Chapter 14
Anti-inflammatory Activity

María Rosario Alonso, Claudia A. Anesini, and Renzo F. Martino

Abstract It is known that inflammation involves a complex series of protective and reparative responses to tissue injury caused by either mechanical and autoimmune stimuli or infection. Inflammation can be either acute or chronic. In the acute phase, in the early stages of inflammation, neutrophils, macrophages, and dendritic cells contribute to cytokine production that spreads the inflammatory events. Although inflammation has a protective role, many diseases have the etiological origin in inflammatory processes such as atherosclerosis, arthritis, cancer, and ischemic heart disease. There are many pathways involving the synthesis and secretion of pro-inflammatory mediators. In this chapter we analyze different intracellular signaling routes related to inflammation. There are two principal types of anti-inflammatory drugs, namely, steroidal anti-inflammatory drugs, which reduce inflammation by binding to cortisol receptors and nonsteroidal anti-inflammatory drugs, which decrease damage by inhibition of cyclooxygenase enzymes. These anti-inflammatory drugs entail many risks, in particular, gastrointestinal ulceration, bleeding, and hepatotoxicity. Over the last decades, the potential of sesquiterpene lactones as anti-inflammatory agents has been pointed out by different authors.

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Abbreviations

AP-1	activator protein-1
ARE	antioxidant response element
C	complement component
Chemokine R	chemokine receptors
COX-2	ciclooxigenase 2
CR	complement receptor
CysLTs	cysteinyl leukotrienes
Cytokine R	cytokine receptors
DAMPs	damage-associated molecular patterns
ERK	extracellular signal-regulated kinase
HO-1	heme oxygenase 1
IFN-γ	interferon-γ
IKK	IκB kinase
IL	interleukins
IL-1ra	IL-1 receptor antagonist
IL-1RAcP	IL-1 receptor accessory protein
IL-1RI	IL-1 type 1 receptor
IL-1RII	IL-1 type 2 receptor
iNOS	inducible type-2 isoform of nitric oxide synthase NOS-2
JAKs	Janus kinases
JNK	c-Jun N-terminal kinase
LPS	lipopolysaccharide
LTs	leukotrienes
MAPKs	mitogen-activated protein kinases
MCP-1	monocyte chemoattractant protein 1
MSU	monosodium urate
NF-κB	nuclear factor kappa B
NLRP3	inflammasome complex Nod-like receptor family pyrin domain containing 3
NLRs	Nucleotide-binding oligomerization-domain protein-like receptors
Nrf2	factor (erythroid-derived 2)-related factor 2
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAMPs	pathogen-associated molecular patterns
PGs	prostaglandins

PLA2	phospholipase A2
PMNs	polymorphonuclear neutrophils
Purine R	purine receptors
RLRs	RIG-I-like (retinoic acid inducible gene 1) receptor family
RNS	reactive nitrogen species
ROS	reactive oxygen species
STATs	signal transducers and activators of transcription
STLs	sesquiterpene lactones
TGF	tumor growth factor
Th	helper T cells
TLRs	Toll-like receptors
TNF-α	tumor necrosis factor alpha
TXs	thromboxanes
TyK2	tyrosine kinase 2

14.1 Introduction

Inflammation is a complex biological response of vascular tissues to harmful stimuli (Ferrero-Miliani et al. 2007; Davicino et al. 2015). This complex reaction is initiated and organized by mediators of different chemical classes derived from plasma proteins or secreted by cells (Robbins et al. 2010). The inflammation process can be classified as either acute or chronic. In the acute phase, the early stages of inflammation are mediated by tissue-resident macrophages and mast cells, Toll-like receptors (TLRs), and nucleotide-binding oligomerization-domain protein-like receptors (NLRs) present in these cells. These components are activated and are responsible for the activation of transcription factors and the production of pro-inflammatory molecules (Medzhitov 2008). Neutrophils, monocytes, and eosinophils access and migrate to the site of infection or injury and contribute to cytokine production tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), which spread inflammatory events. Neutrophils release reactive nitrogen species (RNS), reactive oxygen species (ROS), and enzymes such as proteinase and elastase, which destroy invading microorganisms or necrotic tissues. On the other hand, some interleukins, such as IL-4, IL-9, IL-10, IL-11, IL-13, and IL-19 have anti-inflammatory effects. Interleukin-10 (IL-10) is the most widely studied of the anti-inflammatory interleukins related to the suppression of pro-inflammatory mediators (Zhao et al. 2014). It is noteworthy that a successful acute inflammatory response is followed by resolution and repair. However, if the inflammatory stimulus persists, the acute process progresses to chronic diseases such as cancer, arthritis, atherosclerosis, and ischemic heart disease. The prevention of inflammation and pain is of significant concern particularly for those patients afflicted with arthritis and other musculoskeletal ailments (Fig. 14.1).

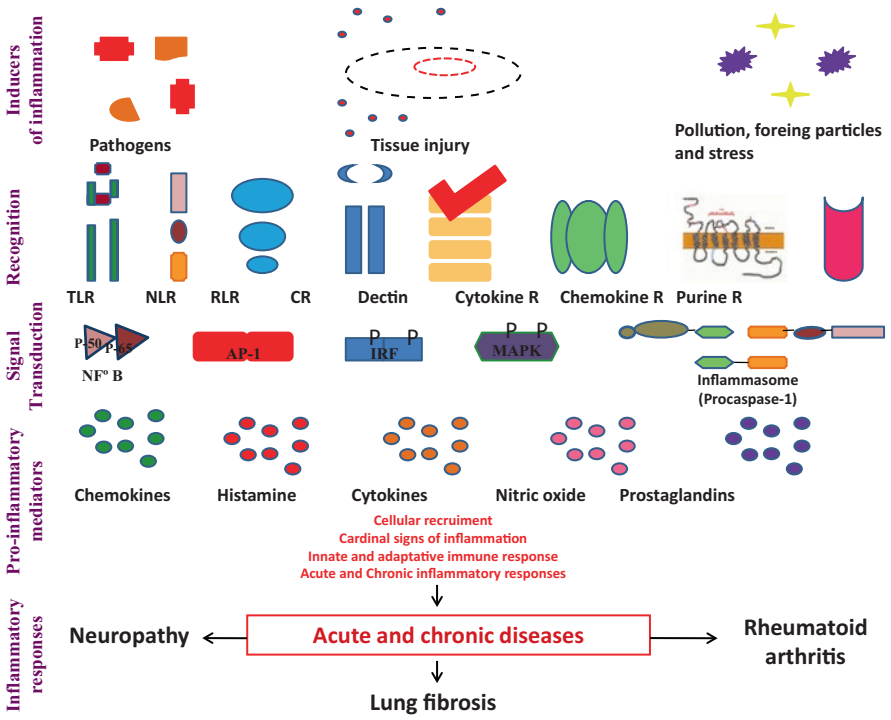

Fig. 14.1 *Summary of inflammatory mediators*. Overview of inflammatory mediators. Firstly, inflammatory stimuli are recognized by specific cell receptors, for example, Toll-like receptors (TLRs), nucleotide-binding oligomerization-domain protein (NOD)-like receptors or NLRs, cytokine receptors (cytokine R), chemokine receptors (chemokine R), purine receptors (purine R), RIG-I-like (retinoic acid-inducible gene 1) receptor family (RLRs), and complement receptor (CR), among others. After recognition, intracellular signaling pathways are activated, such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), which culminate in the activation of transcription factors NF-κB and activator protein-1 (AP-1) upregulation of transcription and, consequently, production of a series of pro-inflammatory mediators (chemokines, cytokines, histamine, prostanoids, and nitric oxide). These molecules mediate responses that are involved in acute and chronic inflammatory conditions, such as leukocyte recruitment, the generation of local exudates, the appearance of cardinal signs of inflammation, immune responses, and consequent diseases. (Adapted from Hohmann et al. 2016)

14.2 Inflammatory Pathways Serving as Pharmacological Targets in Inflammatory Diseases

There are many pathways that involve the synthesis and secretion of pro-inflammatory mediators. In this chapter, we analyze, summarize, and discuss different intracellular signaling routes (Fig. 14.2).

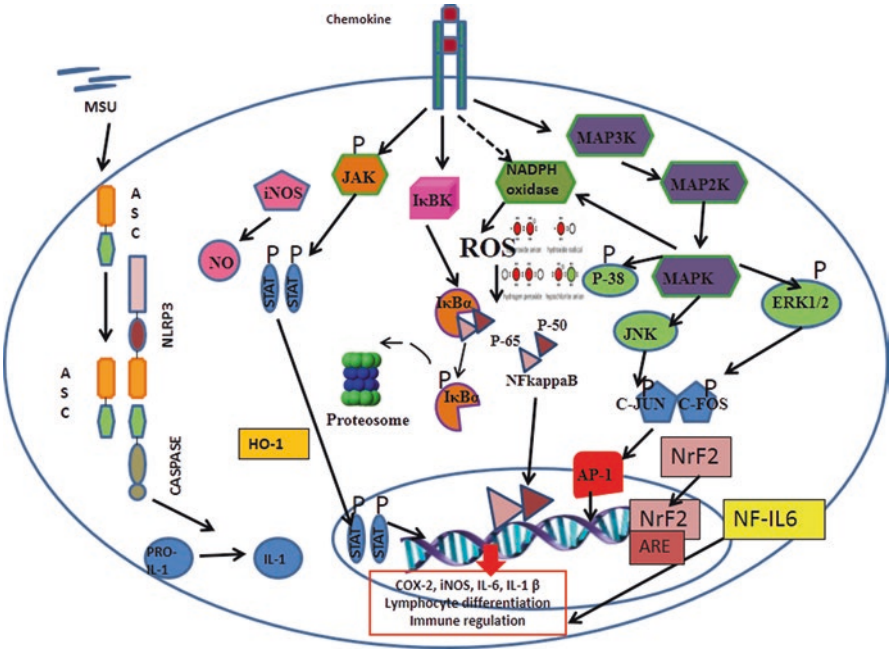

Fig. 14.2 *The most important pathways involved in inflammation*. Activation of nuclear factor kappa B (NF-κB) translocation into nucleus, the expression of NF-IL6; the production of nitric oxide (NO) through the upregulation of iNOS; the activation of extracellular signal-regulated kinase (ERK) 1/2 and activation of the phosphorylation of inhibitor IκBα by IKK, activation of oxidative stress through the inhibition of phase II detoxification genes, such as HO-1, activation of Janus kinase (JAK)/ signal transducer, activation of transcription (STAT) and mitogen-activated protein kinases (MAPK) activation; the activation of inflammasome caspase-1 and NLRP3; and activation of the nuclear factor E2-related factor 2 (Nrf2)/antioxidant response element (ARE). MSU monosodium urate

14.2.1 Inflammatory Cytokines

Cytokines are small secreted proteins, produced predominately by helper T cells (Th) and macrophages, which have a specific effect on the interaction and communication between cells. They can act either on the cells that secrete them (autocrine action), or on nearby cells (paracrine action), or in some instances, on distant cells (endocrine action). They are often produced in a cascade, as one cytokine stimulates its target cells to secrete additional cytokines. Cytokines can also act either synergistically or antagonistically. They are produced as a consequence of physiological or pathological processes. Pro-inflammatory cytokines are produced predominantly by activated macrophages and are involved in the upregulation of inflammatory reactions. Among pro-inflammatory cytokines, interleukins (IL) such as IL-1α and IL-β, IL-6, and TNF-α can be mentioned (Zhang and An 2007).

14.2.1.1 Interleukin-1α and Interleukin-β

IL-1α and IL-β are prototypic pro-inflammatory cytokines that exert pleiotropic effects on a variety of cells and play key roles in acute and chronic inflammatory and autoimmune disorders. There are two IL-1 receptors, namely, type 1 IL-1 receptor (IL-1RI) and type 2 IL-1 receptor (IL-1 RII). The inflammatory action is mediated by the interaction with IL-1RI, while the binding to IL-1RII does not lead to cell signaling, and it is therefore considered a decoy receptor.

Upon the binding of IL-1 to IL-1RI, a second receptor termed IL-1 receptor accessory protein (IL-1RAcP) is recruited at the cell membrane to form a high-affinity binding receptor complex that triggers the intracellular signaling cascade. A third IL-1 family member, IL-1 receptor antagonist (IL-1ra), binds to IL-1 receptors and prevents the interaction of IL-1 with its receptors, acting as a natural IL-1 inhibitor (Dinarello 1996; Braddock and Quinn 2004). In healthy organisms, IL-1β has important homeostatic functions, such as the regulation of feeding, sleep, and body temperature; however, its overproduction is implicated in the pathophysiological changes that occur during different diseases such as rheumatoid arthritis, neuropathic pain, inflammatory bowel disease, osteoarthritis, vascular disease, multiple sclerosis, and Alzheimer's disease (Braddock and Quinn, 2004; Dinarello 2004).

14.2.1.2 Interleukin-6

IL-6 is the principal stimulator for the production of most acute phase proteins (Gitlin and Colten et al. 1987); it participates in the recruitment of leucocytes in vivo, and it is capable of crossing the blood-brain barrier (Banks et al. 1994) to stimulate the synthesis of PGE_2 in the hypothalamus, thereby regulating the body temperature. The IL-6-sIL-6Rα complex can activate endothelial cells to secrete IL-8 and monocyte chemoattractant protein (MCP)-1 and induce expression of adhesion molecules (Romano et al. 1997). IL-6, in combination with its soluble receptor sIL-6Rα, regulates the transition from acute to chronic inflammation by changing the nature of leucocyte infiltrates (from polymorphonuclear neutrophils to monocyte/macrophages). In addition, IL-6 exerts stimulatory effects on T- and B-cells, thus favoring chronic inflammatory responses. IL-6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding IL-6Rα chain (CD126) and the signal-transducing component gp130 (also named CD130). As IL-6 interacts with its receptor, it triggers the gp130 and IL-6R proteins to form a complex, thus activating the receptor. These complexes bring together the intracellular regions of gp130 to initiate a signal transduction cascade through the transcription factors Janus kinases (JAKs) and signal transducers and activators of transcription (STATs) (Heinrich et al. 1998).

Strategies targeting IL-6 and IL-6 signaling pathways have led to the effective prophylaxis and treatment of rheumatoid arthritis and other chronic inflammatory diseases in animal models.

14.2.1.3 Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF-α) is a soluble 17 KDa protein comprising three identical subunits. It is produced by macrophages in response to inflammatory stimuli or infection; TNF-α binds to receptors present on almost all cell types (Vargas Salazar 2009; Bazzoni and Beutler 1996). These receptors are designated p55 and p75, which consist of two identical subunits of transmembrane proteins that form dimers on the cell surface where they bind a TNF-α trimeric form (Mease 2002). The classical inflammatory response attributed to TNF-α, through interaction with p55 and p75, involves thymocyte proliferation, skin necrosis, and apoptosis of activated mature lymphocytes (Peschon et al. 1998). High levels of systemically released TNF-α can modify the anticoagulant properties of endothelial cells, activate neutrophils, and induce the release of other inflammatory cytokines. On the other hand, chronically sustained low levels of TNF-α contribute to the development of the inflammatory response (Choy and Panayi 2001). In this sense the abnormal regulation of TNF-α function plays an important role in the development of chronic inflammatory diseases and infections (Vargas Salazar 2009; Bazzoni and Beutler 1996).

14.2.2 Caspase-1 and the Inflammasome Complex Nod-Like Receptor Family Pyrin Domain Containing the Complex NLRP3

These factors are related to the modulation of cytokine maturation and release. It has been demonstrated that the inhibition of caspase-1 and the complex NLRP3 reduces the maturation rate of pro-inflammatory cytokines IL-1β and IL-18 (Mathema et al. 2012). The inflammasome is a receptor for endogenous danger signals such as ATP, precipitation of monosodium urate (MSU), cholesterol crystals, and β-amyloid. The inappropriate activation of NLRP3 has been demonstrated to be involved in the pathogenesis of different human diseases such as gouty arthritis and atherosclerosis (Li et al. 2014; Kingsbury et al. 2011). This is particularly relevant in patients with chronic inflammation, with chronic or remittent viral or bacterial infections, and with atherosclerosis, since in those conditions, inflammasomes may become activated through damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs). In gout, pro-inflammatory cytokines have an important role in orchestrating the inflammatory reaction to MSU crystals. Recent studies have demonstrated that IL-1β plays a key role by promoting a neutrophil influx into the synovium and joint fluid, which is the pathological expression of the acute attack (Landis and Haskard 2001).

14.2.3 Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a ubiquitous transcription factor that plays an important role in many inflammatory diseases (Baeuerle and Henkel 1994). NF-κB consists of two subunits: the p50 subunit (NF-κB1) and the p65 subunit (RelA). Under physiological conditions, NF-κB is present in the cytoplasm associated with its inhibitory subunit IκBα. In response to different pro-inflammatory stimuli such as stress, cytokines, free radicals, ultraviolet radiation, bacterial, or viral antigens, the IκB kinase (IKK) is activated to phosphorylate IκBα at serine/threonine residues, leading to the release of NF-κB from IκBα. As a consequence, NF-κB translocates into the nucleus, binds to specific sequences in the promoter regions of genes related to inflammation, and activates their transcription (Gilmore 2006).

Antioxidants, which reduce the levels of ROS and RNS, can suppress the activation of NF-κB. The inhibition of NF-κB activation may provide a pharmacological basis to prevent these acute processes.

14.2.4 The Janus Kinase (Jak)/Signal Transducers and Activators of Transcription (STATs) Pathway

Inflammatory cytokines are involved in the activation of these pathways. After the cytokine binds to the corresponding receptor, the JAK tyrosine kinases JAK1, JAK2, and tyrosine kinase 2 (Tyk2) are activated and proceed to tyrosine-phosphorylate cytosolic inert STATs. The phosphorylated STATs homo- or hetero-dimerize and translocate into the nucleus. In addition to tyrosine phosphorylation, STATs may also be phosphorylated on serine residues located on their carboxyl-terminal transactivation domains (Butturini et al. 2011; Decker and Kovarik 2000).The pleiotropic cytokine IL-6 predominantly activates STAT3 binding to gp130 cytokine receptor complex and modulates the expression of genes encoding mediators for the classic physiological acute phase response and for the activation of the apoptotic pathway (Kamimura et al. 2003). The activation of STAT3 leads to the physiological response. The deregulation of this transduction cascade may trigger tissue damage either directly or indirectly, leading to the development of chronic diseases such as psoriasis and Crohn's disease, among others. These diseases are characterized by the hyperactivation of STAT3 (Danese and Mantovani 2010; Atreya and Neurath 2008; Mariotto et al. 2008). Therefore, any treatment aimed at blocking the JAK/STAT pathway will have an anti-inflammatory effect, thus representing a novel anti-inflammatory strategy (de Prati et al. 2005).

14.2.5 Nitric Oxide

Nitric oxide (NO) is synthesized by many cell types involved in immunity and inflammation. The principal enzyme involved in its synthesis is the inducible type-2 isoform of nitric oxide synthase NOS-2 (iNOS), whose expression is mediated by NF-kB. This enzyme produces high sustained levels of NO. Resting cells do not express iNOS, but it is induced by immunological stimuli such as bacterial lipopolysaccharide (LPS) or cytokines such as IL-1, TNF-α, or interferon-γ (IFN-γ). NO is important as a toxic defense molecule against infectious agents, and it also regulates the functional activity, growth, and death of many immune and inflammatory cell types including macrophages, T lymphocytes, antigen-presenting cells, mast cells, neutrophils, and natural killer cells. NO does not act through a receptor, and its target cell specificity depends on its concentration, its chemical reactivity, the vicinity of target cells, and the way that target cells are programmed to respond. At high concentrations, as generated by iNOS, NO is rapidly oxidized to reactive nitrogen oxide species (RNOS) that mediate most of the immunological effects. RNOS can nitrosate thiols to modify key signaling molecules such as kinases and transcription factors. Several key enzymes in mitochondrial respiration are also inhibited by RNOS, and this inhibition leads to a depletion of ATP and cellular energy. NO acts as a pro-inflammatory mediator by inducing vasodilatation and the recruitment of neutrophils, whereas at high concentrations, it downregulates the expression of adhesion molecules and suppresses the activation-inducing apoptosis of inflammatory cells (Ross and Reske-Kunz 2001).

14.2.6 Reactive Oxygen Species

Reactive oxygen species (ROS) are defined as partially reduced oxygen metabolites that have strong oxidizing capacity. While at high concentrations, ROS are deleterious to cells; at low concentrations, they serve complex signaling functions. They are injurious, because they oxidize protein and lipid cellular constituents and damage the DNA, as occurs in the progression of inflammatory disorders where an enhanced ROS generation by polymorphonuclear neutrophils (PMNs) at the site of inflammation causes endothelial dysfunction and tissue injury. The superoxide anion ($O_2^{\cdot-}$), the hydroxyl radical ($OH^{\cdot}$), hydrogen peroxide (H_2O_2), and hypochlorous acid ($HOCl^{\cdot}$) can be mentioned among ROS. The superoxide anion can modulate the activity of kinases upstream NF-κB, resulting in its activation and consequent pro-inflammatory cytokine production and COX-2 expression. If ROS are scavenged, the activation of NF-κB does not occur, with the consequent decrease of inflammation (Mittal et al. 2014). When antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase, or nonenzymatic antioxidants such as ascorbic

acid (vitamin C), α-tocopherol (vitamin E), reduced glutathione, carotenoids, flavonoids, and other antioxidants are at low levels, an imbalance occurs leading to the generation of oxidative stress. The synthesis of antioxidant enzymes is induced by the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2), which is a stress-responsive transcription factor present in the cytoplasm that plays a key role in the induction of stress resistance genes which encode γ-glutamylcysteine synthetase, glutathione peroxidase, glutathione S-transferase, and heme oxygenase-1 (HO-1) through the activation of the antioxidant response element (ARE) (Nakamura et al. 2004; Umemura et al. 2008).

14.2.7 Mitogen-Activated Protein Kinases

The main three mitogen-activated protein kinases (MAPKs), c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 MAPK, are involved in the inflammatory process. MAPKs represent a significant common point for many signaling pathways in the immune response, cell death, and proliferation. MAPKs regulate the activation of downstream transcriptional factors that are important in inflammation. For instance, ERK and JNK and p38 activate the transcription factor activator protein-1 (AP-1) and NF-κB, respectively. On the other hand, anti-inflammatory pathways can also be activated through MAPKs. Another molecule associated with MAPK is Nrf2. When MAPKs are activated, they can activate Nrf2, which is translocated into the nucleus to induce gene expression of heme oxygenase 1 (HO-1). HO-1 plays a key role in the regulation of biological responses such as oxidative stress (where it has cytoprotective/antioxidant roles) and inflammation (Robbins et al. 2010; Haddad 2002).

14.2.8 Lipid Mediators

Lipid mediators are chemical messengers that are released in response to tissue injury, helping tissues to eliminate harmful invaders, such as bacteria. Current evidence suggests that lipid mediators, including prostaglandins (PGs), leukotrienes (LTs), and lipoxins, play an essential role in the different phases of inflammation. The arachidonic acid pathway is involved in the synthesis of PGs, thromboxanes (TXs), and leukotrienes (LTs). The enzymes phospholipase A2 (PLA2) and cyclooxygenase 2 (COX-2) release and metabolize phospholipids from membranes (Teixeira et al. 2003). When cells are activated, phospholipase A2 (PLA2) hydrolyzes glycerophospholipid membranes releasing, among other fatty acids, arachidonic acid, which in turn, is converted into PGs and TXs by COX, and into LTs by the lipoxygenase (LOX) pathways. For example, prostaglandins are generated during inflammation processes by the inducible COX-2 enzyme through the activation of early genes. Though COX-2 is the dominant source of prostaglandins in

inflammation, recent evidences suggest that both COX-1 and COX-2 may contribute to prostanoid production during both acute inflammatory responses and the resolution phase of inflammation (Li et al. 2015; Scarponi et al. 2014).

These mediators are responsible for important events in inflammation such as vasodilatation, increase of vascular permeability, chemotaxis, pain, leucocyte recruitment, and immune modulation. For example, PGE_2 and cysteinyl leukotrienes (cysLTs) promote the increase of early vascular permeability, and leukotriene B4 (LTB_4) stimulates leucocyte chemotaxis. PGs also play additional roles during the acute inflammatory response, including the regulation of local changes in blood flow and pain sensitization (Verri et al. 2006; Xie et al. 2015).

14.3 Which Are the Most Currently Used Drugs to Treat Inflammation?

Nowadays, there are two principal types of anti-inflammatory drugs: the steroidal anti-inflammatory drugs, also known as corticosteroids, which reduce inflammation by binding to cortisol receptors, and the nonsteroidal anti-inflammatory drugs (NSAIDs), which alleviate pain and decrease inflammation signs by inhibition of COX. The use of NSAIDs entails many risks, in particular, the development of gastrointestinal ulcers, bleeding, and hepatotoxicity. The gastrointestinal adverse effects are due to the nonselective capacity of NSAIDs to inhibit both COX-1 and COX-2. Besides, most NSAIDs are organic acids, being their ulcerogenic potential related to their pKa and lipophilicity. NSAIDs with pKa values ranging from 2.8 to 4.4 are most likely to cause ulcers, as they are lipophilic drugs that interact with phospholipids and disrupt gastric mucosal membranes. In contrast, most selective COX-2 inhibitors are not acidic and have much higher pKa values, thus, they are less likely to cause gastrointestinal mucosal irritation (Scarpignato and Hunt 2010; Park et al. 2015; Kim et al. 2011). Nevertheless, selective COX-2 inhibitors are still associated with the potential to cause serious gastrointestinal events in high-risk patients, as these inhibitors block the synthesis of gastroduodenal epithelial COX-2-dependent prostanoid synthesis that accelerate ulcer healing (Robbins et al. 2010). In addition, when COX pathways are blocked by NSAIDs, some arachidonic acid is diverted through the lipoxygenase (LOX) pathway, which increases leukotriene synthesis, which can further propagate mucosal damage. The participation of cytokines, principally an increase in serum TNF-α, has been extensively documented in NSAID-induced gastric injury in rats after the administration of indomethacin (Choy and Panayi 2001). Moreover, selective COX-2 inhibitors have been found to be associated with an increased risk of cardiovascular events, such as risk of recurrent myocardial infarction and death. These adverse effects have been observed even after short-term use (i.e., <1 week), as in the case of the management of acute gouty arthritis flares (Schjerning Olsen et al. 2011). Furthermore, the suppression of COX-2-derived prostacyclin by both nonselective NSAIDs and selective COX-2 inhibitors increases the risk of thrombosis, hypertension, atherosclerosis, and myocardial

infarction (Funk and FitzGerald 2007; Smyth et al. 2009. These drugs also have adverse effects at the renal level, provoking sodium retention, edema, and exacerbation of hypertension. Moreover, they can decrease platelets and red and white blood cells counts, thus increasing the risk of bleeding, anemia, or infection, respectively (Peschon et al. 1998). Furthermore, the side effects of corticosteroids are mainly due to the ability of the steroid-activated glucocorticoid receptor to activate target genes involved in the metabolism of sugars, proteins, fats, muscles, and bones via transactivation and suppression of the hypothalamic-pituitary-adrenal axis via trans repression (De Bosscher and Haegeman 2009; Schäcke et al. 2002). For example, the most common adverse effects associated with steroid use for the management of acute gouty arthritis attacks are hyperglycemia due to the stimulation of gluconeogenesis (related to glucocorticoid-induced upregulation in glucose synthesis, consequence of transactivation of a complex network of hepatic enzymes), mobilization and degradation of proteins, and increased glycogen storage in the liver (De Bosscher and Haegeman 2009; Schäcke et al. 2002). The glucocorticoid therapy is also associated with adverse cardiovascular effects, most notably, hypertension, dyslipidemia, and reduced fibrinolytic potential. Moreover, the acute corticosteroids therapy can cause psychiatric disorders and aggravation of preexisting psychoses, also affecting memory and cognition. Other effects observed with these drugs include an increase in the hemoglobin concentration and red blood cell counts, possibly by retarding erythrophagocytosis. The treatment with corticosteroid also causes an increase of polymorphonuclear leucocytes in blood. In contrast, lymphocytes, eosinophils, monocytes, and basophils decrease in number after administration of glucocorticoids.

Taking into account the role of IL-1β in inflammation, it is clear that the agents that target IL-1β, or prevent the action of IL-1β on cells, are likely to be useful therapies for the treatment or prevention of acute gouty attacks. For example, rilonacept is a recombinant dimeric fusion protein consisting of fragments of interleukin-1 receptor (IL-1R) and the IL-1R accessory protein linked to the Fc portion (fragment crystallizable region) of immunoglobulin G1, which acts as a receptor to neutralize both IL-1β and IL-1α and as a soluble decoy receptor. Canakinumab is a fully human monoclonal antibody that binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors. Nakinra is an IL-1R antagonist that binds to IL-1R1 and blocks IL-1β and IL-1α. These drugs cause adverse effects such as infections, injection-site reactions, hypertension, and headache.

Another drug that is specifically used to treat gouty arthritis is colchicine, which is an antimitotic alkaloid that binds to specific sites on the cytoskeletal protein tubulin and disrupts microtubule polymerization. This disruption of normal cytoskeletal assembly results in a range of biologic effects on essential cell functions, including inhibition of intracellular vesicle transport, decreased secretion of chemokines and cytokines, impairment of cell migration, and inhibition of cell division (Nuki 2008). Colchicine has a narrow therapeutic index between efficacy and treatment-limiting gastrointestinal adverse effects, including diarrhea and abdominal pain caused by increased peristaltic activity (Fig. 14.3).

Since the beginning of human history, plant extracts have been the basis for medical treatments, and such traditional medicine is still widely practiced today.

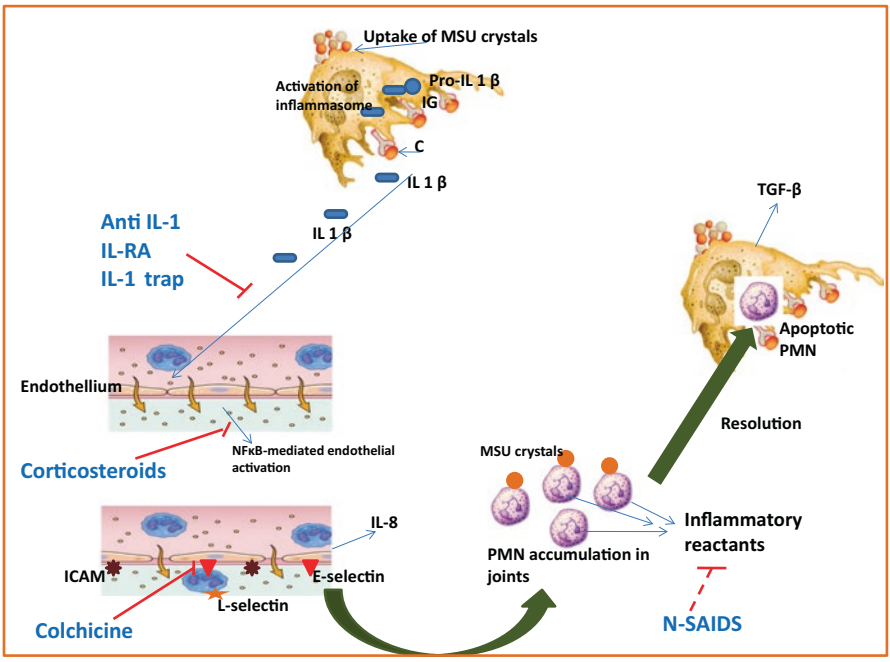

Fig. 14.3 *Mechanism of action of the most commonly anti-inflammatory drugs*. The most common mechanisms of therapeutic anti-inflammatory action of gouty arthritis drugs are colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids which act on many different molecular targets. The mechanisms displayed herein are the most likely targets for reduction of MSU crystal-induced inflammation when these drugs are administered at the recommended therapeutic doses. Anti-IL-1, IL1-RA, and IL-1 trap therapies act specifically to block IL-1β. MSU monosodium urate monohydrate, ICAM intracellular adhesion molecule, IL-1 interleukin-1, IL-RA, IL-1 receptor antagonist, IL-1 trap, IL-1 antagonist, PMN polymorphonuclear leukocytes, TGF tumor growth factor, NF-κB nuclear factor κB, C complement component

Medicinal plants produce chemical compounds as part of their normal metabolic activity, including secondary metabolites which not only are involved in the plant defense against pathogens but also they have effects on humans. Some authors state that plant extracts are more effective and innocuous than synthetic drugs. Among the compounds isolated from plants, sesquiterpene lactones (STLs) are very promising due to their interesting biological activities.

Taking this into account, the aim of this chapter is to review the anti-inflammatory activity and the mechanisms of action of STLs that are used as anti-inflammatory agents, with special interest in their interaction with the cytokine network, lipid mediator production, their effect on the production of reactive oxygen and nitrogen species, their antioxidant capacity, and the effect on the intracellular signaling pathways activated during inflammation. Sesquiterpene lactones can interfere with the production of molecules that initiate and amplify inflammation. Thus, these compounds can modulate events present in both acute and chronic inflammation processes.

14.4 Effects of Sesquiterpene Lactones on Inflammatory Pathways

The effect of some STLs on the inflammatory pathways is reviewed below (Fig. 14.4 and Table 14.1).

14.4.1 Effects on the NF-κB Pathway

One of the most important anti-inflammatory effects exerted by STLs is the inhibition of NF-κB signaling pathway (Siedle et al. 2004; Rummel et al. 2011). Some studies show that STLs can inhibit the NF-κB activity by blocking IκBα degradation

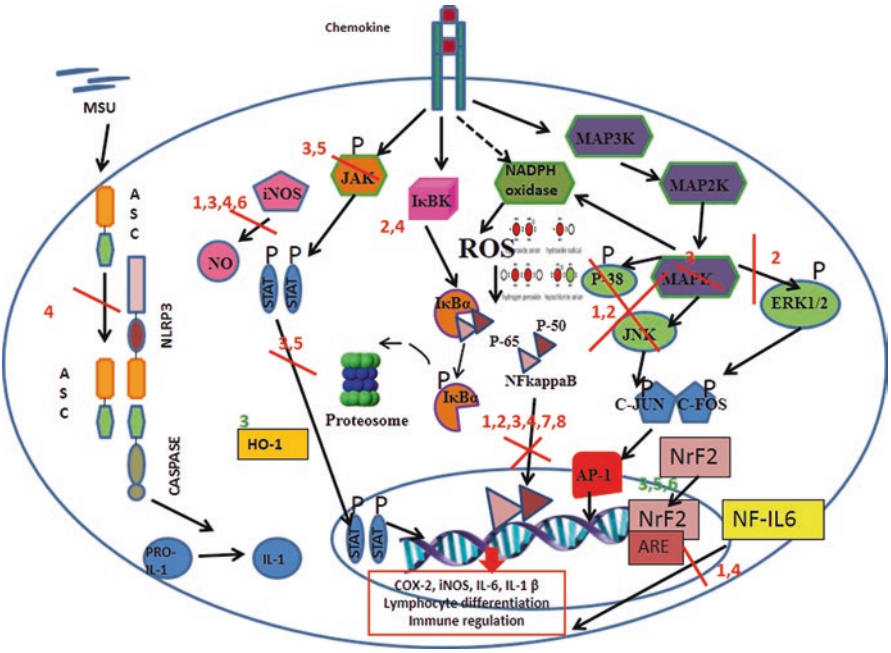

Fig. 14.4 *The anti-inflammatory mechanisms of action of some sesquiterpene lactones*. Atractylenolide I and III (represented as 1) and artemisinin (2) suppress p-38 and c-Jun N-terminal kinase (JNK) activation; 1, 2, costunolide (3), parthenolide (4), budlein A (7), and helenalin (8) inhibit nuclear factor kappa B (NF-κB) induction by targeting p65 subunit; 1 and 4 reduce the expression of NF-IL6; 1, 3, 4, and guaianolide (6) can inhibit the production of NO by downregulating the expression of iNOS; 2 inhibits the activation of extracellular signal-regulated kinase (ERK) 1/2 and decreases the phosphorylation of the inhibitor IκBα by IKK and thus, NF-κB translocation into nucleus. A similar action is observed for 4; 3 suppresses oxidative stress through the induction of phase II detoxification genes, such as HO-1, and inhibits Janus kinase (JAK)/ signal transducer and activator of transcription (STAT) and mitogen-activated protein kinases (MAPK) activation; dehydrocostus lactone (5) inhibits JAK/STAT activation; 4 also reduces the activation of caspase-1 and NLRP3; 3, 5, and 6 increase the nuclear factor E2-related factor 2 (Nrf2)/ antioxidant response element (ARE) activation. MSU, monosodium urate. (Adapted from Hohmann et al. 2016)

Table 14.1 Examples of sesquiterpene lactones with anti-inflammatory effect present in plants and their mechanism of action

Mechanism of action	Sesquiterpene lactones
Inhibition of TNF-α	Artemisinin Budlein A
Inhibition of NF-κB	Atractylenolide I/III Artemisinin Costunolide Parthenolide Mehydrocostus lactone Budlein A Helenalin
Inhibition of JAK-STAT	Costunolide Dehydrocostus lactone
Caspase-1/NLRP3	Parthenolide
Inhibition of NO	Atractylenolide I/III Costunolide Parthenolide Guaianolide
Inhibition of COX	Budlein A Costunolide Artemisinin and parthenolide (mRMA expression of COX-2)
Inhibition of cytokine production (TNF-α, IL-1β)	Parthenolide Budlein A
Inhibition of NF-κB and MAPK	Costunolide Atractylenolide III Artemisinin derivative (SM905)
Effect on the production of lipid mediators: PGs, TX, and LT	Costunolide Parthenolide

or NF-κB translocation into the nucleus, being the latter the most frequent effect (Lyss et al. 1998).

The degradation of IκBα can be blocked by α, β-unsaturated carbonyl moieties of α-methylene-γ-lactones, which react with thiol groups of critical cysteine (Cys-179) in the IKK through a Michael-type addition (Tamura et al. 2012). On the other hand, the prevention of nuclear translocation or DNA binding of NF-κB occurs by alkylation of the critical cysteine residues (Cys38) in the DNA-binding domain of the p65 subunit of NF-κB (Lyss et al. 1998; Tamura et al. 2012). Atractylenolide III, artemisinin, costunolide, budlein A, helenalin, and parthenolide are some examples of STLs that can modulate inflammation by targeting NF-κB activation. For example, it has been demonstrated that costunolide downregulates the LPS-induced expression of TNF-α, IL-1, IL-6, iNOS, monocyte chemotactic protein (MCP)-1, and COX-2 in activated microglia by inhibiting NF-κB and mitogen-activated protein kinases (MAPK) activation, thus reducing brain inflammation (Rayan et al. 2011). Furthermore, costunolide and dehydrocostus lactone reduce the pleural inflammation induced by carrageenan through the inhibition of ICAM-1, P-selectin, NF-κB, and STAT3 upregulation (Butturini et al. 2014). Nevertheless, other mechanisms of

action, apart from the inhibition of NF-κB activation, are involved in the anti-inflammatory action of STLs, for example, atractylenolide III also suppresses receptor-interacting protein-2 (RIP-2) activation and decreases caspase-1 activation and activity, and IL-1β secretion in phorbol-12-myristate 13-acetate plus calcium ionophore A23187 (PMACI)-induced mast cells (Kang et al. 2011). Budlein A inhibits NF-κB DNA binding at very low concentrations (Siedle et al. 2004).

In addition, parthenolide can also suppress the production of inflammatory mediators by inhibiting IκB degradation (Rummel et al. 2011; Siedle et al. 2004; Dai et al. 2010). In vitro studies have shown that parthenolide and artemisinin inhibit the phosphorylation of IKK and RelA/p65, NF-κB translocation into nucleus, and RelA/p65 binding to DNA, which results in significant reduction in cytokine (TNF-α, IL-1β, IL-6, and IL-8) levels and COX-2 mRNA expression (Wang et al. 2011). Moreover, not only does parthenolide attenuate LPS-induced fever, COX-2 expression, and the levels of circulating TNF-α and IL-6 but also reduces the LPS-induced expression of markers for hypothalamic inflammation, such as NF-κB and the nuclear factor for IL-6 expression (NF-IL6) signaling pathways (Rummel et al. 2011).

14.4.2 Effects on Janus Kinase (Jak)/Signal Transducers and Activators of Transcription (STATs) Pathway

It has been demonstrated that dehydrocostus lactone and costunolide inhibit the JAK1 and JAK2 phosphorylation and STAT3 DNA-binding activity in IL-6-activated THP-1 cells (human acute monocytic leukemia cell line). Therefore, STLs also reduce cytokine production and signaling by targeting JAK/STAT (Butturini et al. 2011), thus leading to a significant anti-inflammatory effect.

14.4.3 Effects on Cytokine Production, Maturation, and Release

It has been demonstrated that parthenolide can reduce the maturation of pro-inflammatory cytokines IL-1β and IL-18 by inhibiting the activation of caspase-1 and the inflammasome complex NLRP3 (Mathema et al. 2012). In an experimental stroke model in rats, parthenolide also exerted a protective effect which was partially attributed to a downregulation of caspase-1 expression (Dong et al. 2013). It has been demonstrated that parthenolide can inhibit the proteolysis of pro-IL-1β into active IL-1β through the interaction with caspase-1 by direct alkylation of the active site (Cys285) of the p20 subunit (Juliana et al. 2010). Moreover, this STL inhibits the activation of the NLRP3 inflammasome, possibly by inhibiting its ATPase activity. The ATPase activity of NLRP3 is required to oligomerize the inflammasome protein adaptor ASC and to activate procaspase-1(Juliana et al. 2010).

Furthermore, budlein A, isolated from *Viguiera robusta* (Asteraceae), can inhibit carrageenan-induced mice paw edema, mechanical hyperalgesia (pain), myeloperoxidase activity, and neutrophil recruitment to the peritoneal cavity by a mechanism

related to inhibition of cytokine production (TNF-α, IL-1β, and CXCL1). This STL neither induces the gastric mucosal damage (increased myeloperoxidase activity in the stomach tissue) that is observed after the administration of indomethacin over a 7-day treatment protocol nor the adverse effects provoked by glucocorticosteroids (Valerio et al. 2007). Other authors have also found that budlein A inhibits leukocyte recruitment, adhesion molecule expression, and cytokine production (IL-1β, TNF-α) in vitro (Nicolete et al. 2009).

14.4.4 Effect on Nitric Oxide, Reactive Oxygen Species, Reactive Nitrogen Species, and Antioxidant Contents

It has been demonstrated that STLs exert anti-inflammatory effects by controlling the levels of ROS, RNS, and NO by different mechanisms. Some STLs act by modulating NO levels through the downregulation of iNOS expression, in many cases, through the inhibition of NF-κB and/or MAPK activation. Other STLs control ROS and RNS levels by enhancing antioxidant defenses, which can be either enzymatic or nonenzymatic, via Nrf2/ARE activation. In this sense, parthenolide, costunolide, and atractylenolide I and III are capable of counteracting inflammation by inhibiting the production of NO through the inhibition of NF-κB and/or MAPKs activation (Rayan et al. 2011; Li et al. 2006; Wong and Menendez 1999; Matsuda et al. 2003). The effect on NO production can be studied in vitro on macrophages 264.7, in which the levels of NO can be increased by the action of lipopolysaccharide (LPS). With this model, the anti-inflammatory effect of guaianolides has been demonstrated (Qin et al. 2011).

As for antioxidant enzymes, costunolide and parthenolide, for example, suppress oxidative stress through the increase of endogenous antioxidants such as reduced glutathione and the increase in the activity of the phase II xenobiotic-metabolizing enzymes (γ-glutamylcysteine synthetase, glutathione peroxidase, glutathione S-transferase). These enzymatic activities are induced by the activation of Nrf2/ARE (Jeong et al. 2005).

The antioxidant effect of parthenolide is achieved at low doses, while high doses increase oxidative stress; this effect is responsible for the antiproliferative effect exerted by this compound (Li-Weber et al. 2005). Rummel et al. (2011) have demonstrated that parthenolide exerts antioxidant effects on the rat hypothalamus by reducing LPS-induced mRNA expression of hypothalamic oxidative stress markers (PGC1α/NRF1/TFAM).

14.4.5 Effect on the Production of Lipid Mediators

Some STLs can reduce inflammation by modulating the production of lipid mediators such as PGs, TX, and LT by the inhibition of the enzymes involved in their synthesis. For example, costunolide inhibits the production of PGE2 by suppressing

COX-2 expression (Rodriguez et al. 1976). Sumner et al. (1992) have also demonstrated that parthenolide inhibits TX and LT generation in rat peritoneal leucocytes stimulated with the calcium ionophore A23187 (PMACI).

14.4.6 Effects on Mitogen-Activated Protein Kinase

It has been demonstrated that atractylenolide III can diminish the phosphorylation rate of p38 MAPK and JNK, NF-κB activation, and IL-6 secretion in mast cells induced by phorbol-12-myristate 13-acetate plus the calcium ionophore PMACI (Kang et al. 2011). In addition, an artemisinin derivative (SM905) has proved to inhibit the phosphorylation of ERK, p-38, and JNK and decrease the TNF-α, IL-1β, and IL-6 production induced by LPS in a mouse peritoneal macrophage cell line (Wang et al. 2009; Jung et al. 2010; Lee et al. 2010). In these cases, the inhibition of MAPKs by STLs results in the reduction of cytokine production. As mentioned above, there is a connection between MAPKs and the Nrf2 pathway; for example, costunolide can control TNF-α and IL-6 production induced by LPS by increasing Nrf2 and HO-1 expression (Pae et al. 2007).

14.5 Conclusion

One of the most important mechanisms by which STLs exert anti-inflammatory effects is the inhibition of NF-κB. The inhibition of this nuclear transcription factor leads to the inhibition of the production of pro-inflammatory molecules, such as cytokines and enzymes. As a consequence, inhibition of hypernociception and neutrophil migration occurs, thus achieving control of the inflammation scenario.

The most clinically used inhibitors of NF-κB are the glucocorticosteroids such as dexamethasone, which exerts anti-inflammatory effects. However, this drug is known to cause serious side effects, including osteoporosis, aseptic joint necrosis, adrenal insufficiency, gastrointestinal, hepatic, and ophthalmologic disorders, hyperlipidemia, growth suppression, and probably, congenital malformations.

Sesquiterpene lactones can also exert anti-inflammatory effects by inhibiting the production of lipid mediators by inhibition of COX-2 and LX. The main inhibitors of COX-2 and LX are the nonsteroidal anti-inflammatory drugs (non-NSAID) which are one of the most widely prescribed medications together with corticosteroids. Even though the benefits of NSAIDs are related to their anti-inflammatory and analgesic effects, the use of these agents is not innocuous since they mainly increase the risk of gastrointestinal (GI) and cardiovascular complications. Conversely, sesquiterpene lactones appear to have less side adverse effects.

In summary, sesquiterpene lactones can modulate different inflammatory pathways besides NF-κB inhibition without causing adverse effects, as compared to nonsteroidal and steroidal anti-inflammatory drugs. Therefore, many of these molecules are regarded as promising drug candidates for the treatment of inflammatory diseases.

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