ANTI-INFLAMMATORY POTENTIALS OF Andrographolide AND ITS ANALOGUES IN VARIOUS DISEASES

Shivani Gupta[1], Ravindra Mishra[2], Radharaman Tiwari[3], Harsha Rathore[4]

Abstract

A medicinal herb known as Andrographis paniculata (A. paniculata) is used in both Indian and Chinese traditional medicine for a variety of therapeutic benefits. This is caused by the presence of "Andrographolide," a diterpene lactone. Andrographolide and its natural counterparts are thought to have a number of biological functions, including anti-inflammatory, anti-tumor, anti-hyperglycaemic, anti-fertility, antiviral, cardiac protecting, and hepatoprotective qualities. Studies have revealed the presence of more closely comparable terpenoid analogues from A. paniculate in addition to this diterpene lactone (Andrographolide): This investigation focuses on Andrographolide, a diterpenoid molecule from Andrographis paniculata, which has anti-inflammatory properties. Studies examined the effects of Andrographolide and the characteristics of the target, with a focus on transcription factors. NF-kappaR The DNA binding region, or active site, of NF-kappaB, is discovered to have primarily positive potential. Negative potency is required for a specific inhibitor to have electrostatic complementarity. This substance inhibits the activation of NF-kappaB and reduces the expression of inducible nitric oxide synthase (iNOS), among other anti-inflammatory effects. Additionally, it stops human neutrophils from producing oxygen radicals and stops human fibroblast cells from expressing COX-2.

Key words: Andrographolide, Andrographis paniculata, inflammation, anti-inflammatory effect.

[1*]School of Pharmacy, ITM University. Shivani Gupta**,** ITM University, Gwalior, India. Email: gshivanigupta@gmail.com
[2]Department of Pharmacy, GLA University.
[3]School of Pharmacy, ITM University.
[4]Shriram College of Pharmacy.

***Corresponding Author:** Shivani Gupta
*School of Pharmacy, ITM University. Shivani Gupta**,** ITM University, Gwalior, India. Email: gshivanigupta@gmail.com

DOI: 10.48047/ecb/2023.12.si5a.0487

Introduction

In recent years, the incidence of inflammatory diseases has remained high and patient's life has worsened. Inflammation is a complex pathophysiological process mediated by a variety of singling molecules produced by leukocytes, macrophages and mast cells as well as by the activation of complement factors, which bring about edema formation as a result of extravasations of fluid, proteins, etc and pain at the site of inflammation. Depending upon the defence capacity of host and duration of response, inflammation can be classified into Acute Inflammation and Chronic inflammation (1). Acute and chronic inflammatory responses are both part of natural defence mechanism of the body's innate immune system. The main signs of inflammation are redness (redness or erythema), heat, swelling, and pain which result from local immune, vascular and inflammatory cell responses to infection or injury. Chemical mediators such as histamine are quickly released from mast cell granules and take immediate effect. Other chemical mediators, such as leukotrienes and prostaglandins, must be synthesized from arachidonic acid before they can be released into mast cells, and are therefore responsible for the later effects of prolonging inflammation. The inflammatory response process depends on the exact nature of the initial stimulus and its location in the body. They all share a common mechanism i.e., Recognize cell surface pattern receptors noxious stimuli, inflammatory pathways activation, inflammatory markers are released, and Inflammatory cells are recruited (2,3). Inflammatory responses are accompanied by serious diseases such as septic shock, cancer, atherosclerosis, rheumatoid arthritis implying that inflammatory responses are critical patron to the pathophysiology of several diseases. To date, pharmacotherapy of inflammatory conditions is based on the use of non-steroidal and steroidal anti-inflammatory drugs. Prolonged use of these drugs may cause serious gastrointestinal toxicity, increased blood pressure, greatly increased risk of congestive heart failure. Thus, botanicals have attracted much attention in anti-inflammatory research due to their good pharmacological activity and efficacy (4-9) Flavonoids, terpenoids, steroids, phenols, glycosides, alkaloids and tannins are secondary metabolites of plants and are called natural substances. There is ample scientific evidence supporting the successful treatment of pain and inflammation with natural products. In the plant kingdom, almost every family has representative analgesic and anti-inflammatory herbs. (10-12). Andrographolide paniculate is a traditional herb from Asian countries, also called kalmegh or king of bitters belongs to family acanthaceae. It was first isolated by Boorsma from different parts of A. paniculata and was named as andrographide, untill it was proved that it was structurally a lactone and was renamed as Andrographolide. Andrographolide is bioactive compound Andrographis paniculate is the major labdane diterpenoidal constituents of this plants (13). Previous research has confirmed that Andrographolide has antipyretic and analgesic, anti-inflammatory, antibacterial, antiviral, immune regulatory, anti-tumor, neuroprotective, hepatoprotective, gallbladder protective, and anti-cardiovascular activities. The leaves of the plant are reported to contain Andrographolide, neoAndrographolide, andrographiside, homoAndrographolide, andrographane, andrographanin, andrographone and andrographosterol. The aerial parts of the plant contain Andrographolide, neoan-drographolide, andrographiside 14-deoxyAndrographolide, 14-deoxy-11,12-didehydroAndrographolide, 14-deoxy-11-oxoAndrographolide and β-sitosterol. The roots contain 5-hydroxy-7,8,2-3'-tetramethoxyflavone, Andrographolide andrographonin, apigenin and 7,4-dioxymethylether (14). Of the above chemicals, Andrographolide is the major bioactive constituent responsible for variety of activities. Leaves and stems of plant are used for extracting active phytochemicals; roots are used rarely. Anti-inflammatory and anti-angiogenic activity: A. paniculata as well as extract of Andrographis plant are known to have an anti-inflammatory potential (15). Andrographolide treatment inhibits nuclear factor kappa B (NF-kB) binding to deoxyribonucleic acid, reducing the expression of pro-inflammatory proteins such as cyclooxygenase 2 (Cox-2) and nitric-oxide synthase (16). This article summarizes anti-inflammatory potential of Andrographolide, the anti-inflammatory signalling pathways involved in its effects, discusses the evidence regarding the effectiveness and superiority of Andrographolide and its analogues in anti-inflammation (17).

Inflammation

Inflammation is a pattern of response to injury, Tendency to accumulate cells and exudate in inflamed tissue Protects against further damage. Depending upon the defence capacity of host and duration of response, inflammation can be classified into Acute Inflammation and Chronic inflammation. Acute Inflammation is immediate, is short duration lasting for minutes to hours to days. Upon tissue injury, damaged mast cells and platelets release chemical messengers such as

histamine, serotonin, prostaglandins and leukotrienes into the interstitial fluid and blood. These chemicals affect the blood vessels and nerves in the damaged area. The main signs of inflammation are redness (redness or erythema), heat, swelling, and pain. Redness and heat are caused by increased blood flow to the injured area, Swelling or edema is caused by protein and fluid moving into the interstitial space, Pain results from increased fluid pressure to nerves, especially in confined spaces, and from local nerve stimulation by chemical messengers such as bradykinin. Other common inflammatory symptoms include low-grade fever, malaise, fatigue, headache, and loss of appetite (loss of appetite). If the infection causes inflammation, the fever may be severe, depending on the organism involved. However, high heat can be beneficial if it impedes the growth and reproduction of pathogens. Fever results from the release of pyrogens or pyrogens (eg, interleukin-1) from white blood cells (WBCs) or macrophages. Pyrogens circulate in the blood, triggering the thermoregulatory system and Thermostat and; reset to higher levels of hypothalamus. Thermogenic mechanisms such as shivering are activated and cellular metabolism is increased. Involuntary cutaneous vasoconstriction, characterized by pale, cold skin, reduces body heat loss. Voluntary actions such as curling up or covering yourself conserve heat. These mechanisms continue until body temperature reaches the new higher setting. After the cause is removed, body temperature returns to normal by reversing the mechanism. Chronic inflammation can occur after an acute episode of inflammation if the cause is not fully resolved. Diseases such as rheumatoid arthritis are characterized by chronic inflammation with periodic exacerbations of acute inflammation. Alternatively, chronic irritants such as smoking, certain bacteria, or a long-term abnormal immune response can unknowingly cause inflammation. chronic inflammation is characterized by less swelling and exudate, but more lymphocytes, macrophages, and fibroblasts (connective tissue cells) than acute inflammation. Chronic inflammation often leads to greater tissue destruction. More collagen is produced in this area, forming more fibrous scar tissue. Granulomas, small clumps of cells with a necrotic centre covered with connective tissue, can develop around foreign bodies such as debris or as part of the immune response in some infections, such as tuberculosis (18).

Inflammatory response mechanisms

The inflammatory response is the coordinated activation of signalling pathways that regulate levels of inflammatory mediators in resident tissue cells and inflammatory cells recruited from the blood. Inflammation is a common etiology of many chronic diseases, including cardiovascular disease, bowel disease, diabetes, arthritis, and cancer. Although inflammatory response processes depend on the exact nature and location in the body of the initial stimulus, they all share common mechanisms that can be based on Cell surface pattern receptors recognize noxious stimuli, Inflammatory pathways are activated, Inflammatory markers are released and Inflammatory cells are recruited.

Pattern recognition receptor activation

The innate immune system is a major cause of acute inflammation caused by microbial infection or tissue injury. Innate immunity is also important for the activation of acquired immunity. innate immune cells such as macrophages and Dendritic cells (DCs) play an important role, but non-professional cells such as epithelial, endothelial and fibroblasts also contribute to innate immunity. Germline-encoded pattern recognition receptors (PRRs) serve to detect the presence of microorganisms They do this by recognizing structures that are conserved across microbial species, called pathogen-associated molecular patterns (PAMPs). Recent evidence suggests that PRRs are also involved in recognizing endogenous molecules released by injured cells, termed damage-associated molecular patterns (DAMPs). Four different classes of PRR families have now been identified These families include transmembrane proteins such as Toll-like receptors (TLR) and C-type lectin receptors (CLR), and retinoic acid-inducible gene (RIG)-I-like receptors (RLR) and NOD-like receptors (NLR). These PRRs are not only expressed in macrophages and DCs. but also in various non-professional immune cells. With the exception of some NLRs, PAMP or DAMP sequestration by PRRs upregulates the transcription of genes involved in inflammatory responses. These genes encode proinflammatory cytokines, type I interferons (IFNs), chemokines, antibacterial proteins, and proteins involved in regulating PRR signalling. and many uncharacterized proteins. the Expression patterns of inducible genes differ between activated PRRs.(19)

Activation of inflammatory pathways

Inflammatory pathways influence the pathogenesis of many chronic diseases and involve common inflammatory mediators and regulatory pathways Inflammatory stimuli activate intracellular signalling pathways and activate the production of inflammatory mediators Primary inflammatory

stimuli, including microbial products and cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are mediated by TLRs, IL-1 receptor (IL-1R), IL-6 receptor (IL-6) 6R) and TNF receptor (TNFR) .receptor activation Triggers key intracellular signalling pathways including mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and Janus kinase (JAK) - signal transducers and activators of transcription (STAT Method).(20-22)

Five members comprise the NF-κB protein family: RelA/p65, RelB, c-Rel, p50 and p52. The activation of NF-κB involves two major signalling pathways, the canonical and noncanonical (or alternative) pathways, both being important for regulating immune and inflammatory responses. Canonical pathway activation predominantly occurs through BCR, TCR, TLR4, IL-1R or TNF-R receptors, whereas the non-canonical pathway involves receptor activation of CD40L, BAFF or lymphotoxin-B. The canonical NF-κB pathway responds to diverse stimuli, including ligands of various cytokine receptors, pattern recognition receptors (PRRs), TNF receptor (TNFR) superfamily members, as well as T-cell receptor (TCR) and B-cell receptor (23). The mechanism of canonical NF-κB activation is the inducible degradation of IκBα triggered through its site-specific phosphorylation by a multi-subunit IκB kinase (IKK) complex (24,25**).** IKK is composed of two catalytic subunits (IKKα and IKKβ) and regulatory subunit NF-κB essential modulator (NEMO) or IKKγ (26). IKK can be activated by cytokines, growth factors, mitogens, microbial components and stress agents (27). Upon activation, IKK phosphorylates IκBα at two N-terminal series and, thereby, triggers ubiquitin-dependent IκBα degradation in the proteasome, resulting in rapid and transient nuclear translocation of canonical NF-κB members predominantly the p50/RelA and p50/c-Rel dimers (28,25,29**).** the noncanonical NF-κB pathway selectively responds to a specific group of stimuli, including ligands of a subset of TNFR superfamily members such as LTβR, BAFFR, CD40 and RANK (30,31). In addition, the noncanonical NF-κB activation does not involve IκBα degradation but rather relies on processing of the NF-κB2 precursor protein, p100 (30,32**).** A central signalling molecule for this pathway is NF-κB-inducing kinase (NIK), which activates and functionally cooperates with IKKα to mediate p100 phosphorylation, which in turn induces p100 ubiquitination and processing (33,34). The processing of p100 involves degradation of its C-terminal IκB-like structure, resulting in generation of mature NF-κB2 p52 and nuclear translocation of the noncanonical NF-κB complex p52/RelB (23,30,32). A well-recognized function of NF-κB is regulation of inflammatory responses. In addition to mediating induction of various pro-inflammatory genes in innate immune cells, NF-κB regulates the activation, differentiation and effector function of inflammatory T cells (35,36). This pathway regulates pro-inflammatory cytokine production and inflammatory cell recruitment, which contribute to the inflammatory response.

MAPKs are a family of serine/threonine protein kinases that regulate cellular responses to a variety of stimuli, including osmotic stress, mitogens, heat shock, and inflammatory cytokines (including IL-1, TNF-α, and IL6) that regulate cell proliferation. is., differentiation, cell survival and apoptosis Mammalian MAPKs include the extracellular signalling-regulated kinase ERK1/2. p38 MAP Kinase and c-Jun N-Terminal Kinase (JNK) Each MAPK signalling pathway contains at least three components: MAPK, MAPK kinase (MAPKK), and MAPK kinase kinase (MAPKKK) MAPKKK phosphorylates and activates MAPKK, which in turn phosphorylates and activates MAPKK. ERK is generally activated by mitogenic and differentiation signals, whereas inflammatory stimuli and stress activate JNK and p38 MKK1 and MKK2 activate ERK1/2, MKK4 and MKK7 activate JNK, and MKK3 and MKK6 activate p38 Activation of MAPKs, including Erk1/2 and JNK, leads to phosphorylation and activation of cytoplasmic or nuclear p38 transcription factors, leading to an inflammatory response. (37-41).

The JAK–STAT pathway has been used for intracellular signal transduction in response to cytokines and growth hormones. Different JAK-dependent cytokine receptors signal through different JAKs. Each receptor is composed of multiple subunits, and each subunit associates with a JAK. Activated STAT dimers form a nutcracker-like structure and are commonly the target of STAT inhibitors. Janus Kinase Inhibitors and Autoimmunity 523 receptor chains are able to associate with more than one JAK isoform. Most type I/II cytokine receptors signal through multiple JAKs.(42-54).

Inflammatory markers

Inflammatory markers may be indicative of inflammatory disorders and connect with their origins and effects, including infections, endothelial dysfunctions, and cardiovascular diseases. Inflammatory cytokines, such as IL-1, IL-6, and TNF-, as well as inflammatory proteins and

enzymes are produced when inflammatory cells, such as macrophages and adipocytes, are activated by stimuli (55-57). Inflammatory disorders may be treated more effectively and agent-mediated inflammation could be identified with more accuracy if we had a better understanding of how to control cytokine pathways. High-mobility group box 1 (HMGB1), superoxide dismutase (SOD), glutathione peroxidase (GPx), NADPH oxidase (NOX), inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX)-2 are just a few of the enzymes whose abnormal activation is crucial in the development of inflammation-related diseases like cancer and cardiovascular disease. For instance, stimulation of TLR-coupled signalling pathways may be a mechanism by which extracellular HMGB1 effects are mediated (58-65). The main target of extracellular HMGB1 is TLR4 [68], which sets off intracellular signalling cascades that activate the NF-B and MAPK pathways in a way that depends on MyD88 (66,67). TNF- and other inflammatory cytokines are released as a result. Oxidative stress is influenced by antioxidant defence mechanisms, including antioxidant enzymes. As a result, this cascade can boost the expression of genes that code for chemo kines, inflammatory cytokines, and growth factors (). Numerous diseases, including cardiovascular disease, cancer, diabetes, hypertension, ageing, and atherosclerosis, are linked to oxidative stress and their development. As a result, the by-products of oxidative stress can also serve as indicators of an inflammatory response (69-77).

Cell types in inflammatory responses- Activated macrophages, monocytes, and other cells mediate local responses to tissue damage and infection (78). At sites of tissue injury, damaged epithelial and endothelial cells release factors that trigger the inflammatory cascade, along with chemokines and growth factors, which attract neutrophils and monocytes Inflammation-mediated immune cell alterations are associated with many diseases, including asthma, cancer, chronic inflammatory diseases, atherosclerosis, diabetes, and autoimmune and degenerative diseases (79,80) .Neutrophils are key mediators of the inflammatory response, and program antigen presenting cells to activate T cells and release localized factors to attract monocytes and dendritic cells (81,82). During inflammation, macrophages present antigens, undergo phagocytosis, and modulate the immune response by producing cytokines and growth factors. Activated mast cell release a variety of inflammatory mediators, including cytokines, chemokines, histamine, proteases, prostaglandins, leukotrienes, and serglycin proteoglycans (83). After being recruited by inflammatory stimuli, immune cells amplify and sustain the APR by releasing local inflammatory mediators at the site of recruitment (84).

Role of inflammation in various diseases

The effects of chronic inflammation may be brought on by:

(1) the persistence of acute inflammation;
(2) the consequent tissue destruction;
(3)the scarring brought on by the acute inflammation.
(4)Systemic consequences of persistent inflammation, such as fever, wasting, and weight loss. healing through repair. Long-term amyloidosis formation and chronic disease-related anaemia may also be linked to chronic inflammation (85).

Below are some significant chronic inflammatory disorders and the pathophysiology of their clinical manifestations.

Cardiovascular diseases

From the initial leukocyte recruitment until the rupture of the atherosclerotic plaque, inflammatory mediators play important roles in atherosclerosis (87-90). In the afflicted cardiac tissues, higher levels of endothelial adhesion molecules as well as higher amounts of inflammatory cytokines and chemokines are produced and released (91). The main line of defence for the heart against infections and tissue injury is the innate immune system (92). The most frequent cause of heart injury is myocardial infarction, which frequently occurs from coronary atherosclerosis and involves the abrupt loss of numerous myocardial cells [93]. An inflammatory cascade is started by necrotic cardiac cells to cleanse the infarct of dead cells and debris (94,95). When a cell dies, its internal components are released, activating innate immune systems to start an inflammatory reaction. Cell surface receptors identify endogenous ligands generated after injury as danger signals and trigger inflammation (96,97). TLR-mediated pathways activate NF-B signalling to cause post-infarction inflammatory responses (97-102). Leukocyte-endothelial cell adhesions are facilitated by cytokines, which also attract inflammatory leukocytes to the infarct (103, 105). Additionally, by reducing inflammation, improving myofibroblast phenotypic regulation, and encouraging the deposition of extracellular matrix, TGF- and IL-10 improve cardiac healing [106, 107]. In people with diabetes mellitus, cardiovascular disease—particularly in those with type 2 diabetes (T2D), where it develops 14.6 years

earlier on average (107)—is the leading cause of mortality and disability. Heart attack, stroke, kidney failure, amputation of limbs, blindness, and nerve damage are some of the complications of diabetes. Diabetes is brought on by either defective pancreatic insulin production or by body cells that do not respond by producing insulin (109). Insulin resistance is characterised by a reduced insulin-stimulated glucose uptake and is linked to obesity, age, and inactivity. Insulin secretion and cell mass are increased by pancreatic islet cells in response to insulin resistance. T2D (110), which is increasingly being defined as an inflammatory disease [111, 112], however, arises when islet -cells are unable to make up for insulin resistance. Insulin deficit then follows. Patients with T2D have been found to have higher amounts of circulating acute-phase proteins such as CRP, fibrinogen, serum amyloid A, plasminogen activator inhibitor, and haptoglobin as well as sialic acid, cytokines, and chemokines. Increased levels of IL-1, IL-6, TNF-, and CRP are also indicators of T2D. Prior to the beginning of T2D, IL-1 receptor antagonist (IL-1RA) levels are increased in obesity and prediabetes. Increased amounts of nutrients, such as glucose and free fatty acids, encourage insulin resistance. Additionally, T2D activates the JAK-STAT, MAPK, and NF-B pathways, all of which have the potential to increase tissue inflammation (111, 112, 113). Adipose tissue and other insulin-sensitive tissues are negatively affected by metabolic stresses as well, which increases the release of cytokines and chemokines locally. At the same time, immune cells are drawn in and help cause tissue inflammation. Examples of these cells are mast cells and macrophages. Similar to this, adipose tissue release of cytokines and chemokines into the bloodstream encourages the spread of inflammation to other tissues (114).

Respiratory diseases

The main cause of Respiratory tract inflammation is tissue exposure to bacterial, viral, and/or environmental toxins. Acute inflammation that is too severe and subsequent lung damage can impede gas exchange by causing pulmonary fibrosis. In acute respiratory distress syndrome, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and asthma, unresolved lung injury and persistent inflammation are usually seen (115-117). Approximately 90% of COPD cases are linked to inflammation brought on by cigarette smoking in the small airways and lung parenchyma (118). Smoking is a significant contributor to COPD, which includes pulmonary and systemic inflammation. Long-term smoking can increase the synthesis of chemokines, oxygen radicals, proteases, and cytokines in the lung, including TNF-, IL-6, and IL-8. It can also cause macrophage, neutrophil, and activated T lymphocyte infiltration into airways (119).

Nervous system diseases

Numerous disorders of the central nervous system (CNS), including epilepsy, autoimmune disorders, and neurodegenerative illnesses like Alzheimer's (AD) and Parkinson's (PD), trigger inflammatory reactions in the brain. Neuronal excitability can be increased, cells can be damaged, and the blood-brain barrier can become more permeable to different chemicals as a result of inflammatory responses in the brain (120–122). The activation of the brain's native immune cells and microglia, which produce pro-inflammatory indicators, causes inflammation-associated CNS disorders (123). Like immunological responses to systemic infection, these inflammatory processes also engage both the innate and adaptive immune systems. The main inflammatory mediators in the change from innate to adaptive are cytokines and TLRs. Endogenous ligands identified by TLRs may potentially cause inflammatory responses in the CNS. Inflammatory reactions may be triggered by DAMPs, such as heat shock proteins and extracellular matrix degradation molecules, entering the brain through a compromised blood-brain barrier. Both viral agents and brain injury, such as tissue damage seen after an ischemic, traumatic, or excitotoxic brain injury, or a seizure, trigger a robust CNS inflammatory response (121, 124, 125).

Tumor

Tumor cells produce various cytokines and chemokines that attract leukocytes The inflammatory component of developing neoplasms can include various leukocyte populations, including neutrophils, dendritic cells, macrophages, eosinophils, mast cells and lymphocytes. Cytotoxic mediators including reactive oxygen species, serine and cysteine proteases, MMPs and membrane perforators, and soluble mediators of cell death such as TNF-α, interleukins and interferons (IFNs) (126,127). Monocytes differentiate into immature dendritic cells in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-413. Dendritic cells migrate to inflamed peripheral tissues, where they sequester antigens, and after maturation, migrate to lymph nodes to stimulate T lymphocyte activation Soluble factors such as IL-6 and CSF-1 derived from tumor cells boost myeloid progenitor cells to a macrophage-like phenotype14 Interestingly,

dendritic cells found in neoplastic infiltrates are often immature and defective in their ability to stimulate T cells. Tumor-associated macrophages (TAMs) are important components of inflammatory infiltration in neoplastic tissues, are monocyte-derived and primarily recruited by the monocyte chemoattractant protein (MCP) chemokine. TAMs play a dual role in neoplasia. TAMs can kill neoplastic cells upon activation by IL-2, interferons, and IL-12 (128-129), but many potent angiogenic and lymphangiogenic growth factors, cytokines and proteases. It is a mediator that enhances tumor progression17 TAMs and tumor cells also produce IL-10, which effectively attenuates anti-tumor responses by cytotoxic T cells During melanoma development, activated macrophages produce TGFβ, TNF-α, IL-1α, arachidonic acid metabolites, and extracellular proteases 18. In response, melanocytes express IL-8 and vascular endothelial growth factor (VEGF)-A, thereby inducing angiogenesis under paracrine control (130). Indeed, macrophage invasion is closely related to the depth of invasion of primary melanoma, in part due to tumor-associated angiogenesis regulated by macrophages 19. In addition to altering the local balance of pro-angiogenic factors during melanoma development, TAM expressed her VEGF-C and VEGF-D, and VEGF receptor-3 (VEGFR-3) during human cervical carcinogenesis. increase. All of these are involved in lymphatic vessels. formation and lymph metastasis (131). Placing TAMs at the centre of their recruitment and response to angiogenic and lymphangiogenic stimuli can facilitate tumor spread. TAM also induces her VCAM-1 expression on mesothelial cells.

Importance of medicinal plants and phytocompounds as anti-inflammatory compounds

Herbs and their constituents exert anti-inflammatory activity A number of plants have been reported for anti-inflammatory activity with a significant value than NSAIDs drug and also lack of side effect of causing ulcer and other side effect. Plant activity is attributed to presence of chemical constituents. There is a no. of plant shown below on basis of their constitutes. A number of plants containing triterpenoids such as stem bark of Croton cajucara (132), aerial parts Sideritis candicans (133) and leaves of Broyonia laciniosa (134) showed significant anti-inflammatory activity. plant containing alkaloids such as leaves of Psychotria colorate (135), Chasmentha depends plant (136), seeds of Carum capticum (137) and Myristica fragrans (138) anti-inflammatory activity. Chasmentha dependens (136), dried leaves of Stachytarpheta cayennensis (139) and leucas aspera (140) root containing glycosides showed anti-inflammatory activity. large no of plants containing flavonoids showed anti-inflammatory activity (141). Leaves extract of Vitex negundo (142) and Baphia nitida (143), roots of Calotropis procera (144) and Spilantha acmella (145) showed anti-inflammatory activity. Roots of leucas aspera (140), leaves of Gymnema sylvester (146), leaves of Baphia nitida (143) and whole plant of Chasmentha dependens (136) containing tannins showed anti-inflammatory activity. Many of plant that showed activity had constituents other than above viz. saponin of Gymnema sylvester (146), Caratenoid of Nycanthes arbortristis flowers and iridoids of leaves of Stachytarpheta cryennensis (147).

Current drugs and its limitations

Inflammation is a normal part of the body's Défense to injury or infection, and, in this way, it is beneficial. But inflammation is damaging when it occurs in healthy tissues or lasts too long. Known as chronic Inflammation. (147). Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages. There are many targets of anti-inflammatory action such as

- Stabilization of leucocyte membrane and antagonism of certain action of kinin
- may be contributing to NSAIDs action
- Antagonist action on mediators other than PGs, histamine and bradykinin
- Inhibition of formation of ROS
- Inhibition of chemotaxis
- Inhibition of biosynthesis of mucopolysaccharides
- Stabilization of lysosome membrane fibrinolytic activity
- Inhibition of leucocyte migration and leucocyte phagocytosis

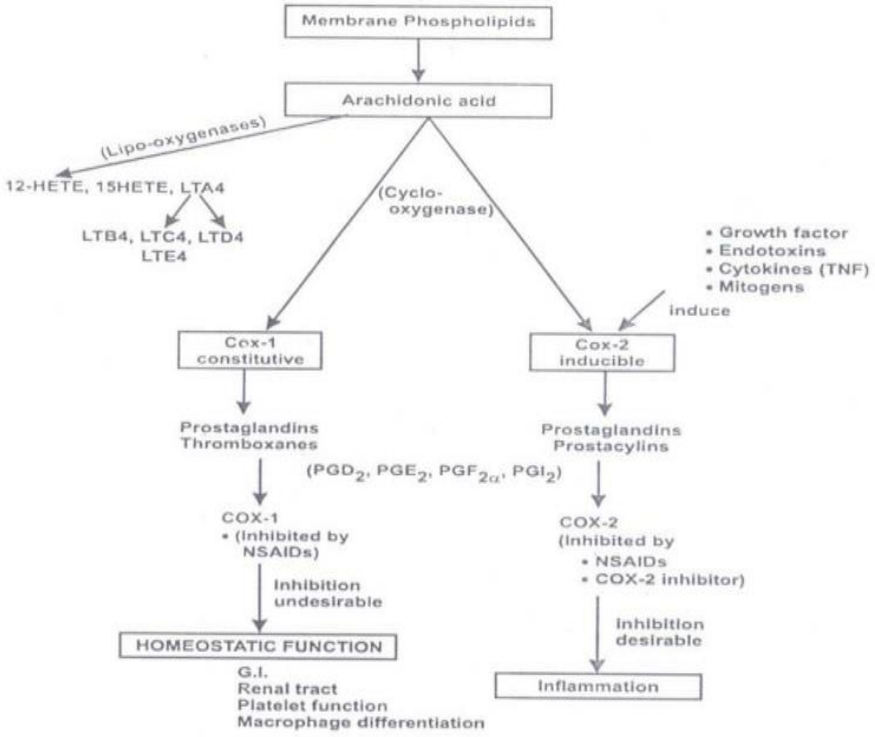
Of all these, inhibition of PGs biosynthesis is said to be important mechanism of action of NSAIDs. Vane and his colleagues in 1971 demonstrated that aspirin and related drugs inhibit prostaglandins (PG's) biosynthesis by inhibition of the enzyme prostaglandin endoperoxides synthase or COX which is involved in PG's synthesis. Inhibition is brought about by steric blockade of receptor active site channel. The table below classifies anti-inflammatory medications.

Anti-inflammatory Drugs Classification

Non -steroidal Anti-inflammatory Drugs			Steroidal Anti-inflammatory Drugs
Non-selective COX inhibitors	selective COX inhibitors		❖ Short-Acting Glucocorticoids (Natural)
❖ Salicylates	Preferential COX2 Inhibitors	Selective COX2 Inhibitors	• Hydrocortisone
• Acetylsalicylic acid (Aspirin)			• Cortisone
• Salicylamide	• Nimesulide	• Celecoxib	❖ Intermediate-Acting Glucocorticoids
❖ Pyrazolone Derivatives	• Meloxicam	• Parecoxib	• Prednisone
• Phenylbutazone	• Nabumeton	• Rofecoxib	• Prednisolone
• Metamizole(Analginm)			• Methylprednisolone
❖ Indole Derivatives			• Triamcinolone
• Indomethacine			❖ Long-Acting Glucocorticoids
❖ Propionic Acid Derivatives			• Betamethasone
• Naproxen			• Dexamethasone
❖ Antranilic Acid Derivatives			• Paramethasone
• Mephenic acid			❖ Topical Acting Glucocorticoids
❖ Aryl Acetic Acid			• Beclomethasone
• Diclophenac sodium			• Budesonide
❖ Oxicam Derivatives			• Fluocortolone
• Piroxicam			
❖ Dihydropyrolizine Carboxylic acid Derivatives			
• Ketorolac			

Mechanism of non-steroidal anti-inflammatory drugs

Inflammation is a normal part of the body's Défense to injury or infection, and in this way, it is beneficial. Inflammation is damaging when it occurs in healthy tissues or lasts too long Known as chronic Inflammation. Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages. There are many targets of anti-inflammatory action such as Stabilization of leucocyte membrane and antagonism of certain action of kinin may be contributing to NSAIDs action, Antagonist action on mediators other than PGs, histamine and bradykinin, Inhibition of formation of ROS, Inhibition of chemotaxis, Inhibition of biosynthesis of mucopolysaccharides ,Stabilization of lysosome membrane fibrinolytic activity ,Inhibition of leucocyte migration and leucocyte phagocytosis Of all these, inhibition of PGs biosynthesis is said to be important mechanism of action of NSAIDs. Vane and his colleagues in 1971 demonstrated that aspirin and related drugs inhibit prostaglandins (PG's) biosynthesis by inhibition of the enzyme prostaglandin endoperoxides synthase or COX which is involved in PG's synthesis. Inhibition is brought about by steric blockade of receptor active site channel. The mechanism of action of non-steroidal anti-inflammatory drugs is shown in Figure. NSAIDs have been shown to be effective in inflammatory conditions such as arthritis, acute trauma, and pain associated with inflammation. Inflammatory mediators at the site of injury mediate vasodilation, protein exudate extravasation, and nociception. This is where prostaglandins, the key players in this process, are inhibited. COX inhibition has been held as the primary mechanism of NSAID anti-inflammatory activity, but other mechanisms loosely termed non-COX mechanisms have been identified. A mechanism has been reported in the literature. NSAIDs have been reported to have quenching effects on nuclear factor (NF)-κB, a transcription factor for proinflammatory proteins such as chemokines, adhesion molecules, and cytokines. NSAIDs also show repression of activated protein 1, membrane stabilization, and inhibition of reactive oxygen species (ROS) production. Although these are thought to contribute at the molecular level, it is unclear how they directly contribute to the clinical benefits of NSAIDs. NSAIDs reduce fever by inhibiting COX-mediated prostaglandin synthesis. Upon exposure to external pyrogens, primarily pathogen-associated molecular patterns (lipopolysaccharides, peptidoglycans, viral RNA, etc.), cells of the innate immune system release endogenous pyrogens to induce fever. Circulating interleukin-1, interleukin-6, and TNFα reach the brain and induce cyclooxygenase-mediated prostaglandin synthesis in the preoptic hypothalamic region of the brain. Prostaglandin E2 (PGE2) binds to EP-3 receptors in the hypothalamic endothelium to reset the body's thermoregulation. Subsequent physiological processes take place to reach this set temperature. By interfering with this process, NSAIDs have been shown to help limit the harmful effects of high and prolonged temperatures by inhibiting COX. It is important to note that it does not affect normal body temperature or abnormally elevated body temperature such as malignant hyperthermia or heat stroke (147). The mechanism of action of non-steroidal anti-inflammatory drugs is shown in Figure.

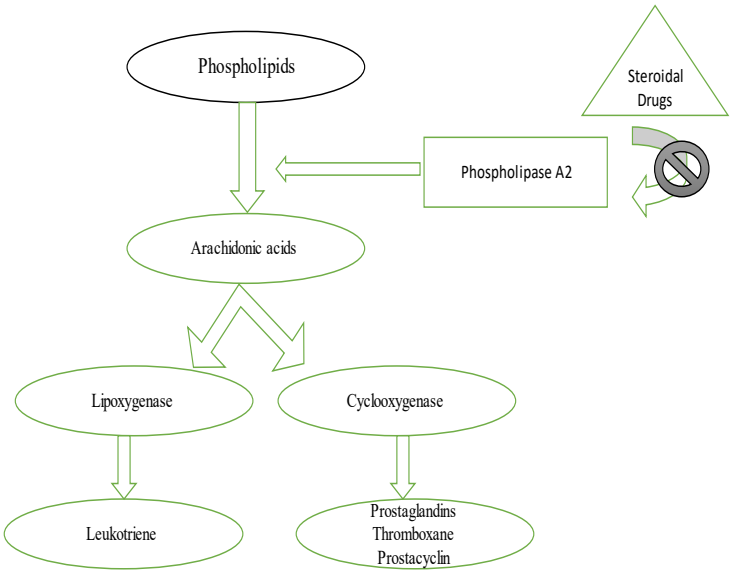


Side effects of NSAIDs

According to COX hypothesis, these drugs exert anti-inflammatory action by blocking COX-2 activity and at the same time, produce unwanted side-effects, mainly gastrointestinal (gastric irritation, erosions and gastric bleeding), hepatic (Hepatic failure and raised transaminase) and renal toxicity (Intestinal nephritis, chronic renal failure), due to inhibition of COX-1 enzyme (148). Almost 5-15% of patients with rheumatoid arthritis (RA) discontinues NSAID therapy within 6-month period of them treatment because of dyspepsia (149). Asthma and anaphylactoid reactions in susceptible individual are also side effect of NSAIDs. Increase in postpartum haemorrhage blood loss, skin reaction, liver disorder CNS (Headache, mental confusion and behavioural disturbances) and bone marrow depression is the main side effect of NSAIDs. Selective COX-2 inhibitor such as celecoxib showed increase in blood pressure and inhibition of platelets (150).

Mechanism of Steroidal Anti-inflammatory Drugs

Steroidal anti-inflammatory drugs are a class of anti-inflammatory drugs used to reduce inflammation in the human body. These agents block the phospholipase A2 enzyme from blocking the inflammatory cascade. Phospholipase, one of the major substances released during inflammation, is rapidly converted to arachidonic acid by phospholipase A2. Arachidonic acid can then enter two different arms of the inflammatory cascade. By following a metabolic pathway, it can be converted into prostaglandins by the enzyme cyclooxygenase. Alternatively, they can be converted to leukotrienes by the enzyme lipoxygenase. Steroidal anti-inflammatory drugs block both arms of the inflammatory cascade.Steroid anti-inflammatory drugs reduce vascular permeability, redness, edema, and pain. Furthermore, it has the added benefit of keeping leukocytes away from the site of inflammation by blocking the lipoxygenase arm of the inflammatory cascade. Steroidal anti-inflammatory drugs may be derived from animal, plant, and human sources. They consist of sex steroids, corticosteroids and anabolic steroids. For corticosteroids, they are used for a variety of conditions, including skin diseases, hormonal imbalances, and tumors. Corticosteroids are also used primarily to treat joint pain and inflammation. However, they have a narcotic effect and can be highly addictive drugs for patients. (151)



Limitation of Steroidal Drugs-

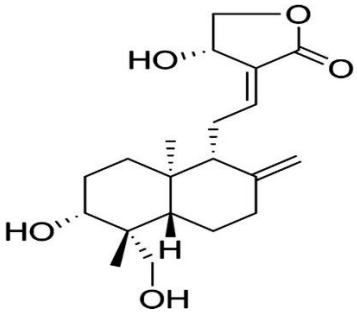
Long-term use and high doses of steroidal anti-inflammatory drugs cause serious side effects similar to Cushing's disease. These side effects may complicate patient treatment and should be considered when examining a patient's medical history. Side effects of steroidal anti-inflammatory drugs include Lymphatic tissue atrophy and low white blood cell count, increased risk of infection, decreased immune response, decreased tissue regeneration), osteoporosis (bone demineralization). muscle wasting, thinning and destruction of skin and mucous membranes (e.g., gastric ulcers), Delayed healing, Delayed growth in children, Sodium and water retention, often leading to hypertension and edema (152,153).

Anti-inflammatory effect of Andrographolide and its analogues

Andrographis paniculate (Burm.f.) Wall. ex Nees., (English name— King of Bitters) is an herbaceous plant. It belongs to Acanthaceae family. It is native to India and Sri Lanka, and it is also found in abundance in Asian countries such as India, Pakistan, Java, Malaysia and Indonesia (154). It is cultivated extensively in China and Thailand, the East and West Indies, and Mauritius. It is normally grown from seeds and grows in pine, evergreen and deciduous forest areas, and also along roads and in villages (155).

The leaves of the plant are reported to contain Andrographolide, neoAndrographolide, andrographiside, omoAndrographolide, andrographane, andrographanin, andrographone and andrographoserol. The aerial parts of the plant contain Andrographolide, neoAndrographolide, andrographiside 14-deoxyAndrographolide, 14-deoxy-11,12-didehydroAndrographolide, 14-deoxy-11-oxoAndrographolide and β-sitosterol. The roots contain 5-hydroxy-7,8,2 3'-tetramethoxyflavone, Andrographolide andrographonin, apigenin and 7,4-dioxymethylether (156). Of the above chemicals, Andrographolide is the major bioactive constituent responsible for variety of activities. Leaves and stems of plant are used for extracting active phytochemicals; roots are used rarely. The leaves contain about 1.0–2.39% of Andrographolide, while the roots, stem, pericarp and seeds contain 0.44,0.20, 0.18 and 0.13% of Andrographolide, respectively (157).

Bicyclic diterpenoid lactone Andrographolide [C20H30O5, (3- [2{decahydro-6hydroxy-5-(hydroxymethyl)-5,8α-dimethyl-2-methylene1-naphthalenyl} ethylidene] dihydro-4-hydroxy-2(3H) furanone)] is concentrated in leaves (Joseph, S.M.,2014). The structure of Andrographolide is shown in Figure



Andrographolides acts on multiple cellular targets in the inflammatory signals. It inhibits NF-kappaB activation, suppresses iNOS expression, inhibits COX-2 expression in human fibro-blast ells, and prevents oxygen radical production by human neutrophils (). According to a recent study, Andrographolide interacts with Arg513 and His90

in the cyclooxygenase site of COX-2 and inhibits PGE2 production in human fibroblast cells.

inhibition of NF-kappaB

Andrographolide inhibited NF-kappaB activation in stimulated endothelial cells, lowering the expression of the cell adhesion molecule E-selectin and preventing E-selectin-mediated leukocyte adhesion under flow. It also prevented cytokine- and endotoxin-induced neutrophil peritoneal deposition, septic shock, and allergic lung inflammation in vivo. Notably, it had no effect on IkappaB degradation, nuclear translocation of p50 and p65, or cell growth rates (Xia et al., 2004). PAF-induced NF-kappaB luciferase activity was inhibited by Andrographolide. However, Andrographolide had no effect on the phosphorylation of p38 MAPK or ERKl/2, nor on the degradation of IkappaB induced by PAF and fMLP. It also reduced NF-kappaB DNA binding in whole cells and nuclear extracts induced by PAF and fMLP. It is concluded that Andrographolide exerts anti-inflammatory effects by inhibiting NF-kappaB binding to DNA, thereby reducing the expression of proinflammatory proteins like COX-2 (158-170)

Suppression of inducible nitric oxide synthase (iNOS) expression:

High levels of NO have the potential to be cytotoxic and can harm the nearby cells and tissues without regard for context, either by themselves or by the creation of ONoo-. Additionally, it's conceivable that reduction of iNOS protein expression and NO generation in response to immunological stimulation and/or bacterial infection could partially account for Andrographolide's anti-inflammatory effects.

Prevention of oxygen radical production

Andrographolide's capacity to block neutrophil adhesion/transmigration by suppressing Mac-1 overexpression may account for its anti-inflammatory effects. According to Shen et al. (2002), the inhibitory impact of Andrographolide on Mac-1 expression may be caused via a mechanism that reduces ROS generation but does not require calcium (159).

Inhibition on PAF-induced platelet aggregation

The effects of Andrographolide on the production of eicosanoids and platelet-activating factor were examined (PAF). It was demonstrated that Andrographolide suppresses PAF-induced human blood platelet aggregation in a dose-dependent manner, although isolated human Polymorph-Nuclear Leukocytes (PMNL) showed no effect on the biosynthesis (171).

Inhibition of COX-2 expression

It has been demonstrated that the minor diterpenoid molecule Andrographolide and its counterpart, neoAndrographolide, interact with Arg513 and His90 at the cyclooxygenase site of COX-2. Andrographolide -11.7963 kcal mol-1 and neoAndrographolide -7.4339 kcal mol-1 require only a modest amount of energy to interact (calculated using AutoDockTools 3.0.5). These findings suggest that the exchanges will occur naturally and favourably (Levita et al., 2009a, b, 2010). When human fibroblast cells were stimulated with LPS, the inhibitory action of Andrographolide to COX-2 enzyme was measured by detecting PGE2 generation. These results demonstrated that Andrographolide's anti-inflammatory action also involved COX-2 expression inhibition (170).

Conclusion

The mechanism of Andrographolide in the treatment of inflammatory diseases, we found that Andrographolide has good anti-inflammatory and immunomodulatory effects and is a promising drug for inflammatory diseases. Andrographolide can exert anti-inflammatory effects through a variety of targets and signalling pathways, including blocking the NF-κB, MAPK, PI3K/Akt, NLRP3 and other pathways. Further research is needed to explore the pharmacological mechanism of action, its toxicity and adverse reactions, its pharmacokinetics and optimal therapeutic dose.

References

1. Brooks PM, Day RO. Nonsteroidal anti-inflammatory drugs-differences and similarities. N Engl J Med. 1991:324(241:171 6-25. Brooks PM and Day RO, 1991
2. Libby P. Inflammatory mechanisms: the molecular basis of inflammation and disease. Nutr Rev. 2007; 65:S140-S146. Libby P,2007
3. Lawrence T. The Nuclear Factor NF-κB Pathway in Inflammation. CSH Perspect Biol. 2009; https://doi.morg/10.1101/cshperspect.a001651
4. St Clair 8N. Tides of inflammation: impact of biologics. J R heumatol Suppl. 2002; 65:22--6.
5. Canvin JM, E – Gaalavry HS. Anti-inflammatoty therapy. P hys Med Rehabil Clin N Am. 1999;10(2):30 1-17.

6. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. N Engl J Med. 1999;340'(24):1388-99.
7. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reaction as cause of admission to hospital: Prospective analysis of 18 820 patients.BMJ.2004;329(7456):15-9.
8. McCarberg B, Gibofsky A. Need to develop new nonsteroidal anti-inflammatory drug formulations. Clin Ther. 2012;34(9): 1954-63.
9. Smith AB, BH. Toder, P.J. Carroll and J.Donohue, 1982. Andrographolide: An x-ray Crystallographic analysis. J.Chem. Crystallography,12: 309-319.
10. Harborne, J. B. (ed). The Flavonoids: Advances in research since 1986. New York: Chapman and Hall 1994.
11. Okoli, C. O., Akah P. A., Nwafor, S. V. (). Anti-inflammatory activity of plants. J. Nat. Remed, 2003; 3: 1-30. (Okoli CO, Akah PA, Nwafor SV,2003)
12. Ohadoma SC, Akah PA, Enye JC. Pharmacological assessment of the antinociceptive anti-inflammatory effects of the methanol extract and fractions of Lupinus arboreus.
13. Smith AB, BH. Toder, P.J. Carroll and J.Donohue, 1982. Andrographolide: An x-ray Crystallographic analysis. J.Chem. Crystallography,12: 309-319.
14. Joselin, J., Jeeva, S.; Andrographis paniculata: A review of its traditional uses, phytochemistry and pharmacology; Med Aromat Plants, (2014); 3(4): 1–15
15. Chiou, W.F., Chen, C.F., Lin, J.J.; Mechanisms of suppression of inducible nitric oxide synthase (iNOS) expression in RAW 264.7 cells by Andrographolide; Br J Pharmacol, (2000); 129: 1553–1560
16. Hidalgo, M.A., Romero, A., Figueroa, J., Cortes, P., Concha, I.I., Hancke, J.L. et al.; Andrographolide interferes with binding of nuclear factor-kb to DNA in HL-60-derived neutrophilic cells; Br J Pharmacol, (2005); 144: 680–686.
17. Kishore, V., Yarla, N. S., Bishayee, A., Putta, S., Malla, R., Neelapu, N. R., et al. (2017). Multi-targeting Andrographolide and its natural analogs as potential therapeutic agents. Curr. Top. Med. Chem. 17 (8), 845–857. doi:10.2174/ 1568026616666160927150452
18. White MJ. Mediators of inflammation and the inflammatory process. J Allergy Clin Immunology 1999; 103:378-381.
19. Akira, S., Uematsu, S., and Takeuchi, O. (2006). Pathogen recognition and innate immunity. Cell 124, 783–801.
20. Hendrayani SF, Al-Harbi B, Al-Ansari MM, Silva G, Aboussekhra A. The inflammatory/cancer-related IL-6/ STAT3/NF-κB positive feedback loop includes AUF1 and maintains the active state of breast myofibroblasts. Oncotarget. 2016; 7:41974–41985. https://doi.org/10.18632/ oncotarget.9633
21. Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev 2001; 81:807–869
22. Henríquez-Olguín C, Altamirano F, Valladares D, López JR, Allen PD, Jaimovich E. Altered ROS production, NFκB activation and interleukin-6 gene expression induced by electrical stimulation in dystrophic mdx skeletal muscle cells. BBA-Mol Basis Disc. 2015; 1852:1410–1419
23. Zhang H, Sun SC. NF-kappaB in inflammation and renal diseases. Cell Biosci 2015; 5: 63.
24. Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol 2009; 1: a000034.
25. Karin M, Delhase M. The I kappa B kinase (IKK) and NF-kappa B: key elements of proinflammatory signalling. Semin Immunol 2000; 12: 85–98.
26. Sun SC, Ley SC. New insights into NF-kappaB regulation and function. Trends Immunol 2008; 29: 469–478
27. Israel A. The IKK complex, a central regulator of NF-kappaB activation. Cold Spring Harb Perspect Biol 2010; 2: a000158.
28. Beinke S, Ley SC. Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. Biochem J 2004; 382: 393–409
29. Hayden MS, Ghosh S. Shared principles in NF-kappaB signaling. Cell 2008; 132: 344–362. 11 Sun SC. The noncanonical NF-kappaB pathway. Immunol Rev 2012; 246: 125–140.
30. Sun SC. The noncanonical NF-kappaB pathway. Immunol Rev 2012; 246: 125–140.
31. Sun SC, Liu ZG. A special issue on NF-kappaB signaling and function. Cell Res 2011; 21: 1–2.
32. Sun SC. Non-canonical NF-kappaB signaling pathway. Cell Res 2011; 21: 71–85.
33. Xiao G, Harhaj EW, Sun SC. NF-kappaB-inducing kinase regulates the processing of NF-kappaB2 p100. Mol Cell 2001; 7: 401–409

34. Senftleben U, Cao Y, Xiao G, Greten FR, Krahn G, Bonizzi G et al. Activation by IKK alpha of a second, evolutionary conserved, NF-kappa B signaling pathway. Science 2001; 293: 1495–1499.
35. Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol 2009; 1: a001651.
36. Tak PP, Firestein GS. NF-kappaB: a key role in inflammatory diseases. J Clin Invest 2001; 107: 7–11.
37. Kaminska B. MAPK signalling pathways as molecular targets for anti-inflammatory therapy--from molecular www.impactjournals.com/oncotarget 7214 Oncotarget mechanisms to therapeutic benefits. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics. 2005; 1754:253–262.
38. Pearson G, Robinson F, Beers GT, Xu BE, Karandikar M, Berman K, Cobb MH. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocr Rev. 2001; 22:153–183.
39. Kim EK, Choi EJ. Pathological roles of MAPK signaling pathways in human diseases. BBA-Mol Basis. 2010; 1802:396–405.
40. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007; 26:3279– 3290
41. Raingeaud J, Whitmarsh AJ, Barrett T, Dérijard B, Davis RJ. MKK3- and MKK6-regulated gene expression is mediated by the p38 mitogen-activated protein kinase signal transduction pathway. Mol Cell Biolog. 1996; 16:1247– 1255
42. O'Shea JJ, Kontzias A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis. 2013;72(Suppl. 2):ii111–5. doi:10.1136/annrheumdis-2012-202576.
43. Kaul A, Gordon C, Crow MK, et al. Systemic lupus erythematosus. Nat Rev Dis Primers. 2016;2:16039. doi:10.1038/nrdp. 2016.39.
44. Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem. 2014;57(12):5023–38. doi:10.1021/jm401490p.
45. Leonard WJ, O'Shea JJ. Jaks and STATs: biological implications. Ann Rev Immunol. 1998;16:293–322. doi:10.1146/ annurev.immunol.16.1.293
46. Decker T. Emancipation from transcriptional latency: unphosphorylated STAT5 as guardian of hematopoietic differentiation. EMBO J. 2016;35(6):555–7. doi:10.15252/embj.201693974.
47. Mohr A, Chatain N, Domoszlai T, et al. Dynamics and noncanonical aspects of JAK/STAT signalling. Eur J Cell Biol. 2012;91(6–7):524–32. doi:10.1016/j.ejcb.2011.09.005.
48. O'Shea JJ, Schwartz DM, Villarino AV, et al. The JAK–STAT pathway: impact on human disease and therapeutic intervention. Ann Rev Med. 2015;66:311–28. doi:10.1146/annurev-med051113-024537
49. Liongue C, Ward AC. Evolution of the JAK–STAT pathway. JAK–STAT. 2013;2(1):e22756. doi:10.4161/jkst.22756.
50. Brooks AJ, Dai W, O'Mara ML, et al. Mechanism of activation of protein kinase JAK2 by the growth hormone receptor. Science. 2014;344(6185):1249783. doi:10.1126/science.1249783.
51. Mavers M, Ruderman EM, Perlman H. Intracellular signal pathways: potential for therapies. Curr Rheumatol Rep. 2009;11(5):378–85.
52. Mao X, Ren Z, Parker GN, et al. Structural bases of unphosphorylated STAT1 association and receptor binding. Mol Cell. 2005;17(6):761–71. doi:10.1016/j.molcel.2005.02.021.
53. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 2013;368(2):161–70. doi:10.1056/NEJMra1202117.
54. Hofmann SR, Ettinger R, Zhou YJ, et al. Cytokines and their role in lymphoid development, differentiation and homeostasis. Curr Opin Allergy Clin Immunol. 2002;2(6):495–506. doi:10. 1097/01.all.0000044534. 45448.bf
55. Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Rubin SM, Ding J, Simonsick EM, Harris TB. Inflammatory markers and onset of cardiovascular events. Circulation. 2003;108: 2317–2322.
56. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. Thorax. 2000; 55:114–120.
57. Pecoits-Filho R, Heimbürger O, Bárány P, Suliman M, Fehrman-Ekholm I, Lindholm B, Stenvinkel P. Associations between circulating inflammatory markers and residual
58. Ross AC. Relationship between Inflammatory Markers, Endothelial Activation Markers, and Carotid Intima-Media Thickness in HIV-

Infected Patients Receiving Antiretroviral Therapy. Cli Infect Dis. 2009; 49:1119–1127.
59. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ. Inflammatory markers and the risk of coronary heart disease in men and women. New Engl J Med. 2004; 351:2599–2610.
60. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Hum Hypertens. 2005; 19:149–154.
61. Carrero JJ, Yilmaz MI, Lindholm B, Stenvinkel P. Cytokine Dysregulation in Chronic Kidney Disease: How Can We Treat It? Blood Purificat. 2008; 26:291–299.
62. Machowska A, Carrero JJ, Lindholm B, Stenvinkel P. Therapeutics targeting persistent inflammation in chronic kidney disease. Translat Res J La Clin Med. 2016; 167:204–213.
63. Goldstein BI, Kemp DE, Soczynska JK, Mcintyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psych. 2009; 70:1078–1090.
64. Miller AH, Maletic V, Raison CL. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. Biol Psych. 2009; 65:732–741.
65. Lindahl B, Toss H, Siegbahn A, Venge P Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. New Engl J Med. 2000; 343:1139–1147. 56. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. Circulation. 2003; 107: 87–92.
66. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, Shah VO, Balakrishnan VS, Guzman NJ, Girndt M. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrolog Cjasn. 2012; 7:1938–1946.
67. Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. BBA-Mol Cell Res.2014; 1843:2563–2582.
68. Czaja AJ. Hepatic inflammation and progressive liver fibrosis in chronic liver disease. World J Gastroenter. 2014; 20:2515–2532.
69. Liu Z, Wang Y, Wang Y, Ning Q, Zhang Y, Gong C, Zhao W, Jing G, Wang Q. Dexmedetomidine attenuates inflammatory reaction in the lung tissues of septic mice by activating cholinergic anti-inflammatory pathway. Int Immunopharmacol. 2016; 35:210–216.
70. Eckersall PD, Bell R. Acute phase proteins: Biomarkers of infection and inflammation in veterinary medicine. Vet J. 2010; 185:23–27.
71. Murata H, Shimada N, Yoshioka M. Current research on acute phase proteins in veterinary diagnosis: an overview. Vet J. 2004; 168:28–40.
72. Murakami A, Ohigashi H. Targeting NOX, INOS, COX2 in inflammatory cells: chemoprevention using food phytochemicals. Int J Cancer. 2007; 121:2357–2363.
73. Lopresti AL, Maker GL, Hood SD, Drummond PD. A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. Prog neuro-psychoph. 2014; 48:102–111.
74. Huang W, Tang Y, Li L. HMGB1, a potent proinflammatory cytokine in sepsis. Cytokine. 2010; 51:119–126.
75. Schierbeck H, Lundbäck P, Palmblad K, Klevenvall L, Erlandssonharris H, Andersson U, Ottosson L. Monoclonal anti-HMGB1 (high mobility group box chromosomal protein 1) antibody protection in two experimental arthritis models. Mol Med. 2011; 17:1039–1044.
76. Cheng Y, Wang D, Wang B, Li H, Xiong J, Xu S, Chen Q, Tao K, Yang X, Zhu Y. HMGB1 translocation and release mediate cigarette smoke–induced pulmonary inflammation in mice through a TLR4/MyD88-dependent signaling pathway. Mol Biol Cell. 2017; 28:201–209.
77. Asavarut P, Zhao H, Gu J, Ma D. The role of HMGB1 in inflammation-mediated organ injury. Acta Anaesthesiol Taiwanica. 2013; 51:28–33.
78. Stramer BM, Mori R, Martin P. The inflammation-fibrosis link? A Jekyll and Hyde role for blood cells during wound repair. J Invest Dermatol. 2007; 127:1009–1017.

79. Van LS, Miteva K, Tschöpe C. Crosstalk between fibroblasts and inflammatory cells. Cardiovasc Res. 2014; 102:258–269.
80. Robb CT, Regan KH, Dorward DA, Rossi AG. Key mechanisms governing resolution of lung inflammation. Semin Immunopathol. 2016; 38:425–448.
81. Nathan C. Neutrophils and immunity: challenges and opportunities. Nat Rev Immunol. 2006; 6:173–182.
82. Fujiwara N, Kobayashi K. Macrophages in inflammation. Current Drug Targets Inflam Allergy. 2005; 4:281–286.
83. Huang C, Šali A, Stevens RL. Regulation and Function of Mast Cell Proteases in Inflammation. J Clin Immunol. 1998; 18:169–183
84. Aggrey AA, Srivastava K, Ture S, Field DJ, Morrell CN. Platelet induction of the acute-phase response is protective in murine experimental cerebral malaria. J Immunol. 2013; 190:4685–4691
85. Jackson JR, Seed MP, Kircher CH, Willoughby DA and Winkler JD (1997) The co-dependence of angiogenesis and chronic inflammation. FASEB Journal 11: 457–465.
86. Packard RRS, Peter L. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem. 2008; 54:24–38.
87. Packard RRS, Peter L. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem. 2008; 54:24–38.
88. Libby P. History of Discovery: Inflammation in Atherosclerosis. Arteriosclerosis Thrombosis Vascular Biology. 2012; 32:2045–2051.
89. Libby P. Atherosclerosis in Inflammation. Nature. 2002; 420:868–874.
90. Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. Circulation J. 2010; 74:213–220.
91. Glezeva N, Baugh JA. Role of inflammation in the pathogenesis of heart failure with preserved ejection fraction and its potential as a therapeutic target. Heart Fail Rev. 2014; 19:681–694
92. Askevold ET, Gullestad L, Dahl CP, Yndestad A, Ueland T, Aukrust P. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. Curr Heart Fail Reports. 2014; 11:146–155.
93. Jennings RB, Murry CE, Steenbergen C Jr, Reimer KA. Development of cell injury in sustained acute ischemia. Circulation. 1990; 82:II2–12.
94. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990; 81:1161–1172.
95. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet. 2006; 367:356–367.
96. Frangogiannis NG. The immune system and cardiac repair. Pharmacol Res. 2008; 58:88–111.
97. Beg AA. Endogenous ligands of Toll-like receptors: implications for regulating inflammatory and immune responses. Trends Immunol. 2002; 23:509–512.
98. Frantz S, Ertl G, Bauersachs J. Mechanisms of Disease: Toll-like receptors in cardiovascular disease. Nat Clin Pract Card. 2007; 4:444–454.
99. Nijmeijer R, Lagrand WK, Visser CA, Meijer CJ, Niessen HW, Hack CE. CRP, a major culprit in complement mediated tissue damage in acute myocardial infarction? Int Immunopharmacol. 2001; 1:403–414.
100. Giordano FJ. Oxygen, oxidative stress, hypoxia, and heart failure. J Clin Invest. 2005; 115:500–508.
101. Griendling KK, Fitzgerald GA. Oxidative Stress and Cardiovascular Injury: Part I: Basic Mechanisms and In Vivo Monitoring of ROS. Circulation. 2003; 108:1912– 1916.
102. Hall G, Hasday JD, Rogers TB. Regulating the regulator: NF-κB signaling in heart. J Mol Cell Cardiol. 2006; 41:580–591.
103. Gerard C, Rollins BJ. Chemokines and disease. Nat Immunol. 2001; 2:108–115.
104. Moser B, Loetscher P. Lymphocyte traffic control by chemokines. Nat Immunol. 2001; 2:123–128.
105. Kaur K, Dhingra S, Slezak J, Sharma AK, Bajaj A, Singal PK. Biology of TNFα and IL-10, and their imbalance in heart failure. Heart Fail Rev. 2009; 14:113–123.
106. Frangogiannis NG. Targeting the transforming growth factor (TGF)-β cascade in the remodelling heart: Benefits and perils. J Mol Cell Cardiol. 2014; 76:169–171.
107. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet. 2006; 368:29–36

108. Pradeep T, Haranath C. A Review on Diabetes Mellitus Type II. Int J Pharma Res Rev. 2014; 3:23–29.
109. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY. Interleukin-1– receptor antagonist in type 2 diabetes mellitus. New Engl J Med . 2007; 356 :1517–1526.
110. Donath MY, Schumann DM, Faulenbach M, Ellingsgaard H, Perren A, Ehses JA. Islet inflammation in type 2 diabetes. Diabetes care. 2008; 31:S161-S164.
111. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pr. 2014; 105:141–150.
112. Dinarello CA, Donath MY, Mandrup-Poulsen T. Role of IL-1β in type 2 diabetes. Curr Opin Endocrinol. 2010; 17:314–321.
113. Turner MD. The identification of TNFR5 as a therapeutic target in diabetes. Taylor Francis. 2017; 21:349–351
114. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011; 11:98–107.
115. Leitch AE, Duffin R, Haslett C, Rossi AG. Relevance of granulocyte apoptosis to resolution of inflammation at the respiratory mucosa. Mucosal Immunol. 2008; 1:350–363.
116. Brusselle G, Bracke K. Targeting immune pathways for therapy in asthma and chronic obstructive pulmonary disease. Annals of the American Thoracic Society. 2014; 11:329–335.
117. Wong J, Magun BE, Wood LJ. Lung inflammation caused by inhaled toxicants: a review. Int J of Copd. 2016; 11:1391–1401.
118. Mroz RM, Noparlik J, Chyczewska E, Braszko JJ, Holownia A. Molecular basis of chronic inflammation in lung diseases: new therapeutic approach. J Physiol Pharmacol. 2007; 58:453–460.
119. Kawayama T, Kinoshita T, Matsunaga K, Kobayashi A, Hayamizu T, Johnson M, Hoshino T. Responsiveness of blood and sputum inflammatory cells in Japanese COPD patients, non-COPD smoking controls, and non-COPD nonsmoking controls. Int J Copd. 2016; 11:295–303
120. Nelson PT, Soma LA, Lavi E. Microglia in diseases of the central nervous system. Annals Med. 2002; 34:491–500. www.impactjournals.com/oncotarget 7218 Oncotarget
121. Vezzani A, Granata T. Brain Inflammation in Epilepsy: Experimental and Clinical Evidence. Epilepsia. 2005; 46:1724–1743.
122. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neuro. 2007; 8:57–69.
123. Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. P Natl Acad of Sci USA. 2003; 100:13632–13637.
124. Koltsakis GC, Stamatelos AM. Cytokines and acute neurodegeneration. Nat Rev Neuro. 2001; 2:734–744.
125. Jankowsky JL, Patterson PH. The role of cytokines and growth factors in seizures and their sequelae. Prog Neurobio. 2001; 63:125–149.
126. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. J Intern Med 2000; 248:171–183. [PubMed: 10971784]
127. Wahl LM, Kleinman HK. Tumor-associated macrophages as targets for cancer therapy. J Natl Cancer Inst 1998; 90:1583–1584. [PubMed: 9811301].
128. Brigati C, Noonan DM, Albini A, Benelli R. Tumors and inflammatory infiltrates: friends or foes? Clin Exp Metastasis 2002; 19:247–258. [PubMed: 12067205]
129. Tsung K, Dolan JP, Tsung YL, Norton JA. Macrophages as effector cells in interleukin 12-induced T cell-dependent tumor rejection. Cancer Res 2002; 62:5069–5075. [PubMed: 12208763]
130. Torisu H, et al. Macrophage infiltration correlates with tumor stage and angiogenesis in human malignant melanoma: possible involvement of TNFα and IL-1α. Int J Cancer 2000;85:182–188. [PubMed: 10629075
131. Schoppmann S, et al. Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis. Am J Pathol 2002; 161:947–956. [PubMed: 12213723].
132. Campos AR, Albuquerque FAA, Rao VSN, Pinto AC. Investigation on the antinociceptive activity of crude extracts from Croton cajucaraI leaves in mice. Fitoterapia 2002; 73(2):116-20.
133. Hernandez PM, Sanchez MCC, Montalbetti MY, Rabanal RM. Studies on the analgesic and anti-inflammatory effects of Sideritis candicans aerial parts. J Ethnopharmacology 2004; 93(2-3):279-84.
134. Gupta M, Mazumdar UK, Sivakumar T, Vamsi MLM. Evaluation of Anti-

inflammatory activity of chloroform extract of Bryonia laciniosa in experimental animal models. Biol Pharma Bull 2003; 26(9):1342-4.
135. Elisabetsky E, Amador TA, Albuquerque,RR, Nunes DS, Carvalho,Ado C. Analgesic activities of Psychotria colorate (Wild ex R. and S). Muel alkaloids. J Ethnopharmacology 1995; 48(2):77-83.
136. Onabanjo AO, John Th.A., Sokale AA, Samuel OT. Analgesic and Anti-inflamatory effects of Chasmentha dependens. Int J Pharmacology 1991; 29(1):24-8.
137. Thangam C, Dhananjayan R. Anti-inflammatory potential of the seeds of Carum copticum. Indian J Pharmacology 2003; 35:388-91.
138. Sonavane G, Sarveiya V, Kasture V, Kasture SB. Behavioural actions of Myristica fragrans. Indian J pharmacology 2001; 33: 417-24.
139. Schapoval ES, Maran R, Winter V, Chaves CG, Bridi R, Zuanazzi JA, Henriques AT. Antiinflammatory and antinociceptive activities of extracts and isolated compounds from Stachytarpheta cayennensis. J Ethnopharmacology 1998; 60:53-59.
140. Rahman MS, Sadhu SK, Hasan CM. Preliminary antiocciceptive, antioxidant and cytotoxic activites of Leucas aspera. Fitoterapia 2007; 78(7-8):552-5.
141. Alcaraz MJ, Jimenez M. Flavonoids as anti-inflammatory agents. Fitoterapia 1988; 59: 25-38.
142. Telang RS, Chatterjee S, Varshneya C. Studies on analgesic and anti-inflammatory activites of Vitex negundoi. Indian J Pharmacology 1999; 31: 363-6.
143. Onwukaeme ND. Antiinflammtory activities of flavonoids of Baphia nitida on mice and rats. J Ethnopharmacology 1995; 46:121-24.
144. Alencar NMN, Figueriredo IST, Vale MR, Bitencurt FS, Oliveria JS, Riberiro RA, Ramos MV. Anti-inflammatory effect of the latex from the Calotropis procera in three different experimental models, Peritonitis, Paw oedema and Hemorrhagic cystitis. Planta Med 2004; 70:1144-49
145. Chakrabory A, Devi RKB, Sharatchandra K, Singh T. Preliminary studies on anti-inflammatory and analgesic activities of Spilanthes acmella. Indian J Pharmacology 2004; 36(3):148-50.
146. Malik JK, Manvi FV, Alagawadi KR, Noolvi M. Evaluation of anti-inflammatory activity of Gymnea Sylvester leaves extracts in rats. Indian J Green Pharmacy 2008; 2(2):114-16.
147. Campbell WB. Lipid derived autocoids; Eicosanoidsand platelet activating factors; In: Gillmans AG, Roll TW, Neis A.S., Taylor P. (editors). Goodman's and Gillman's : The Pharmacological basis of Therapeutics, 8th ed. New York pergaman press, 1991:607-8.
148. Fitz GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345:433–42
149. Vane JR, Botting BRM. The future of NSAIDs therapy selective COX-2 inhibitors. In J Clin Pract 2000; 54(1):7-9.
150. Marcelo NM, Nathalie V, Fina L, Christopher R, Susan NE, Samuel A, John LW. Selective cyclo-oxygenase-2 inhibition with celecoxib elevates blood pressure and promotes leukocyte adherence. Br J Pharmacol 2000; 129:1423-30.
151. FLOWER, R. J. Background and discovery of lipocortins. Agents Actions 17: 255-262; 1985.
152. WALLNER, B. P.; MATTALIANO, R. J.; HESSION, C.; CATE, R. L.; TIZARD, R.; SINCLAIR, L. K.; FOELLER, C.; Cuow, E. P.; BROWNING, J. L.; RAMACHANDRAN, K. L.; PEPINSKY, R. B. Cloning and expression of human lipocortin, a phospholipase A2 inhibitor with potent anti-inflammatory activity. Nature (London) 320: 77-81; 1986.
153. DAVIDSON, F. F.; DENNIS, E. A.; POWELL, M.; GLENNEY, J. R., JR. Inhibition of phospholipase A2 by "lipo- 96 VANE AND BOlTING cortins" and calpactins.J. Biol. Chem. 262: 1698-1705; 1987.
154. Joseph, S.M.; Scientific aspects of the therapeutic use of A.paniculata (kalmegh): A review; Int J Pharm Sci Rev Res, (2014); 27(1): 10–13.
155. Mishra, S.K., Sangwan, N.S., Sangwan, R.S.; Phcog rev.: Plant review A.paniculata (Kalmegh): A review; Pharmacogn Rev, (2007); 1(2): 283–296.
156. Joselin, J., Jeeva, S.; Andrographis paniculata: A review of its traditional uses, phytochemistry and pharmacology; Med Aromat Plants, (2014); 3(4): 1–15.
157. Benoy, G.K., Animesh, D.K., Mandal, A., Dubey, K.P., Halder, S.; An overview on A.paniculata (Burm.F.) Nees; Int J Res Ayurveda Pharm, (2012); 3(6): 752–760.
158. Chiou, W.F., C.F. Chen and J.J. Lin, 2000. Mechanisms of suppression of inducible nitric oxide synthase (iNOS) expression in RAW 264. 7 cells by Andrographolide

159. Shen, Y.C., C.F. Chen and W.F. Chiou, 2002. Andrographolide prevents oxygen radical production by human neutrophils: Possible mechanisms involved in its anti-inflammatory effect. Br. J. Pharmacol., 135: 399-406.
160. Satyanarayana, C., D.S. Deevi, R. Rajagopalan, N. Srinivas and S. Rajagopal, 2004. DRF 3188 a novel semi-synthetic analog of Andrographolide: Cellular response to MCF7 breast cancer cells. BMC Cancer, 4: 1-8.
161. Wang, T., B. Liu, W. Zhang, B. Wilson and J.S. Hong, 2004. Andrographolide reduces inflammation- mediated dopaminergic neurodegeneration m mesenphalic neuronglia cultures by inhibiting microglial activation. J. Pharmacol. Exp. Therapeutics, 308: 975-983.
162. Xia, Y.F., B.Q. Ye, Y.D. Li, J.G. Wang and X.J. He et al., 2004. Andrographolide attenuates inflammation by inhibition of NF-kB activation through covalent modification of reduced cysteine62 of p50. J. Immunol., 173: 4207-4217.
163. Hidalgo, M.A., A Romero, J. Figueroa, P. Cortes,I.I. Concha, J.L. Haneke and R A Burgos, 2005. Andrographolide interferes with binding of nuclear factor-kB to DNA in HL-60-derived neutrophilic cells. Br. J. Pharmacol., 144: 680-685.
164. Sheeja, K., P.K. Shihab and G. Kuttan, 2006. Antioxidant and anti-inflammatory activities of the plant andrographis paniculata nees. Immunopharmacol. Immunotoxicol., 28: 129-140
165. Abu-Ghefreh, A.A, H. Canatan and C.I. Ezeamuzie, 2009. In vitro and in vivo anti-inflammatory effects of Andrographolide. Int. Immunopharmacol., 9: 313-318.
166. Bao, Z., S. Guan, C. Cheng, S. Wu and S.H. Wong et al., 2009. A novel antiinflammatory role for Andrographolide in asthma via inhibition of the nuclear factor-kB pathway. Am. J. Respir. Crit. Care Med., 179: 657-665.
167. Suebsasana S., P. Pongnaratorn, J. Sattayasai,T. Arkaravichien, S. Tiamkao and C. Aromdee, 2009. Analgesic, antipyretic, anti-inflammatory and toxic effects of Andrographolide derivatives in experimental animals. Arch. Pharm. Res., 32: 1191-1200.
168. Chandrasekaran, C.V., A Guptaa and A Agarwal, 2010. Effect of an extract of Andrographis paniculata leaves on inflammatory and allergic mediators in vitro. J. Etnopharmacol., 129: 203-207.
169. Chao, W.W., Y.H. Kuo and B.F. Lin, 2010. Anti-inflammatory activity of new compounds from Andrographis paniculata by NF-kappaB transactivation inhibition. J. Agric. Food Chem., 58: 2505-2512.
170. Levita, J., A Nawawi, A Mutholib and S. Ibrahim, 2010. Andrographolide inhibits COX-2 expression in human fibroblast cells due to its interaction with arginine and histidine in cyclooxygenase site. J. Applied Sci., 10: 1481-1484.
171. Amroyan, E., E. Gabrielian, A Panossian, G. Wikman and H. Wagner, 1999. Inhibitory effect of Andrographolide from Andrographis paniculata on PAF-induced platelet aggregation. Phytomedicine, 6: 27-31.
172. Levita, J., E.P. Istyastono, A Nawawi, A Mutholib, I.J.P. de Esch and S. Ibrahim, 2009a. Analyzing the interaction of Andrographolide and neoAndrographolide, diterpenoid compounds from Andrographis paniculata (Burm. F) Nees, to COX-2 enzyme by docking simulation. ITB J. Sci., 41A: 110-119.
173. Levita, J., Novriyanti, M., Muchtaridi, M. Moektiwardoyo and E. Halimab, 2009b. Molecular modeling study of Andrographolide as inhibitor of nuclear factor-kappaB p50 DNA binding. Pekan Ilmiah Universitas Padjadjaran,http://www.lppm. unpad. ac.id/wp-content/uploads/2009/11 /jadwal- seminar.pdf.