Neutrophils in Rheumatoid Arthritis: A Target for Discovering New Therapies Based on Natural Products

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Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disorder with an important inflammatory component in joints. Neutrophils are the most abundant leukocytes in inflamed joints, and play an essential role in the initiation and progression of RA. Neutrophil effector mechanisms include the release of proinflammatory cytokines, reactive oxygen and nitrogen species (ROS and RNS), and granules containing degradative enzymes, which can cause further damage to the tissue and amplify the neutrophil response. Therefore, the modulation of neutrophil migration and functions is a potential target for pharmacological intervention in arthritis. The pharmacologic treatment options for RA are diverse. The current treatments are mostly symptomatic and have side effects, high costs, and an increased risk of malignancies. Because of these limitations, there is a growing interest in the use of natural products as therapies or adjunct therapies. Herbal products have attracted considerable interest over the past decade because of their multiple beneficial effects such as their antioxidant, anti-inflammatory, antiproliferative, and immunomodulatory properties. This chapter focuses on the role of neutrophils in the pathogenesis of arthritis and the action of substances from natural products as putative antirheumatic therapies.

Keywords: neutrophils, rheumatoid arthritis, herbal products, polyphenols, flavonoids, tetranortriterpenoids, inflammation

1. Introduction

Arthritis is an inflammatory joint disorder that can cause edema, pain, and loss of function. The most common types of arthritis are osteoarthritis, gout, and rheumatoid arthritis [1, 2]. Rheumatoid arthritis is a systemic, autoimmune disorder with an important inflammatory
component in which genetic and environmental risk factors contribute to disease development. Its prevalence in the world population is between 0.3 and 1%, and it affects three times more women than men [3, 4].

The pathophysiology of RA is complex and appears to be initiated when the adaptive immune system (cellular or humoral) recognizes self-joint antigens as non-self, which triggers a variety of distinct inflammatory effector mechanisms, including the recruitment of leukocytes [5–8]. RA is characterized by intense inflammatory processes and joint damage that are mediated by the influx of immune system cells to the synovial space such as neutrophils, macrophages, and lymphocytes [1, 2]. A critical factor that contributes to tissue damage is the excessive production of inflammatory mediators by resident and/or infiltrated cells. Among the primary mediators involved in joint damage are free radicals, enzymes that degrade the matrix, and pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β, as well as chemokines such as CXCL-8, lipid mediators, such as leukotriene B₄ (LTB₄) [9, 10], and endothelin (ET) [11, 12]. Inflamed synovial tissue is invasive and called pannus, which can be formed by synovial cell proliferation, angiogenesis, and the accumulation of macrophages, lymphocytes, and neutrophils [13].

Neutrophils are crucial cells that have significant roles in diverse inflammatory diseases, including acute, chronic, autoimmune, infectious, and non-infectious conditions [14]. The most well-known effector function of neutrophils is their role in innate immunity. However, recent studies have identified neutrophils as active cells during adaptive immunity, facilitating the recruitment and activation of antigen-presenting cells or directly interacting with T cells. Neutrophils are the most abundant leukocytes in inflamed joints, and the importance of these cells in the initiation and progression of human RA as well as in murine models has been demonstrated [15–18]. Therefore, neutrophils play an essential role in joint inflammation, and the modulation of neutrophil functions is considered a potential target for pharmacological intervention in arthritis [19–21].

The pharmacologic treatment options for arthritis are diverse. The current treatments are mostly symptomatic and include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologic therapies. High costs and an increased risk of malignancies limit the use of these agents, in addition to the potential side effects that all therapies possess. Plant-derived products, such as polyphenols, sesquiterpenes, flavonoids, and tetranortriterpenoids, which are herbal metabolites with anti-inflammatory activity, may provide new therapeutic agents and cost-effective treatments [22, 23]. This chapter focuses on the role of neutrophils in the pathogenesis of arthritis and the action of substances from natural products as putative antirheumatic therapies.

2. Role of neutrophils in rheumatoid arthritis

2.1. Neutrophil trafficking from blood to the synovial cavity

Neutrophil recruitment is an important stage in the inflammatory development process, including autoimmune diseases such as RA. Among the circulating cells, neutrophils are the first ones to reach the synovium and are the most abundant cells in the synovial fluid [24]. In this section,
we discuss the cascade of events that culminates in neutrophil entry into inflamed joints. The leukocyte recruitment cascade involves the following commonly recognized steps: capture, rolling, firm adhesion, and finally transendothelial migration.

Neutrophil release from the bone marrow to the circulating blood occurs immediately after the first signal of inflammation, serving to increase the number of neutrophils available for recruitment into the tissue in response to inflammation [25]. The mobilization of neutrophils from the bone marrow is orchestrated by the hematopoietic cytokine granulocyte colony-stimulating factor (G-CSF). G-CSF mobilizes neutrophils indirectly by shifting the balance between CXCR4 and CXCR2 ligands [26]. In response to the release of inflammatory mediators such as TNF-α and IL-17, the adjacent vascular endothelium becomes activated. Cell surface proteins of the selectin family termed E- and P-selectin and their ligands (L-selectin) mediate this initial neutrophil capture. Neutrophil rolling through the endothelium facilitates their contact with chemotactic factors that promotes neutrophil activation [27]. Chemokines (CXCR-1 or 2 ligands, such as IL-8), the C5a fragment of the complement system, and leukotriene B₄ (LTB₄) are responsible for neutrophil mobilization to the synovial fluid [28–30].

Firm adhesion is mediated by interactions between β₂ integrins (LFA-1, CD11a/CD18, and MAC-1, CD11b/CD18) and their ligand (ICAM-1). Integrins are usually in an inactive state on neutrophil and become activated after the triggering of G protein-coupled receptors such as chemokine receptors [31]. The binding of integrins to their ligands activates signaling pathways in neutrophils stabilizing adhesion and initiating cell motility [32, 33]. This signaling also regulates actin polymerization, which controls the direction of neutrophil movement [34, 35]. The final stage in the adhesion cascade is the ultimate migration of the neutrophil from the vasculature into the inflamed tissue. Passage through the endothelial cell layer occurs both paracellularly (between endothelial cells) and by a transcellular route (over the endothelial cell). Paracellular migration of neutrophils is mediated by binding to endothelial proteins that target neutrophils to intercellular junctions and facilitate their passage through them. To reach the inflamed joint, neutrophils must pass over the basal membrane, which occurs through the degradation of extracellular matrix molecules by proteases stored inside the cells, such as matrix metalloproteinases (MMPs) and serine proteases [14].

In inflammatory foci, neutrophils find immune complexes on the synovium that bind to Fcγ receptors on the neutrophil membrane, triggering their degranulation and reactive oxygen species (ROS) production [36]. In RA pathology, oxidative stress is a result of inadequate ROS release by neutrophils [37]. Oxygen radicals cause DNA damage and oxidation of lipids, proteins, and lipoproteins and may be involved in immunoglobulin mutations that lead to rheumatoid factor (RF) formation [38, 39]. Moreover, proteins from neutrophil degranulation are found at high concentrations in the RA synovial fluid and could be responsible for cartilage and tissue damage, activation of cytokines and soluble receptors, inhibition of chondrocyte proliferation and activation of synoviocytes proliferation and invasion [40–43]. In addition, activated neutrophils also generate chemoattractants (such as IL-8 and LTB₄) that promote further neutrophil recruitment and amplify the inflammatory response (see Figure 1).
2.2. Neutrophil action in rheumatoid arthritis

Neutrophils are key cells in articular inflammation that are abundant in the synovial fluid and pannus of patients with active RA [44], a typical knee joint may have $2 \times 10^9$ cells, of which 90% are neutrophils [24]. These cells are mobilized to synovial tissue by chemoattractant mediators, such as CXCL1, CXCL2, endothelin (ET)-1, and leukotriene $B_4$, a process in which resident macrophages play a central role [11, 45, 46].

For many years, the major contribution of neutrophils to the pathology of RA was thought to be their cytotoxic potential, since neutrophils participate in the pathogenesis of arthritis by promoting the inflammatory process and cartilage degradation, as well as bone resorption. However, neutrophils are now recognized to have an active role in orchestrating the progression of inflammation through regulating the functions of other immune cells [47, 48], and current research has shown that these cells are involved in RA onset [49, 50].

In the synovial cavity, activated neutrophils exhibit an increased expression of plasma membrane receptors such as major histocompatibility complex (MHC) class II molecules and present antigens to T lymphocytes, an immune function that they share with macrophages and dendritic cells (DCs) [51]. In addition, the interaction of neutrophils with other cells induces the secretion of MMP-8 and MMP-9, and a repertoire of cytokines (IL-1β, IL-12, IL-18, IL-23,
and TNF-α) and chemokines (CCL-2, CCL-4, CCL-5, and CXCL-8), including TNF ligand superfamily member (RANKL) \[52, 53\] and TNFSF13B (also known as BLyS or BAFF) \[54\], which are implicated in the activation of osteoclasts and B lymphocytes, respectively, regulate the function of other immune cells \[48, 55–57\].

Neutrophils from patients with RA are functionally very different from those isolated from healthy individuals. RA blood neutrophils are already primed for ROS production \[58\] and striking differences in gene and protein expression exist between peripheral blood neutrophils from patients with RA and their healthy counterparts \[18\], including higher levels of membrane-expressed TNF and myeloblastin (also known as PR-3 or cANCA antigen) in RA \[59\].

In RA patients, neutrophils can be activated by immune complexes, such as RF or anti-citrullinated protein antibodies (ACPAs), both within the synovial fluid and deposited on the articular cartilage surface \[60\]. These complexes engage Fcγ receptors and thereby trigger neutrophil activation, which release ROS and RNS \[61, 62\], collagenases, gelatinases, neutrophil myeloperoxidase (MPO), elastase, and cathepsin G into the synovial fluid and joints \[14, 55, 56, 63\] due to frustrated phagocytosis \[60\].

### 2.2.1. Pain in rheumatoid arthritis and neutrophils

One of the most prevalent symptoms of RA is the increase in sensitivity to joint pain (hyperalgesia), which causes movement limitations. Despite its clinical relevance, strategies for the treatment of arthralgia remain limited. In animal models, hyperalgesia (inflammatory pain) is defined as hypernociception (a decreased nociceptive threshold) \[64\]. It is broadly accepted that articular hypernociception results mainly from the direct and indirect effects of inflammatory mediators on the sensitization (increased excitability) of primary nociceptive fibers that innervate the inflamed joints \[65–67\]. Prostaglandins and sympathetic amines are the key mediators of this process. Furthermore, other mediators, such as the cytokines TNF-α, IL-1β, IL-6, and IL-17 play a crucial role in the pathogenesis of arthritis, increasing the recruitment of neutrophils into the joint and driving the enhanced production of chemokines and degradative enzymes \[68–70\]. In addition, endothelin-1 (ET-1), acting directly or indirectly, also sensitizes primary nociceptive neurons \[71–74\].

During the inflammatory process, the migrating neutrophils participate in the cascade of events leading to mechanical hypernociception, by mediating the release of hyperalgesic molecules (such as MPO, MMPs, hypochlorite, superoxide anion, and PGE\(_2\)) capable of activating nociceptive neurons and causing pain \[17, 75–78\].

Indeed, decreased inflammation and joint destruction have been directly correlated with reduced neutrophil influx into the joints, as observed in mouse models by means of antibody blockade or the gene deletion of chemoattractant receptors such as CXCR1, CXCR2, and BLT1 (LTB\(_4\) receptor) \[15, 79\]. Therefore, the blockade of neutrophil migration could be a target in the development of new analgesic drugs \[77\].

### 2.2.2. Citrullinated autoantigens and NETs in rheumatoid arthritis

Citrullination is the natural posttranslational conversion of arginine to citrulline mediated by peptidyl arginine deiminases (PADs), enzymes present in macrophages, dendritic cells, and
neutrophils. Experimental evidence indicates that citrullination is involved in the breakdown of immune tolerance and may generate neoantigens (neoAgs) that become additional targets during epitope spreading [80]. Citrullinated residues stimulate the production of anti-citrullinated protein antibodies (ACPAs) in predisposed individuals. It has been observed that ACPAs can be present for several years before any clinical signs of arthritis appear [81–83]. A substantial increase in the number and titer of many antibodies against posttranslationally modified proteins is also seen shortly before the onset of arthritis. Citrullinated Ags have increased immunogenicity and arthritogenicity, and their presence in arthritic joints correlates with disease severity [80, 84–86].

Osteoclasts are dependent on citrullinating enzymes for their normal maturation and display citrullinated antigens on their cell surface in a non-inflamed state. In humans, the binding of ACPAs to osteoclasts in the bone compartment induces IL-8 secretion. In turn, IL-8 sensitizes and/or activates sensory neurons by binding to CXCR chemokine receptor (CXCR) 1 and CXCR2 on peripheral nociceptors [87–90], producing IL 8 dependent joint pain that is associated with ACPA-mediated bone loss.

IL-8 release contributes to the chemoattraction of neutrophils [49], which play critical roles in initiating and maintaining joint-inflammatory processes that have been described in experimental arthritis [36, 91]. However, the exact roles that neutrophils play in the posttranslational modification of proteins and disease initiation and progression in RA remain unclear. Recent evidence suggests that, among the various mechanisms by which neutrophils cause tissue damage and promote autoimmunity, aberrant formation of neutrophil extracellular traps (NETs) could play important roles in the pathogenesis of RA [50].

NETs are released during a process of cellular death named NETosis. NETosis occurs with neutrophils upon contact with bacteria, fungi [92], or under several inflammatory stimuli. This process is associated with changes in the morphology of the cells, which eventually lead to cell death with extrusion of NETs [93, 94]. This process requires calcium mobilization, reactive oxygen species (ROS) produced by NADPH oxidase, neutrophil chromatin decondensation mediated by neutrophil elastase (NE) and myeloperoxidase (MPO), and chromatin modification via the citrullination of histones by peptidyl arginine deiminase 4 (PAD4) [95–99]. NETs are a network of extracellular fibers, which contain nuclear compounds as DNA and histones and that are covered with antimicrobial enzymes and granular components, such as MPO, NE, cathepsin G, and other microbicidal peptides [93, 94]. In the extracellular environment, NET fibers entrap microorganisms, and their enzymes and granular substances reach locally high concentrations and are thus able to cleave virulence factors and kill microorganisms [95, 100, 101].

Although NETs play a key role in the defense against pathogens, they may cause undesirable effects to the host, which has increased the interest in the role of neutrophils and NETs in autoimmunity. Augmented NET formation was first described in preeclampsia and ANCA-associated vasculitis and followed by the description in a series of autoimmune conditions, including psoriasis, systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), and RA [50, 100, 102–105]. Neutrophil extracellular traps are an obvious source of nuclear material. Among these are a range of cytoplasmic and extracellular citrullinated antigens, well-established
targets of the ACPAs found in RA [50, 100]. The protein contents of NETs not only serve as targets for autoantibody and immune complex formation but also induce further NETosis, resulting in a harmful positive-feedback loop. These factors form an inflammatory microenvironment that may trigger a strong autoimmune response in individuals with the corresponding susceptibility [106, 107]. Pro-inflammatory cytokines, such as TNF-α and IL-17, as well as autoantibodies stimulate the formation of NETs and affect their protein composition [50]. Additionally, NETs have been shown to stimulate autoimmunity via the production of interferons and activation of the complement cascade. Interferons activate both the innate and adaptive immune systems, inducing a Th1 immune response and stimulating B cells toward the generation of autoantibodies [108]. The deposition of NETs observed in various inflammatory pathologies is associated with the circulating cell-free DNA (cfDNA) levels in biological fluids, such as plasma and serum, from patients [100, 101, 109]. Therefore, circulatory cfDNA could eventually be utilized as a marker of NETs in these pathologies, while the determination of the DNA levels might facilitate the monitoring of disease activity and assessment of the effectiveness of a selected therapeutic strategy.

Neutrophils have been traditionally viewed as short-lived cells that die at sites of inflammation; however, some evidence suggests that they can prolong their life span upon specific stimuli and transmigrate away from inflammatory loci [48, 110, 111]. Conditions within the synovial joint, such as hypoxia [112] and the presence of antiapoptotic cytokines (including TNF, granulocyte-macrophage colony-stimulating factor (GM CSF), and IL 8) [113, 114], can increase neutrophil survival for up to several days [115, 116], which contributes to enhanced tissue damage.

As described above, neutrophils play an essential role on innate and adaptive immunity in RA physiopathology, contributing to tissue lesions in RA, and therefore represent a promising pharmacological target in RA. Pharmacological strategies that inhibit or reduce neutrophil mobilization or activation could be successful in RA treatment.

3. Neutrophils as therapeutic targets

Animal models have been extensively used in studies of RA pathogenesis. Despite the inherent limitations of all animal models, several rodent models have greatly contributed to the overall knowledge of important processes/mediators in the generation of inflammation, cartilage destruction, and bone resorption. In addition, the pharmaceutical industry has used these models for testing potential anti-arthritic agents, leading to important advances in therapeutic interventions for this destructive disease [117]. Such models include collagen-induced arthritis, collagen antibody-induced arthritis, zymosan-induced arthritis, the methylated BSA model, and genetically manipulated or spontaneous arthritis models such as the TNF-α-transgenic mouse, K/BxN mouse, and Skg mouse [118]. Many of these models show that neutrophils are the first immune cells to enter the arthritic joint, and that early measures of joint inflammation correlate with neutrophil infiltration [45, 119, 120]. In this section, we highlight pharmacological approaches targeting neutrophil recruitment and activity, which present a therapeutic benefit to patients with RA.
The current treatments available to RA patients include glucocorticoids, non-steroidal anti-inflammatory drugs, and disease-modifying antirheumatic drugs. Only disease-modifying agents—and to some extent glucocorticoids—can impede or halt the inflammatory and destructive disease processes [121]. With a more complete understanding of the immune-inflammatory events that occur in the pathogenesis of RA, scientists have developed therapeutic strategies that include monoclonal antibodies and receptor constructs, which target specific soluble or cell-surface molecules of interest. Biological agents such as monoclonal antibodies and recombinant proteins that target TNF-α, CD20, CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), and the IL-1 receptor as well as therapies based on the blockade of T-cell and B-cell functions have shown efficacy in controlling the physical signs and pain associated with RA [122, 123].

Many interventions used to treat RA exert inhibitory effects on neutrophil responses in inflammation. However, non-steroid anti-inflammatory drugs (NSAIDS), DMARDs, and biologics do not specifically target neutrophil function [124].

Most NSAIDs inhibit the action of the cyclo-oxygenase-1 and -2 (COX-1 and -2) enzymes, which metabolize arachidonic acid into inflammatory mediators of the prostaglandin family. NSAIDs have been shown to inhibit neutrophil adherence, decrease degranulation and oxidant production, inhibit neutrophil elastase activity, and induce neutrophil apoptosis [125–127]. Corticosteroids induce anti-inflammatory signals by several mechanisms; a major one may be to reduce the expression of cytokine-induced genes. They enter all cells and bind to the cytoplasmic steroid receptor, and then this complex translocates to the nucleus where it is recognized by specific DNA sequences. The major effect of binding to DNA is the suppression of transcription by opposing the activation of the transcription factors AP-1 and NF-κB [128]. Corticosteroids have been shown to inhibit neutrophil degranulation and ROS production, decrease production of inflammatory mediators, and prevent neutrophil adhesion and migration into RA joints [44, 129–131]. The most widely used DMARD in clinic settings is methotrexate, a compound that blocks folic acid metabolism. Its benefits in RA include the stimulation of neutrophil apoptosis [116], inhibition of the NF-κB pathway [132], and reduced adhesion molecule expression and LTB₄ production [133], consequently decreasing neutrophil recruitment and ROS production [134].

Anti-TNF-α therapies are also widely used for the treatment of RA patients. TNF primes the neutrophil respiratory burst, upregulates the expression of adhesion molecules, cytokines and chemokines, and at high local concentrations can stimulate ROS production in adherent neutrophils [135–138]. Three different TNF inhibitors are available for RA patients who fail to respond adequately to standard DMARD therapy. Infliximab and adalimumab are monoclonal antibodies against TNF, whereas etanercept is a TNFRII fusion protein. All three drugs sequester soluble TNF [139]. Reports regarding the direct effect of anti-TNF agents on neutrophils have been published, and these drugs have been shown to decrease the mobilization of neutrophils from the peripheral blood to inflamed joints [140], decrease ex vivo neutrophil ROS production [20], and reduce neutrophil chemotactic and adhesive properties [141].
Tocilizumab, a monoclonal antibody that blocks the soluble and tissue-expressed IL-6 receptor, is also proving to be a highly effective biologic agent in RA treatment [142]. Neutrophils are a major source of soluble IL-6 receptors, which they shed in large quantities when activated, and their accumulation in high numbers within the synovial joint could contribute significantly to IL-6 signaling within the synovium through trans-signaling [143]. In vivo therapeutic blockade of IL-6 with tocilizumab induces transient neutropenia caused by apoptosis or phagocytosis of apoptotic neutrophils but does not impair antibacterial neutrophil functions [144].

Despite the clinical efficacy of these therapies, many patients do not exhibit significant responses or discontinue treatment because of adverse effects. In addition, the limited availability of biological agents in developing countries, the need for parenteral administration of these products, and the high cost restrict access to such therapies for many RA patients worldwide, and this promotes a continuous search for new therapeutic targets and the development of new drugs [145]. Due to these limitations, interest has grown in the use of alternative treatments and herbal therapies for arthritis patients [146, 147] (Table 1).

| Therapy                          | Effect on neutrophil response                                                                 | Reference    |
|---------------------------------|------------------------------------------------------------------------------------------------|--------------|
| Non-steroidal anti-inflammatory drugs (NSAIDS) | Inhibit neutrophil adherence, decrease neutrophil degranulation and ROS production, inhibit neutrophil elastase activity, and induce neutrophil apoptosis | [125–127]   |
| Corticosteroids                 | Inhibit neutrophil degranulation and ROS production, decrease the production of inflammatory mediators, and prevent neutrophil adhesion and migration into RA joints | [44, 129–131]|
| Disease-modifying antirheumatic drugs (DMARDs) | Stimulate neutrophil apoptosis, inhibit the NF-κB pathway, and reduce adhesion molecule expression, LTB₄ production, neutrophil recruitment, and ROS production | [116, 132–134]|
| TNF-α inhibitors                | Decrease neutrophil mobilization from the peripheral blood to inflamed joints and reduce ex vivo neutrophil ROS production and neutrophil chemotactic and adhesive properties | [20, 140, 141]|
| IL-6 inhibitor                  | Induce transient neutropenia caused by apoptosis or phagocytosis of apoptotic neutrophils but not impair antibacterial neutrophil functions | [144]        |

Table 1. Current therapeutic targets for arthritis and their effect on neutrophils.
4. Plant-derived molecules as emerging therapies for arthritis

Current arthritis treatments result in unwanted side effects and tend to be expensive, and natural products devoid of such disadvantages offer a novel opportunity. The use of natural products represents a promising alternative to treat rheumatic diseases, in particular by acting as therapeutic adjuvants to reduce the daily doses of conventional drugs that RA patients administer [148–150]. In this section, we highlight future perspectives in the treatment of RA with natural compounds, mainly herbal compounds, to minimize the harmful effects of the over-activation of neutrophils.

Decreased inflammation and joint destruction have been directly correlated with reduced neutrophil influx into the joints, as observed in mouse models by means of antibody blockade or the gene deletion of chemoattractant receptors such as CXCR1, CXCR2, and BLT1 (LTB4 receptor) [15, 79]. The prospect of new drugs obtained from herbal products (or from structures of herbal products) plays a compelling role in drug discovery and development [151].

As previously mentioned, pharmacologic treatment options for arthritis are diverse and present several side effects. Furthermore, the high costs and increased risk of malignancies limit the use of such agents. Because of these limitations, there is a growing interest in the use of natural products as therapies or adjunct therapies [22]. Plant-derived products such as polyphenols, sesquiterpenes, flavonoids, and tetranortriterpenoids, which are herbal metabolites, are considered to have potential activity to block inflammation, and they may provide new therapeutic agents and cost-effective treatments [22, 23]. These natural products have attracted considerable interest over the past decade because of their multiple beneficial effects, such as their antioxidant, anti-inflammatory, antiproliferative, and immunomodulatory properties. In this section, we discuss the plant-derived products that have been most studied in RA experimental models and/or clinical trials (Table 2).

4.1. Quercetin

Quercetin (Figure 2a) is the major dietary flavonol found in fruits, vegetables, and beverages, such as tea and red wine [152]. Several epidemiological and experimental studies support the antioxidant, anti-inflammatory, antiangiogenic, antiproliferative, and proapoptotic effects of this molecule [153–155]. Preclinical studies on primary cells and animal models, as

| Compound               | Chemical class     | Arthritis experimental model     | Reference |
|------------------------|--------------------|----------------------------------|-----------|
| Quercetin              | Flavonoid          | Adjuvant-induced arthritis       | [156]     |
| Methyl gallate         | Polyphenol         | Zymosan-induced arthritis        | [171]     |
| Gedunin                | Tetranortriterpenoid| Zymosan-induced arthritis        | [176]     |
| Epigallocatechin gallate| Polyphenol         | Collagen-induced arthritis       | [179]     |
| Curcumin               | Polyphenol         | Collagen-induced arthritis       | [191]     |

Table 2. Herbal products that exhibit anti-arthritic potential in animal models.
well as clinical studies, suggest an inhibitory action of quercetin in RA. Quercetin has been reported to lower the levels of IL-1β, C-reactive protein, and monocyte chemotactic protein-1 (MCP-1), and restore plasma antioxidant capacity. In addition, quercetin increased the expression of hemeoxygenase-1 in the joints of arthritic rats. Finally, quercetin inhibited the twofold increase in NF-κB activity observed in joints after arthritis induction [156].

There are divergent data on the effect of quercetin in neutrophils. For instance, in vitro, quercetin inhibited myeloperoxidase activity [157] but had no effect on lipopolysaccharide-induced neutrophil surface expression of the adhesion molecules L-selectin (CD62L) and β2 integrin (CD11b/Mac1), [158] which are related to rolling and firm adhesion, respectively [159]. In paw edema induced by carrageen, quercetin did not inhibit the increase in myeloperoxidase, which is used as a marker of neutrophil recruitment [160]. Therefore, it seems unlikely that quercetin would inhibit neutrophil recruitment [158]. On the other hand, quercetin inhibits the fMLP-induced increase in intracellular calcium, [158] which is necessary for actin polymerization and consequently neutrophil migration [159]. In addition, in vitro, quercetin blocked human neutrophil mobilization through the inhibition of the cellular signaling responsible for actin polymerization in association with the down-regulation of adhesion molecules [161], indicating that treatment with this flavonoid is a conceivable approach to control excessive neutrophil recruitment during inflammation and to prevent neutrophil-mediated tissue lesions [162] (Table 3).

4.2. *Schinus terebinthifolius* and methyl gallate

*S. terebinthifolius* Raddi (Anacardiaceae) is a native plant from South America. It has been used in folk medicine as teas, infusions, or tinctures, as an anti-inflammatory, febrifuge, analgesic,
Quercetin

Inhibits IL-1β, C-reactive protein, and MCP-1 levels. Restores plasma antioxidant capacity, increases HO-1 expression, and inhibits NF-κB activity in joints

Inhibits myeloperoxidase activity in neutrophils and blocks neutrophil mobilization

Methyl gallate

Reduces edema formation, total leukocyte accumulation, neutrophil migration and IL-6, TNF-α, CXCL-1, IL-1β, LTB₄, and PGE₂ production in zymosan-induced arthritis. Impairs neutrophil chemotaxis and adhesion

Gedunin

Attenuates zymosan-induced articular edema, neutrophil migration, hypernociception, and the production of IL-6, TNF-α, LTB₄, and PGE₂, and prevents increases in lipid bodies. Decreases neutrophil shape changes, chemotaxis, and lipid body formation

Epigallocatechin gallate

Ameliorates the severity of arthritis and regulates the expression of cytokines, chemokines, MMPs, ROS, NO, COX-2, and PGE₂. Affects neutrophil functionality and inhibits IL-8 and MIP-3α expression

Curcumin

Suppresses collagen-induced arthritis by reducing cellular infiltration, synovial hyperplasia, cartilage destruction, and bone erosion. Blocks neutrophil recruitment

Table 3. Major molecular targets and anti-arthritic mechanisms of herbal products.

and depurative agent and to treat urogenital system illnesses [163]. Scientific reports demonstrated that *S. terebinthifolius* extracts and fractions are rich in polyphenols and display antioxidant, antibacterial, and antiallergic properties in different experimental models [164–166]. The HPLH chromatograms of hydroalcoholic extracts from *S. terebinthifolius* leaves (ST-70) reveal that methyl gallate (MG, Figure 2b) is one of the major polyphenol components of the ST-70 extract [167]. Methyl gallate has been extensively studied because of its antioxidant, antitumor, and antimicrobial activities [168–170]. Pharmacological studies have shown that ST-70 and MG also have an anti-inflammatory effect and may have potential activity against arthritis. Pretreatment with ST-70 or MG markedly reduced knee-joint thickness, total leukocyte (mainly neutrophil) infiltration, and reduced the production of inflammatory mediators associated with arthritis such as CXCL-1/KC, IL-6, TNF-α, IL-1β, LTB₄, and PGE₂. ST-70 and MG also inhibited murine neutrophil chemotaxis induced by CXCL-1/KC *in vitro*, and
MG impaired the adhesion of these cells to TNF-α-primed endothelial cells [167, 171]. These results provide some evidence that MG inhibits neutrophil activation and adhesion molecules expression and consequently prevents the neutrophil entry into inflammatory sites (Table 3).

Moreover, unlike potassium diclofenac, the long-term oral administration of ST-70 does not induce lethality or gastric damage in mice, which suggests that ST-70 could be used to treat inflammatory conditions such as arthritis with less toxicity [167].

4.3. Carapa guianensis and gedunin

*C. guianensis* Aublet is a member of the Meliaceae family that is widely used in folk medicine in Brazil and other countries surrounding the Amazon rainforest [172]. Anti-inflammatory and analgesic activities are among the most remarkable properties attributed by ethnopharmacological research to the oil extracted from *C. guianensis* seeds, mainly for rheumatic pain and arthritis [172, 173]. *C. guianensis* oil and six different tetranortriterpenoids (TNTP) isolated from the oil were able to significantly inhibit zymosan-induced knee joint edema formation and protein extravasation. TNTP pretreatment inhibited the increase in total leukocyte and neutrophil numbers in the synovial fluid. TNTP also impaired the production of TNF-α, IL-1β, and CXCL-8/IL-8, and significantly inhibited the expression of the NF-κB p65 subunit [174].

Gedunin (Figure 2c) is a natural tetranortriterpenoid isolated from vegetal species of the Meliaceae family and is known to inhibit the stress-induced chaperone heat shock protein (Hsp) 90 [175]. Mouse pretreatment and posttreatment with gedunin impaired zymosan-induced edema formation and total leukocyte influx mainly due to the inhibition of neutrophil migration and reduced articular hypernociception. Gedunin also reduced the in situ expression of preproET-1 mRNA and IL-6, TNF-α, LTB₄, and PGE₂ production and prevented increases in the number of lipid bodies in synovial leukocytes [176]. Lipid bodies are important sites for the synthesis and storage of lipid mediators and they increase in number during inflammatory responses [177]. In neutrophils, gedunin impaired ET-1-induced shape changes, blocked ET-1- and LTB₄-induced chemotaxis, decreased ET-1-induced lipid body formation and impaired neutrophil adhesion to TNF-α-primed endothelial cells [176]. The combined in vitro and in vivo effects of gedunin reveal its potential as an anti-arthritic candidate, especially its direct effect on key cells involved in articular inflammation such as neutrophils (Table 3).

4.4. Epigallocatechin gallate

Epigallocatechin gallate (EGCG, Figure 2d) is one of the main components of green tea [178]. It has antioxidative, anti-inflammatory, antitumor, and chemopreventive properties. The potential disease-modifying effects of green tea on arthritis have been reported; for example, in a mouse model of RA, the induction and severity of arthritis was ameliorated by the prophylactic administration of green tea polyphenols [179]. Subsequent studies suggested that EGCG possesses remarkable potential to prevent chronic diseases like OA and RA [180–184]. The anti-inflammatory and anti-arthritic effects of EGCG are supported by in vitro and in vivo data indicating that EGCG can regulate the expression of cytokines, chemokines, MMPs,
ROS, nitric oxide (NO), COX-2, and PGE\textsubscript{2} in cell types relevant to the pathogenesis of RA [179–184]. In \textit{in vivo} studies, EGCG was found to inhibit inflammation in mouse models by affecting the functioning of T cells and neutrophils [185, 186]. IL-8 is the most powerful chemo-attractant for neutrophils in the target tissue. EGCG is a very effective inhibitor of IL-1β and of TNF-α-induced IL-8 and macrophage-inflammatory protein-3α (MIP-3α) expression in different cell types [187–189]. These \textit{in vitro} and \textit{in vivo} observations indicated the efficacy of EGCG and demonstrate that it can modulate multiple signal transduction pathways in a fashion that suppresses the expression of inflammatory mediators that play a role in the pathogenesis of arthritis (Table 3).

4.5. Curcumin

Curcumin (Figure 2e) is a yellow-colored polyphenol found in the rhizome of turmeric. It has antioxidant, anti-inflammatory, antiapoptotic, and anticarcinogenic properties [190]. Oral administration of curcumin suppressed type II collagen-induced arthritis (CIA) in mice by reducing cellular infiltration, synovial hyperplasia, cartilage destruction, and bone erosion. Moreover, the production of MMP-1 and MMP-3 was inhibited by curcumin in CIA and in TNF-α-stimulated RA fibroblast-like synoviocytes (RA-FLS) and chondrocytes [191].

\textit{In vitro}, it has been reported that curcumin decreases IL-1β-induced expression of the pro-inflammatory cytokine IL-6 and vascular endothelial growth factor (VEGF) in RA-FLS [192]. In addition, curcumin blocks neutrophil recruitment through the inhibition of cellular signaling responsible for actin polymerization in association with the down-regulation of adhesion molecules [193]. It has also been shown to induce apoptosis of RA-FLS (which are resistant to apoptosis) by increasing the expression of the proapoptotic protein Bax and down-regulating the expression of the antiapoptotic protein Bcl-2 [190]. Some molecular mechanisms related to curcumin have been identified. In a human synovial fibroblast cell line (MH7A) stimulated with IL-1β, curcumin blocked the activation of the NF-κB pathway and induced deactivation of the ERK-1/2 pathway [192]. In addition, this polyphenol inhibited activating phosphorylation of protein kinase Cδ (PKCδ) in CIA, RA-FLS, and chondrocytes. Curcumin also suppressed JNK and c-Jun activation in those cells [191].

In a clinical trial with RA patients, curcumin reduced reported pain, tenderness, and swelling of joints [194]. A curcumin-based medicine, Meriva®, demonstrated efficacy in clinical trials with patients with osteoarthritis by reducing reported pain [195]. In another clinical trial, treatment with Meriva® reduced stiffness and physical signs of RA (treadmill test) along with IL-1, IL-6, and VCAM-1 production [196] (Table 3).

5. Conclusion

In RA, neutrophils are key cells that are recognized to play an active role in orchestrating the progress of inflammation, through the release of pro-inflammatory cytokines, ROS, RNS, and NETs, which potentially affect the activities of both neutrophils and other cell types, such as resident mononuclear cells and chondrocytes. In addition, neutrophils participate in the
cascade of events leading to mechanical hypernociception. Therefore, neutrophils participate in the pathogenesis of arthritis by promoting the inflammatory process, degradation of cartilage, and bone resorption. The modulation of neutrophil migration and functions in RA can be considered a potential target for pharmacological intervention in arthritis. The pharmacologic treatment options for arthritis are diverse. High costs and an increased risk of malignancies limit the use of these agents, in addition to the potential for side effects that all therapies possess. Nevertheless, herbal metabolites with anti-inflammatory activity and inhibitory action in neutrophils may provide new therapeutic agents and cost-effective treatments.

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References

[1] Wong SH, Lord JM. Factors underlying chronic inflammation in rheumatoid arthritis (in Eng). Archivum Immunologiae et Therapiae Experimentalis (Warsz). Nov-Dec 2004;52(6):379–388

[2] Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis (in Eng). Lancet. Sep 2010; 376(9746):1094–1108

[3] Helmick CG. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I (in Eng). Arthritis & Rheumatology. Jan 2008;58(1):15–25

[4] Singh JA. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis (in Eng). Arthritis & Rheumatology. Jan 2016;68(1):1–26
[5] Arend WP. The pathophysiology and treatment of rheumatoid arthritis (in Eng). Arthritis & Rheumatology. Apr 1997;40(4):595–597

[6] Issekutz AC, Meager A, Otterness I, Issekutz TB. The role of tumour necrosis factor-alpha and IL-1 in polymorphonuclear leucocyte and T lymphocyte recruitment to joint inflammation in adjuvant arthritis (in Eng). Clinical & Experimental Immunology. Jul 1994;97(1):26–32

[7] Kasama T, Miwa Y, Isozaki T, Odai T, Adachi M, Kunkel SL. Neutrophil-derived cytokines: potential therapeutic targets in inflammation (in Eng). Current Drug Targets—Inflammation & Allergy. Jun 2005;4(3):273–279

[8] Mitani Y, Honda A, Jasin HE. Polymorphonuclear leukocyte adhesion to articular cartilage is inhibited by cartilage surface macromolecules (in Eng). Rheumatology International. Jul 2001;20(5):180–185

[9] Maini RN, Taylor PC. Anti-cytokine therapy for rheumatoid arthritis (in Eng). Annual Review of Medicine. 2000;51:207–229

[10] Feldmann M, Charles P, Taylor P, Maini RN. Biological insights from clinical trials with anti-TNF therapy (in Eng). Springer Seminars in Immunopathology. 1998;20(1–2):211–228

[11] Conte FEP. Endothelins modulate inflammatory reaction in zymosan-induced arthritis: Participation of LTB4, TNF-alpha, and CXCL-1 (in Eng). Journal of Leukocyte Biology. Sep 2008;84(3):652–660

[12] Henriques MG. New Therapeutic Targets for the Control of Inflammatory Arthritis: A Pivotal Role for Endothelins, Innovative Rheumatology, Dr. Hiroaki Matsuno (Ed.), InTech. Jan 2013.

[13] Dayer JM. The pivotal role of interleukin-1 in the clinical manifestations of rheumatoid arthritis (in Eng). Rheumatology (Oxford). May 2003;42(Suppl 2):ii3–ii10

[14] Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation (in Eng). Nature Review Immunology. Mar 2013;13(3):159–175

[15] Wipke BT, Allen PM. Essential role of neutrophils in the initiation and progression of a murine model of rheumatoid arthritis (in Eng). Journal of Immunology. Aug 2001;167(3):1601–1608

[16] Bombini G, Canetti C, Rocha FA, Cunha FQ. Tumour necrosis factor-alpha mediates neutrophil migration to the knee synovial cavity during immune inflammation (in Eng). European Journal of Pharmacology. Aug 2004;496(1-3):197–204

[17] Guerrero AT. Involvement of LTB4 in zymosan-induced joint nociception in mice: Participation of neutrophils and PGE2 (in Eng). Journal of Leukocyte Biology. Jan 2008;83(1):122–130

[18] Wright HL, Moots RJ, Edwards SW. The multifactorial role of neutrophils in rheumatoid arthritis (in Eng). Nature Review Rheumatology. Oct 2014; 10(10):593–601
[19] Kraan MC, de Koster BM, Elferink JG, Post WJ, Breedveld FC, Tak PP. Inhibition of neutrophil migration soon after initiation of treatment with leflunomide or methotrexate in patients with rheumatoid arthritis: Findings in a prospective, randomized, double-blind clinical trial in fifteen patients (in Eng). Arthritis & Rheumatology. Jul 2000;43(7):1488–1495

[20] den Broeder AA, Wanten GJ, Oyen WJ, Naber T, van Riel PL, Barrera P. Neutrophil migration and production of reactive oxygen species during treatment with a fully human anti-tumor necrosis factor-alpha monoclonal antibody in patients with rheumatoid arthritis (in Eng). Journal of Rheumatology. Feb 2003;30(2):232–237

[21] Ferrandi C. Phosphoinositide 3-kinase gamma inhibition plays a crucial role in early steps of inflammation by blocking neutrophil recruitment (in Eng). Journal of Pharmacology & Experimental Therapy. Sep 2007;322(3):923–930

[22] Khanna D. Natural products as a gold mine for arthritis treatment (in Eng). Current Opinion in Pharmacology. Jun 2007;7(3):344–351

[23] Singh R, Akhtar N, Haqqi TM. Green tea polyphenol epigallocatechin-3-gallate: Inflammation and arthritis [corrected] (in Eng). Life Science. Jun 2010;86(25-26):907–918

[24] Cross A, Bakstad D, Allen JC, Thomas L, Moores RJ, Edwards SW. Neutrophil gene expression in rheumatoid arthritis (in Eng). Pathophysiology. Oct 2005;12(3):191–202

[25] Sadik CD, Kim ND, Luster AD. Neutrophils cascading their way to inflammation (in Eng). Trends in Immunology. Oct 2011;32(10):452–460

[26] Semerad CL, Liu F, Gregory AD, Stumpf K, Link DC. G-CSF is an essential regulator of neutrophil trafficking from the bone marrow to the blood (in Eng). Immunity. Oct 2002;17(4):413–423

[27] Sanz MJ, Kubes P. Neutrophil-active chemokines in in vivo imaging of neutrophil trafficking (in Eng). European Journal of Immunology. Feb 2012;42(2):278–283

[28] Chen M. Neutrophil-derived leukotriene B4 is required for inflammatory arthritis (in Eng). Journal of Experimental Medicine. Apr 2006;203(4):837–842

[29] Chou RC. Lipid-cytokine-chemokine cascade drives neutrophil recruitment in a murine model of inflammatory arthritis (in Eng). Immunity. Aug 2010;33(2):266–278

[30] Sadik CD, Kim ND, Iwakura Y, Luster AD. Neutrophils orchestrate their own recruitment in murine arthritis through C5aR and FcγR signaling (in Eng). Proceedings of the National Academy of Sciences United States of America. Nov 2012;109(46):E3177–E3185

[31] Tarrant TK, Patel DD. Chemokines and leukocyte trafficking in rheumatoid arthritis (in Eng). Pathophysiology. Feb 2006;13(1):1–14

[32] Cicchetti G, Allen PG, Glogauer M. Chemotactic signaling pathways in neutrophils: From receptor to actin assembly. (in Eng). Critical Reviews in Oral Biology & Medicine. 2002;13(3):220–228
[33] Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: The leukocyte adhesion cascade updated. (in Eng), Nature Reviews Immunology. Sep 2007;7(9):678–89

[34] Stillie R, Farooq SM, Gordon JR, Stadnyk AW. The functional significance behind expressing two IL-8 receptor types on PMN (in Eng). Journal of Leukocyte Biology. Sep 2009;86(3):529–543

[35] Futosi K, Fodor S, Mócsai A. Neutrophil cell surface receptors and their intracellular signal transduction pathways (in Eng). International Immunopharmacology. Nov 2013;17(3):638–650

[36] Pillinger MH, Abramson SB. The neutrophil in rheumatoid arthritis (in Eng). Rheumatic Disease Clinics of North America. Aug 1995;21(3):691–714

[37] Cedergren J, Forslund T, Sundqvist T, Skogh T. Intracellular oxidative activation in synovial fluid neutrophils from patients with rheumatoid arthritis but not from other arthritis patients (in Eng). Journal of Rheumatology. Nov 2007;34(11):2162–2170

[38] Hitchon CA, El-Gabalawy HS. Oxidation in rheumatoid arthritis (in Eng). Arthritis Research & Therapy. 2004;6(6):265–278

[39] Rasheed Z. Hydroxyl radical damaged immunoglobulin G in patients with rheumatoid arthritis: Biochemical and immunological studies (in Eng). Clinical Biochemistry. Jun 2008;41(9):663–669

[40] Elsaid KA, Jay GD, Chichester CO. Detection of collagen type II and proteoglycans in the synovial fluids of patients diagnosed with non-infectious knee joint synovitis indicates early damage to the articular cartilage matrix (in Eng). Osteoarthritis Cartilage. Sep 2003;11(9):673–680

[41] Katano M. Implication of granulocyte-macrophage colony-stimulating factor induced neutrophil gelatinase-associated lipocalin in pathogenesis of rheumatoid arthritis revealed by proteome analysis (in Eng). Arthritis & Research Therapy. 2009;11(1):R3

[42] Wang CH. Expression of CD147 (EMMPRIN) on neutrophils in rheumatoid arthritis enhances chemotaxis, matrix metalloproteinase production and invasiveness of synoviocytes (in Eng). Journal of Cell & Molecular Medicine. Apr 2011;15(4):850–860

[43] Lefrançais E. IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G (in Eng). Proceedings of the National Academy of Sciences United States of America. Jan 2012;109(5):1673–1678

[44] Wittkowski H. Effects of intra-articular corticosteroids and anti-TNF therapy on neutrophil activation in rheumatoid arthritis (in Eng). Annals in Rheumatic Diseases. Aug 2007;66(8):1020–1025

[45] Conte FP, Menezes-de-Lima O, Verri WA, Cunha FQ, Penido C, Henriques MG. Lipoxin A4 attenuates zymosan-induced arthritis by modulating endothelin-1 and its effects (in Eng). British Journal of Pharmacology. Oct 2010;161(4):911–924
[46] Mathis S, Jala VR, Haribabu B. Role of leukotriene B4 receptors in rheumatoid arthritis (in Eng). Autoimmunity Reviews. Nov 2007;7(1):12–17

[47] Firestein, GS. Immunologic Mechanisms in the Pathogenesis of Rheumatoid Arthritis. Journal of Clinical Rheumatology. June 2005; 11(3):S39–S44

[48] Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity (in Eng). Nature Review Immunology. Aug 2011;11(8):519–531

[49] Catrina AI, Svensson CI, Malmström V, Schett G, Klareskog L. Mechanisms leading from systemic autoimmunity to joint-specific disease in rheumatoid arthritis (in Eng). Nature Review Rheumatology. Feb 2017;13(2):79–86

[50] Khandpur R. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis (in Eng). Science Translational Medicine. Mar 2013;5(178):178ra40

[51] Cross A, Bucknall RC, Cassatella MA, Edwards SW, Moots RJ. Synovial fluid neutrophils transcribe and express class II major histocompatibility complex molecules in rheumatoid arthritis (in Eng). Arthritis & Rheumatology. Oct 2003;48(10):2796–2806

[52] Woodfin A, Voisin MB, Nourshargh S. Recent developments and complexities in neutrophil transmigration (in Eng). Current Opinion in Hematology. Jan 2010;17(1):9–17

[53] Chakravarti A, Raquil MA, Tessier P, Poubelle PE. Surface RANKL of Toll-like receptor 4-stimulated human neutrophils activates osteoclastic bone resorption (in Eng). Blood. Aug 2009;114(8):1633–1644

[54] Assi LK, et al. Tumor necrosis factor alpha activates release of B lymphocyte stimulator by neutrophils infiltrating the rheumatoid joint (in Eng). Arthritis & Rheumatology. Jun 2007;56(6):1776–1786

[55] Cascão R, Rosário HS, Souto-Carneiro MM, Fonseca JE. Neutrophils in rheumatoid arthritis: More than simple final effectors (in Eng). Autoimmunity Review. Jun 2010;9(8):531–535

[56] Németh T, Mócsai A. The role of neutrophils in autoimmune diseases (in Eng). Immunology Letters. Mar 2012;143(1):9–19

[57] Soehnlein O, Steffens S, Hidalgo A, Weber C. Neutrophils as protagonists and targets in chronic inflammation. Nature Review Immunology, Apr 2017; 17(4):248–261

[58] Eggleton P, Wang L, Penhallow J, Crawford N, Brown KA. Differences in oxidative response of subpopulations of neutrophils from healthy subjects and patients with rheumatoid arthritis (in Eng). Annals in Rheumatic Diseases. Nov 1995;54(11):916–923

[59] Wright HL, Chikura B, Bucknall RC, Moots RJ, Edwards SW. Changes in expression of membrane TNF, NF-[kappa]B activation and neutrophil apoptosis during active and resolved inflammation (in Eng). Annals in Rheumatic Diseases. Mar 2011;70(3):537–543
[60] Rollet-Labelle E, Vaillancourt M, Marois L, Newkirk MM, Poubelle PE, Naccache PH. Cross-linking of IgGs bound on circulating neutrophils leads to an activation of endothelial cells: Possible role of rheumatoid factors in rheumatoid arthritis-associated vascular dysfunction (in Eng). Journal of Inflammation (London). Jul 2013;10(1):27

[61] Kundu S, Ghosh P, Datta S, Ghosh A, Chattopadhyay S, Chatterjee M. Oxidative stress as a potential biomarker for determining disease activity in patients with rheumatoid arthritis (in Eng). Free Radical Research. Dec 2012;46(12):1482–1489

[62] Khojah HM, Ahmed S, Abdel-Rahman MS, Hamza AB. Reactive oxygen and nitrogen species in patients with rheumatoid arthritis as potential biomarkers for disease activity and the role of antioxidants (in Eng). Free Radical Biology Medicine. Aug 2016;97:285–291

[63] Murphy G, Nagase H. Reappraising metalloproteinases in rheumatoid arthritis and osteoarthritis: destruction or repair? (in Eng). Nature Clinical Practice Rheumatology. Mar 2008;4(3):128–135

[64] Ren K, Dubner R. Interactions between the immune and nervous systems in pain (in Eng). Nature Medicine. Nov 2010;16(11):1267–1276

[65] McDougall JJ. Arthritis and pain. Neurogenic origin of joint pain (in Eng). Arthritis & Research Therapy. 2006;8(6):220

[66] Schaible HG, Ebersberger A, Von Banchet GS. Mechanisms of pain in arthritis (in Eng). Annals of the New York Academy of Sciences. Jun 2002;966:343–354

[67] Schaible HG, Grubb BD. Afferent and spinal mechanisms of joint pain (in Eng). Pain. Oct 1993;55(1):5–54

[68] Arend WP, Dayer JM. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor alpha in rheumatoid arthritis (in Eng). Arthritis & Rheumatology. Feb 1995;38(2):151–160

[69] Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis (in Eng). Journal of Clinical Investigation. Nov 2008;118(11):3537–3545

[70] Pinto LG, et al. IL-17 mediates articular hypernociception in antigen-induced arthritis in mice (in Eng). Pain. Feb 2010;148(2):247–256

[71] Ferreira SH, Romitelli M, de Nucci G. Endothelin-1 participation in overt and inflammatory pain (in Eng). Journal of Cardiovascular Pharmacology. 1989;13(Suppl 5):S220–2

[72] Verri WA, Schivo IR, Cunha TM, Liew FY, Ferreira SH, Cunha FQ. Interleukin-18 induces mechanical hypernociception in rats via endothelin acting on ETB receptors in a morphine-sensitive manner (in Eng). Journal of Pharmacology & Experimental Therapy. Aug 2004;310(2):710–717

[73] Verri WA, et al. IL-15 mediates immune inflammatory hypernociception by triggering a sequential release of IFN-gamma, endothelin, and prostaglandin (in Eng). Proceedings of the National Academy of Science United States of America. Jun 2006;103(25):9721–9725
[74] Verri WA, et al. Antigen-induced inflammatory mechanical hypernociception in mice is mediated by IL-18 (in Eng). Brain Behavioral Immunology. Jul 2007;21(5):535–543

[75] Wang ZQ, et al. A newly identified role for superoxide in inflammatory pain (in Eng). Journal of Pharmacology & Experimental Therapy. Jun 2004;309(3):869–878

[76] Ting E, et al. Role of complement C5a in mechanical inflammatory hypernociception: potential use of C5a receptor antagonists to control inflammatory pain (in Eng). British Journal of Pharmacology. Mar 2008;153(5):1043–1053

[77] Cunha TM, et al. Crucial role of neutrophils in the development of mechanical inflammatory hypernociception (in Eng). Journal of Leukocyte Biology. Apr 2008;83(4):824–832

[78] Gokin AP, Fareed MU, Pan HL, Hans G, Strichartz GR, Davar G. Local injection of endothelin-1 produces pain-like behavior and excitation of nociceptors in rats (in Eng). Journal of Neuroscience. Jul 2001;21(14):5358–5366

[79] Tanaka D, Kagari T, Doi H, Shimozato T. Essential role of neutrophils in anti-type II collagen antibody and lipopolysaccharide-induced arthritis (in Eng). Immunology. Oct 2006;119(2):195–202

[80] Kidd BA, et al. Epitope spreading to citrullinated antigens in mouse models of autoimmune arthritis and demyelination (in Eng). Arthritis & Research Therapy. 2008;10(5):R119

[81] Brink M, et al. Anti-carbamylated protein antibodies in the pre-symptomatic phase of rheumatoid arthritis, their relationship with multiple anti-citrulline peptide antibodies and association with radiological damage (in Eng). Arthritis & Research Therapy. Feb 2015;17:25

[82] Sokolove J, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis (in Eng). PLoS One. 2012;7(5):e35296

[83] van de Stadt LA, et al. Development of the anti-citrullinated protein antibody repertoire prior to the onset of rheumatoid arthritis (in Eng). Arthritis Rheumatology. Nov 2011;63(11):3226–3233

[84] Lundberg K, et al. Citrullinated proteins have increased immunogenicity and arthritogenicity and their presence in arthritic joints correlates with disease severity (in Eng). Arthritis & Research Therapy. 2005;7(3):R458–67

[85] Sokolove J, Zhao X, Chandra PE, Robinson WH. Immune complexes containing citrullinated fibrinogen costimulate macrophages via Toll-like receptor 4 and Fcγ receptor (in Eng). Arthritis Rheumatology. Jan 2011;63(1):53–62

[86] Kinloch A, et al. Identification of citrullinated alpha-enolase as a candidate autoantigen in rheumatoid arthritis (in Eng). Arthritis & Research Therapy. 2005;7(6):R1421–9

[87] Cunha TM, Verri WA, Silva JS, Poole S, Cunha FQ, Ferreira SH. A cascade of cytokines mediates mechanical inflammatory hypernociception in mice (in Eng). Proceedings of the National Academy of Sciences United States of America. Feb 2005;102(5):1755–1760
[88] Guerrero AT, et al. Toll-like receptor 2/MyD88 signaling mediates zymosan-induced joint hypernociception in mice: Participation of TNF-α, IL-1β and CXCL1/KC (in Eng). European Journal of Pharmacology. Jan 2012;674(1):51–57

[89] Qin X, Wan Y, Wang X. CCL2 and CXCL1 trigger calcitonin gene-related peptide release by exciting primary nociceptive neurons (in Eng). Journal of Neuroscience Research. Oct 2005;82(1):51–62

[90] Zhang ZJ, Cao DL, Zhang X, Ji RR, Gao YJ. Chemokine contribution to neuropathic pain: respective induction of CXCL1 and CXCR2 in spinal cord astrocytes and neurons (in Eng). Pain. Oct 2013;154(10):2185–2197

[91] Matsubara S, Yamamoto T, Tsuruta T, Takagi K, Kambara T. Complement C4-derived monocyte-directed chemotaxis-inhibitory factor. A molecular mechanism to cause polymorphonuclear leukocyte-predominant infiltration in rheumatoid arthritis synovial cavities (in Eng). American Journal of Pathology. May 1991;138(5):1279–1291

[92] Papayannopoulos V, Zychlinsky A. NETs: A new strategy for using old weapons (in Eng). Trends in Immunology. Nov 2009;30(11):513–521

[93] Brinkmann V, et al. Neutrophil extracellular traps kill bacteria (in Eng). Science. Mar 2004;303(5663):1532–1535

[94] Steinberg BE, Grinstein S. Unconventional roles of the NADPH oxidase: signaling, ion homeostasis, and cell death (in Eng). Science STKE. Mar 2007;2007(379):pe11

[95] Fuchs TA, et al. Novel cell death program leads to neutrophil extracellular traps (in Eng). Journal of Cell Biology. Jan 2007;176(2):231–241

[96] Remijsen Q, Kuijpers TW, Wirawan E, Lippens S, Vandenabeele P, Vanden Berghe T. Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality (in Eng). Cell Death Differentiation. Apr 2011;18(4):581–588

[97] Wang Y, et al. Histone hypercitrullination mediates chromatin decondensation and neutrophil extracellular trap formation (in Eng). Journal of Cell Biology. Jan 2009;184(2):205–213

[98] Martinod K, et al. Neutrophil histone modification by peptidylarginine deiminase 4 is critical for deep vein thrombosis in mice (in Eng). Proceedings of the National Academy of Sciences United States of America. May 2013;110(21):8674–8679

[99] Gupta AK, Giaglis S, Hasler P, Hahn S. Efficient neutrophil extracellular trap induction requires mobilization of both intracellular and extracellular calcium pools and is modulated by cyclosporine A (in Eng). PLoS One. 2014;9(5):e97088

[100] Sur Chowdhury C, Giaglis S, Walker UA, Buser A, Hahn S, Hasler P. Enhanced neutrophil extracellular trap generation in rheumatoid arthritis: Analysis of underlying signal transduction pathways and potential diagnostic utility (in Eng). Arthritis & Research Therapy. Jun 2014;16(3):R122
Wang Y, et al. Increased neutrophil elastase and proteinase 3 and augmented NETosis are closely associated with β-cell autoimmunity in patients with type 1 diabetes (in Eng). Diabetes. Dec 2014;63(12):4239–4248

Kessenbrock K, et al. Netting neutrophils in autoimmune small-vessel vasculitis (in Eng). Nature Medicine. Jun 2009;15(6):623–625

Lande R, et al. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus (in Eng). Science Translational Medicine. Mar 2011;3(73):73ra19

Leffler J, Stojanovich L, Shoenfeld Y, Bogdanovic G, Hesselstrand R, Blom AM. Degradation of neutrophil extracellular traps is decreased in patients with antiphospholipid syndrome (in Eng). Clinical Experimental Rheumatology. Jan-Feb 2014;32(1):66–70

Villanueva E, et al. Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus (in Eng). Journal of Immunology. Jul 2011;187(1):538–552

Kaplan MJ, Radic M. Neutrophil extracellular traps: Double-edged swords of innate immunity (in Eng). Journal of Immunology. Sep 2012;189(6):2689–2695

Brinkmann V, Zychlinsky A. Neutrophil extracellular traps: Is immunity the second function of chromatin? (in Eng). Journal of Cell Biology. Sep 2012;198(5):773–783

Giaglis S, Hahn S, Hasler P. The NET outcome: Are neutrophil extracellular traps of any relevance to the pathophysiology of autoimmune disorders in childhood? (in Eng). Frontiers in Pediatrics. 2016;4:97

Sur Chowdhury C, Hahn S, Hasler P, Hoesli I, Lapaire O, Giaglis S. Elevated levels of total cell-free DNA in maternal serum samples arise from the generation of neutrophil extracellular traps (in Eng). Fetal Diagnosis and Therapy. 2016;40(4):263–267

Giaglis S, et al. Neutrophil migration into the placenta: Good, bad or deadly? (in Eng). Cell Adhesion and Migration. Mar 2016;10(1-2):208–225

Mayadas TN, Cullere X, Lowell CA. The multifaceted functions of neutrophils (in Eng). Annual Review of Pathology. 2014;9:181–218

Cross A, Barnes T, Bucknall RC, Edwards SW, Moots RJ. Neutrophil apoptosis in rheumatoid arthritis is regulated by local oxygen tensions within joints (in Eng). Journal of Leukocyte Biology. Sep 2006;80(3):521–528

Lally F, et al. A novel mechanism of neutrophil recruitment in a coculture model of the rheumatoid synovium (in Eng). Arthritis & Rheumatology. Nov 2005;52(11):3460–3469

Parsonage G, et al. Prolonged, granulocyte-macrophage colony-stimulating factor-dependent, neutrophil survival following rheumatoid synovial fibroblast activation by IL-17 and TNFalpha (in Eng). Arthritis and Research Therapy. 2008;10(2):R47
Raza K, et al. Synovial fluid leukocyte apoptosis is inhibited in patients with very early rheumatoid arthritis (in Eng). Arthritis and Research Therapy. 2006;8(4):R120

Weinmann P, et al. Delayed neutrophil apoptosis in very early rheumatoid arthritis patients is abrogated by methotrexate therapy (in Eng). Clinical and Experimental Rheumatology. Nov-Dec 2007;25(6):885–887

Bendele A. Animal models of rheumatoid arthritis (in Eng). Journal of Musculoskeletal and Neuronal Interactions. Jun 2001;1(4):377–385

Asquith DL, Miller AM, McInnes IB, Liew FY. Animal models of rheumatoid arthritis (in Eng). European Journal of Immunology. Aug 2009;39(8):2040–2044

Verri WA, et al. IL-33 induces neutrophil migration in rheumatoid arthritis and is a target of anti-TNF therapy (in Eng). Annals in Rheumatic Diseases. Sep 2010;69(9):1697–1703

Verri WA, Cunha TM, Parada CA, Poole S, Cunha FQ, Ferreira SH. Hypernociceptive role of cytokines and chemokines: Targets for analgesic drug development? (in Eng). Pharmacological Therapy. Oct 2006;112(1):116–138

Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis (in Eng). Lancet. Dec 2007;370(9602):1861–1874

Burmester GR, Feist E, Dörner T. Emerging cell and cytokine targets in rheumatoid arthritis (in Eng). Nature Reviews Rheumatology. Feb 2014;10(2):77–88

McInnes IB, Liew FY. Cytokine networks—Towards new therapies for rheumatoid arthritis (in Eng). Nature Clinical Practice Rheumatology. Nov 2005;1(1):31–39

Wright HL, Moots RJ, Bucknall RC, Edwards SW. Neutrophil function in inflammation and inflammatory diseases (in Eng). Rheumatology (Oxford). Sep 2010;49(9):1618–1631

Derouet M, et al. Sodium salicylate promotes neutrophil apoptosis by stimulating caspase-dependent turnover of Mcl-1 (in Eng). Journal of Immunology. Jan 2006;176(2):957–965

Pillinger MH, et al. Modes of action of aspirin-like drugs: Salicylates inhibit ERK activation and integrin-dependent neutrophil adhesion (in Eng). Proceedings of the National Academy of Sciences United States of America. Nov 1998;95(24):14540–14545

Neal TM, Vissers MC, Winterbourn CC. Inhibition by nonsteroidal anti-inflammatory drugs of superoxide production and granule enzyme release by polymorphonuclear leukocytes stimulated with immune complexes or formyl-methionyl-leucyl-phenylalanine (in Eng). Biochemical Pharmacology. Aug 1987;36(15):2511–2517

Dinarello CA. Anti-inflammatory agents: Present and future (in Eng). Cell. Mar 2010;140(6):935–950

Liu L, et al. Rapid non-genomic inhibitory effects of glucocorticoids on human neutrophil degranulation (in Eng). Inflammation Research. Jan 2005;54(1):37–41
[130] Crockard AD, Boylan MT, Droogan AG, McMillan SA, Hawkins SA. Methylprednisolone-induced neutrophil leukocytosis—Down-modulation of neutrophil L-selectin and Mac-1 expression and induction of granulocyte-colony stimulating factor (in Eng). International Journal of Clinical and Laboratory Research. 1998;28(2):110–115

[131] Youssef PP, et al. Neutrophil trafficking into inflamed joints in patients with rheumatoid arthritis, and the effects of methylprednisolone (in Eng). Arthritis and Rheumatology. Feb 1996;39(2):216–225

[132] Majumdar S, Aggarwal BB. Methotrexate suppresses NF-kappaB activation through inhibition of IkappaBalpha phosphorylation and degradation (in Eng). Journal of Immunology. Sep 2001;167(5):2911–2920

[133] Sperling RI, Benincaso AI, Anderson RJ, Coblyn JS, Austen KF, Weinblatt ME. Acute and chronic suppression of leukotriene B4 synthesis ex vivo in neutrophils from patients with rheumatoid arthritis beginning treatment with methotrexate (in Eng). Arthritis and Rheumatology. Apr 1992;35(4):376–384

[134] Wessels JA, Huizinga TW, Guchelaar HJ. Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis (in Eng). Rheumatology (Oxford). Mar 2008;47(3):249–255

[135] Dewas C, Dang PM, Gougerot-Pocidalo MA, El-Benna J. TNF-alpha induces phosphorylation of p47(phox) in human neutrophils: partial phosphorylation of p47phox is a common event of priming of human neutrophils by TNF-alpha and granulocyte-macrophage colony-stimulating factor (in Eng). Journal of Immunology. Oct 2003;171(8):4392–4398

[136] Fujishima S, et al. Regulation of neutrophil interleukin 8 gene expression and protein secretion by LPS, TNF-alpha, and IL-1 beta (in Eng). Journal of Cell Physiology. Mar 1993;154(3):478–485

[137] Cross A, Moots RJ, Edwards SW. The dual effects of TNFalpha on neutrophil apoptosis are mediated via differential effects on expression of Mcl-1 and Bfl-1 (in Eng). Blood. Jan 2008;111(2):878–884

[138] Ginis I, Tauber AI. Activation mechanisms of adherent human neutrophils (in Eng). Blood. Sep 1990;76(6):1233–1239

[139] Mitoma H, et al. Mechanisms for cytotoxic effects of anti-tumor necrosis factor agents on transmembrane tumor necrosis factor alpha-expressing cells: comparison among infliximab, etanercept, and adalimumab (in Eng). Arthritis and Rheumatology. May 2008;58(5):1248–1257

[140] Taylor PC, et al. Reduction of chemokine levels and leukocyte traffic to joints by tumor necrosis factor alpha blockade in patients with rheumatoid arthritis (in Eng). Arthritis and Rheumatology. Jan 2000;43(1):38–47
Dominical VM, et al. Neutrophils of rheumatoid arthritis patients on anti-TNF-α therapy and in disease remission present reduced adhesive functions in association with decreased circulating neutrophil-attractant chemokine levels (in Eng). Scandinavian Journal of Immunology. Apr 2011;73(4):309–318

Smolen JS, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): A double-blind, placebo-controlled, randomised trial (in Eng). Lancet. Mar 2008;371(9617):987–997

Marin V, Montero-Julian F, Grès S, Bongrand P, Farnarier C, Kaplanski G. Chemotactic agents induce IL-6Ralpha shedding from polymorphonuclear cells: Involvement of a metalloproteinase of the TNF-alpha-converting enzyme (TACE) type (in Eng). European Journal of Immunology. Oct 2002;32(10):2965–2970

Wright HL, Cross AL, Edwards SW, Moots RJ. Effects of IL-6 and IL-6 blockade on neutrophil function in vitro and in vivo (in Eng). Rheumatology (Oxford). Jul 2014;53(7):1321–1331

Yen JH. Treatment of early rheumatoid arthritis in developing countries. Biologics or disease-modifying anti-rheumatic drugs? (in Eng). Biomedicine & Pharmacotherapy. Dec 2006;60(10):688–692

Kikuchi M, Matsuura K, Matsumoto Y, Inagaki T, Ueda R. Bibliographical investigation of complementary alternative medicines for osteoarthritis and rheumatoid arthritis (in Eng). Geriatrics & Gerontology International. Mar 2009;9(1):29–40

Marcus DM. Therapy: Herbals and supplements for rheumatic diseases (in Eng). Nature Reviews Rheumatology. Jun 2009;5(6):299–300

Ernst E. Prevalence of use of complementary/alternative medicine: A systematic review (in Eng). Bulletin of the World Health Organization. 2000;78(2):252–257

Steinhubl SR. Why have antioxidants failed in clinical trials? (in Eng). American Journal of Cardiology. May 2008;101(10A):14D–19D

Haseeb A, Haqqi TM. Immunopathogenesis of osteoarthritis (in Eng). Clinical Immunology. Mar 2013;146(3):185–196

Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010 (in Eng). Journal of Natural Products. Mar 2012;75(3):311–335

Rothwell JA, et al. Phenol-Explorer 3.0: A major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content (in Eng). Database (Oxford). 2013;2013:bat070

Kelly GS. Quercetin. Monograph (in Eng). Alternative Medicine Review. Jun 2011;16(2):172–194

Lamson DW, Brignall MS. Antioxidants and cancer, part 3: Quercetin (in Eng). Alternative Medicine Review. Jun 2000;5(3):196–208
[155] Russo M, Spagnuolo C, Tedesco I, Bilotto S, Russo GL. The flavonoid quercetin in disease prevention and therapy: Facts and fancies (in Eng). Biochemical Pharmacology. Jan 2012;83(1):6–15

[156] Gardi C, et al. Quercetin reduced inflammation and increased antioxidant defense in rat adjuvant arthritis (in Eng). Archives of Biochemistry and Biophysics. Oct 2015;583:150–157

[157] Pincemail J, Deby C, Thirion A, de Bruyn-Dister M, Goutier R. Human myeloperoxidase activity is inhibited in vitro by quercetin. Comparison with three related compounds (in Eng). Experientia. May 1988;44(5):450–453

[158] Suri S, et al. A comparative study of the effects of quercetin and its glucuronide and sulfate metabolites on human neutrophil function in vitro (in Eng). Biochemical Pharmacology. Sep 2008;76(5):645–653

[159] Petri B, Phillipson M, Kubes P. The physiology of leukocyte recruitment: An in vivo perspective (in Eng). Journal of Immunology. May 2008;180(10):6439–6446

[160] Valério DA, et al. Quercetin reduces inflammatory pain: Inhibition of oxidative stress and cytokine production (in Eng). Journal of Natural Products. Nov 2009;72(11):1975–1979

[161] Suyenaga ES, et al. Beyond organoleptic characteristics: The pharmacological potential of flavonoids and their role in leukocyte migration and in L-selectin and β2-integrin expression during inflammation (in Eng). Phytotherapy Research. Sep 2014;28(9):1406–1411

[162] Souto FO, et al. Quercetin reduces neutrophil recruitment induced by CXCL8, LTB4, and fMLP: Inhibition of actin polymerization (in Eng). Journal of Natural Products. Feb 2011;74(2):113–118

[163] Medeiros KCP, Monteiro JC, Diniz MFFM, Medeiros IA, Silva BA, Piuvezam MR. Effect of the activity of the Brazilian polyherbal formulation: Eucalyptus globulus Labill, Peltodon radicans Pohl and Schinus terebinthifolius Raddi in inflammatory models. Brazilian Journal of Pharmacognosy, Mar 2007; 17:23–28

[164] Cavalher-Machado SC, et al. The anti-allergic activity of the acetate fraction of Schinus terebinthifolius leaves in IgE induced mice paw edema and pleurisy (in Eng). International Immunopharmacology. Nov 2008;8(11):1552–1560

[165] de Lima MR, et al. Anti-bacterial activity of some Brazilian medicinal plants (in Eng). Journal of Ethnopharmacology. Apr 2006;105(1-2):137–147

[166] Velázquez E, Tournier HA, Mordujovich de Buschiazzo P, Saavedra G, Schinella GR. Antioxidant activity of Paraguayan plant extracts (in Eng). Fitoterapia. Feb 2003;74(1-2):91–97

[167] Rosas EC, et al. Anti-inflammatory effect of Schinus terebinthifolius Raddi hydroalcoholic extract on neutrophil migration in zymosan-induced arthritis (in Eng). Journal of Ethnopharmacology. Dec 2015;175:490–498
[168] Whang WK, et al. Methyl gallate and chemicals structurally related to methyl gal-
late protect human umbilical vein endothelial cells from oxidative stress (in Eng). Exper-
imental & Molecular Medicine. Aug 2005;37(4):343–352

[169] Acharyya S, Sarkar P, Saha DR, Patra A, Ramamurthy T, Bag PK. Intracellular and
membrane-damaging activities of methyl gallate isolated from Terminalia chebula
against multidrug-resistant Shigella spp. (in Eng). Journal of Medical Microbiology.
Aug 2015;64(8):901–909

[170] Lee SH, et al. Antitumor activity of methyl gallate by inhibition of focal adhesion for-
mation and Akt phosphorylation in glioma cells (in Eng). Biochimica et Biophysica
Acta. Aug 2013;1830(8):4017–4029

[171] Correa LB, et al. Anti-inflammatory effect of methyl gallate on experimental arthritis:
Inhibition of neutrophil recruitment, production of inflammatory mediators, and activ-
ation of macrophages (in Eng). Journal of Natural Products. Jun 2016;79(6):1554–1566

[172] Henriques M, Penido C. The therapeutic properties of Carapa guianensis (in Eng).
Current Pharmaceutical Design. 2014;20(6):850–856

[173] Hammer ML, Johns EA. Tapping an Amazôñian plethora: Four medicinal plants of
Marajó Island, Pará (Brazil) (in Eng). Journal of Ethnopharmacology. Sep 1993;40(1):53–75

[174] Penido C, Conte FP, Chagas MS, Rodrigues CA, Pereira JF, Henriques MG. Anti-
inflammatory effects of natural tetranortriterpenoids isolated from Carapa guianensis
Aublet on zymosan-induced arthritis in mice (in Eng). Inflammation Research. Nov
2006;55(11):457–464

[175] Patwardhan CA, Fauq A, Peterson LB, Miller C, Blagg BS, Chadli A. Gedunin inacti-
vates the co-chaperone p23 protein causing cancer cell death by apoptosis (in Eng).
Journal of Biological Chemistry. Mar 2013;288(10):7313–7325

[176] Conte FP, et al. Effect of gedunin on acute articular inflammation and hypernociception
in mice (in Eng). Molecules. 2015;20(2):2636–2657

[177] Bozza PT, Bakker-Abreu I, Navarro-Xavier RA, Bandeira-Melo C. Lipid body function
in eicosanoid synthesis: An update (in Eng). Prostaglandins, Leukotrienes, & Essential
Fatty Acids. Nov 2011;85(5):205–213

[178] Khan N, Afaq F, Saleem M, Ahmad N, Mukhtar H. Targeting multiple signaling path-
ways by green tea polyphenol (-)-epigallocatechin-3-gallate (in Eng). Cancer Research.
Mar 2006;66(5):2500–2505

[179] Haqqi TM, et al. Prevention of collagen-induced arthritis in mice by a polyphenolic
fraction from green tea (in Eng). Proceedings of the National Academy of Sciences
United States of America. Apr 1999;96(8):4524–4529

[180] Ahmed S, Wang N, Lalonde M, Goldberg VM, Haqqi TM. Green tea polyphenol epigal-
locatechin-3-gallate (EGCG) differentially inhibits interleukin-1 beta-induced expres-
sion of matrix metalloproteinase-1 and -13 in human chondrocytes (in Eng). Journal of
Pharmacological & Experimental Therapy. Feb 2004;308(2):767–773
[181] Ahmed S, Anuntiyo J, Malemud CJ, Haqqi TM. Biological basis for the use of botanicals in osteoarthritis and rheumatoid arthritis: A review (in Eng). Evidence Based Complementary and Alternative Medicine. Sep 2005;2(3):301–308

[182] Ahmed S, et al. Epigallocatechin-3-gallate inhibits IL-6 synthesis and suppresses trans-signaling by enhancing soluble gp130 production (in Eng). Proceedings of the National Academy of Sciences United States of America. Sep 2008;105(38):14692–14697

[183] Singh R, Ahmed S, Islam N, Goldberg VM, Haqqi TM. Epigallocatechin-3-gallate inhibits interleukin-1beta-induced expression of nitric oxide synthase and production of nitric oxide in human chondrocytes: Suppression of nuclear factor kappaB activation by degradation of the inhibitor of nuclear factor kappaB (in Eng). Arthritis & Rheumatology. Aug 2002;46(8):2079–2086

[184] Yun HJ, Yoo WH, Han MK, Lee YR, Kim JS, Lee SI. Epigallocatechin-3-gallate suppresses TNF-alpha -induced production of MMP-1 and -3 in rheumatoid arthritis synovial fibroblasts (in Eng). Rheumatology International. Nov 2008;29(1):23–29

[185] Aktas O, et al. Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis (in Eng). Journal of Immunology. Nov 2004;173(9):5794–5800

[186] Donà M, et al. Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis (in Eng). Journal of Immunology. Apr 2003;170(8):4335–4341

[187] Westacott CI, Sharif M. Cytokines in osteoarthritis: Mediators or markers of joint destruction? (in Eng). Seminars in Arthritis & Rheumatology. Feb 1996;25(4):254–272

[188] Porath D, Rieger C, Drewe J, Schwager J. Epigallocatechin-3-gallate impairs chemokine production in human colon epithelial cell lines (in Eng). Journal of Pharmacology & Experimental Therapy. Dec 2005;315(3):1172–1180

[189] Netsch MI, Gutmann H, Aydogan C, Drewe J. Green tea extract induces interleukin-8 (IL-8) mRNA and protein expression but specifically inhibits IL-8 secretion in caco-2 cells (in Eng). Planta Medica. Jun 2006;72(8):697–702

[190] Park C, et al. Curcumin induces apoptosis and inhibits prostaglandin E(2) production in synovial fibroblasts of patients with rheumatoid arthritis (in Eng). International Journal of Molecular Medicine. Sep 2007;20(3):365–372

[191] Mun SH, et al. Oral administration of curcumin suppresses production of matrix metalloproteinase (MMP)-1 and MMP-3 to ameliorate collagen-induced arthritis: Inhibition of the PKCdelta/JNK/c-Jun pathway (in Eng). Journal of Pharmacological Science. Sep 2009;111(1):13–21

[192] Kloesch B, Becker T, Dietersdorfer E, Kiener H, Steiner G. Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes (in Eng). International Immunopharmacology. Feb 2013;15(2):400–405

[193] Kim DC, Lee W, Bae JS. Vascular anti-inflammatory effects of curcumin on HMGB1-mediated responses in vitro (in Eng). Inflammation Research. Dec 2011;60(12):1161–1168
[194] Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis (in Eng). Phytotherapy Research. Nov 2012;26(11):1719–1725

[195] Di Pierro F, Rapacioli G, Di Maio EA, Appendino G, Franceschi F, Togni S. Comparative evaluation of the pain-relieving properties of a lecithinized formulation of curcumin (Meriva®), nimesulide, and acetaminophen (in Eng). Journal of Pain Research. 2013;6:201–205

[196] Belcaro G, et al. Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients (in Eng). Alternative Medicine Review. Dec 2010;15(4):337–344