$_2$, LpPLA$_2$ and sPLA$_2$	Phospholipids containing arachidonic acid at sn-2 position	Arachidonic acid	Generation of precursor (arachidonic acid) for eicosanoid synthesis, release of free radicals	28–30, 32, 33
COX	COX-1 and **COX-2**	Arachidonic acid	PGE_2, TXA_2	Vasodilation, neutrophil infiltration, extracellular matrix degradation, angiogenesis, induction of pain and edema, platelet aggregation, smooth muscle contraction, endothelial cell migration	43–45, 48
LOX	**5-LOX,** 12-LOX and15-LOX	Arachidonic acid	LTB_4	Leukocytes infiltration, expression of pathogenic TNF-α and IL-1β, activation of neutophils to release superoxides and MMPs	50, 54
MMPs	**MMP-1, MMP-2,** MMP-3, **MMP-9,** MMP-12, **MMP-13** and MMP-14	Collagen and proteoglycans	-------	Degradation of cartilage and bone, osteoclast resorption, and angiogenesis	68–70
NOS	bNOS, ecNOS, **iNOS**	L-arginine	NO	Production of TNF-α, IL-1β, IFN-γ and MMPs	93, 94
IDO	-------	Tryptophan	Kynurenine	Reduction in autoreactive T cells, and development of immune tolerance, induction of regulatory T cells, control of the accumulation of Th1 and Th17 pathogenic T cells	100–103

The isoforms shown in bold font are the key enzymes in that group. bNOS- brain nitric oxide synthase, COX- cyclooxygenase, cPLA$_2$- cytosolic phospolipase A$_2$, ecNOS- endothelial cell nitric oxide synthase, IDO- indoleamine 2,3-dioxygenase, IL- interleukin, iNOS- inducible nitric oxide synthase, iPLA$_2$- calcium independent phospolipase A$_2$, LOX- lipooxgenase, LpPLA$_2$- platelet activating factor acetyl hydrolase/oxidized lipid lipoprotein associated phospolipase A$_2$, LTB$_4$- leukotriene B4, MMPs- matrix metalloproteases, NO- nitric oxide, PGE$_2$- prostaglandin E$_2$, sPLA$_2$- secreted phospolipase A$_2$, TNF- tumor necrosis factor and TXA$_2$- thromboxane A$_2$.

Table 2

Functions of the key molecular mediators associated with the pathogenesis of RA

Molecular mediators	Function	Reference
Signaling molecules		
ERK	Production of proinflammatory cytokines and MMPs, lymphocyte activation and differentiation	117–119, 121, 122, 124, 125
P38	Release of proinflammatory cytokines, COX-2 and MMPs	127, 128
JNK	Expression of cytokines, growth factors, cell surface receptors, cell adhesion molecules and MMPs	135
Nuclear factors		
NF-kB	Expression of cytokines (TNF-α, IL-1β, IL-6, IL-6, IL-17, IFN-γ, etc.), chemokines (MCP-1, MCP-4, CCL18, etc.), adhesion molecules (E-selectin, ICAM-1, VCAM-1, etc.), MMPs, VEGF, NOS and COX	141
AP-1	Activation of cytokine production, T-cell differentiation, interaction with and trans-repression of the glucocorticoid receptor, and MMP expression	149–151

COX- cyclooxygenase, ICAM- intracellular adhesion molecule, IFN- interferon, IL- interleukin, MCP- monocyte chemoattractant protein, MMPs- matrix metalloproteases, NOS- inducible nitric oxide synthase, TNF- tumor necrosis factor, VCAM- vascular cell adhesion molecule and VEGF- vascular endothelial growth factor.

Table 3

Examples of herbs that target biochemical mediators of inflammation

Herb	Origin	Active compound(s)	Reference
1.1. Herbs targeting PLA_2, COX-2, LOX, PGE_2 and/or LTB_4			
Allium cepa	Multiple	Quercetin	6
Aralia cordata	Korea	7-oxosandaracopimaric acid	164
Boswellia serrata	India	Boswellic acid	20, 165
Camellia sinensis	China	Epigallocatechin-3-gallate	166
Curcuma longa	China/India	Curcumin	10, 12
Gentiana macrophylla	China		19
Ocimum sanctum	India	Ursolic acid	60
Sinomenium acutum	China	Sinomenine	167
Tripterygium wilfordii	China	Triptolide, triptonide and celastrol	8, 168, 169
Turpinia arguta	China	Flavonoids	7
Vitis vinifera	Multiple	Resveratrol	62, 170
Zingiber officinale	China/India	Gingerol and Zingerone	11
1.2. Herbs targeting MMPs and/or TIMPs			
Achyranthes bidentata	China	Oleanolic acid	171
Camellia sinensis	China	Epigallocatechin-3-gallate	13
Cibotium barametz	Multiple	Cibotinoside, cyathenosin A	172
Magnolia officinalis	Asia	Magnolol	173
Ocimum sanctum	India	Ursolic acid	4, 61
Paeonia lactiflora	China	Paeoniflorin	9
Sinomenium acutum	China	Sinomenine	174
Triphala guggulu	India	Guggulsterone, Guggulsterol	75
1.3. Herbs targeting NO, iNOS and/or SOD			
Brassica sp.	Multiple	Indole-3-carbinol	17
Celastrus aculeatus	China	Celastrol	18
Cynodon dactylon	India	----37	175
Helenium microcephalum	Multiple	Bis(helenalinyl)glutarate	176
Sinomenium acutum	China	Sinomenine	167
Trewia polycarpa	India	--------	5

Herbs mentioned in bold font were studied in the adjuvant arthritis (AA) model. Active compound identified in each herbal extract is listed. Some of these compounds have been tested for their specific inhibitory activity.

Table 4

Examples of herbs targeting molecular mediators of inflammation

Herb	Origin	Active compound(s)	Reference
2.1. Herbs targeting cell signaling molecules (ERK, p38 MAP kinase and/or JNK)			
Aralia cordata	Korea	7-oxosandaracopimaric acid	164
Bidens pilosa	Taiwan	Phenylheptatriyne, linolic acid and linolenic acid	16
Curcuma longa	China/India	Curcumin	177
Epimedium koreanum	Korea	Ikarisoside A	14
Tanacetum parthenium	Europe	Parthenolide	178
Zingerber officinale	China/India	Zingerone	140
2.2. Herbs targeting nuclear factors (NF-kB and/or AP-1)			
Aralia cordata	Oriental region	7-oxosandaracopimaric acid	164
Commiphora mukul	India	Guggulsterone, cembranoids	61
Dictamnus dasycarpus	Korea	Dictamnine, obacunone and fraxinellone	179
Epimedium koreanum	Korea	Ikarisoside A	14
Magnolia officinalis	Asia	Magnolol	173
Sinomenium acutum	China	Sinomenine	167
Tripterygium wilfordii	China	Triptolide, triptonide and celastrol	15, 63, 180
Withania somnifera	India	Withanolides	64

Herbs mentioned in bold font were studied in the adjuvant arthritis (AA) model. Active compound identified in each herbal extract is listed. Some of these compounds have been tested for their specific inhibitory activity.