Plant based anti-inflammatory secondary metabolites

P. Pushpangadan, T.P. Ijinu and V. George

Amity Institute for Herbal and Biotech Products Development, 3 Ravi Nagar, Peroorkada Post Office, Thiruvananthapuram 695 005, Kerala, India

Received March 20, 2015: Revised April 15, 2015: Accepted April 20, 2015: Published online June 30, 2015

Abstract

Inflammation is the body’s natural response to harmful stimuli arising in tissue in response to traumatic, infectious, post-ischaemic, toxic or autoimmune injury. The resolution inflammation requires the termination of pro-inflammatory signaling pathways and clearance of inflammatory cells allowing the restoration of normal tissue functions. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most well recognized drugs worldwide for the treatment of inflammation and associated diseases. However, prolonged use of NSAIDs causes adverse gastrointestinal complications, immunodeficiency and humoral disturbances, leading to chronic problems. In this context, the identification of new chemical entities with high efficacy and safety has a paramount importance. Natural products are considered to be a promising avenue for the discovery of new drug molecules. The discovery of aspirin was a basis for the treatment of inflammatory diseases. This review summarizes the molecular mechanisms through which several phytochemicals may inhibit inflammation.

Key words: Inflammation, plant bioactives, NSAIDs, cyclooxygenase, NF-κB, cytokines

1. Introduction

Inflammation is a complex set of interactions among soluble factors (cytokines) and cells that can arise in any tissue in response to traumatic, infectious, post-ischaemic, toxic or autoimmune injury. The process normally leads to recovery from infection and to healing, however, if targeted destruction and assisted repair are not properly phased, inflammation can lead to persistent tissue damage by leukocytes, lymphocytes or collagen (Nathan, 2002). Chronic inflammation can contribute to diseases such as arthritis, heart attacks, Alzheimer’s disease and also makes individuals susceptible to many forms of cancer. The culprits that drive this process are inflammatory cells and signaling molecules of the innate immune system, which recognizes potential threats without previous exposure to them (Balkwill and Coussens, 2004; Mantovani, 2005).

Natural products, including those derived from plants have over the years contributed to the development of modern therapeutic drugs. Recently, much interest has been generated for a wide range of phytoconstituents with reports demonstrating their role in the modulation of inflammatory responses. Several natural product drugs of plant origin are in clinical use and some are undergoing Phase II and III clinical trials. The understanding of the cellular and molecular mechanisms involved in the inflammatory process has increased considerably in recent decades and this has permitted the discovery of many promising targets for the development of new drugs to treat inflammatory diseases.

1.1 Inflammatory cascade

Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages and there are many targets for anti-inflammatory action. A major component of the inflammation process is the arachidonic acid (AA) pathway because arachidonic acid is immediately derived from the traumatized cellular membranes by the action of enzyme phospholipase A2 (PLA2). This membrane based arachidonic acid catalysed by cyclooxygenases (two isofoms, namely; COX-1 and COX-2), results in the formation of prostaglandin G2 (PGG2) and in a subsequent peroxidase reaction PGG2 undergoes a two-electron reduction to PGH2. PGH2 may then be acted upon by various enzymes to yield prostaglandins (PGD2 PGE2 PGF2α), prostacyclin (PGI2) and thromboxane (THA2). Prostaglandins play a key role in the generation of the inflammatory response. They promote inflammation that is necessary for healing, but also results in pain, and fever, support the blood clotting function of platelets and protect the lining of the stomach from the damaging effects of acid. Among the prostaglandins, PGE2 has received the most attention because of its contribution to nociception and inflammation. PGE2 stereospecifically exerts potent (i.e., within the nanomolar to micromolar range) tissue and cell type selective actions. PGE2 is not only thought to play a key role in nociception (e.g., intradermal PGE2 is largely responsible for hyperalgesia in the peripheral nervous system) but also appears to be involved in a wide variety of other functions, including vasodilatation, altered microvascular permeability, and febrile responses (Pountos et al., 2011; Ricciotti and Gerald, 2010).

PGE2 is a potent vasodilator and inhibitor of platelet adhesion to the endothelium. It inhibits platelet aggregation through stimulation of adenylate cyclase leading to an increase in cyclic AMP in the platelets. THA2 is a potent vasoconstrictor and its production is
enhanced during inflammation and tissue injury, and following platelet activation. It is important in producing arterial vasoconstriction when a vessel is cut and bleeding (haemostatic function) (Ricciotti and Gerald, 2010).

Along with the cyclooxygenase pathway, the lipoxygenase (LOX) pathway is also a strong mediator of inflammation. Lipoxygenase (LOX) catalyzes the insertion of one molecular oxygen into the 5-, 12- or 15- carbon position of arachidonic acid and are termed 5-LOX, 12-LOX and 15-LOX accordingly (Funk, 2001). The primary products are 5S-, 12S-, or 15S-hydroperoxyeicosa-tetraenoic acid (5-, 12-, or 15-HPETE), which can be further reduced by glutathione peroxidase to the hydroxy forms, 5-, 8-, 12-, 15-HETE, respectively. Further, 5-LOX has a unique activity of catalyzing 5-HPETE to either 5-HETE or the unstable epoxide leukotriene A4 (LTA4) (Peters-Golden, 1998; Funk, 2001). This is later catalyzed to either LTB4 (a potent neutrophil chemoattractant and stimulator of leukocyte adhesion to endothelial cells) or LTC4. LTC4 might be converted to LTD4, which can be further converted to LTE4. The LTC4, LTD4, and LTE4 are called peptidoleukotrienes or cysteinyl leukotrienes (Chen, 2011; Pountos et al., 2011). The arachidonic acid depended pathway of inflammation is shown in Figure 1.

![Figure 1: Cyclooxygenase and lipoxygenase pathways of inflammatory cascade](image-url)
1.2 NF-κB in inflammation

The nuclear factor κB (NF-κB) is an inducible transcription factor comprised of homo- and hetero-dimers of the NF-κB and Rel protein family (Hoffmann et al., 2006). It has been reported that NF-κB plays major roles in leukemia, inflammatory bowel disease, arthritis, sepsis, asthma, multiple sclerosis, colitis, diabetic neuropathy and AIDS (Cameron and Cotter, 2008). The NF-κB proteins are localized in the cytoplasm of the cell and are associated with a family of inhibitory proteins known as IkB (Gupta et al., 2001; Wang et al., 2004a). The IkB proteins are normally bound to NF-κB and block their nuclear localization signal. A variety of provoking stimuli can degrade the IkB and result in the nuclear translocation of NF-κB to be free to activate the gene expression of inflammatory cytokines (Maroon et al., 2010). They include pro-inflammatory cytokines (e.g., IL-1, IL-2, IL-6, TNF-α, etc.), chemokines (e.g., IL-8, MIP-1α, MCP1, RANTES, eotaxin, etc.), adhesion molecules (e.g., ICAM, VCAM, E-selectin), inducible enzymes (COX-2 and iNOS), growth factors, some of the acute phase protein and immune receptors. All these inflammatory cytokines play a critical role in controlling most of the inflammatory processes (Barnes and Karin, 1997; Ghosh and Karin, 2002). Therefore, NF-κB is the master switch for inflammation.

Gene expression of inflammatory cytokine leads to another stage of the inflammatory cascade. In conjunction with chemokines and various co-stimulatory molecules, proinflammatory molecules facilitate the recruitment of effector cells, such as monocytes and neutrophils, to the site of disturbance. Neutrophils create a cytotoxic environment by releasing noxious chemicals from cytoplasmatic granules (a process called degranulation). Rapid release of these chemicals requires consumption of both glucose and oxygen, known as the respiratory burst. Toxic chemicals released include reactive oxygen species (ROS) and reactive nitrogen species (RNS), respectively and various proteinases. These substances are destructive to both pathogens and hosts and essentially induce liquefaction of surrounding tissue to stave off microbial metastasis (Nathan 2002; Ashley et al., 2012). These effector mechanisms are thus major contributors to host collateral damage. The net effect of these interactions culminates in the stereotypical cardinal signs of local inflammation: heat, swelling, redness, pain, and loss of function (Ashley et al., 2012).

1.3 NSAIDS and their mechanism of action

Salicylic acid and salicylates, obtained from natural sources, have long been used as medicaments. Salicylic acid was chemically synthesized in 1860 and was used as antiseptic, antipyretic and antirheumatic. Almost 40 years later, aspirin was developed as a more palatable form of salicylate. Soon after, other drugs having similar actions to aspirin were discovered, and the group was termed the ‘aspirin-like drugs’ (also now termed the nonsteroidal anti-inflammator drugs (NSAIDs) (Vane and Botting, 1998). In 1971, Vane discovered the mechanism by which aspirin exerts its anti-inflammatory, analgesic and antipyretic actions. He proved that aspirin and other NSAIDs inhibit the activity of the enzyme cyclooxygenase which leads to the formation of prostaglandins (PGs) that cause inflammation, swelling, pain and fever. In 1982, he was awarded the Nobel Prize in Physiology or Medicine (Vane and Botting, 1996; Vane and Botting, 2003; Botting, 2010). This discovery by John Vane, was followed twenty years later by the discovery of COX-2 and the rapid development of selective inhibitors of this enzyme (Botting, 2010).

Mostly NSAIDs inhibit the activity of both COX-1 and COX-2, and thereby the synthesis of prostaglandins, prostacycline and thromboxane. The constitutive COX-1 is responsible for physiological functions and inducible COX-2 involved in inflammation. Inhibition of COX explains both the therapeutic effects (inhibition of COX-2) and side effects (inhibition of COX-1) of NSAIDs. NSAIDs which selectively inhibit COX-2 are likely to retain maximal anti-inflammatory efficacy combined with less toxicity (Vane and Botting, 1996). According to the results of various studies on the ranking scheme in terms of COX-2 selectivity, one can consider rofecoxib, celecoxib, and meloxicam as posing the higher COX-2 selectivity, followed by ibuprofen, diclofenac and piroxicam. Aspirin, indomethacin and ketorolac have the lowest COX-2 selectivity (Brooks et al., 1999; Warner et al., 1999). Aspirin, sodium salicylate, rofecoxib and ibuprofen also inhibit of NF-κB, and in addition to this aspirin and sodium salicylate have shown to inhibit activator protein-1 (AP-1) (Budsberg, 2010).

Several NSAIDs affect the production or actions of cytokines and this property has been considered to be a component of their actions, positive or negative. Indomethacin and some other NSAIDs may increase production of IL-1 or TNF-α and these effects have been considered important in the development of gastrointestinal ulcers and asthma attributed to these drugs. However, some other NSAIDs such as nimesulide inhibit IL-6 and TNF-α (Rainsford, 2005) while ibuprofen inhibits TNF-α (Jiang et al., 1998). TNF-α induction of the NF-κB/IκB signalling pathway is inhibited by salicylate at the level of the activity of IκB kinase and cAMP-response element binding protein (CREB) (Rainsford, 2004).

The inhibitory effects on signalling pathways, especially those involving NF-κB/IκB and MAP kinases, may have particular significance in subsequent inhibition of the expression of mRNAs and the proteins of COX-2, iNOS and PLA2 (Rainsford, 2004; Rainsford, 2007). With nimesulide there is also an interesting additional property that this drug activates glucocorticoid receptors leading to down-regulation of a number of cytokines, metalloprotease enzymes, COX-2, iNOS and PLA2 (Rainsford, 2005). Some NSAIDs also affect the response of T-cells to IL-2 (Hall and Wolf, 1997) and this together with reduction in the effects of PGE2, due to blockade of the production of this prostanoid by NSAIDs, may form a component of their immuno-regulatory effects (Smith et al., 1971; Goodwin et al., 1977, 1978; Rainsford, 2007). Recent findings have exposed the fatal side effects associated with NSAIDs, and considering these harmful outcomes, a range of novel therapeutically relevant biological targets, which particularly include NF-κB and Jak/STAT signaling pathways, have received growing attention.

1.4 Plant derived bioactives

Many plant-derived compounds have been used as drugs, either in their original or semi-synthetic form. Plant secondary metabolites can also serve as drug precursors, drug prototypes and pharmacological probes (Salim et al., 2008). Despite the recent interest in drug discovery by molecular modeling, combinatorial chemistry, and other synthetic chemistry methods, natural product derived compounds are still proving to be an invaluable source of medicines for human well being. At present, numerous studies
have established that the plant bioactives contribute protective effects against acute and chronic inflammatory diseases. Traditionally several plants are used against inflammatory diseases and many of the natural compounds isolated from these plants show potent anti-inflammatory action in in vitro and in vivo animal models. They work by inhibiting the inflammatory pathways in a similar manner as NSAIDs.

Several mechanisms of action have been proposed to explain the anti-inflammatory actions of phytochemicals, such as (i) Antioxidative and radical scavenging activities; (ii) Modulation of cellular activities of inflammation-related cells (mast cells, macrophages, lymphocytes, and neutrophils); (iii) Modulation of proinflammatory enzyme activities such as PLA2, COX and LOX and the NO producing enzyme, NOS; (iv) Modulation of the production of other proinflammatory molecules and (v) Modulation of proinflammatory gene expression (Bellik et al., 2013). Some of the potent anti-inflammatory bioactives isolated from plants in recent years and their anti-inflammatory mechanisms are described below:

**Acetylsalicylic acid or aspirin**

It is one of the most widely used drugs worldwide and is a starting point for the treatment of inflammation and associated diseases. It was derived from salicylic acid found in the bark of the *Spiraea ulmaria*, which has traditionally been used to treat fever and inflammation (Recio et al., 2012). In antithrombotic and anti-inflammatory actions, it acetylates COX-1 and COX-2, thereby, irreversibly blocking the conversion of arachidonic acid to prostanoids for the production of prostaglandins, thromboxanes and prostacyclins, the essential fatty acid signalling molecules (Ammann and Peskar, 2002; Vane and Botting, 2003; Bala et al., 2008). Recently Alfonso et al. (2014) raised the intriguing possibility that aspirin may interact and acetylate cellular molecules such as RNA, and metabolites such as CoA, leading to a change in their function. Research in this area will provide a greater understanding of the mechanisms of action of this drug.

![Acetylsalicylic acid](image)

**Epigallocatechin-3-gallate**

The compound (-)-epigallocatechin-3-gallate (EGCG) is the major catechin found in *Camellia sinensis*. It has shown remarkable anti-inflammatory and cancer chemopreventive effects in many animal tumor bioassays, cell culture systems and epidemiological studies (Ahmad et al., 2000; Le Marchand, 2002). Hwang et al. (2007) have reported that the anti-inflammatory action is through the activation of AMPK. Activation of AMPK has been shown to inhibit the production of several proinflammatory mediators including TNF-α, IL-1β, IL-6, MCP-1, iNOS and COX-2 with LPS stimulation (Jeong et al., 2009). Another study indicates that EGCG inhibits the IL-1β-induced production of NO in human chondrocytes by interfering with the activation of NF-κB through a novel mechanism (Singh et al., 2002; Ahmed et al., 2002). EGCG has also been shown to inhibit metalloproteinases (Rasheed et al., 2009), COX-2, PGE2, MAPKs and AP-1 (Singh et al., 2003) in IL-1β stimulated human osteoarthritic chondrocytes.

![Epigallocatechin-3-gallate](image)

**Triptolide**

It is a diterpenoid triepoxide purified from a Chinese herb, *Tripterygium wilfordii*. Triptolide inhibits both Ca²⁺-dependent and Ca²⁺-independent pathways and affects T-cell activation through inhibition of IL-2 transcription at a site different from the target of cyclosporin A. It also shows inhibitory effects on a variety of proinflammatory cytokines and mediators and on the expression of adhesion molecules by endothelial cells (Chen, 2001). It inhibits the transcriptional activation of the IL-2 gene by inhibiting activation of the purine-box regulator of NFAT target DNA sequence in the IL-2 enhancer and by inhibiting NF-κB activation (Qu et al., 1999). Wen et al. (2013) reported triptolide treatment significantly attenuates cardiac inflammation and fibrosis through suppressing the activity and the expression of NF-κB, resulting in improved left ventricular function in experimental diabetic cardiomyopathy.

![Triptolide](image)

**Boswellic acid**

In *Ayurveda*, the plant *Boswellia serrata* has long been used for the treatment of inflammatory diseases. Boswellic acids were isolated from the gum resin of this plant and is inhibited the leukotriene synthesis via 5-LOX (Ammon et al., 1993). Clinical studies also suggest its efficacy in some autoimmune diseases including rheumatoid arthritis, Crohn’s disease, ulcerative colitis and bronchial asthma (Ammon, 2006).

![Boswellic acid](image)
Andrographolide
It is a diterpene lactone found in the plant Andrographis paniculata, which is widely used in traditional Indian and Chinese medicines. It shows a reduction of the production of proinflammatory mediators, such as COX-2, NO and iNOS (Anand et al., 2007; Jurenka, 2009; Prasad et al., 2014). Traditionally these plants are used against a variety of inflammatory and neuronal diseases (Liou et al., 2003; Ou et al., 2007). Andrographolide inhibits a number of cell-signaling pathways that are important to inflammation by reducing COX-2-induced exacerbation. It also inhibited the production of NO and PGE2 by inhibiting iNOS and suppression of NF-κB signaling pathway and suppression of NF-κB regulated gene expression.

Honokiol
It is a major component isolated from the bark, root and stem of various Magnolia species (Wang et al., 2004b). Traditionally these plants are used against a variety of inflammatory and neuronal diseases. Hamalainen et al. (2007) study shows that genistein and daidzein reduced inflammatory cytokines, including IL-1β, IL-6 and COX-2 expression. The increased release and expression of inflammatory cytokines, including TNF-α, IL-6, adiponectin and leptin serum concentrations and significantly improved rheumatoid arthritis symptoms.

Genistein and Daidzein
The main bioactive isoflavones are genistein and daidzein, which are abundant in soybean and soy products. Epidemiologic studies in humans indicate that increased soy consumption could be cardioprotective. The main bioactive isoflavones are genistein and daidzein, which are abundant in soybean and soy products. Epidemiologic studies in humans indicate that increased soy consumption could be cardioprotective. Hamalainen et al. (2007) study shows that genistein inhibited activation of STAT-1 and NF-κB. Genistein also inhibited the production of NO and PGE2 by inhibiting iNOS and COX-2 expression. The increased release and expression of inflammatory cytokines, including IL-1β, TNF-α, by LPS, were also markedly reduced by genistein (Jeong et al., 2014). Mohammad-Shahi et al. (2011) study shows that genistein and daidzein reduced the TNF-α, IL-6, adiponectin and leptin serum concentrations and significantly improved rheumatoid arthritis symptoms.

Ellagic acid
It is a phenolic acid naturally occurring in many food plants like strawberries, raspberries, blackberries and walnuts and also in some medicinal plants. Favarin et al. (2013) reported, ellagic acid as a potential therapeutic agent for acute lung injury-associated inflammation by reducing COX-2-induced exacerbation. It also inhibits a number of cell-signaling pathways that are important to tumor growth, including inflammatory signaling such as TNF-α induced COX-2 protein expression and NOS inhibition (Adams et al., 2006; Chiang et al., 2003). Adams et al. (2006) found that Punica granatum fruit juice containing ellagic acid significantly suppressed TNF-α induced COX-2 protein expression in human colon cancer cells. Ellagitannins and punicalagin from P. granatum have also been reported to inhibit cancer cell proliferation and apoptosis through the modulation of NF-κB signaling pathway and suppression of NF-κB regulated gene expression.
Myrtucommulone
It is a nonprenylated acylphloroglucinol contained in the leaves of Myrtus communis, a Mediterranean shrub used as a culinary spice and as a folk medicine. Myrtucommulone has been reported to suppress the biosynthesis of eicosanoids by inhibition of 5-LOX and COX-1 in vitro and to inhibit the release of elastase and the formation of ROS in activated polymorphonuclear leukocytes (Rossi et al., 2009).

According to Koetherle et al. (2009), myrtucommulone is the first natural product to inhibit mPGES-1 that efficiently suppresses PGE2 formation without significant inhibition of the COX enzymes. Rossi et al. (2009) demonstrated that myrtucommulone attenuates the production of TNF-α and IL-1 in pleural exudates and lungs of carrageenan-treated mice.

![Myrtucommulone](image)

Arzanol
The acylphloroglucinol arzanol has recently been suggested as an active ingredient responsible for the anti-inflammatory effects of the plant Helichrysum italicum, grows in the Mediterranean area. Arzanol is a potent inhibitor of 5-LOX and mPGES-1 in both cell-free and cell-based assays (Bauer et al., 2010; 2011). It also inhibits the activation of inflammatory transcription factor NF-κB, HIV replication in T cells, release of IL-1β, IL-6, IL-8, and TNF-α (Appendino et al., 2007; Kothavade et al., 2013).

![Arzanol](image)

Thymoquinone
It is one of the most active ingredients of Nigella sativa seeds (Ragheb et al., 2009; Woo et al., 2012). Chehl et al. (2009) reported that anti-inflammatory activity of thymoquinone in PDA cells, is by the inhibition of NF-κB. The study results of Taka et al. (2014) suggest that thymoquinone could have a neuroprotection potential and may provide a means for the treatment of neurodegenerative diseases such as Alzheimer and Parkinson’s diseases. Thymoquinone also attenuates allergic airway inflammation by inhibiting Th2 cytokines and eosinophil infiltration into the airways (El Guzzar et al., 2006).

![Thymoquinone](image)

Shikonin
It is an analog of naphthoquinone pigments isolated from the root of Lithospernum erythrorhizon. Results suggest that shikonin exerts anti-inflammatory properties in LPS-mediated ALI, possibly through inhibition of the NF-κB signaling pathway (Liang et al., 2013). It can be also mediated by suppression of TNF-α promoter activity (Stanforth et al., 2004) or by regulation of TNF-α pre-mRNA splicing (Chiu and Yang, 2007). Shikonin treatment substantially affected transgenic and/or endogenous expression of TNF-α, GM-CSF and other cytokine genes in mouse skin tissues in vivo (Su et al., 2008) and in DCs or monocytes ex-vivo (Chiu et al., 2010). Several other studies demonstrated that shikonin has a significant antitumor potential, inducing cell death and inhibiting the cell growth by sequential activation of caspases in various types of cancer cell lines (Wu et al., 2004; Hsu et al., 2004; Min et al., 2008; Mao et al., 2008; Thangapazham et al., 2008; Chen et al., 2012).

![Shikonin](image)

Emodin-8-O-β-D-glucoside
It is extracted from the traditional Chinese medicinal herb Polygonum cuspidatum and is widely used to treat acute hepatitis. Wang et al. (2007) reported that emodin-8-O-β-D-glucoside is able to provide neuroprotection against cerebral ischemia-reperfusion injury and glutamate induced neuronal damage. Emodin-6-O-β-D-glucoside, isolated from Reynoutria japonica, has shown to exert potent anti-inflammatory and barrier protective effects in HUVE cells and also in animal model (Lee et al., 2014).

![Emodin-8-O-β-D-glucoside](image)

Resveratrol
It is a naturally occurring stilbene, considered to have a number of beneficial effects, including anticancer, antiatherogenic, antioxidative, anti-inflammatory, antimicrobial and estrogenic activity (Piotrowska et al., 2012). It is found in many plants including grapes, peanuts, berries and medicinal plants, such as Polygonum cuspidatum (Baur and Sinclair, 2006).

The anti-inflammatory mechanisms of action, mostly in inhibition of COX activity, inhibition of some activated immune cells, and proinflammatory mediators, and inhibition of transcriptional factor like NF-κB and activator protein (Das and Das, 2007). In addition to COX inhibition resveratrol also suppress the activity of NF-κB and IκB kinase (Kundu et al., 2006), reduced the production of PGE2 and the formation of ROS in LPS activated microglial cells (Candelario-Jalil et al., 2007; Kim et al., 2007).

![Resveratrol](image)
Resveratrol

It is a phenolic stilbenoid and a metabolite of resveratrol. Piceatannol was first isolated from the seeds of *Euphorbia legasus* (Ferrigni et al., 1984; Wieder et al., 2001). Piceatannol commonly exhibits anti-inflammatory, antiplatelet, and antiproliferative activity (Ko et al., 2013). When examined for the mechanism, Ashikawa et al. (2002) found that piceatannol inhibited TNF-induced IκBα phosphorylation, p65 phosphorylation, p65 nuclear translocation, and IκBα kinase activation. Although piceatannol has been shown to induce apoptosis in cancer cells and also inhibits Syk kinase, which plays a crucial role in the coordination of immune recognition receptors and orchestrates multiple downstream signaling pathways in various hematopoietic cells (Piotrowska et al., 2012).

Apocynin

The apocynin was first described by Schmiedeberg in 1883 and was isolated from the roots of *Apocynum cannabinum*, and its extract used as remedy for dropsy and heart troubles. In 1971, apocynin was identified during activity-guided isolation of immunomodulatory constituents from the root of *Picrorhiza kurroa*, a native plant grown in the mountains of India, Nepal, Tibet and Pakistan. Apocynin has been used as an efficient inhibitor of the complex NADPH-oxidase in many experimental models involving phagocytic and nonphagocytic cells (Lafeber et al., 1999; Zhang et al., 2005). NADPH-oxidase mediated superoxide plays an important role in the pathogenesis of brain injury and that inhibition of NADPH-oxidase by apocynin can attenuate brain injury following experimental ischemic stroke (Tang et al., 2007).

Moreover, another study showed that apocynin prevented COX-2 expression in stimulated human monocyte (Barbieri et al., 2004) and the prevention of the activation of NF-κB (Barnes and Karin, 1997; Hougee et al., 2006). Recently, Ghosh et al. (2012) reported that diapocynin exhibits profound neuroprotective effects in a animal model of Parkinson’s disease by attenuating oxidative damage and neuroinflammatory responses.

Celastrol

It is a triterpene molecule, a major active ingredient of Chinese herb, *Tripterygium wilfordii*, has exhibited a broad spectrum of pharmacological activities, including anti-inflammation, anticancer and immunosuppression (Yang et al., 2014). It attenuates excessive production of NO and proinflammatory cytokines such as TNF-α and IL-1β in LPS-stimulated BV-2 cells. Thus, it may be an effective therapeutic candidate for use in the treatment of neurodegenerative human brain disorders (Jung et al., 2007). Celastrol also decreased the induced expression of class II MHC molecules by microglia (Allison et al., 2001). Yang et al. (2014) demonstrated that celastrol significantly reduced nociceptive pain through CB2 signaling.

Wilforlide A

*Tripterygium wilfordii* has a long history of use in China for more than 2,000 years. Traditionally, it has been used as an anticancer drug, male contraceptive, a drug used to suppress the immune system and as an anti-inflammatory agent. The anti-inflammatory and immunosuppressive effect of wilforlide A, a triterpene isolated from this plant was studied and compared to that of triptolide (Xue et al., 2010). They used several models of inflammation and the results indicate that wilforlide A has obvious anti-inflammatory properties. Wilforlide A serves as a quality control standard of Tripterygium Glycosides, is effective in the treatment of patients with a variety of inflammatory and autoimmune diseases and is listed in Drug Standard of Ministry of Public Health, China (Xue et al., 2010).

Asiaticoside

It is isolated from *Centella asiatica*, which has been used for a long time as a memory enhancer drug in India. It is a triterpenoid molecule found to exhibit antioxidant and anti-inflammatory activities in several experimental animal models. These effects could be associated with the inhibition of proinflammatory mediators, including TNF-α and IL-6 levels, COX-2 expression and PGE2 production, as well as MPO activity, which might be mediated by...
the upregulation of HO-1 (Wan et al., 2013). The neuroprotective effect against transient cerebral ischemia and reperfusion in mice might be associated with the anti-inflammation via inhibiting over activation of p38 MAPK pathway (Chen et al., 2014).

### Helenalin
The sesquiterpene lactone helenalin, which can be isolated from several plant species of the Asteraceae family such as Arnica montana and A. chamissonis ssp. foliosa, are used traditionally as anti-inflammatory remedy. Lyss et al. (1997) and Lim et al. (2012) reported inhibition activity of transcription factor NF-κB. In human granulocytes, helenalin inhibited both the 5-LOX and LTC-4 synthase in a concentration and time-dependent fashion (Tomhamre et al., 2001).

### Cucurbitacin E
It is a triterpenoid compound isolated from Cucurbitaceae plants, possesses a wide range of biological activities including anti-inflammatory properties. The anti-inflammatory effect is through the suppression of NF-κB nuclear translocation leading to a decreased expression of TNF-α and IL-1β in LPS-stimulated RAW 264.7 cells (Qiao et al., 2013) and inhibition of COX-2 (Abdelwahab et al., 2011; Jang et al., 2008). Dong et al. (2010) reported Cucurbitacin E is an effective drug candidate against tumor angiogenesis by inhibiting VEGFR2 mediated Jak-STAT3 and mitogen activated protein kinases signaling pathways.

### Dihydrocucurbitacin B
It is a triterpenoid isolated from roots of Cayaponia tayuya. Dihydrocucurbitacin B modified the evolution of the clinical symptoms, reducing the swelling of bone and tissue damage along with the development of the disease, modifying the cell infiltration and the expression of both NOS and COX-2. In addition, it decreased the TNF-α and IL-1β production in lymphocytes (Escandell et al., 2006). Moreover, the analysis of inflamed tissues showed that dihydrocucurbitacin B reduced the presence of the most relevant cytokines implicated in these processes, including IL-1β, IL-4, and TNF-α. Dihydrocucurbitacin B was also found to inhibit the proliferation of phytohemagglutinin-stimulated human T lymphocytes, halting the cell cycle in the G phase. Finally, dihydrocucurbitacin B was found to exert a selective inhibition on NFAT cells in human lymphocytes. Thus, it curbs DTH reactions by inhibiting NFAT, which in turn suppresses the proliferation of the most relevant cells involved in DTH reactions, namely the T cells (Escandell et al., 2007).

### Madecassoside
It is also a triterpenoid product isolated from Centella asiatica. Results suggest that madecassoside can effectively alleviate inflammatory response on collagen induced arthritis. The inhibition of proinflammatory mediators, including COX-2 expression, PGE2 production, TNF-α and IL-6 levels and the up-regulation anti-inflammatory molecule IL-10 also attributed the anti-inflammatory effect of madecassoside (Li et al., 2009). In another study, Won et al. (2010) reported that the anti-inflammatory effects of madecassic acid are caused by iNOS, COX-2, TNF-α, IL-1β, and IL-6 inhibition via the downregulation of NF-κB activation in RAW 264.7 macrophage cells.

### Parthenolide
It is a sesquiterpene lactone isolated from the medicinal herb, Tanacetum parthenium. It appears to inhibit the pro-inflammatory enzymes 5-LOX, phosphodiesterase-3 and phosphodiesterase-4 (Kwok et al., 2001). It also inhibited the release of pro-inflammatory mediators NO, PGE2 and TNF-α from macrophages and TNF-α, IL-2, IFN-γ and IL-4 from human peripheral blood mononuclear cells (Wong et al., 2008). Study on molecular mechanisms supporting the potential use of parthenolide in periodontitis treatment (Zhang et al., 2014). These therapeutic effects have been attributed mostly to inhibition of NF-κB. However, in addition to its anti-NF-κB activity, Juliana et al. (2010) reported that parthenolide is a potent inhibitor of NLRP3 inflammasome.
Dihydrocucurbitacin B

Embelin
It is identified primarily from the *Embelia ribes*. Embelin possesses anti-inflammatory and anticarcinogenic properties *in vivo*, and these features have been related to interference with multiple targets including XIAP (Wehrkamp *et al.*, 2014), NF-κB (Ahn *et al.*, 2007), STAF-3 (Dai *et al.*, 2014), Akt and mTOR (Kim *et al.*, 2013; Huang *et al.*, 2014). Schaiblea *et al.* (2013) revealed human 5-LOX and microsomal mPGES-1 as direct molecular targets of embelin and suppressed the biosynthesis of eicosanoids. Kumar *et al.* (2011) reported anti-inflammatory activity of embelin both in acute and chronic irritant contact dermatitis *in vivo*.

Embelin

Pinitol
It is a component of *Abies pindrow*, reported to suppress NF-κB activation both induced by inflammatory stimuli and carcinogens and constitutive NF-κB activation noted in most tumor cells. The suppression of NF-κB activation by pinitol occurred through inhibition of the activation of IκBα kinase, leading to sequential suppression of IκBα phosphorylation and degradation, p65 phosphorylation and nuclear translocation, and NF-κB-dependent reporter gene expression. The inhibition of NF-κB activation thereby led to down-regulation of gene products involved in inflammation (COX-2), proliferation (cyclin D1 and c-Myc), invasion (MMP-9), angiogenesis (VEGF), and cell survival (cIAP1, cIAP2, XIAP, Bcl-2, and Bcl-xL). Suppression of these gene products by pinitol enhanced the apoptosis induced by TNF and chemotherapeutic agents and suppressed TNF-induced cellular invasion (Sethi *et al.*, 2008; Aggarwal *et al.*, 2011).

Pinitol

Abruquinone
It is the isoflavavanquinone isolated from the roots of *Abrus precatorius* have strong anti-inflammatory and antiallergic effects. Wang *et al.* (1995) suggests that the anti-inflammatory effect of abruquinone is mediated partly by suppressing the release of chemical mediators from mast cells and partly by preventing vascular permeability changes caused by mediators.

Abruquinone

Flavocoxid
Altavilla *et al.* (2009) studied the anti-inflammatory activity of flavocoxid, a mixed extract containing baicalin and catechin from *Acacia catechu* that acts as a dual inhibitor of COX and 5-LOX enzymes. It significantly inhibited COX-2, 5-LOX and inducible iNOS expression in LPS-stimulated peritoneal rat macrophages.

Flavocoxid

Marmelin
It is an ethyl acetate fraction of *Aegle marmelos* extracts, suppressed, TNF-α mediated activation and translocation of NF-κB, inhibited AKT and ERK phosphorylation both *in vitro* and in tumor xenografts (Subramaniam *et al.*, 2008).

Marmelin

Emodin
It is an active component from *Aloe vera*, exerts anti-inflammatory effects through the suppression activity of NF-κB in human umbilical vein endothelial cells in a dose- and time-dependent manner. Emodin inhibited degradation of IκB, an inhibitory subunit of NF-κB. Thus, emodin also downmodulated adhesion molecules like ICAM-1, VCAM-1, and ELAM-1 contain NF-κB binding sites in their promoter region in endothelial cells (Kumar *et al.*, 1998).

Emodin

Azadirachtin
*Azadirachta indica* is known for its medicinal properties since ancient time. A recent report indicated that azadirachtin obtained from this plant possesses antitumor property and has the potential to target NF-κB (Thoh *et al.*, 2010).
Berberine

Berberine isolated from the plant *Berberis aristata*, was shown to abolish NF-κB activation induced by various inflammatory agents and carcinogens. This alkaloid also suppressed constitutive NF-κB activation found in certain tumor cells. Suppression of NF-κB activation occurred through the inhibition of phosphorylation and degradation of IκB-α by the inhibition of IκB kinase activation, leading to suppression of phosphorylation and nuclear translocation of p65, and finally to inhibition of NF-κB reporter activity. Inhibition of IκB kinase by berberine was direct and could be reversed by reducing agents. Berberine also suppressed the expression of NF-κB-regulated gene products involved in antiapoptosis, proliferation, inflammation and invasion. Suppression of antiapoptotic gene products correlated with enhancement of apoptosis induced by TNF and chemotherapeutic agents and with inhibition of TNF induced cellular invasion (Pandey *et al.*, 2008).

Guggulsterone

It is a plant sterol derived from the gum resin (guggulu) of the tree *Commiphora mukul*. Guggulsterone mediates gene expression through regulation of various transcription factors, including NF-κB (Shishodia and Aggarwal, 2004), STAT-3 (Ahn *et al.*, 2008) and various steroid receptors such as androgen receptor and glucocorticoid receptors (Burris *et al.*, 2005).

Citral

It is isolated from *Cymbopogon citratus*, showed reduction in the release of pro-inflammatory mediators TNF-α and NO, significantly indicating an anti-inflammatory effect (Tiwari *et al.*, 2010).

Rohitukine

It is a chromane alkaloid, a precursor of flavopiridol, a promising anticancer compound. Rohitukine was first reported from *Amoora rohituka* followed by that in *Dysoxylum binectariferum* (Mohanakumara *et al.*, 2010). Flavopiridol is known as potent inhibitor of several CDKs and currently undergoes Phase III clinical trial. Flavopiridol suppressed NF-κB in a dose and time dependent manner in several cell types. Flavopiridol also inhibited the expression of the TNF induced NF-κB-regulated gene products cyclin D1, COX-2, and MMP-9 (Takada and Aggarwal, 2004; Takada *et al.*, 2008).
Rohitukine

Anethole
Dried fruits of *Foeniculum vulgare* possess a fragrant odour and a pleasant aromatic taste. Anethole, a chief constituent of this plant, has been shown to block both inflammation and carcinogenesis. Pretreatment with anethole decreased LPS-induced histopathological changes. The anti-inflammatory mechanism of anethole is by suppression of NF-κB by blocking IκB-α degradation (Kang *et al*., 2013). Besides NF-κB, anethole also suppressed TNF-induced activation of the transcription factor AP-1, c-jun N-terminal kinase and MAPK kinase (Chainy *et al*., 2000).

Gambogic acid
It is an active component of *Garcinia cambogia*. Pandey *et al*. (2007) reported that gambogic acid enhanced apoptosis induced by TNF and chemotherapeutic agents, inhibited the expression of gene products involved in antiapoptosis, proliferation, invasion and angiogenesis, all of which are known to be regulated by NF-κB. Gambogic acid suppressed NF-κB activation induced by various inflammatory agents and carcinogens and this, accompanied by the inhibition of TAK1/TAB1 mediated IκB kinase activation, inhibited IκB-α phosphorylation and degradation, suppressed p65 phosphorylation and nuclear translocation, and finally abrogated NF-κB dependent reporter gene expression.

Indirubin
It is an active principle from *Indigofera tinctoria*, has been demonstrated that it had anti-inflammatory and anticancer activities through suppression of NF-κB. Sethi *et al*. (2006) reported that indirubin suppressed NF-κB activation induced by various inflammatory agents and carcinogens. NF-κB reporter activity induced by TNFR1, TNF receptor-associated death domain, TRAF2, TAK1, NF-κB-inducing kinase, and IκB kinase-β was inhibited by indirubin.

Armepavine
It is an active compound from *Nelumbo nucifera*, has been shown to exert immunosuppressive effects both in *vitro* and in *vivo* through inhibition of NF-κB activation pathways (Weng *et al*., 2009). *In vitro*, armepavine suppressed NF-κB activation and MAPK phosphorylations and *in vivo* it attenuated the mRNA expression levels of col1α2, TGF-β1, TIMP-1, ICAM-1, iNOS, and IL-6 genes. Armepavine also shown the downregulation of iNOS and TNF-α expression via NF-κB modulation another active compound (Weng *et al*., 2009).

Ursolic acid
It is a pentacyclic triterpene acid from *Ocimum sanctum*, has been reported to suppress NF-κB activation induced by various carcinogens including TNF, phorbol ester, okadaic acid, H₂O₂, and cigarette smoke. Ursolic acid inhibited degradation and phosphorylation of IκB-α, IκB kinase activation, p65 phosphorylation, p65 nuclear translocation, and NF-κB-dependent reporter gene expression. The inhibition of NF-κB activation correlated with suppression of NF-κB-dependent cyclin D1, COX-2, and MMP-9 expression (Shishodia *et al*., 2003). It also inhibited both constitutive and IL-6-inducible STAT3 activation in a dose and time dependent manner in multiple myeloma cells (Pathak *et al*., 2007).

Picroliv
It is an iridoid glycoside derived from *Picrorhiza kurroa*, interfered the activation of NF-κB signal cascade. Picroliv abrogated TNF-induced activation of NF-κB through inhibition of IκB kinase, leading to inhibition of phosphorylation and degradation of IκB-α.
It also inhibited phosphorylation and nuclear translocation of p65. NF-κB inhibition by picroliv leads to suppression of NF-κB-regulated proteins, including those linked with cell survival (inhibitor of AP-1, Bcl-2, Bcl-xL, survivin, and TNF receptor-associated factor 2), proliferation (cycin D1 and COX-2), angiogenesis (VEGF), and invasion (intercellular adhesion molecule-1 and matrix metalloproteinase-9). Suppression of these proteins enhanced apoptosis induced by TNF (Gaddipati et al., 1999; Anand et al., 2008; Aggarwal et al., 2011).

**Piperine**
The fruits of *Piper longum* and *P. nigrum* contain the alkaloid piperine, possess inhibitory activities on prostaglandin and leukotrien COX-1 inhibitory effect, as well as on NF-κB activation (Stohs et al., 2001; Singh et al., 2008).

**Plumbagin**
The root of *Plumbago zeylanica* is a major source of plumbagin, has been used in the Indian medicine since the period of Charaka, from 750 B.C. (Tilak et al., 2004). Plumbagin has been shown to exert anticancer and antiproliferative activities in animal models as well as in cells in culture. Sandur et al. (2006) suggest that plumbagin may be effective against cancer not only by suppressing invasion but also by inhibiting angiogenesis and inflammation through inhibition of the NF-κB signaling pathway. Plumbagin inhibited both constitutive and interleukin 6-inducible STAT3 phosphorylation in human multiple myeloma cells and this correlated with the inhibition of c-Src, JAK-1, and JAK-2 activation (Sandur et al., 2010).

**Mollugin**
The roots of the plant *Rubia cordifolia* is used traditionally as anti-inflammatory, haemostatic, antidiysenteric, antipyretic, analgesic and anthelmentic agent. Mollugin, one of the active compounds obtained from the plant was shown to inhibit TNF-α induced expression of inflammatory molecules by inhibiting NF-κB activation in colon cancer cells (Kim et al., 2009).

**Sesamin**
Harikumar et al. (2010) found that sesamin, a lignan from *Sesamum indicum*, inhibited the proliferation of a wide variety of tumor cells including leukemia, multiple myeloma, and cancers of the colon, prostate, breast, pancreas, and lung. Sesamin also potentiated TNF-induced apoptosis and this correlated with the suppression of gene products linked to cell survival (Bcl-2 and survivin), proliferation (cycin D1), inflammation (COX-2), invasion (MMP-9, ICAM-1), and angiogenesis (VEGF). Sesamin downregulated constitutive and inducible NF-κB activation induced by various inflammatory stimuli and carcinogens, and inhibited the degradation of IκBα, through the suppression of phosphorylation of IκB-α and inhibition of activation of IκB kinase, thus resulting in the suppression of p65 phosphorylation and nuclear translocation (Aggarwal et al., 2011).

**Brucine and brucine N-oxide**
Brucine and brucine N-oxide isolated from the dried seeds of *Strychnos nux-vomica* are reported to exert anti-inflammatory effects through reduction of PGE2 release (Yin et al., 2007).

**Amarogentin**
The secoiridoid glycoside, amarogentin, isolated from the plant *Swertia chirata* is reported to suppress COX-2 (Saha et al., 2006) and also possesses various biological activities such as chemopreventive, antibacterial, anticholinergic and antihepatitis activity.
Eugenol

_Syzygium aromaticum_ is traditionally used to treat respiratory and digestive ailments. Eugenol, the principle component of this plant has been shown to have ROS scavenging activity and antitumor potentials targeting COX-2, cMyc, H-Ras (Banerjee _et al._, 2006).

Octacosanol

It is a straight chain aliphatic 28-carbon primary fatty alcohol. Octacosanol isolated from _Tinospora cordifolia_ downregulates VEGF gene expression by inhibiting nuclear translocation of NF-kappaB and its DNA binding activity (Thrippleswamy _et al._, 2008).

Diosgenin

It is a steroidal saponin present in _Trigonella foenum-graecum_ and some other plants, has been shown to suppress inflammation, inhibit proliferation, and induce apoptosis in a variety of tumor cells. It down-regulates TNF-α induced expression of NF-xB-regulated gene products involved in cell proliferation, antiapoptosis and invasion (Shishodia _et al._, 2006). It also inhibits STAT3 signaling pathway leading to suppression of proliferation and chemosensitization of human hepatocellular carcinoma cells (Li _et al._, 2010).

Withanolides

The plant _Withania somnifera_ also known as Indian ginseng, is widely used in the Ayurvedic system of medicine. Withanolides isolated from this plant suppressed NF-xB activation induced by a variety of inflammatory and carcinogetic agents, including TNF-α, IL-1β, doxorubicin, and cigarette smoke condensate. It also suppressed both inducible and constitutive NF-xB activation. The suppression occurred through the inhibition of inhibitory subunit of IxB-α kinase activation, IxB-α phosphorylation, IxB-α degradation, p65 phosphorylation, and subsequent p65 nuclear translocation (Ichikawa _et al._, 2006). Withanolide sulfoxide, another active compound of this plant inhibits COX-2 expression (Mulabagal _et al._, 2009).

2. Conclusion

Inflammation has been associated with many diseases like cancer, diabetes, neurological disorders, _etc._ There has been some concern over the use of synthetic COX-2 inhibitors such as rofecoxib and valdecoxib for therapeutic interventions because of fatal side effects, some of these therapeutic products are either withdrawn or made to carry a warning by the Food and Drug Authority (FDA) (Naesdal and Brown, 2006). Due to risk of cardiovascular and skin related toxicities, rofecoxib and valdecoxib were withdrawn from the market in September 2004 and March 2005, respectively (Greenberg _et al._, 2009).

Since ancient times traditional herbal medicines are used for the treatment of inflammatory and related disorders. Inhibition of the synthesis or action of COX, LOX, PLA2, pro-inflammatory cytokines and NO are important targets for the treatment of inflammatory diseases. Various medicinal plants which are used in Ayurveda for the treatment of inflammation and associated diseases have been found to contain chemical constituents that inhibit inflammatory mediators like TNF-α, IL-1, NF-xB, COX, LOX, _etc._ in various _in vitro_ and _in vivo_ studies.

Guggulsterone isolated from _Commiphora mukul_, curcumin form _Curcuma longa_, boswellin / boswellic acid from _Boswellia serrata_, salicin from _Populus tremula_, _etc._ are clinically tested and shown effective against inflammatory diseases by reducing post surgical edema, tenderness, pain; improved disease conditions of osteoarthritis and rheumatoid arthritis, _etc._ Some of the traditional formulations marketed in India, for inflammatory diseases or as immunomodulatory agents are Shallaki (_Boswellia serrata_), Hadjod (_Cissus quadrangularis_), Curril capsules (_Ocimum sanctum_), Ashwagandharista (_Withania somnifera_), Himalaya Guduchi (_Tinospora cordifolia_), Himcolin (_Vitex negundo_), _etc._ Development of standardized, safe and effective herbal formulations with proven scientific evidence can provide an alternative in treatment for inflammatory diseases. Thus, plants have the potential to serve as a source of new chemical entities for the development of future drugs in the treatment of various inflammatory diseases.

Acknowledgements

The authors express their sincere thanks to Dr. Ashok K. Chauhan, Founder President, Ritnand Balved Education Foundation (RBEF) and Amity Group of Institutions for constant support and encouragement and to Dr. Atul Chauhan, President, RBEF and Chancellor, AUUP, Noida for facilitating this work.
Conflict of interest

We declare that we have no conflict of interest.

References


