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Review

Inflammation: What's There and What's New?

Ricardo C. Calhelha [1,2,*], Hala Haddad [1,2], Lúcia Ribeiro [1,2], Sandrina A. Heleno [1,2], Márcio Carocho [1,2] and Lillian Barros [1,2]

[1] Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal
[2] Laboratório para a Sustentabilidade e Tecnologia em Regiões de Montanha (SusTEC), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal
* Correspondence: calhelha@ipb.pt; Tel.: +351-273303285

Abstract: Since the dawn of man, inflammation has been known to humanity, as it is marked by pain. Inflammation processes are related to serious chronic diseases with irreversible damage to the organism, being crucial for the development of anti-inflammatory agents. Among the existing anti-inflammatory drugs, non-steroidal and glucocorticoids are commonly used; however, these compounds have been described as responsible for the increased risk of upper gastrointestinal complications and many other side effects. Therefore, it is not shocking that ethnobotany leads most modern studies on the discovery of anti-inflammatory agents obtained from natural matrices. Extracts from plants and isolated substances have demonstrated anti-inflammatory effects in a set of in vitro and in vivo anti-inflammatory models. This review describes inflammation processes with an emphasis on the most common related diseases, while also describing the most promising natural anti-inflammatory agents, by reporting on their obtention processes, mechanisms of action, and applications.

Keywords: inflammation; synthetic anti-inflammatory agents; natural anti-inflammatory agents; mechanisms of action; in vitro and in vivo anti-inflammatory assays

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1. Introduction

Inflammation is a defense mechanism designed to eradicate microbes or irritants, thus protecting living tissues from infection injuries and enhancing tissue repair. This process can lead to changes in blood flow and also to an increase in blood vessels' permeability, fluid migration, proteins, and white blood cells (leukocytes) from the circulation system to the site of the damaged tissue. If the inflammatory response lasts for a few days, it is called acute inflammation; however, if it lasts for a longer time, it is referred to as chronic inflammation and can cause physiological decomposition, organ dysfunction, and eventually even death [1].

The inflammation process is characterized by five cardinal signs: (i) rubor (redness, attributed to hyperemia); (ii) tumor (swelling due to the increase in the permeability of the microvasculature and leakage of protein into the interstitial space); (iii) color (heat related to an increase in blood flow caused by the metabolic activity of the cellular inflammation mediators); (iv) dolor (pain, attributed to changes in the per vasculature and nerve endings); and (v) function lease (dysfunction of the involved organs) [2].

Common anti-inflammatory drugs can calm the symptoms or limit the deleterious effects of inflammation in organisms. Usually, there are two types of anti-inflammatory drugs, non-steroidal drugs and glucocorticoids. These drugs can be applied in different forms, namely by oral treatment, suppository, inhalation, infusion, local application via an ointment, eye drops, among others); however, these anti-inflammatory drugs have serious side effects [3]. The use of oral steroids, aspirin, and acetaminophen at doses of approximately 2 g each is associated with a double increase in the risk of upper gastrointestinal complications; non-steroidal anti-inflammatory drugs are associated with a nearly fourfold

increase in this risk [3]. Therefore, it is crucial to find new and efficient anti-inflammatory drugs that can eliminate infection without undesired side effects. Thus, the aim of the present work is to describe different methods of studying the anti-inflammatory process, namely by testing natural ingredients as inflammatory agents, as natural products have a huge diversity of bioactive molecules with anti-inflammatory capacity [4].

2. Inflammatory Mechanisms

2.1. Initiation of the Inflammatory Response

2.1.1. Vasodilatation, Fluid Exudation, and Leukocyte Migration

Vasodilatation is a typical characteristic of acute inflammation that is manifested at the injury site by redness associated with a warming of the site. The vasodilator response promotes the local delivery of soluble mediators and inflammatory cells, usually vasodilating prostaglandins and nitric oxide (NO). Upon exposure to microbial agents or pro-inflammatory cytokines, the activated leukocytes develop nitric oxide synthase (NOS) enzymes derived from L-arginine. There are three known isoforms of NOS: neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3), which are formed constitutively. Through cyclic guanosine monophosphate (cGMP)-dependent pathways, the formed NO induces subsequent smooth muscle relaxation [1].

Prostacycline (PGI2), PGD2, PGE2, and PGF2a are the main vasodilatory prostaglandins [1] formed by the activities of phospholipase and cyclooxygenase from arachadonic acid [5]. Vasodilatation caused by inflammation first requires arterioles accompanied by the formation of new micro-vascular beds. Highly spread vasodilatation can induce systemic hypotension, as well as shock, in cases of severe systemic inflammation, such as sepsis. Such physiological modifications are potentiated by myocardial depression caused by the sepsis stage, a condition triggered by the activities of nitric oxide and pro-inflammatory cytokines, namely tumor necrosis factor-a (TNF-a) [6]. Another indication of inflammation is edema formation; the trans-vascular movement from the intravascular compartment into the interstitium of protein-rich fluid is caused by the activities of histamine, bradykinin, leukotrienes, complement elements, substance P, and platelet-activating factor (PAF). The mentioned processes significantly affect the membrane activity of small blood vessels and improve the permeability of both water and protein capillaries and venules [7].

Capillary hydrostatic pressure at the injury site also increases earlier during damage caused by inflammatory processes, triggered by local vasodilatation. The spillage of fluids rich in proteins induces erythrocyte aggregation in small vessels and increases blood viscosity. This flow of trans-vascular fluid gradually returns to normal intravascular pressure at the inflammation site. At the same time, plasma protein loss reduces oncotic pressure intravascularly [1]. The increase in vascular permeability, the increase in the capillary hydrostatic pressure, and the decrease in plasma oncotic pressure work together to cause trans-vascular fluid and protein to flow into the interstitium with inflammation. The main purpose of these actions is to facilitate the release of antibodies, for example, to the injury site. However, extreme systemic inflammation can lead to intense vascular permeability, which can contribute to the development of edema in the lungs and extremities. In critically ill patients, the fluid that accumulates in the lungs causes serious respiratory distress syndrome, which can lead to morbidity and death [8].

Vasodilation and fluid exudation occur during leukocyte adhesion and migration. In an infection or inflammatory site, neutrophils are the first and most abundant leukocytes to emerge. The migration of neutrophils from the intravascular space to the inflamed interstitium takes place primarily in the systemic circulation of postcapillary venules and in the pulmonary capillaries of the lung. Transmigration can be divided into many phases, including imagination, turning, membership, diapedesis, and chemotaxis [9]. The process of neutrophil migration from the main bloodstream to the vessel's periphery is named marginalization; this process is facilitated by stasis after fluid exudation and contact established by erythrocytes and neutrophils. Poor adhesive association occurs after imagination by neutrophils and endothelial vascular cells, allowing neutrophils to remain

close to the vascular endothelium. Neutrophil action is stimulated by the tension of moving erythrocytes, with the speed being in accordance with the speed of red cells [10]. Selectins and their ligands promote the adhesive interaction that causes leukocyte rolling. Selectins are a family of surface molecules of glycoprotein expressed on leukocytes (L-selectin), endothelial cells (E-selectin), and platelets (Pselectin) that bind adjacent cells to sialylated carbohydrate determinants. A strong affinity in the adhesive association denominated as conformity occurs when rolling continues. For the subsequent neutrophil diapedesis and chemotaxis, adherence is needed and can occur through the activity of integrins and respective ligands. The most commonly researched and understood are the β-2 integrins, which are composed of different subunits that are bound to a specific β- subunit (CD11a, CD11b, and CD11c) (CD18). B-2 integrins appear in the neutrophils and interact with ligands on the endothelial surface, especially intercellular adhesion molecule-1 (ICAM-1). In neutrophils and endothelial cells, beta-2 integrins and ICAMs are constitutively present, with their expression being significantly up-regulated when inflammation occurs, and help in the transition from rolling to strict adherence [11]. After the adhesion process, to reach the extravascular inflammatory environment, the neutrophil must enter the endothelium and basement membrane. Neutrophils migrate via endothelial cells, a mechanism partially supported by endothelial retraction. Diapedesis is also promoted by the adherence of compounds such as platelet-endothelial cell adhesion molecule-1 (PECAM-1), which is usually present both on the endothelial cells and on neutrophils. PECAM-1 bonds can reduce neutrophils' adherence to ICAM-1, which results in the inhibition of adherence and diapedesis. Rolling, adhesion, and diapedesis mechanisms are regulated via the interaction of neutrophil-adherent molecules with endothelial cells. The end purpose of such processes is to promote neutrophils' movements at sites of infection or damage from the intravascular compartment and into the interstitium [12]. To promote their migration to the damaged tissue, neutrophils and other leukocytes often need chemoattractants, soluble compounds that help to attract leukocytes to damaged tissues, which are usually by-products of a bacterial origin, complementary agents, and chemokines. Several chemoattractants are unique to subsets of leukocytes and can be categorized depending on the sensitivity of the leukocyte. Classical chemoattractants may be bacteria-produced N-formylated peptides, complementary agents, as well as leukotrienes [13].

Injury or invasion of tissue can lead to significant growth in the place of chemokine production, causing a selective captation of leukocytes to the injured tissue. The analysis of chemokine secretion due to the inflammatory stimulus defines the type of the inflammatory penetration of the damaged site. Chemokine receptors regulate the migration of leukocytes that are cell-type and chemokine-type specific. With seven transmembrane regions, these receptors are G-protein-coupled proteins that present an identic chemical structure, but have different functions. These molecules display ligand and leukocyte specificity, thereby evaluating the inflammatory infiltrate's type [14].

2.1.2. Coagulation Cascade Profile in Inflammatory Processes

During an infection, a coagulation cascade occurs, and it can be split into two pathways that eventually converge, resulting in thrombin activation and fibrinogen division into fibrin. The intrinsic pathway is a collection of plasma proteins controlled by Hageman factor (factor XII), a liver-produced protein that regulates collagen, basement membranes, and activated platelets by attaching to them [15]. When the Hageman effect is switched on, it causes a series of events that contribute to the development of thrombin. The intrinsic pathway is most frequently stimulated by directed tissue pain.

The production of tissue factor, on the other hand, stimulates the extrinsic pathway [16]. Tissue factor acts on tissues that are not normally accessible to the vascular compartment, such as subcutaneous tissues and blood vessel adventitial layers. Moreover, during inflammatory processes, endothelial cells and stimulated monocytes generate tissue factor in response to TNF-a, IL-1, IL-6, and C-reactive protein [17]. The presence of tissue factor activates factor VII, forming a complex with tissue factor and eventually inducing the production of

thrombin through the stimulation of coagulating agents. The activation of the coagulation cascade is relevant to the development of fibrin clots and to pro-inflammatory processes. Pro-inflammatory activity has been linked to factor Xa, thrombin, and the tissue factor–VIIa complex. Thrombin and the tissue factor–VIIa complex, in particular, cause mononuclear and endothelial cells to release pro-inflammatory cytokines, such as TNF-a [18]. Such an effect is usually regulated through the linking of particular factors on the membrane of target cells to protease-activated receptors. The inflammatory process then initiates coagulation, which will further amplify the immune process.

During inflammation, the clotting cascade is activated, but is restricted by many factors. It inhibits pro-coagulant pathways from unregulated induction. Anti-thrombin, the C protein system, and tissue factor pathway inhibitor (TFPI) are the main well-defined factors. After formation in the liver, anti-thrombin immediately establishes bonds with inactivated thrombin. Heparin, as well as glycosaminoglycans, greatly potentiate this bonding. The association of anti-thrombin with the endothelial cell surface in rodents stimulates the release of PGI2, which inhibits monocyte production of TNF-α by inhibiting the activation of the nuclear factor-kB (NF-kB) transcription factor. Thus, besides coagulation control, anti-thrombin also presents anti-inflammatory effects [18].

Protein C is a circulating protein that activates endothelial cells through the thrombin–thrombomodulin complex. Through the inactivation of Va and VIIIa, the activation of protein C decelerates the clotting cascade. The induction of thrombin synthesis by TNF-a through monocytes is also inhibited due to the activation of protein C by the inhibition of the activation of NF-kB and AP-1. Thus, protein C acts as an anti-coagulant and as an anti-inflammatory agent. During a sepsis situation, because of the intake and the induction of inflammation and down-regulation of thrombomodulin, the depletion of activated protein C may occur. This contributes to unregulated thrombin production, leading to rapid coagulation and elevated pro-inflammatory activity. Increased mortality in septic patients with low activated protein C levels has shown the significance of protein C in controlling thrombin production during sepsis [19].

TFPI is the third critical element in the regulation of thrombin production. On endothelial cells, TFPI is present and bonded to lipoproteins. Through the formation of a quaternary structure with tissue factor and factor VIIa, TFPI inactivates tissue factor. During inflammation, the induction of tissue factor activity inhibits the extrinsic clotting pathway. It has also been shown that TFPI infusion reduces the formation of pro-inflammatory cytokines in baboons; nonetheless, in humans, it does not occur [17].

2.2. Complement System

This is a collection of microbial-activated proteins, helping and facilitating inflammation and microbial degradation. The nutrient cascade is also likely to be active in a tissue injury situation, being important in cell damage related to severe injuries, such as those resulting from burning [20]. Three different methods have been described that trigger this complement cascade: the classical pathway, alternative pathway, and lectin pathway; each one is activated through different mechanisms. The classic pathway is activated by the antibodies IgM or IgG that bind to the microbial structures, while the alternative pathway is activated by microbial compounds binding to the C3 component supplement; finally, lectin pathway activation occurs through the bonding established by mannose-lectin that establishes interactions with glycoproteins, for instance [1].

The complement portion can be cleaved by these three different pathways into C3a and C3b. C3a acts as a chemoattractant for neutrophils and C3b binds to microbes to promote phagocyte detection and enable phagocytosis [21]. Furthermore, C3b establishes a proteolytic structure with complementary agents to allow C5 to be cleaved into C5a and C5b [22]. C5a is a chemotactic driver of neutrophils, causing at the same time alterations in the vascular permeability in the inflamed area. C5b attaches to microbe structures, developing a membrane attack complex consisting of C6, C7, C8, and C9 [23]. This complex causes the eventual death of the microbe's cells.

2.3. Amplification of the Inflammatory Response

2.3.1. Immune Response

This may be split into natural and adaptive responses regarding tissue injury or infection. The primary response to tissue invasion is supported by the innate immune system. The vasodilatation processes described above can improve vascular permeability and cellular infiltration. Macrophages, dendritic cells, natural killer cells (NK), and neutrophils are the main cell agents of the innate immune response. Besides the mentioned elements, effector proteins, namely complement, acute-phase reactants, and the cascade of coagulation are very relevant to our immunity response [1].

The extent of innate reaction is primarily determined by the production of cytokines and non-cytokine inflammation mediators. Cytokines are polypeptides formed by immune system cells when these cells are exposed to an infection process, and significant work to control inflammatory and the immune reactions begins. Cytokine production is limiting, but certain cytokines can exist in the circulatory system for long periods, with these reactions being pleiotropic and repetitive. For instance, interferon-α (IFN-) induces macrophage activation and isotype-switching induction in B-cells, causing the output of opsonizing antibody of IgG and activating the differentiation of T-helper-1 (Th1) cells to T-cells. However, TNF-α and IL-1 have the ability to trigger fever, activate the liver to manufacture acute-phase proteins, and cause the activation of endothelial cells. Therefore, cytokines can have multiple different functions. Blocking a single cytokine can, for this reason, also have a minimal impact on the response to an inflammation process [24]. The innate immune system's classical cytokine-secreting cells are macrophages. Dendritic cells have been identified as relevant factors for microbial identification and the development of cytokines in the immune response. These cells and macrophages possess the capacity to respond to a range of microbial products through pattern-recognition receptor components.

It has been shown that toll-like receptors (TLRs), proteins from the surface, are essential for pathogen-associated molecular pattern recognition and subsequent cytoplasmic signaling. TLRs can be associated with many components to build complexes in the cell's surface receptors that are specific for some ligands, namely Gram-negative lipopolysaccharides, Gram-positive lipoproteins, and bacterial DNA. However, these complexes have similar signaling paths, but certain signaling processes for individual TLR complexes are likely to be distinct [25].

The processes that stimulate the production of the transcriptors NF-kB and AP-1 have the highest profile. Multiple cytoplasmic signaling proteins, such as the MyD88 adaptor protein and the IL-1 receptor-associated kinase are recruited as ligands to bind to the TLR complex (IRAK). Autophosphorylation, as well as the separation of IRAK from MyD88, is induced by the recruitment of IRAK. TNF-R-associated factor 6 (TRAF-6) is stimulated by phosphorylated IRAK, which further induces the NF-kB (IkB) cascade inhibitor and further breakdown of protein IkB, as well as the production of NF-kB in the cytoplasm.

To promote the binding of the gene-promoting region and to control the gene transcription that encodes mediators of inflammation, including TNF-a, IL-1b, IL-6, and iNOS, the factor NF-kB is translocated to the nucleus [26]. TRAF-6 stimulation also activates the mitogen-activated protein (MAP) kinase cascade, which triggers the release of the transcription factor AP-1. AP-1, alongside NF-kB, attaches to the binding site of pro-inflammatory mediator genes and activates the output of pro-inflammatory cytokines [27]. TNF-α is a well-known pro-inflammatory cytokine. TNF-α is predominantly unfettered by macrophages TNF-α, activates antimicrobial resistance pathways, and removes tissue before the infection is eradicated by triggering an inflammatory reaction at locations of regional infection or inflammation [28]. It is an important phagocyte modulator for neutrophils and mononuclear phagocytes, as well as a fibroblast-growing and angiogenesis factor.

However, a devastating series of events that can result in tissue damage, organ failure, and possibly death can be precipitated by the secretion of TNF-α. The effects of TNF-α include fever, enhancement of liver acute-phase protein secretion, the induction of the coagulation cascade, myocardial suppression, the induction of hypotensive systemic vasodilators, catabolism, as well as hypoglycemia. Several scientific reports have described

that organisms' responses that simulate the systemic inflammatory reaction seen during sepsis and after serious injury occur after the administration of TNF-α to animals during scientific experiments. TNF–receptor II (TNF-RII) complex activation mediates almost all of the pro-inflammatory and metabolic effects. This receptor links proteins (TRAFs), with six of them being known (TRAF-1 to TRAF-6) [29]. These factors provoke pro-inflammatory gene expression by transducing signals that stimulate the transcription factors NF-kB and AP-1. A further significant consequence of TNF-a can be the capacity to cause apoptosis after binding to the TNF-RI complex. The active TNF-RI allows the TNF receptor death domain (TRADD) to be recruited to the plasmatic tissue.

TRADD attracts certain proteins, including FAS-associated death-domain protein (FADD), which is responsible for the caspase-8 activation, resulting in the stimulation of a caspase cascade that triggers apoptosis. TNF-α's biochemical actions are almost similar to those of IL-1. IL-1, on the other hand, does not really damage the cells or induce apoptosis on its own, though it can enhance the harmful effects of TNF-α. While IL-1 receptor blockers (IL-1r β) attach to the IL-1 receptor, they do not activate it; they tend to act as IL-1 antagonists that compete with each other. IL-18-binding protein works in the same manner, preventing IL-18 from performing its role. Surprisingly, their roles are somewhat different, despite the fact that IL-1 and IL-18 signal via similar processes [30].

IL-6 is yet another cytokine produced during inflammation that has a large influence. IL-6 functions as a lymphocyte growth and differentiation factor and induces the release of acute-phase proteins in the liver. Even though IL-6 does not seem to be a direct mediator of tissue injury, chronic plasma IL-6 elevation is related to undesirable outcomes in trauma and patients in sepsis conditions. During this situation, IL-6 can be used to continue the inflammation [31].

IL-8 is generated by the macrophages and is also a highly studied chemokine in inflammation settings. IL-8 is an effective chemoattractant for the mobilization of inflammatory foci from neutrophils. Different scientific reports stated that IL-8 is relevant for the mediation of tissue damage in the sense of trauma and burn injury, particularly in the lungs [32]. Other chemokines are also likely to be powerful in the mediation of inflammation. IL-12, for instance, is released by macrophages and dendritic cells that are activated, with its most significant function being the promotion of the T-cell and NK cell development of IFN-g. Furthermore, IL-12 mediates the early immune response to intracellular microorganisms and adaptive immunity stimulation [33]. The release of IL-12, which functions in combination with IL-15 and IL-18 to induce IFN-g production by NK cells, is induced by several types of microbes. IFN-g is a cytokine that is implicated in the amplification of an inflammatory process, specifically the induction of cytokine release by macrophages and phagocytosis. To improve these immune responses, IL-12 and IFN-g work together. In more detail, IL-12 released by macrophages and dendritic cells prompts NK cells to release IFN-g. In exchange, macrophage inflammation activities, including the output of further IL-12, are potentiated by NK cell-derived IFN-g. Therefore, during immune responses, the early development of IL-12 and IFN-g potentiates the inflammatory response. Thus, during septic shock, a blockade of IL-12 or IFN-g development or function has been shown to substantially decrease the deleterious inflammatory effects [33].

Several other mediators that are not cytokines also participate in systemic inflammatory response syndrome pathogenesis (SIRS). Platelet-activating factor (PAF) is an autocoid phospholipid released by endothelial cells that regulates cytokine release and amplifies the pro-inflammatory response [34]. The adhesion of neutrophils to endothelial cells seems to be an important factor. PAF's extended involvement in the serum of SIRS patients is associated with a negative outcome. Eicosanoids are metabolites of arachadonic acid that regulate different processes and reactions during the inflammation response. Leukotrienes (LTC4–LTE4) promote the contraction of endothelial cells, leading to capillary leakage. Thromboxane A2, a catalyst originating from the macrophages and platelets, causes platelet accumulation, as well as vasoconstriction [1].

The response from the immune system is closely regulated and typically acts successfully to decrease inflammation and facilitate tissue recovery. Pro-inflammatory mediators (TNF-a, IL-1, IL-12, and IFN-g) and anti-inflammatory mediators are typically balanced (IL-10, converting growth factor-b and some prostaglandins). IL-10 is an activated macrophage and dendritic cell inhibitor, and acts as an effective inflammatory response regulator. Following a bacterial endotoxin or intact bacteria challenge, mice that are deficient in IL-10 display hyper-inflammation. Supplementation with exogenous IL-10 increases the anti-inflammatory potential. The first effect of IL-10 is that activated macrophages and dendritic cells inhibit IL-12 development. This causes the subsequent suppression of the development of IFN-g by NK cells and activated T-cells, allowing the pro-inflammatory response to inhibit IL-12/IFN-g-mediated amplification [35].

Granulocyte colony-stimulating factor is another cytokine with anti-inflammatory effects (G-CSF). For improved killing operations, G-CSF induces neutrophil production from bone marrow and primes neutrophils. At the same time, by communicating with G-CSF receptors on monocytes and macrophages, G-CSF inhibits the development of TNF-a, IL-1, and IL-12. In addition, the contents of IL-1ra and TNF receptors are increased by G-CSF therapy. G-CSF thus facilitates local anti-microbial defense by improving the roles of neutrophils while systemically exerting anti-inflammatory effects [36].

Extreme systemic inflammation, namely sepsis and SIRS, can ensue in cases where the pro-inflammatory response predominates. In comparison, the predominance of the anti-inflammatory response can contribute to the creation of a state of relative immunosuppression.

This condition also occurs in the post-septic state following major trauma or thermal damage and has been dubbed counter-anti-inflammatory reaction syndrome (CARS). A high number of scientific reports state that the predominance of IL-10 contributes to post-inflammatory immunosuppression growth. CARS-exhibiting patients may be more vulnerable to contagious complications. As a consequence of extreme inflammation, if the pro- and anti-inflammatory paths are out of control, organs can start to fail and a patient can die [37].

2.3.2. Acquired Immune Response

The innate immune response enhances the acquired immunity, which is mainly mediated by IL-12 that induces the activation of T-cells and facilitates the segregation of immature T-cells into the Th1 phenotype [38]. However, the adaptative immune response is mainly triggered by the introduction of "strange" antigens to T-cells CD4+ and CD8+ T. The activation of CD4+ T-cells triggers the subsequent development of cytokines and stimulates both immune systems (innate and acquired). At the time of antigen presentation, the different cytokines generated by CD4+ cells depend upon the immunological environment. CD4 T-cells are the best-defined subsets of Th1 and Th2 cells, which are characterized by the cytokines generated by them. IFN-g is the principal cytokine formed by Th1 cells. In fact, IFN-g increases the pro-inflammatory reaction by inducing the activation of macrophages and activating the cytolytic functions of CD8 T-cells [39]. IFN-g also activates B-cells to develop IgG2a antibodies that are opsonizing and complement binding [40]. Helminths and susceptibility to allergens induce the differentiation of Th2. Such stimuli induce sustained stimulation of T-cells without a relevant innate response or macrophage activation.

Two more T-cell subsets are Th3 and T-regulatory 1 (Tr1) cells. The first ones generate TGF-b and participate in the development of immune tolerance [41].

3. Relationship between Inflammatory Processes and Chronic Diseases

Several diseases, such as type 2 diabetes, obesity, Alzheimer's disease, heart disease, and allergies, have few common factors. Still, in common, they are all primarily lifestyle diseases and are usually related to chronic inflammation. In order to change the traditional thinking about inflammation diseases, a generic model was proposed, because traditional thinking claimed the chronic diseases of various organ systems as their own, and the research on the pathophysiology was reductionist. However, these chronic diseases have several mechanisms in common, so these models highlight these shared pathophysiologic mechanisms [42]. The

epithelial and mesenchymal cells of the affected organs are two prototypic cell types induced by signals resulting from interactions between the innate and adaptative immune systems. These signals induce some responses, such as the recruitment of leukocytes participating in chronic inflammation, extracellular matrix remodeling, and cell death, among others [42]. Atherosclerosis, interstitial lung disease, rheumatoid arthritis, and cirrhosis present similar mechanisms and mediators; however, they act in totally different ways [43,44].

In many organs, helper T-cells bind to the damaged tissue of chronic inflammation, including atherosclerotic plaques, forms of chronic hepatidites, rheumatoid synovium, and a number of pulmonary diseases. Histocyte, microglia, or alveolar macrophages are also found in such lesions. Every type of tissue involved has specific epithelial cells: the vascular endothelial cells in atherosclerosis, the glomerular or tubular epithelial cells in renal disease, and enterocytes in inflammatory bowel diseases. Similarly, depending on the organ involved, inflammatory and immune mechanisms have different types of structures of mesenchymal cells, arterial smooth muscle cells, fibroblasts, myofibroblasts, synoviocytes, or mesangial cells. The first step of an inflammatory process involves the selective and sequential migration of blood cells and the second step is their interaction with resident tissue cells. Only some elements of this inflammatory process can be exhibited by some conditions. However, the key inflammatory mediators are dominant, but outside of the context of classic inflammatory processes.

For instance, in osteoporosis, mediators such as IL-1, IL-6, and TNF-α are primarily furnished by resident stromal cells to regulate bone turnover unaccompanied by different agents of the classic response. A normal defense mechanism can be coaxed into an injurious response due to a persistent stimulus.

3.1. Chronic Diseases

In Table 1, some examples of chronic diseases directly related to inflammation processes can be seen. For the displayed diseases, the inflammation process and the common therapeutic treatment are available and allow disease control over a long period of time. Nevertheless, particular attention should be paid to chronic diseases, such as Atherosclerosis and Alzheimer's, which cause severe and irreversible damage.

3.1.1. Atherosclerosis

Atherosclerosis is a disease in which plaque builds up within an artery, narrowing it. There are normally no signs in the early stages, but depending on the form and position of the compromised arteries, it may cause serious issues, including coronary heart problems, strokes, coronary artery disease, and kidney disorders [44].

Vascular endothelial cells resist long periods of contact with leucocytes when exposed to activating agents, such as modified lipoproteins, microbial agents, or pro-inflammatory cytokines; nonetheless, they release a variety of vascular cell adhesion molecule-1 (VCAM-1) and elements of the selectin family, including P- as well as E-selectin [45]. Monocytes pass straight through the artery wall after adhering to the endothelial surface, assisted by chemokines, such as monocyte chemoattractant protein-1 (MCP-1) [46]. These monocytes transform into macrophages and proliferate after being exposed to activating and co-mitogenic mediators, such as macrophage colony-stimulating factor in the arterial intima (M-CSF) [47]. These macrophages produce an excessive amount of scavenger receptors, which wrap transformed lipoprotein particles in endocytotic droplets and then absorb cholesterol (CE), which is a feature of the formation of atherosclerotic plaques, in cytoplasmatic droplets, resulting in a foamy cell [48]. The inflammatory and immune processes contribute to acute thrombosis, which is one of the ultimate complications of atherosclerosis [46].

Signal transmission occurs between T cells, mononuclear phagocytes, and vessel wall cells as the intima of the artery becomes inflamed. As a result of reduced collagen production or increased deterioration, this mechanism causes the fibrous plaque to degrade. Proteinases mediated by inflammatory signaling mediate decreased synthesis, while IFN- mediates increased

breakdown. The expression of tissue factor, a significant cause of thrombus development, is improved by CD40 ligation, increasing the thrombogenicity of the lipid core [49].

3.1.2. Alzheimer's Disease

This is a chronic neurodegenerative disease that progressively worsens. Cognitive deterioration and the involvement of amyloid plaques and neurofibrillary tangles define this chronic condition [50]. In pathologically susceptible areas of Alzheimer's disease, localized peripheral inflammatory responses of high complexity have been observed. Inflammation is caused by degenerative tissue and the aggregation of deeply insoluble pathological chemicals, as well as injured neurons and neurites, highly insoluble amyloid peptide deposition, and neurofibrillary tangles. The local upregulation of complement, cytokines, acute process reactants, and other inflammatory mediators is frequently discrete, microlocalized, and permanent, as these symptoms are discrete, microlocalized, and stable from the preclinical to late stages of Alzheimer's disease. Explicit and indirect damage from Alzheimer's disease to inflammatory pathways accumulates through time and is predicted to play a major role in the pathogenic processes. As per clinical trials and animal models, inflammation plays a significant part in the pathogenesis of Alzheimer's disease [51].

Table 1. Examples of chronic diseases related to inflammation.

Disease	Description	Inflammatory Mechanism	Treatment	Ref.
Chronic obstructive pulmonary disease (COPD)	A chronic inflammatory lung disease that causes obstructed airflow from the lungs.	Both innate (macrophages/neutrophils) and adaptive inflammatory immune cells (CD4, CD8, and B lymphocytes) that develop lymphoid follicles increase the tissue volume of the bronchial wall characterized by the infiltration of the wall.	Phosphatidylcholine (PC) (natural) 18:1 PC (cis) and 1, 2-dioleoyl-sn-glycerol-3-phosphocholine (DOPC) (synthetic).	[52]
Alcoholic fatty liver disease (AFLD)	A build-up of fats in the liver caused by drinking a large amount of alcohol.	Expression of the following inflammatory molecules in the liver: tumor necrosis factor α (TNF-α), monocyte chemotactic protein 1 (MCP-1), chemokine (C-X-C motif) ligand 1 (CXCL-1), and interleukin 1 beta (IL-1β).	Phosphoesterase complex (Pho).	[53]
Obesity	A complex disease involving an excessive amount of body fat.	Abnormal cytokine production, increased synthesis of acute-phase reactants, and activation of inflammatory signaling pathways	Weight loss and physical activity.	[54]
Chronic kidney disease	A long-term condition where the kidneys do not work as well as they should.	Activation of the prototypical proinflammatory signaling pathway, the best characterized being NF-κB and AP-1, mainly based on the stimulation of multiple mediators, including proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α).	Ramipril, enalapril, lisinopril. atorvastatin, simvastatin, vitamin D, furosemide, and cyclophosphamide.	[55]
Autoimmune diseases (SLE, RA, and Sjogren's Syndrome)	A condition in which the immune system mistakenly attacks the body.	Substitution of the AU-rich element (ARE) in the IFN- 3 'untranslated region (called ARE-Del) with random nucleotides, which results in a weak, but chronic, expression of IFN-γ.	Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (Motrin and Advil) and naproxen (Naprosyn).	[56]
Myocardial infarction (MI)	A heart attack occurring when blood flow to a part of the heart decreases or stops, causing damage to the heart muscle.	Inhibition of the signaling pathways of nuclear transcription factor κB (NF-κB), p38, c-Jun NH2-terminal kinase (JNK), and transforming growth factor β (TGF-β).	Thrombolytics, aspirin, nitroglycerin, beta-blockers, and ACE inhibitors.	[57]
Psoriasis	A skin condition that causes red, flaky, crusty patches of skin covered with silvery scales.	Heightened innate and adaptive immune activation. T helper (Th)1 and Th17 cells drive pro-inflammatory cytokines, including TNF-α, interferon-γ, IL17A, and IL23.	Anti-TNF-α therapy, topical—creams and ointments, phototherapy.	[58]

4. Common Treatments of the Inflammatory Process

4.1. Corticosteroids

Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex of vertebrates. There are two main classes of corticosteroids, namely glucocorticoids and mineralocorticoids, which are both involved in the regulation of the inflammatory response (Table 2). This class of drugs represents a natural starting point for empirical anti-inflammatory therapy. The most broadly active anti-inflammatory/immunosuppressive agents in clinical use are glucocorticoids [59]. The suppression of neutrophil's adherence, aggregation, phagocytosis, and accumulation, suppression of monocyte accumulation, inhibition of prostaglandin and leukotriene production, lympholysis, inhibition of immunoglobulin production, and impairment of delayed hypersensitivity are known specific actions of corticosteroids.

Steroids have been widely used in the treatment of idiopathic inflammatory diseases of the central nervous system (CNS), including lupus cerebritis and temporal arteritis, as well as to treat multiple sclerosis. Nevertheless, there are serious drawbacks (Table 2) to clinical trials of this class of drugs for Alzheimer's disease. A high dose of corticosteroids can cause toxic effects, such as hypertension, hyperglycemia, fluid retention, and the exacerbation of congestive heart failure, psychiatric syndromes, including psychosis, mania, and depression, gastrointestinal ulceration or perforation, increased susceptibility to infection, osteoporosis with vertebral compression fractures, aseptic necrosis of bones, myopathy, truncal obesity, accelerated atherogenesis, glaucoma, adrenal suppression, and cataracts [60].

4.2. Non-Steroidal Anti-Inflammatory Drugs

These drugs are members of a drug class that reduces pain, decreases fever, prevents blood clots, and decreases inflammation in higher doses (Table 2).

The first-line drugs for inflammatory diseases, such as rheumatoid arthritis and gout, are non-steroidal anti-inflammatory drugs. Their main role is the inhibition of neutrophil function and prostaglandin synthesis [61]. Non-steroidal anti-inflammatory drugs interact primarily with the pro-inflammatory cytokines interleukin (IL)-1a, IL1b, IL-6, and tumor necrosis factor (TNF-α) [62]. The cardinal signs of inflammation occur because of the increase in the TNF-α concentration; they also stimulate white cell phagocytosis and the production of inflammatory lipid prostaglandin E2 (PGE2). The major mechanism that leads to the success of these medications is their ability to interfere with the production of prostaglandin during the inflammatory cascade [63]. Steroidal and non-steroidal anti-inflammatory medications have significant side effects in reducing the inflammatory response [64].

From Table 2, it can be deduced that corticosteroid and non-steroidal anti-inflammatory drugs are molecules containing at least one functional group, such as hydroxyl, methyl, and ketone. These functional groups are described as being the main groups responsible for the anti-inflammatory activity.

4.3. Natural Anti-Inflammatory Agents

Most anti-inflammatory medications are linked to an elevated risk of severe upper gastrointestinal problems. The level of risk for particular anti-inflammatory drugs has been estimated through epidemiological studies. Through the use of oral steroids or low-dose aspirin, the likelihood of upper gastrointestinal tract leakage or perforation rises by almost twice with the use of non-aspirin, non-steroidal, anti-inflammatory medicines. Overall, with more than one anti-inflammatory drug administered concurrently, the risk is dose-dependent and higher. Therefore, in order to minimize the risk of severe upper gastrointestinal complications, anti-inflammatory drugs should be prescribed as monotherapies and at the lowest effective dose possible [3].

Table 2. Mechanism of action, structure, and side effects of some steroidal and non-steroidal anti-inflammatory drugs.

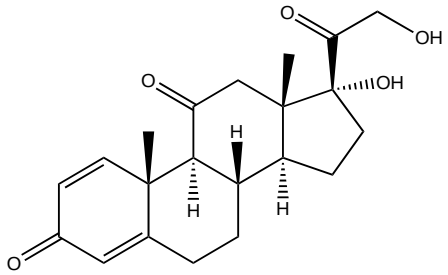
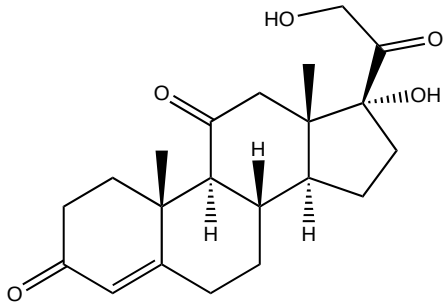
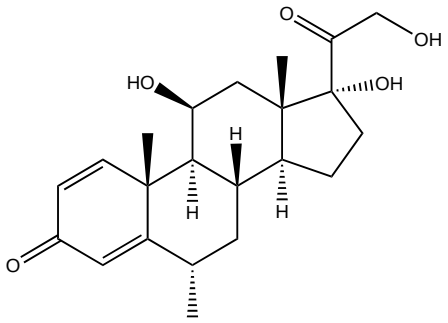
Drug Type	Mechanism of Action	Chemical Structure	Side Effects	Reference
Corticosteroid Drugs				
Prednisone	Decreases inflammation through the suppression of the migration of polymorphonuclear leukocytes and reversing increased capillary permeability. It also suppresses the immune system by reducing the function and the size of the immune system.		Nausea, vomiting, loss of appetite, heartburn, trouble sleeping, increased sweating, and acne.	[65]
Cortisone	Switches off multiple activated inflammatory genes through the inhibition of HAT and recruitment of HDAC2 activity to the inflammatory gene transcriptional complex.		Confusion, excitement, restlessness, headaches, nausea, vomiting, skin problems, including acne, thin skin, heavy sweating, and redness, and trouble sleeping.	[66]
Methylprednisolone	The methylprednisolone–glucocorticoid receptor complex binds and blocks promoter sites of pro-inflammatory genes, promotes the expression of anti-inflammatory gene products, and inhibits the synthesis of inflammatory cytokines, mainly by blocking the function of transcription factors, such as nuclear factor kappa-B (NF-kB).		Upset stomach, stomach irritation, vomiting, headache, dizziness, insomnia, restlessness, depression, anxiety, acne, increased hair growth, easy bruising, and irregular or absent menstrual periods.	[67]

Table 2. *Cont.*

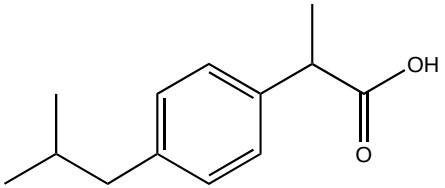
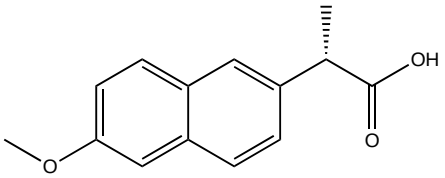
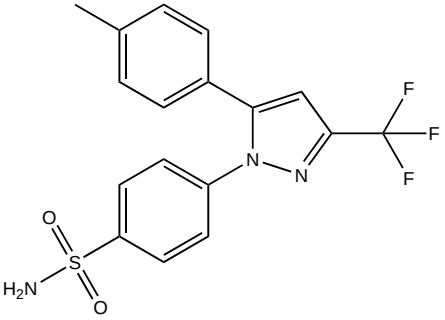
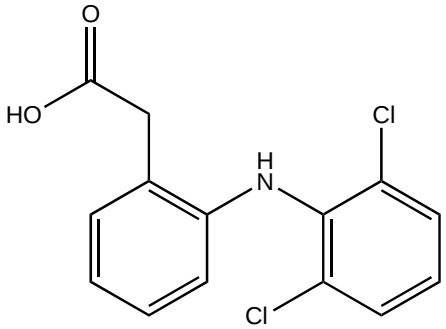
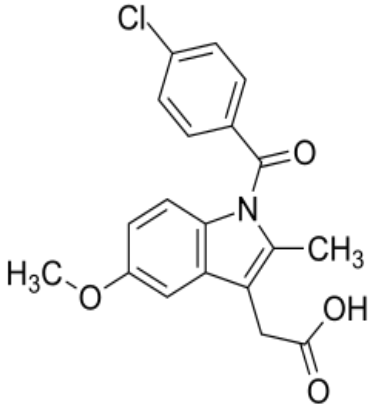
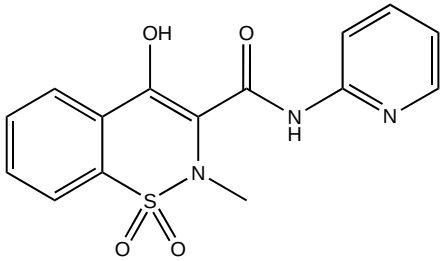
Drug Type	Mechanism of Action	Chemical Structure	Side Effects	Reference
Non-steroidal Anti-Inflammatory Drugs NSAIDs				
Ibuprofen	Non-selective, reversible inhibition of the cyclooxygenase enzymes COX-1 and COX-2 (coded for by PTGS1 and PTGS2, respectively).		Headaches, feeling dizzy, feeling sick (nausea), being sick (vomiting), wind, indigestion, and swollen ankles.	[68]
Naproxen	Blocks arachidonate binding to competitively inhibit both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, resulting in analgesic and anti-inflammatory effects.		Confusion, headaches, ringing in the ears, changes in vision, tiredness, drowsiness, dizziness, and rashes.	[69]
Celecoxib	Selective inhibition of cyclooxygenase-2 (COX-2), which is responsible for prostaglandin synthesis, an integral part of the pain and inflammation pathway.		Stomach pain, heartburn, gas, diarrhea, constipation, nausea, vomiting, swelling in the hands or feet; dizziness, and cold symptoms.	[70]

Table 2. *Cont.*

Drug Type	Mechanism of Action	Chemical Structure	Side Effects	Reference
Diclofenac	Inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) with relative equipotency.		Headaches, dizziness, stomach pain, feeling or being sick, diarrhea, and rashes.	[71]
Indomethacin	Inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).		Vomiting, upset stomach, heartburn, diarrhea, a feeling of bowel fullness, constipation, bloating, gas, rectal irritation, dizziness, drowsiness, and nervousness.	[72]
Piroxicam	Inhibition of cyclooxygenase (COX-1 and COX-2). Piroxicam is a potent inhibitor of prostaglandin (PG) synthesis in vitro.		Abnormal liver function tests, urination problems, upset stomach, heartburn, loss of appetite, stomach pain, nausea, vomiting, gas, diarrhea, constipation, dizziness, headaches, itching, rashes, and ringing in the ears.	[73]

Owing to the substantial side-effect profiles of steroidal and NSAID drugs, there is greater interest in natural compounds, such as nutritional supplements and herbal medicines, which have been used for centuries to reduce pain and inflammation. Many of these natural compounds often act in a similar fashion to NSAIDs by inhibiting inflammatory pathways. Many natural compounds function to inhibit the inflammatory pathways of nuclear factor-kB (NF-kB) in addition to the COX pathway [4].

4.3.1. Omega-3 EFAs (Fish Oil)

One of the most effective natural anti-inflammatory agents available are omega-3 polyunsaturated fatty acids [74]. After acknowledging that vascular inflammation is the root cause of coronary artery disease, the American Heart Association advises eating seafood and taking fish oil supplements to avoid this disease [75]. Eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) are active ingredients in fish oil, and they can help COX convert to prostaglandin E3, a natural anti-inflammatory agent. Prostaglandin E3 competes with arachidonic acid for its conversion to prostaglandin E2, a potent inflammatory mediator. It also prevents the production of the inflammatory cytokines TNF-α and IL-1b. By competitive inhibition, EPA and DHA, which transform arachidonic acid into inflammatory leukotrienes, can also block the 5-LOX pathway [4,76].

4.3.2. White Willow Bark; Salix Alba (Carl Linnaeus)

One of the strongest herbal remedies for pain and inflammation is the bark of the white willow tree. The inhibition of inflammatory prostaglandins by nonselective antagonists of COX-1 and COX-2 is a mechanism of action shared by white willow bark and aspirin [77]. White willow bark has been found to have comparable potency to synthetic anti-inflammatory drugs in some studies that compared it with non-steroidal anti-inflammatory drugs. However, white willow bark may cause a few side effects as a result of the liver's conversion of salicin to salicylic acid [78].

4.3.3. Green Tea

Green tea has been used as an anti-inflammatory agent in the treatment of arthritic disease, as well as in the prevention of cardiovascular disease and cancer. Catechins and epigallocatechin-3 gallate are the most common polyphenols found in green tea. Epigallocatechin-3 gallate blocks IL-1, causing proteoglycan secretion and type 2 collagen breakdown in cartilage explants [62]. In addition, it inhibits IL-1b and reduces the expression of the transcriptional factor NF-kB in human in vitro human models. Green tea also reduces the synthesis of aggrecanases, which are cartilage-degrading enzymes [4].

4.3.4. Ginger; Zingiber Officinale (Roscoe)

In ancient civilizations, herbal practitioners relied on herbs to strengthen the body's immune system. In several countries, ginger and its derivatives are used to improve the immune system. Gingerol, shogaol, and other structurally related compounds in ginger block the biosynthesis of prostaglandin and leukotriene by blocking 5-lipoxygenase or prostaglandin synthetase. In addition, they can also inhibit the synthesis of pro-inflammatory cytokines, such as IL-1, TNF-α, and IL-8. Studies have shown that ginger extract in liver cancer-induced rats can suppress the elevated expression of NFκB. Similarly, elevated expression of TNF-α has also been inhibited by the treatment with ginger extract in liver cancer rats. It is obvious that ginger can serve as an anti-cancer and anti-inflammatory agent by blocking NFκB activation through the inhibition of TNF-α, a pro-inflammatory cytokine [79,80].

4.3.5. Bryonia Dioica (Jacq.)

The mitochondria-mediated cascade (the destruction of mitochondria, the activation of caspase-9 and -3, the cleavage of PARP, and the degradation of PUMA) may be activated by *Bryonia dioica* aqueous extract in Burkitt's lymphoma cell line BL41. Phytochemical

screening revealed the presence of bioactive compounds, such as flavonoids, triterpenes, and sterols, that may lead to the apoptogenic role of the *Bryonia dioica* aqueous extract. *Bryonia dioica* may also be considered a possible source of new treatments for Burkitt's lymphoma [81,82].

4.3.6. Other Natural Matrices

Table 3 shows the commonly used techniques (in vitro and in vivo), as well as the active compounds and their anti-inflammatory effects. Regarding in vitro studies, anti-inflammatory activity is exhibited by EC_{50} (μg/mL) (corresponding to the sample concentration that inhibits 50% of NO production) for various studied plants, meaning that a low EC_{50} concentration results in high anti-inflammatory activity. Concerning in vivo studies, three different methods have been described: (i) inhibition of the croton oil-induced ear edema in mice, in which the anti-inflammatory activity was expressed as a percentage of the edema reduction in treated mice compared with the control mice; (ii) the carrageenan-induced rat paw edema assay, in which the result was expressed as the decrease in volume percentage compared with the control group at various time intervals; and finally (iii) the detection of ROS and NO production in an established zebrafish model, where the output of NO and ROS was calculated.

As stated in Table 3, aloe-emodin, perilla aldehyde, phenolic acids, flavonoid glycoside, flavan-3-ols, peraksine derivatives, methyl (1-hydroxy-4-oxocyclohexa-2,5- dien-1-yl), acetate (jacaranone), ethyl ester, verbascoside, artemisinin, scopoletin, chrysosplenetin, eupatin, sitosterol-3-O-β-d—glucopyranoside, essential oils, trans-sabinene hydrate, methyl-ether, 1,2-epoxy-menth-4-ene21, acteoside terpenoids, alkaloids, and triterpenoids are the most important bioactive molecules found in natural matrices that have chemical features responsible for the anti-inflammatory properties. These molecules present chemical groups in their structure, such as hydroxyl, methyl, and ketone, similar to synthetic drugs, thus corroborating the efficacy of these functional groups in the treatment of inflammation processes. Hydroxyl and ketone groups are required for glucocorticoid activity in the immune system; glucocorticoids are part of the feedback process that decreases certain facets of immune function, such as inflammation. Therefore, they are used in medicine to combat conditions, such as allergies, asthma, inflammatory diseases, and sepsis, that are caused by an overactive immune system.

Table 3. In vitro and in vivo anti-inflammatory activities of natural matrices.

Natural Matrix	Anti-Inflammatory Assay	Active Compounds	Mechanism of Action	Anti-Inflammatory Activity	References
In vitro assessment					
				(EC_{50}) µg/mL	
Acacia tortilis (Forssk.)	Inhibition of nitric oxide (NO) production in a cell-based model of lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophage-like cell line.	(epi)-Gallocatechin derivatives	Inhibition of cyclooxygenase-1 (COX-1) and COX-2 enzymes that are involved in the inflammatory response.	88 ± 4	[83]
Aloe vera (Carl Linnaeus)		Aloe–emodin	Active against the human colon cancer cell lines DLD-1 and HT2.	8.6 ± 0.1	[84]
Ammodaucus leucotrichus fruits (Coss. and Dur.)		Perilla aldehyde and limonene	Active against skin pathologies.	11.70	[85]
Bauhinia variegata L.		Phenolic acids and flavonoid glycoside	-	255 ± 16	[86]
Calendula arvencis L.		-	-	321 ± 4	[87]
Carissa macrocarpa (Eckl.) A.DC		Phenolic acids, flavan-3-ols, and flavonols	-	179 ± 6	[88]
Rauvolfia vomitoria (Afzel)		Peraksine derivatives	-	17.52−20.99	[89]
Jacaranda arborea (Bignoniaceae) (Urban)		Methyl (1-hydroxy-4-oxocyclohexa-2,5-dien-1-yl)acetate (jacaranone) (1) and its ethyl ester 2	Inhibition of the production of TNF-a in LPS-treated macrophages with low toxicity.	0.99 (uM)	[90]
Acanthus montanus (Nees) T.	Inhibition of nitric oxide (NO) production in a cell-based model of lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophage-like cell line and inhibition of COX-2 expression.	Verbascoside	-	91.50 ± 0.95 92.55 ± 0.64	[91]
Brillantaisia owariensis P. (P.Beauv.)		-	-	71.01 ± 0.65 71.01 ± 0.65	[91]

Table 3. *Cont.*

Natural Matrix	Anti-Inflammatory Assay	Active Compounds	Mechanism of Action	Anti-Inflammatory Activity	References
Asteraceaeherba-alba Asso (Bercht. and J. Presl)	Inhibition of nitric oxide (NO) production in a cell-based model of lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophage-like cell line.	-	-	60	[92]
Asteraceae annua L. (C.Winkl.).		Artemisinin scopoletin, chrysosplenetin, eupatin, and sitosterol-3-*O*-β-d–glucopyranoside	-	87.43	[93]
Cassia fistula L. (Collad.)		-	-	83	[94]
Eucalyptus camaldulensis (Dehnh)	Lipoxygenase inhibition activity (LOX).	Essential oils	-	36.79	[95]
Biophytum umbraculum (Welw.)	Inhibition of nitric oxide (NO) production in a cell-based model of lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophage-like cell line.	-	-	39.6 ± 6.8	[96]
Nigella sativa L. (Mill.)		Essential oils, trans-sabinene hydrate methyl ether 19, and 1,2-epoxy-menth-4-ene21	-	6.3	[97]
Buddleja salviifolia (Lam)		Acteoside	-	42	[94]
Rubus rosifolius (Sm.)		Essential oils	-	56	[94]
Morinda citrifolia (Carl Linnaeus)		-	-	67	[94]

Table 3. *Cont.*

Natural Matrix	Anti-Inflammatory Assay	Active Compounds	Mechanism of Action	Anti-Inflammatory Activity	References
		In vivo assessment			
				Percentage of edema reduction (%)	
Borago officinalis (Carl Linnaeus)	Inhibition of the croton oil-induced ear edema in mice.	Phenolic compounds	-	21	[98]
Capparis sicula subsp. *Sicula* (Carl Linnaeus)			-	24	[98]
Malva sylvestris (Carl Linnaeus)			-	21	[98]
Mentha aquatic (Carl Linnaeus)			-	27	[98]
Raphanus raphanistrum subsp. *Raphanistrum* (Carl Linnaeus)			-	25	[98]
				Percent inhibition of edema volume after 1 h (%)	
Terminalia bellarica (Gaertn.) Roxb.	Reducing the carrageenan-induced mice paw edema volume.	Flavonoids, terpenoids, and alkaloids	Inhibition of COX-2 activity.	32.85 ± 0.013	[99]
Terminalia chebulla (Retz.)		Flavonoids, terpenoids, and alkaloids	Inhibition of COX-2 activity.	34.28 ± 0.016	[99]
Zanthoxylm armatum, (DC.)		-	Prevention of pro-inflammatory mediators of edema synthesis and their release at the target site.	43 ± 0.2	[100]
				Output of NO and ROS	
Patrinia heterophylla (Benth.)	Detection of ROS and NO production in an established zebrafish model.	Natural iridoids	Down-regulation of iNOS and COX-2 expression.	ROS and NO increase after treatment of zebrafish embryos with LPS.	[101]
Lantana camara (Carl Linnaeus)		Triterpenoids	Down-regulation of iNOS.		[102]

5. Methods for Assessing Anti-Inflammatory Activity

5.1. In Vivo Assessment

There are several in vivo anti-inflammatory methods commonly used by the scientific community, such as: (i) "*Cotton Pellet Method of Meier, Schuler and Desaulles*", based on the fact that anti-inflammatory medication decreases the deposition of granulation tissue. This assay basically consists of the insertion of pellets in mice that are further injected with anti-inflammatory agents. Afterward, the mice are sacrificed, the pellets are extracted, the extraneous tissue is cut off, and the pellets are dried overnight. The pellets are measured again and the volume of granulation tissue is calculated [103]; (ii) the "*Inhibition of the Tuberculin Reaction in B.C.G. Sensitized Guinea Pigs*" method, also in use, is based on the findings that some fractions of liquor ice extract are as active as cortisone. In this assay, white guinea pigs are sensitized to tuberculin and are subcutaneously injected with the anti-inflammatory agent with the aim of analyzing the inflammation-reducing capacity [104]; (iii) The "*Rat Foot Test*", in which a formaldehyde solution is injected into the right rear foot plantar aponeurosis and the degree of swelling is measured. The difference between the amounts in the injected and non-injected feet can be contrasted with the percentage change in regulation as measured as a percentage of that in the non-injected foot [105]; (iv) "*Granuloma Pouch Method*", in which a volume of air is gradually inserted under the skin of the rat's back through a fine hypodermic needle. Anti-inflammatory medicine reduces pouch wall thickening and fluid exudation into the sac [106]; (v) "*Topical anti-inflammatory activity*" has been tested in mice as an inhibition of the ear edema caused by croton oil. Croton oil suspended in aqueous ethanol is applied to the inner surface of the right ear. Its anti-inflammatory activity has been demonstrated as a proportion of the decrease in edema in treated mice. Indomethacin, a non-steroidal anti-inflammatory drug (NSAID), was used as a guideline [98]; (vi) The "*Carrageenan-induced rat paw edema assay*" uses carrageenan-induced rat paw edema. By the subplanar injection of carrageenan (1 percent w/v), edema is briefly caused on the right hind paw. The amounts in the injected and contralateral paws are measured after inflammatory activation using a plethysmometer (Orchid Scientific Laboratory). The value is calculated as a decrease in volume percentage compared with the control group at various time intervals [100]. (vii) "*Detection of ROS and NO production in an established zebrafish model*"; ROS are often over-released as an inflammatory response occurs, in addition to extreme NO as an indication of inflammation response. A zebrafish model is commonly used as a convenient and economical animal screening model to test anti-inflammatory effects in vivo, where the outputs of NO and ROS are calculated [102].

5.2. In Vitro Assessment

Regarding in vitro assessments, a wide range of assays are used to perform a first screening to select the most promising anti-inflammatory agents.

The "*PhagoBurst Assay*" consists of kits that use flow cytometry to examine the phagocytic activity of granulocytes and monocytes in the whole blood. The Phagotest allows for the quantitative evaluation of leukocyte phagocytosis (bacterial uptake). It specifies the percentage and activity (number of bacteria per cell) of phagocytes that ingest fluorescein–isothiocyanate (FITC)-labeled opsonized bacteria [107].

In the "*Anti-inflammatory bioassay*", a reaction mixture consisting of egg albumin, phosphate-buffered saline, and various concentrations of the anti-inflammatory agent is incubated with egg albumin under controlled experimental conditions. Then, the absorbance is measured and the percentage inhibition of protein denaturation is calculated by using the following formula [108].

$$\% \text{ inhibition} = 100 \times [\text{Vt}/\text{Vc} - 1]$$

where Vt is the absorbance of the test sample and Vc is the absorbance of the control.

The "*Cyclooxygenase inhibitors*", is also an in vitro approach used for more than two decades and is based on the incubation of arachidonic acid with COX-1-containing sheep seminal

vesicle microsomes. However, distilled COX-2 and COX-1 were used in 2000 and 2004, respectively, by the same community. To identify the COX inhibitory effect of plant extracts, various parameters were tested. To be considered active, some researchers set a minimum COX inhibition of 50% for water extracts and 70% for organic solvent extracts. The standards where the Inhibition was below 20 percent were considered negligible. COX inhibition activity is known to be marginal between 20 and 40%, mild between 40 and 70%, and strong anti-inflammatory activity above 70 [109].

Regarding "*Lipoxygenase inhibitors*", it is interesting to note that leukotrienes are another class of inflammatory mediators formed by LOX enzymes from arachidonic acid metabolism. It has been documented that leukotrienes are responsible for binding white blood cells to the endothelium of weakened blood vessels and function as phagocyte chemoattractants. In addition, leukotriene development has been linked to clinical symptoms of pathological disorders, such as asthma and anaphylaxis. Leukotrienes, formed by 5-LOX in inflammatory cells, such as polymorphonuclear neutrophils, basophils, mast cells, eosinophils, and macrophages, are the most actively examined [109].

Finally, the "*Inhibition of nitric oxide (NO)*", potentially the most used method, is based on the ability of anti-inflammatory agents to suppress inflammatory processes through the inhibition of nitric oxide (NO) production in a cell-based model of lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophage-like cell line [83].

6. Trends in the Treatment of Inflammatory Processes

Targeting Glycolysis with Small Molecules to Elicit an Anti-Inflammatory Effect

Several models of infection and inflammation have shown an anti-inflammatory response after the inhibition of hexokinase by 2-DG and GAPDH by heptelidic, acid as well as tetramerization and the activation of the pyruvate kinase activity of PKM2 by TEPP-46 [27]. Targeting the glucose transporter Glut1 is one of the novel, promising targeted therapies to limit inflammation (Figure 1).

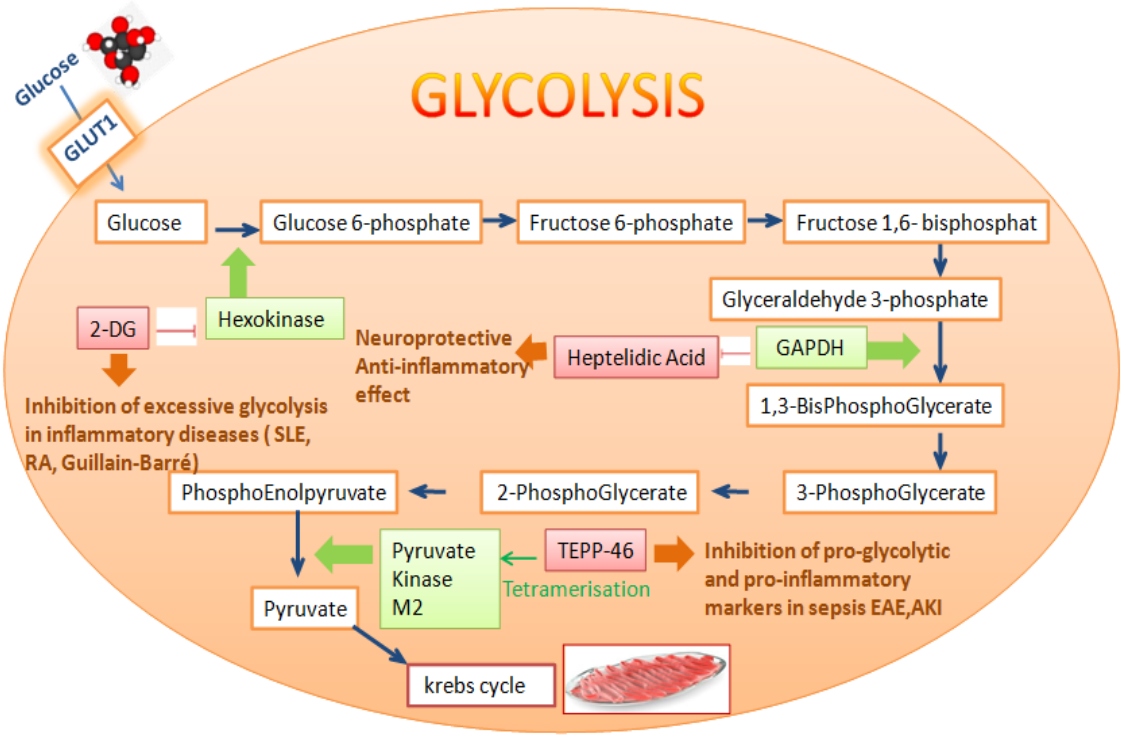


Figure 1. Targeting enzymes of glycolysis as an anti-inflammatory strategy. Glut-1, glucose transporter-1; 2-DG, 2-deoxyglucose; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; EAE, experimental autoimmune encephalomyelitis; AKI, acute kidney injury.

Molecular docking has been consistently used to highlight ligand–receptor molecular interactions and is thus a valuable method supporting drug discovery and development. It is one of several computational methodologies that have been developed to help researchers classify candidates for new drugs and investigate them. Molecular docking analysis was then used to elucidate the structural criteria for the interaction of compounds with various anti-inflammatory drug targets.

The Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB, http://www.rcsb.org/pdb/home/home.do; accessed on 25 March 2022) provides three-dimensional coordinates of various inflammation-related drug targets, such as cyclo-oxygenase-2, tumor necrosis factor-α, inducible nitric oxide synthase, and galectin-3.

The graphical user interface of the Biovia Exploration Studio Visualizer and MGLTools packages can be used to prepare all input files for docking. It is possible to extract native co-crystallized ligands, water molecules, and cofactors from each PDB and Gasteiger file, and process and use them to assign partial atomic charges. After combining non-polar hydrogens, each rotatable bond of a ligand can be allocated. The 2D structure can be transformed by the MM2 process implemented in ChemBio3D Ultra 12.0 into its 3D coordinates and energy-reduced form. For molecular docking simulation using the Lamarckian genetic algorithm technique, AutoDock 4.2 and AutoDock Vina 1.1 are included. The default docking protocol needs to be introduced with 100 individual runs for a rigid protein and a fluid ligand [110].

Compared with the co-crystallized ligands, the observed root-mean-square deviation (RMSD) of the docked ligands with minimal binding energy should be around 2.0 Å, suggesting that the scoring parameters implemented in both AutoDock 4.2 and AutoDock Vina 1.1 are accurate [110].

7. Conclusions

Inflammation is a protective mechanism intended to remove bacteria or irritants in order to protect living tissues from infection and damage, and to potentiate tissue repair. However, inflammatory processes have a direct relationship with serious diseases, such as atherosclerosis and Alzheimer's disease. Different types of synthetic substances are used in the treatment of inflammation, but, unfortunately, they have been strongly associated with harmful side effects; therefore, there is a crucial need to find natural alternatives with higher efficiency and safety. Some natural agents, mostly obtained from plants, have already been explored and have successfully been used to inhibit inflammation, a fact that is corroborated by the chemical features of these natural molecules that present similar functional groups in their chemical structures, similar to the ones present in synthetic drugs, including hydroxyl, methoxy, and ketone groups.

In the available literature, there have been few in vivo and in vitro studies on methods to analyze anti-inflammatory activity. There have also been several findings that point to new methods for treating inflammation, such as iron chelation for cystic fibrosis lung inflammation, nanosystems for ocular inflammation, and in silico applications based on network pharmacology for the treatment of acute skin inflammation.

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