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## Abstract

**Background:** Medicinal plant and plant products have shown tremendous potentials and are used beneficially in the treatment of inflammation and in the management of diseases with significant inflammatory components. Many medicinal plants employed as anti-inflammatory and anti-phlogistic remedies lack the gastro-erosive side effects of non-steroidal anti-inflammatory drugs (NSAID) or the plethora of unwanted side effects associated with steroidal anti-inflammatory drugs. In order to harness and optimise the applications of these herbs in inflammatory diseases, there is a need to understand how these herbs produce their anti-inflammatory actions.

**Materials and Methods:** This paper is a review of some anti-inflammatory herbs and their molecular mechanisms of action. A literature search and analysis of published manuscript was employed to x-ray research findings that show how medicinal plants produce anti-inflammatory activities.

**Results:** Many studies have shown that anti-inflammatory activities of herbal extracts and herb-derived compounds are mainly due to their inhibition of arachidonic acid (AA) metabolism, cyclo-oxygenase (COX), lipo-oxygenase (LOX), pro-inflammatory cytokines, inducible nitric oxide, and transcription activation factor (NF- $\kappa$ B). Some anti-inflammatory medicinal herbs are reported to stabilize lysosomal membrane and some cause the uncoupling of oxidative phosphorylation of intracellular signalling molecules. Many have also been shown to possess strong oxygen radical scavenging activities.

**Conclusion:** Most of the mechanisms by which anti-inflammatory medicinal plants act are related and many herbal products have been shown to act through a combination of these molecular pathways.

**Key words:** Medicinal plants, antiinflammatory, mechanism of action, molecular pathways.

## Introduction

There are several proposed cellular actions or mechanisms explaining *in vivo* anti-inflammatory activity of medicinal plants. These mechanisms include antioxidative and radical scavenging activities, regulation of cellular activities of the inflammation-related cells: mast cells, macrophages, lymphocytes, and neutrophils (for instance, some inhibit histamine release from mast cells and others inhibit T-cell proliferation), modulation of the enzymatic activities of arachidonic acid (AA) metabolizing enzymes such as phospholipase A2 (PLA2), cyclooxygenase (COX), and lipoxygenase (LOX) and the nitric oxide (NO) producing enzyme, nitric oxide synthase (NOS) (Vane and Botting, 1987; Chen, 2011). Inhibitions of these enzymes by anti-inflammatory medicinal plants products (AIMP) reduce the production of AA, prostaglandins (PG), leukotrienes (LT), and NO, which are crucial mediators of inflammation (Khanapure *et al.*, 2007). Thus, the inhibition of these enzymes by AIMP is one of the important cellular mechanisms of anti-inflammation. In recent years, many lines of evidence support the idea that certain AIMP are the modulators of gene expression, especially the modulators of pro-inflammatory gene expression, thus leading to the attenuation of the inflammatory response. Here, we have highlighted the relevance of these mechanisms as they relate to the activities of herbal products used in the treatment of inflammation.

### 1.0 Inhibition of Phospholipase A2

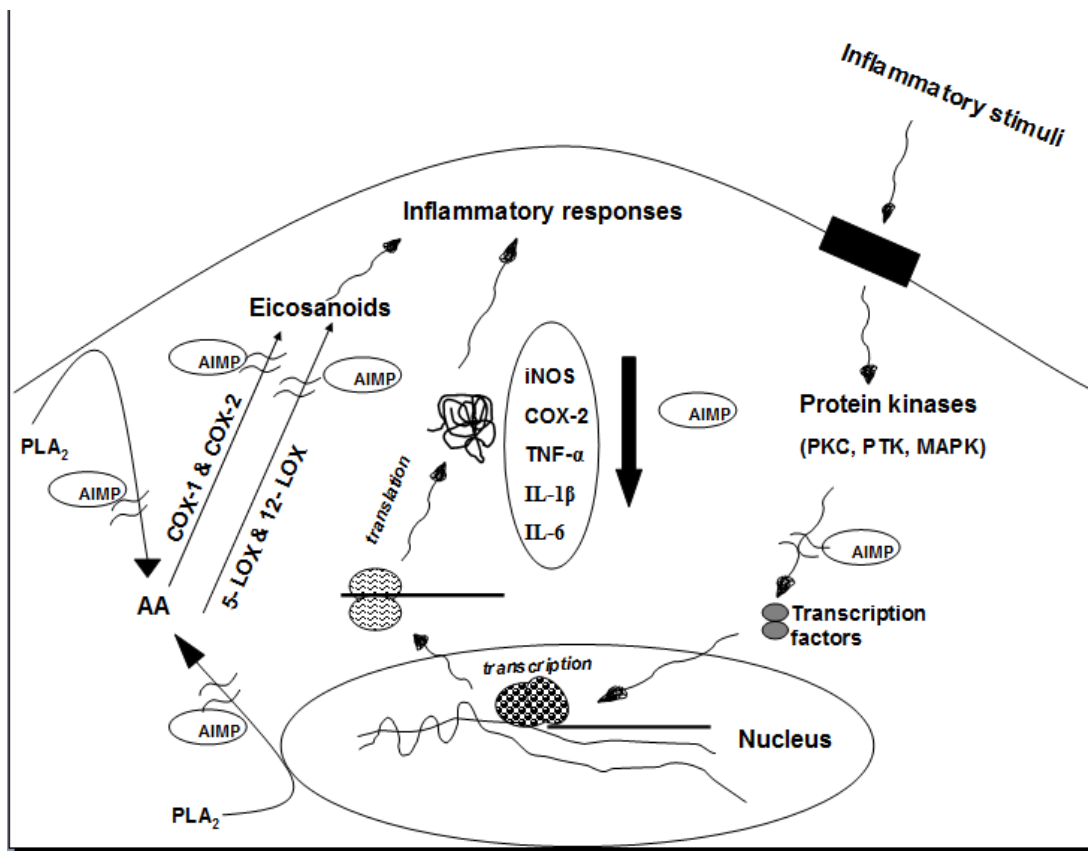
During inflammatory response, arachidonic acid (AA), a precursor of eicosanoids, is released mostly from membrane lipids in cells. The enzyme responsible for this release is Phospholipase A2 (PLA2), although some portion is attributed to the combined action of phospholipase C and diacylglycerol lipase (Ito *et al.*, 2002). AA mobilization by PLA2 and subsequent prostaglandins synthesis is considered to be a pivotal event in inflammation. Therefore, drugs that inhibit PLA2 thus block the cyclo-oxygenase (COX) and lipo-oxygenase (LOX) pathways in the AA cascade are effective in the treatment of inflammatory processes. PLA2 catalyses the hydrolysis of the acyl group attached to the 2-position of intracellular membrane phosphoglycerides which releases arachidonic acid from membrane phosphoglycerides. Arachidonic acid is the precursor of prostaglandins (PGs), thromboxanes, and leukotrienes. Some anti-inflammatory medicinal plants inhibit PLA2 (Figure 1) and this inhibition is mediated via lipocortine or by direct interaction with the enzyme itself. The former mechanism utilizes a protein known as lipocortine, the synthesis of which is induced by steroidal hormones and steroidal plant metabolite, triterpenoids (Barnes, 1998). The other mechanism involves a direct binding with the enzyme itself, a mechanism that is yet to be exploited in therapeutics but with great promise. It is known that betulinic acid, a triterpene act by direct binding to phospholipase A2 (Wiert, 2006).



The inhibitory activity of several flavonoid derivatives against AA metabolizing enzymes was initially reported in 1980 (Bauman *et al.*, 1980). Thereafter, investigators have studied the inhibitory effect of flavonoids on these enzymes (Kim *et al.*, 2004). Up to date, many isoforms of PLA2 have been discovered (Murakami and Kudo, 2004). They are mainly classified into three large categories, secretory PLA2 (sPLA2), cytosolic PLA2 (cPLA2), and calcium independent PLA2 (iPLA2). These PLA2s are distributed in wide varieties of tissues and cells. In some conditions, they are coupled to COXs depending on the cells and agonists used (Murakami and Kudo, 2004). For instance, group IIA sPLA2 was found in arthritic synovial fluid, and group IV cPLA2 are coupled to COXs and 5-LOX to produce eicosanoids (Murakami and Kudo, 2004). Therefore, a modulation of sPLA2 and/or cPLA2 activity is important in the control of inflammatory processes.

The first flavonoid inhibitor of PLA2 to be identified was quercetin, which inhibited PLA2 from human neutrophils (Lee *et al.*, 1982).

Quercetin was repeatedly found to inhibit PLA<sub>2</sub> from several sources. It inhibited PLA<sub>2</sub> from rabbit peritoneal neutrophils with an IC<sub>50</sub> of 57-100 μM (Lanni and Becker, 1985). It was also demonstrated that quercetin selectively inhibited group II sPLA<sub>2</sub> from *Vipera russelli* with less inhibition of PLA<sub>2</sub> from porcine pancreas, PLA<sub>2</sub>-IB (Lindahl and Tagesson, 1993). While flavanones including flavanone, hesperetin, and naringenin showed less inhibition, flavonols such as kaempferol, quercetin, and myricetin were found to considerably inhibit snake venom PLA<sub>2</sub>, indicating an importance of the C-ring-2,3-double bond (Welton *et al.*, 1986).

In many other studies, other herbal extracts and phytoconstituents have been reported to exhibit significant anti-inflammatory effects through an inhibition of various PLA<sub>2</sub>. Extract of *Trichilia catigua* (Meliaceae) completely inhibited PLA<sub>2</sub> at a concentration of 120 μg/ml (Barbosa *et al.*, 2004). Ethanol extract of *Baccharis uncinella* DC (Asteraceae) were reported to contains among other constituents two triterpenoids (oleanolic and ursolic acids) and one flavonoid (pectolinaringenin) which exhibited anti-inflammatory effects against inflammatory reactions induced by phospholipase A<sub>2</sub> (from *Crotalus durissus terrificus* venom) (Zalewski *et al.*, 2011). It was shown recently that the water extract of *Aloe vera* leaf skin (AVLS) extract exhibited anti-PLA<sub>2</sub> activity with an IC<sub>50</sub> = 0.22 mg/ml (Kammoun *et al.*, 2011). Also recently, it was shown that the neuroprotective effect of *Ginkgo biloba* extract (EGb761) was mediated, at least in part, through inhibition of cytosolic cPLA<sub>2</sub> activation (Zhao *et al.*, 2011). In a study to evaluate the effects of the flavonoid, quercetin, on *Crotalus durissus terrificus* secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>), it was reported that the protein was chemically modified by treatment with quercetin, which resulted in modifications in the secondary structure as evidenced through circular dichroism (Kim *et al.*, 2004). In addition, quercetin was able to inhibit the enzymatic activity and some pharmacological activities of sPLA<sub>2</sub>, including its antibacterial activity, its ability to induce platelet aggregation, and its myotoxicity by approximately 40% (Cotrim *et al.*, 2011). *Cochinchina momordica* seed extract (SKMS10) was also shown to exhibit anti-inflammatory activities by down-regulating cPLA<sub>2</sub> among other molecular mechanisms of action (Kang *et al.*, 2009).



**Figure 1: The proposed mechanism of action of anti-inflammatory medicinal plants (AIMP).** “” and “” denote enzyme inhibition and down-regulation of the expression, respectively.

## 2.0 Inhibitors of cyclooxygenases (COX)

COX that produces prostaglandins (PGs) and thromboxanes (TX) from arachidonic acid exists in two different isoforms (COX-1 and -2). COX-1 is a constitutive enzyme existing in almost every cell type, catalysing the conversion of AA into cytoprotective PGs and blood pro-aggregatory TXs. On the other hand, COX-2 is an inducible enzyme and in most cases causes the production of large amount of PGs (Needleman and Isakson, 1997). COX-2 is highly expressed in the inflammation-related cell types including macrophages and mast cells, when they are stimulated with pro-inflammatory cytokines and/or bacterial lipopolysaccharide (LPS) (Needleman and Isakson, 1997). Inhibition of both COX-1 and COX-2 has been found to be the molecular target of many anti-inflammatory herbal extracts and herb-derived compounds (Figure 1). COX-2 that produces PGs is closely associated with inflammatory disorders of acute as well as chronic types. Actually, COX-2 selective inhibitors possess anti-inflammatory activity with reduced side effects frequently seen with COX-1/COX-2 non-selective inhibitors (McMurray and Hardy, 2002).

Devil's claw, *Harpagophytum procumbens* DC (Pedaliaceae) used in South Africa for the management of pain and inflammation is an example of medicinal plant whose anti-inflammatory activities is based on reported inhibition of COX (Kundu *et al.*, 2005). Anti-inflammatory effects of seven lignans and one dihydrochalcone isolated from the leaves of two Lauraceae species (*Pleurothyrium cinereum* and *Ocotea macrophylla*), were found to be potent inhibitors of COX-2/5-LOX (Coy-Barrera and Cuca-Suarez, 2011). Ethyl acetate-soluble extract of the stems of *Macrocochilus pomiferus* was found to inhibit COX-2 (Su *et al.*, 2004). (S)-coriolic acid and (+/-)-glycerol 1-monolinolate isolated from ethylacetate-soluble extract of the seeds of *Hernandia ovigera* showed selective inhibitory activity with cyclooxygenase-2 (Jang *et al.*, 2004). The compound, 2, 4, 5-trimethoxybenzaldehyde isolated from *Daucus carota* seed extracts inhibited COX-2 enzyme very significantly at a concentration of 100 µg/ml (Momin *et al.*, 2003). Some flavonoids such as luteolin, 3', 4'-dihydroxyflavone, galangin, and morin were found as inhibitors of COX (Bauman *et al.*, 1980). When their structural activity relationships were compared, several flavone derivatives such as flavone and apigenin were found to be COX inhibitors, while some flavonol derivatives such as quercetin and myricetin were preferential LOX inhibitors. Also, certain flavonoids such as flavone, kaempferol, and quercetin were repeatedly found to be inhibitors of COX from rat peritoneal macrophages (Welton *et al.*, 1986). After these reports, many studies have been done to figure out the inhibitory activity of flavonoids on COX, mostly COX-1. For instance, flavonoids such as quercetin and xanthomicrol were reported to inhibit sheep platelet COX-1; while the IC<sub>50</sub> values of flavones such as cirsiolol, hypolaetin, and diosmetin were more than 100 µM (Ferrandiz *et al.*, 1990). Furthermore, flavones and flavonols including chrysin, flavone, galangin, kaempferol, and quercetin were repeatedly revealed to inhibit TXB2 formation from mixed leukocyte suspension probably by COX-1 inhibition (Laughton *et al.*, 1991).

### 3.0 Inhibition of lipoxygenases (LOX)

Arachidonate 5-lipoxygenase is the key enzyme in leukotriene biosynthesis and catalyses the initial steps in the conversion of arachidonic acid to biologically active leukotrienes. Leukotrienes are considered as potent mediators of inflammatory and allergic reactions, and regarding their pro-inflammatory properties the inhibition of 5-lipoxygenase pathway is considered to be interesting in the treatment of a variety of inflammatory diseases. Lipoxygenases (LOX) are present in leucocytes, tracheal cells, keratinocytes, and the epithelium of stomach and airways and they catalyse the introduction of a molecule of oxygen to the 5-position of AA to give the intermediate 5(S)-hydroxy-(6E, 8Z, 11Z, 14Z)-eicosatetraenoic acid, 5-HETE, which is immediately followed by the re-arrangement of 5-HETE to leukotrienes. This is another target for anti-inflammatory medicinal plants that inhibit the biogenesis of leukotrienes and 5-HETE (Figure 1). Medicinal plants that inhibit LOX hold some other useful therapeutic potential in the treatment of asthma, psoriasis, arthritis, allergic rhinitis, cancer, osteoporosis, and atherosclerosis.

**Table 1:** Examples of some anti-inflammatory medicinal plants reported to inhibit the 5-lipoxygenase.

Plant species/Family	Extract/plant part used	Active constituent/fraction	References
<i>Longifolia nees</i> (Asteracantha)	Methanol seed extract		Kumar et al., 2000
<i>Gomphrena perennis</i> L. (Amaranthaceae)	Methanol extract of aerial part	Ethylacetate fraction	Matsunaga et al., 2000
<i>Vitis amurensis</i> Rupr. (Ampelidaceae)	Ethanol root extract	Amurensin	Huang et al., 2000
<i>Pistacia terebinthus</i> L. (Anacardiaceae)	Methanol extract of gall	Masticadienolic acid, Morolic acid, Oleanolic acid	Giner-Larza et al., 2001; Giner-Larza et al., 2002
<i>Toxicodendron radicans</i> L. (Anacardiaceae)	Ethanol fruit extract	Urushiol	Wagner et al., 1989
<i>Xylopiia frutescens</i> Aubl (Annonaceae)	n-Hexane seed extract		Braga et al., 2000
<i>Ilex aquifolium</i> L. (Aquifoliaceae)	Ethanol leaf extract		Müller et al., 1998
<i>Achillea ageratifolia</i> Boiss. (Asteraceae)		Hexadeca-2E,7Z-diene-10-ynoic acidpyrrolide	Müller-Jakic et al., 1994
<i>Echinacea purpurea</i> (L.) Moench (Asteraceae)	Root	Polyunsaturated isobutylamides	Wagner et al., 1989
<i>Cannabis sativa</i> L (Cannabinaceae)		Cannipren	El Sohly et al., 1990
<i>Phyllanthus emblica</i> (Euphorbiaceae)	Diethyl ether leaf extract		Ihantola-Vormisto et al., 1997
<i>Cassia fistula</i> L. (Fabaceae)	Methanol fruit extract		Sunil Kumar and Müller, 1998
<i>Salvia aethiopis</i> L. (Lamiaceae)	Root	Aethiopinone	Benrezzouk et al., 2001
<i>Allium cepa</i> L. (Liliaceae)	Chloroform extract of the bulb	Methyl-1-propenylthiosulfinate, Propyl-1-propenylthiosulfinate, Cepaenes	Wagner et al., 1990
<i>Allium sativum</i> L. (Liliaceae)	Chloroform extract of the bulb	Methylajoene, Dimethylajoene, Ajoene, Allicin	Sendl et al., 1992
<i>Ardisia japonica</i> Blume (Myrsinaceae)	Methanol extract of the wood	Ardisianone A and B, Maesanin	Fukuyama et al., 1993
<i>Punica granatum</i> L. (Punicaceae)	Seed oil	Flavonoids	Schubert et al., 1999
<i>Solanum xanthocarpum</i> Schrad. (Solanaceae)	Methanol leaf extract		Kumar et al., 2000
<i>Curcuma longa</i> L. (Zingiberaceae)	Petroleum ether extract of the rhizome	Curcumine	Ammon et al., 1992

A potential source for new 5-lipoxygenase inhibitors is undoubtedly provided by medicinal plants used in traditional medicine. The *Ardisia* species and other Myrsinaceae family produce very unusual series of dimeric benzoquinones known as ardisiaquinones, which are known to inhibit the enzymatic activity of 5-LOX. This feature could explain the frequent use of *Ardisia* species to treat inflammatory conditions. One such compound is Ardisiaquinone G which was isolated from *Ardisia teysmanniana* and is known to inhibit LOX (Yang *et al.*, 2001; Fuiishi *et al.*, 2001). The Asteraceae family is one of the richest source of LOX inhibitors and three different types of principles exhibiting remarkable LOX inhibition have been isolated and characterised. Helenalin, a sesquiterpene lactone, which can be isolated from several plant species of the Asteraceae family possess potent anti-inflammatory and antineoplastic agent. Helenalin inhibited 5-LOX (IC<sub>50</sub> 9 mM after 60 min pre-incubation) in a concentration and time-dependent fashion in human granulocyte culture (Tornhamre *et al.*, 2001). Polyacetylenes from *Artemisia monosperma* showed some levels of activity against LOX (Stavri *et al.*, 2005). The third groups of LOX inhibitors in this family are the bornyl cinnamoyl derivatives from *Verbenisa species*, such as bornyl caffeate from the South American herb *Verbenisa turbacensis* Kunth. Another compound, friedelin isolated from the bark of *Commiphora berryi* showed significant soybean lipoxygenase (SBL) inhibitory activity with IC<sub>50</sub> of 35.8 μM (Kumari *et al.*, 2011).

Generally, an enormous number of different plant-derived compounds from various species have been found to interfere with 5-LOX activities. In general, it appears that lipophilic, often fatty acid-like compounds with (i.e. phenols) and without (i.e. triterpenes and polyacetylenes) reducing properties interfere with 5-LOX and the majority are phenolic structures including flavonoids, quinones, (that become hydroxylated to hydroquinones), hydroxylated coumarines, and many other polyphenols. Apparently a combination of iron-reducing and iron-chelating properties of these phenolic compounds is responsible for 5-LOX inhibitions (Werz, 2007)

#### 4.0 Inhibition of nitric oxide synthetase (NOS)

The NOS is an important enzyme involved in the regulation of inflammation, vascular tone, neurotransmission, and cancer. NO is a toxic free radical that can cause substantial tissue damage in high concentration. In stroke, large amount of NO is released from nerve cells and causes extensive damage to surrounding tissues including neurones and myocytes (Shah *et al.*, 2011)

The NO is biochemically generated via oxidation of the terminal guanidine nitrogen atom from L-arginine by NOS. NO is one of the cellular mediators of physiological and pathological process (Moncada *et al.*, 1991; Nathan, 1992; Mollace *et al.*, 2005). Three different isoforms of NOS are now recognised: endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS) (Venema *et al.*, 1997; Stuehr, 1999). The former two are constitutively expressed in the body, whereas the latter type is an inducible enzyme highly expressed by inflammatory stimuli in certain cells such as macrophages. iNOS is involved in overproduction of NO in response to pro-inflammatory mediators such as interleukine-1β (IL-1β), tumour necrosis factor-α (TNF-α), and bacterial lipopolysaccharide (LPS). While a small amount of NO synthesized by eNOS and nNOS is essential for maintaining normal body function (homeostasis), a significantly increased amount of NO synthesized by iNOS participates in provoking inflammatory process and acts synergistically with other inflammatory mediators (Mollace *et al.*, 2005). Many herbal extracts and compounds of herbal origin have shown strong inhibition of iNOS and NO over-production (Figure 1). Search for herb-based compounds which can reduce NO production by inhibiting iNOS without affecting eNOS or nNOS is very desirable for anti-inflammatory agents.

Recently, we reported the inhibition of inducible NO production by the methanol extract of *Spondias mombin* (Nworu *et al.*, 2011). LPS-stimulated NO production by bone marrow-derived macrophages was significantly inhibited at 25 μg/ml and 100 μg/ml of the methanol extract (Nworu *et al.*, 2011). Artemisinin, a sesquiterpene used in the treatment of malaria was demonstrated to inhibit NO synthesis in cytokine-stimulated human astrocytoma T67 cells (Aldieri *et al.*, 2003). Several studies suggest that sesquiterpene lactones inhibit NO synthetase. For example, ambrosanolides-type sesquiterpene known as cumanin isolated from *Ambrosia psilostachya* inhibited NO activity with an IC<sub>50</sub> value of 9.38 μM (Lastra *et al.*, 2004). Ursolic acid and 2α-hydroxy ursolic acid, triterpenes from *Prunella vulgaris* L., inhibited NO from murine leukaemic monocytes macrophages (RAW 264.7) with IC<sub>50</sub> of 17 μM and 27 μM, respectively (Ryu *et al.*, 2000). Bigelovin, 2,3-dihydroaromaticin, and ergolide isolated from *Inula species* showed potent inhibition of LPS-induced NOS in RAW 264.7 cells with IC<sub>50</sub> values of 0.46 mM, 1.05 mM, and 0.69 mM, respectively (Lee *et al.*, 2002).

Inhibition of iNOS is not a general behaviour of flavonoids, but they inhibit NO production which means they down-regulate the expression of iNOS and not the activity of already produced enzymes. Flavone and several other amino-substituted flavones were reported to inhibit NO production (Krol *et al.*, 1995). Flavonoids that down-regulate iNOS expression include flavones such as apigenin and oroxylin A; flavonols such as kaempferol and quercetin; biflavonoids such as bilobetin and ginkgetin, and some prenylated flavonoid such as sanggenons and kuwanon C (Kim *et al.*, 2004).

#### 5.0 Inhibitions of pro-inflammatory cytokines

Several cytokines are associated with inflammatory diseases. A number of pro-inflammatory cytokines also regulate inflammatory reactions either directly or by their ability to induce the synthesis of cellular adhesion molecules or other cytokines in certain cell types. The major pro-inflammatory cytokines that are responsible for early responses are IL1-alpha (IL-1α), IL1-beta (IL-1 β), IL-6, and TNF-alpha (TNF-α). Other pro-inflammatory mediators include leukemia inhibitory factor, (LIF), interferon-gamma (IFN-γ), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), tumour growth factor-beta (TGF-β), granulocyte macrophage colony-stimulating factor (GM-CSF), IL-8, IL-11, IL-12, IL-17, IL-18, and a variety of other chemokines that chemoattract inflammatory cells. Inhibition of the expression of these cytokines has been demonstrated as the target for many anti-inflammatory medicinal plants and their compounds (Figure 1; Table 1). Steroidal anti-inflammatory drugs (SAIDs) such as prednisolone and dexamethasone are also known to reduce the production of these pro-inflammatory cytokines (Newton, 2000).

#### 6.0 Modulation of pro-inflammatory gene expression

The cellular mechanisms through which anti-inflammatory medicinal plants modulate gene expression have also been extensively studied. The most prominent points of cellular regulation affected by these herbs and herb-based compounds are the various protein kinases involved in signal transduction including protein kinase C (PKC) and mitogen activated protein kinase (MAPK) (Figure 1). Through the inhibition of these enzymes, DNA-binding capacity of transcription factors such as nuclear factor-κB (NF-κB) or activator protein-1 (AP-1) is



regulated (Kim *et al.*, 2004). Thereby, the expression rate of the target gene is controlled. Flavonoids inhibit the enzyme activities of various signal transduction protein kinases (Kim *et al.*, 2004). The best example is PKC inhibition (Ferriola *et al.*, 1989) and protein tyrosine kinase inhibition (Chang and Geahlen, 1992) by various flavonoid derivatives. MAPKs are also key elements in signal transduction. In macrophages, LPS activates three kinds of MAPKs, extracellular signal related kinase (ERK), p38 MAPK, and Jun N-terminal kinase/ stress activated protein kinase (JNK/SAPK) (Weinstein *et al.*, 1992). It was shown that a plant flavonoids, quercetin, inhibited inducible nitric oxide synthetase (iNOS) expression by inhibiting p38 MAPK (Wadsworth and Koop, 2001) and inhibited TNF- $\alpha$  -induction from LPS-induced RAW cells by inhibiting JNK/SAPK, leading to the inhibition of AP-1-DNA binding (Wadsworth *et al.*, 2001). In a separate pathway, quercetin inhibited ERK 1/2 and p38 MAPK to regulate the post-transcriptional level of TNF- $\alpha$ . It has been shown that quercetin inhibited NF- $\kappa$ B activation by ERK and p38 kinase inhibition (Cho *et al.*, 2003). Another plant flavonoid, wogonin, inhibited monocyte chemotactic protein-1 gene expression of 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced human endothelial cells by AP-1 repression through ERK 1/2 and JNK inhibition (Chang *et al.*, 2001).

Studies have shown clearly that anti-inflammatory medicinal plants inhibited the expression of various inflammation-related proteins/enzymes, at least partly, by suppressing activation of transcription factors such as NF- $\kappa$ B and AP-1 (Kim *et al.*, 2004). These suppressions might be mediated via inhibition of several protein kinases involved in the signal transduction pathway.

**Table 2:** Examples of some anti-inflammatory medicinal plants reported to decrease the expression of some pro-inflammatory cytokines

Cytokine	Medicinal plant	Model used	References
<b>IL-1</b>	<i>Curcuma longa</i>	<i>In vitro</i> , Human	Chan, 1995
	<i>Polygala tenuifolia</i>	<i>In vitro</i> , Murine	Kim et al, 1998
	<i>Smilax glabra</i>	<i>Ex vivo</i> , Human	Jiang and Xu, 2003
	<i>Uncaria tomentosa</i>	<i>In vitro</i> , Murine	Lemaire et al, 1999
<b>IL-1<math>\alpha</math></b>	<i>Allium sativum</i>	<i>In vitro</i> , Human	Hodge et al, 2002
<b>IL-1<math>\beta</math></b>	<i>Ampelopsis brevipedunculata</i>	<i>In vitro</i> , Human	Kuo et al, 1999
	<i>Harpagophytum procumbens</i>	<i>In vitro</i> , Human	Fiebich et al, 2001
	<i>Ludwigia octovalvis</i>	<i>In vitro</i> , Human	Kuo et al, 1999
	<i>Pinus maritima</i>	<i>In vitro</i> , Murine	Cho et al, 2001
	<i>Rhus semialata</i>	<i>In vitro</i> , Human	Kuo et al, 1999
	<i>Tabernaemontana divaricata</i>	<i>In vitro</i> , Human	Kuo et al, 1999
<b>IL-6</b>	<i>Allium sativum</i>	<i>In vitro</i> , Human	Hodge et al, 2002
	<i>Astragalus membranaceus</i>	<i>In vitro</i> , Human	Shon et al, 2002
	<i>Coptis spp.</i>	<i>In vivo</i> , Murine	Iizuka et al, 2000
	<i>Harpagophytum procumbens</i>	<i>In vitro</i> , Human	Fiebich et al, 2001
<b>TNF</b>	<i>Acanthopanax senticosus</i>	<i>In vitro</i> , Murine	Yi et al, 2002
	<i>Acer nikoense</i>	<i>In vitro</i> , Murine	Fujiki et al, 2003
	<i>Allium sativum</i>	<i>In vitro</i> , Human	Hodge et al, 2002
	<i>Ampelopsis</i>	<i>In vitro</i> , Human	Kuo et al, 1999
	<i>Curcuma longa</i>	<i>In vitro</i> , Human	Chan, 1995
	<i>Dichroa febrifuga</i>	<i>In vitro</i> , Murine	Kim et al, 2000
	<i>Harpagophytum procumbens</i>	<i>In vitro</i> , Human	Fiebich et al, 2001
	<i>Ludwigia octovalvis</i>	<i>In vitro</i> , Human	Kuo et al, 1999
	<i>Perilla frutescens</i>	<i>In vivo</i> , Murine	Ueda and Yamazaki, 1997
	<i>Polygala tenuifolia</i>	<i>In vitro</i> , Murine	Hong et al, 2002
	<i>Polygala tenuifolia</i>	<i>In vitro</i> , Murine	Kim et al, 1998
	<i>Rhus semialata</i>	<i>In vitro</i> , Human	Kuo et al, 1999
	<i>Rosa davurica</i>	<i>In vitro</i> , Murine	Kim et al, 1999
	<i>Scutellaria baicalensis</i>	<i>In vitro</i> , Murine	Kim et al, 2001
	<i>Sinomenium acutum</i>	<i>In vitro</i> , Murine	Kim et al, 1999
	<i>Smilax glabra</i>	<i>In vivo</i> , Murine	Jiang and Xu, 2003
	<i>Tabernaemontana divaricata</i>	<i>In vitro</i> , Murine	Kuo et al, 1999
<i>Tinospora cordifolia</i>	<i>In vivo</i> , Murine	Dhuley, 1997	
<i>Uncaria tomentosa</i>	<i>In vitro</i> , Murine	Sandoval et al, 2002	
<i>Withania somnifera</i>	<i>In vivo</i> , Murine	Davis and Kuttan, 1999	
<b>IL-8</b>	<i>Coriolus versicolor</i>	<i>In vitro</i> , Human	Hsieh et al, 2002
	<i>Curcuma longa (Curcumin)</i>	<i>In vitro</i> , Human	Hidaka et al, 2002
	<i>Paeonia suffruticosa</i>	<i>In vitro</i> , Bovine	Oh et al, 2003
<b>IL-12</b>	<i>Allium sativum</i>	<i>In vitro</i> , Human	Hodge et al, 2002

## 7.0 SOME NIGERIAN ANTI-INFLAMMATORY HERBS

The use of anti-inflammatory herbs for health improvement has a long and successful history in traditional medicine in Nigeria. Many herbal preparations are used to treat fever and inflammation in the traditional folklore medicine. The hope of discovering novel therapeutic agents capable of suppressing, reducing, or relieving pain as well as inflammation is high.

Many human and animal diseases, such as arthritic disorders, lupus erythematosus, asthma, bronchitis, inflammatory bowel disease,

ulcerative colitis, pancreatitis, ascities, hepatitis, cancer, infections are associated with different degrees of inflammation. Malaria and malaria fever can also be viewed as inflammatory disorders (Perlmann and Troye-Blomberg, 2000). The infection of the liver and the red blood cells by the hepatic and erythrocytic plasmodia schizonts leads to severe inflammation of hepatocytes. The clinical manifestations of malaria, fever and chills, are associated with the synchronous rupture of the infected erythrocytes and the release of metabolites with potent pro-inflammatory activities (Perlmann and Troye-Blomberg, 2000). For this reason, antipyretic and anti-inflammatory therapies are often essential in the treatment of malaria. This could explain the benefits and instant relief experienced by malaria patients when they use anti-inflammatory medications, including some herbal medications with known antiphlogistic properties.

**Table 3:** Some local medicinal plants used in folklore medicine to treat inflammation, rheumatism, and fever

Plant	Family	Parts of plant/ and preparation
<i>Gymnema sylvestris</i>	Asclepiadaceae	leaf
<i>Acanthus montanus</i> (Nees)	Acanthaceae	Infusion of leaves taken 3 times daily
<i>Schwenkia americana</i> (Linn)	Solanaceae	Whole plant; Crushed and used as poultice
<i>Zanha golungensis</i> Hiern	Sapindaceae	Leaves; Chopped fresh leaves applied on inflamed sores
<i>Cardiospermum grandio</i> Florum Swart	Sapindaceae	Whole plant; leaves mixed with castor oil and used orally to treat rheumatism and lumbago
<i>Paullinia pinnata</i> Linn	Sapindaceae	Boil leaves and drink as desired
<i>Allophylus africana</i> P. Beauv	Sapindaceae	Bark, root, and leaves; boiled in water and used as tea
<i>Achyranthes aspera</i> Linn	Amaranthaceae	Whole plant; Boiled in water and used as tea
<i>Cyathula prostrata</i> (L.) Blume	Amaranthaceae	Leaves; Crushed with alcohol and used as poultice
<i>Alternanthera repens</i> (L.) Kuntze	Amaranthaceae	Leaves; Decoction used as tea
<i>Monodora myristica</i> (Gaertn) Dumal	Annonaceae	Leaves and bark; Chopped fresh leaves applied on fresh sores
<i>Ocimum basilicum</i> Linn	Labiatae	Whole plant; Infusion drunk once daily
<i>Entadrophragma cylindricum</i> Sprague	Meliaceae	Bark; macerated in alcohol and used as a drink
<i>Ekebergia senegalensis</i> A. Juss	Meliaceae	Leaves; Infusion drunk as tea
<i>Lecaniodiscus cupanioides</i> (Planch)	sapindaceae	Roots and leaves; Extracts are taken orally for a long time for rheumatism and arthritis
<i>Chassalia kolly</i> (Schumach.) Heppner	Rubiaceae	Leaves; Extract of bark taken as tea
<i>Securidaca longipedunculata</i> Fres	Polygalaceae	Leaves and roots; Paste of root bark and leaves is applied externally on sores and to cure rheumatism
<i>Strophanthus hispidus</i> Oliv	Apocynaceae	Leaves; Decoction taken as tea
<i>Astonia boonei</i> De Wild	Apocynaceae	Leaves, sap, and stem bark; Topical application of the latex on the swollen part and leaf infusion drunk as desired
<i>Funtumia Africana</i> (Benth) Stapf.	Apocynaceae	Leaves; Decoction taken as tea
<i>Abrus precatorius</i> L.	Fabaceae	Leaves and stem; decoction and infusion are drunk
<i>Ageratum conyzoides</i> Linn	Asteraceae	Leaves and flowers; fresh leaves applied on fresh sores and infusion drunk
<i>Tetrapleura tetraptera</i> (Taub)	Fabaceae	Fruits; decoction and infusion drunk
<i>Alchornea cordifolia</i>	Euphorbiaceae	Leaves; Ground leaves applied to wounds and aches
<i>Aspillia africana</i> C.D. Adams	Compositae	Chopped leaves applied on inflamed sores
<i>Combretum racemosum</i> P. Beauv	Combretaceae	Leaves; Leaf infusion administered orally
<i>Salacia palleescens</i> Oliv	Celastraceae	Leaves; Crushed with alcohol and used as poultice
<i>Desmodium triflorum</i> DC	Papilionaceae	Whole plant; a powder is made and taken with pap
<i>Plumbago zeylanica</i> Linn	Plumbaginaceae	Roots and leaves; Decoction is drunk
<i>Peperomia pellucida</i> L. HBK	Piperaceae	Aerial part; Squeezed juice used for eye inflammation and headaches
<i>Anchomanes difformis</i> Engl	Araceae	Aqueous decoction of the Rhizome taken orally
<i>Anthocleista d'jalonsensis</i> A. Chev	Loganiaceae	Ethanol decoction of stem bark taken orally
<i>Diodium sarmentosa</i> Swartz	Rubiaceae	Aqueous leaf extract taken orally and applied locally
<i>Hexalobus monopetalous</i> Engl	Anonaceae	Aqueous infusion of root bark extract taken orally
<i>Mitracarpus scarber</i> Zucc	Rubiaceae	Aqueous decoction of leaf extract taken orally
<i>Morinda lucida</i> Benth	Rubiaceae	Alcoholic infusion of leaf taken orally and applied externally
<i>Palisota hirsuta</i> K. Schum	Commelineaceae	Aqueous infusion of leaf taken orally
<i>Pentaclethra macrophylla</i> Benth	Mimosaceae	Aqueous decoction of seed taken orally
<i>Securidaca longipedunculata</i> Fresen	Polygalaceae	Aqueous infusion of leaf taken orally and applied externally
<i>Strophamus hispidus</i> Oliv	Apocynaceae	Aqueous decoction of leaf extract taken orally
<i>Emilia sonchifolia</i> Linn	Asteraceae	Fresh juice squeezed from the leaves promote wound healing and is commonly applied to fresh wounds
<i>Spondias mombin</i> Linn	Anacardiaceae	Decoction of the leaves is taken orally and commonly used to treat laryngitis, sour throat, and tooth decay
<i>Ficus exasperata</i>	Moraceae	Leaves of <i>F. exasperata</i> are mashed and prepared as poultices that are placed on swellings, wounds, and arthritic joints to relieve swelling. The leaf and stalk are used to mitigate itching/inflammation as well.

The treatment of rheumatic disorders (inflammation) is one area in which Nigerian traditional medical practitioners enjoy patronage and success. A good number of plant species are available for this purpose, and the method of usage differs from one area to another. The most common practice involves taking the extracts orally as decoctions or infusions; washing the inflamed part (e.g. swollen knee) with the extracts; applying squeezed herb as poultice on inflamed part (Akah and Nwambie, 1994; Akah *et al.*, 2003a,b; Akah *et al.*, 2004, 2007). Evaluation and understanding the mechanisms behind the anti-inflammatory activities of some of these medicinal plants has been the focus of some of our recent studies (Nworu *et al.*, 2011, 2012, 2013; Okoye *et al.*, 2013). These medicinal plants have been the focus. Some of these local medicinal plants which have been used in folklore medicine to treat inflammation, fever, and rheumatic ailments are shown in Table 3.

## 8.0 Conclusion

Inflammation acts as a central executor in the pathogenesis of many diseases such as rheumatoid arthritis, arteriosclerosis, myocarditis, infections, cancer, metabolic disorders, and many more. Monocytes and macrophages are the key players in inflammatory responses and are also the major sources of pro-inflammatory mediators and enzymes including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukins (ILs), cyclooxygenase (COX), and nitric oxide synthase (NOS). These genes of pro-inflammatory mediators are strongly induced during inflammation and are responsible for its initiation and persistence. TNF- $\alpha$  and IL-1 $\beta$  are the cytokines that act as signalling molecules for immune cells and coordinate the inflammatory responses. Cyclooxygenase-2 (COX-2) is an enzyme which is necessary for the production of pro-inflammatory prostaglandins and thus has been a target for many present anti-inflammatory medicinal plants. Nitric oxide (NO) is a free radical that mediates many physiological and pathophysiological processes, including neurotransmission and inflammation. Expression of the inducible isoform of NOS (iNOS) in activated macrophages is mainly responsible for production of pathological concentration of NO during inflammation. Therefore suppression of iNOS synthetase expression is an important target through which many anti-inflammatory medicinal plants mediate their activities. It is established that nuclear factor- $\kappa$ B (NF- $\kappa$ B) and AP-1 play the most important roles in the immune system. NF- $\kappa$ B is reported to regulate the expression of nearly all inflammatory mediators involved in inflammation. Nuclear translocation of NF- $\kappa$ B and AP-1 in response to various pro-inflammatory stimuli is associated with the activation of inflammatory cascade and therefore, these transcriptional factors are primary target of many anti-inflammatory medicinal plants and their compounds.

Since anti-inflammatory medicinal plant extracts are usually multi-component, it is likely that they act on multiple targets to impact the complex equilibrium of whole cellular networks of immune cells. This could be more favourably than agents that act on a single target since complementary actions on many genes might be needed to modify inflammatory disease processes. In other words, the efficacy of herbal therapy and herb-based anti-inflammatory compounds might depend on the perturbation of more than one target.

## References

1. Akah PA, Nwambie AI (1994). Evaluation of Nigerian traditional medicines: 1. Plants used for rheumatic (inflammatory) disorders, J. Ethnopharmacol. 42: 179-182.
2. Akah PA, Ezike AC, Nwafor SV, Okoli CO, Enwerem NM (2003a). Evaluation of the anti-asthmatic property of *Asytasia gangetica* leaf extracts. J. Ethnopharmacol. 89: 25-36.
3. Akah PA, Okoli CO, Nwafor SV (2003b). Anti-inflammatory plants. J. Natr. Remed. 3: 1-30.
4. Akah PA, Okoli CO (2004). Mechanism of the anti-inflammatory activity of the leaf extract of *Culcasia scandens*. P. Baeuv (Araceae). Pharm. Biochem. Bev. 79: 473-481.
5. Akah PA, Okpi O, Okoli CO (2007). Evaluation of the anti-inflammatory, analgesic and antimicrobial activities of the bark of *Afzelia Africana*. Nig. J. Nat. Prod. Med. 11: 48-52.
6. Ammon HPT, Anazodo MI, Safayhi H, Dhawan BN, Srimal RC (1992). Curcumin: a potent inhibitor of leukotriene B4 formation in rat peritoneal polymorphonuclear neutrophils (PMNL). Planta Med 58: 226.
7. Amos S, Okwuasaba FK, Gamaniel K, Akah PA, Nwambebe C. Anti-inflammatory and muscle relaxant effects of aqueous extract of *Pavetta cressipes* leaves. Fitoterapia 69: 425-428.
8. Barbosa NR, Fischmann L, Talib LL, Gattaz WF (2004). Inhibition of platelet phospholipase A2 activity by catuaba extract suggests anti-inflammatory properties. Phytother Res. 18(11):942-944.
9. Bauman J, Bruchhausen FV, Wurm G (1980). Flavonoids and related compounds as inhibitors of arachidonic acid peroxidation. Prostaglandins. 20:627-639.
10. Benrezzouk R, Terencio MC, Ferrandiz ML, Hernandez-Perez M, Rabanal R, Alcaraz MJ (2001). Inhibition of 5-lipoxygenase activity by the natural anti-inflammatory compound aethiopinone. Inflamm Res 50: 96-101.
11. Braga FC, Wagner H, Lombardi JA, Braga de Oliveira A (2000). Screening Brazilian plant species for in vitro inhibition of 5-lipoxygenase. Phytomedicine 6: 447-452.
12. Chan MM (1995). Inhibition of tumor necrosis factor by curcumin, a phytochemical. Biochem Pharmacol 49:1551-1556.
13. Chang CJ, Geahlen RL (1992). Protein-tyrosine kinase inhibition: mechanism-based discovery of antitumor agents. J Nat Prod. 55:1529-1590.
14. Chang YL, Shen JJ, Wung BS, Chen JJ, Wang DL (2001). Chinese herbal remedy wogonin inhibits monocyte chemotactic protein-1 gene expression in human endothelial cells. Mol Pharmacol. 60: 507-513.
15. Chen S (2011). Natural products triggering biological targets - a review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis. Curr Drug Target 12(3):288-301.
16. Cho KJ, Yun CH, Packer L, Chung AS (2001). Inhibition mechanisms of bioflavonoids extracted from the bark of *Pinus maritima* on the expression of pro-inflammatory cytokines. Ann N Y Acad Sci 928:141-156.
17. CS, Song JC, Jeong KS (2003). Quercetin suppresses pro-inflammatory cytokines production through MAP kinases and NF-KB pathway in lipopolysaccharide-stimulated macrophage. Mol Cell Biochem. 243:153-160.
18. Cotrim CA, de Oliveira SC, Diz Filho EB, Fonseca FV, Baldissera L Jr, Antunes E, Ximenes RM, Monteiro HS, Rabello MM, Hernandes MZ, de Oliveira Toyama D, Toyama MH (2011). Quercetin as an inhibitor of snake venom secretory phospholipase A2. Chem Biol Interact. 89(1-2):9-16.
19. Coy-Barrera ED, Cuca-Suarez LE (2011). In vitro anti-inflammatory effects of naturally-occurring compounds from two Lauraceae

- plants. An Acad Bras Cienc. Oct 21. pii: S0001-37652011005000044.
20. Crofford LJ, Oates JC, McCune WJ, Gupta S, Kaplan MJ, Catella-Lawson F, Morrow JD, McDonagh KT, Schmaier AH (2000). Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase 2 inhibitors. A report of four cases. *Arthritis Rheum.* 43: 1891–1896.
  21. Davis L, Kuttan G (1999). Effect of *Withania somnifera* on cytokine production in normal and cyclophosphamide treated mice. *Immunopharmacol Immunotoxicol* 1999;21:695-703.
  22. Dhuley JN (1997). Effect of some Indian herbs on macrophage functions in ochratoxin A treated mice. *J. Ethnopharmacol.* 58:15-20.
  23. Ekpendu TO, Akah PA, Adesomuju AA, Okogun JI (1994). Anti-inflammototy and anti- microbial activities of *Mtracarpus scaber* Int. J. Pharmacog. 32: 191-196
  24. El Sohly H, Little T, El Sohly JR, El Sohly M. (1990). Canniprene: a prototype anti-inflammatory natural product. *Planta Med* 56: 662–663.
  25. Ferrandiz ML, Ramachandran Nair AG, Alcaraz MJ (1990). Inhibition of sheep platelet arachidonate metabolism by flavonoids from Spanish and Indian medicinal herbs. *Pharmazie.* 45:206–208.
  26. Ferriola PC, Cody V, Middleton E (1989). Protein kinase C inhibition by plant flavonoids. Kinetic mechanisms and structural-activity relationships. *Biochem. Pharmacol.* 38:1617–1624.
  27. Fiebich BL, Heinrich M, Hiller KO, Kammerer N (2001). Inhibition of TNF-alpha synthesis in LPS-stimulated primary human monocytes by Harpagophytum extract SteiHap 69. *Phytomedicine* 8:28-30.
  28. Fujiki H, Suganuma M, Kurusu M, Okabe S, Imayoshi Y, Taniguchi S, Yoshida T (2003). New TNF-alpha releasing inhibitors as cancer preventive agents from traditional herbal medicine and combination cancer prevention study with EGCG and sulindac or tamoxifen. *Mutat. Res.* 523-524:119-125.
  29. Fukuishi N, Takada T, Fukuyama Y, Akagi M (2001). Antiallergic effect of ardisiaquinone A: a potent 5-lipoxygenase inhibitor. *Phytomedicine* 8:460-464.
  30. Fukuyama Y, Kiriyama Y, Okino J, Kodama M, Iwaki H, Hosozawa S, Matsui K (1993). Naturally occurring 5-lipoxygenase inhibitor. II. Structures and syntheses of ardisianones A and B, and maesanin, alkenyl-1, 4 benzoquinones from the rhizome of *Ardisia japonica*. *Chem Pharm Bull* 41: 561–565.
  31. Giner-Larza EM, Máñez S, Recio MC, Giner RM, Prieto JM, Cerdá-Nicolás M, Ríos JL (2001). Oleanonic acid, a 3-oxotriterpene from Pistacia, inhibits leukotriene synthesis and has anti-inflammatory activity. *Eur. J. Pharmacol.* 428: 137– 143.
  32. Giner-Larza EM, Máñez S, Giner RM, Recio MC, Prieto JM, Cerdá-Nicolás M, Ríos JL (2002). Anti-inflammatory triterpenes from Pistacia terebinthus Galls. *Planta Med* 68: 311–315.
  33. Hidaka H, Ishiko T, Furuhashi T, Kamohara H, Suzuki S, Miyazaki M, Ikeda O, Mita S, Setoguchi T, Ogawa M (2002). Curcumin inhibits interleukin 8 production and enhances interleukin 8 receptor expression on the cell surface: impact on human pancreatic carcinoma cell growth by autocrine regulation. *Cancer* 95:1206-1214.
  34. Hodge G, Hodge S, Han P (2002). Allium sativum (garlic) suppresses leukocyte inflammatory cytokine production in vitro: potential therapeutic use in the treatment of inflammatory bowel disease. *Cytometry* 48:209-215.
  35. Hong T, Jin GB, Yoshino G, Miura M, Maeda Y, Cho S, Cyong JC (2002). Protective effects of Polygalae root in experimental TNBS-induced colitis in mice. *J Ethnopharmacol* 79:341- 346.
  36. Hsieh TC, Kunicki J, Darzynkiewicz Z, Wu JM (2002). Effects of extracts of *Coriolus versicolor* (Γ'm-Yunity) on cell-cycle progression and expression of interleukins-1 beta, -6, and -8 in promyelocytic HL-60 leukemic cells and mitogenically stimulated and nonstimulated human lymphocytes. *J. Altern. Compl. Med* 8: 591-602.
  37. Huang KS, Lin M, Yu LN, Kong M (2000). Four novel oligostilbenes from the roots of *Vitis amurensis*. *Tetrahedron* 56: 1321–1329.
  38. Ihtola-Vormisto A, Summanen J, Kankaanranta H, Vuorela H, Asmawi ZM, Moilanen E (1997). Anti-inflammatory activity of extracts from leaves of *Phyllanthus emblica*. *Planta Med* 63: 518–524.
  39. Iizuka N, Miyamoto K, Hazama S, et al. (2000). Anticachectic effects of *Coptidis rhizoma*, an anti-inflammatory herb, on oesophageal cancer cells that produce interleukin 6. *Cancer Lett* 158:35-41.
  40. Ito M, Tchoua U, Okamoto M, Tojo H (2002). Purification and Properties of a Phospholipase A2/Lipase Preferring Phosphatidic Acid, Bis(monoacylglycerol) Phosphate, and Monoacylglycerol from Rat Testis J. Biol. Chem. 277(10): 43674–43681
  41. Jang DS, Cuendet M, Su BN, Totura S, Riswan S, Fong HH, Pezzuto JM, Kinghorn AD (2004). Constituents of the seeds of *Hernandia ovigera* with inhibitory activity against cyclooxygenase-2. *Planta Med.* 70(10):893-896.
  42. Jiang J, Xu Q (2003). Immunomodulatory activity of the aqueous extract from rhizome of *Smilax glabra* in the later phase of adjuvant-induced arthritis in rats. *J Ethnopharmacol* 85:53-59.
  43. Kammoun M, Miladi S, Ben Ali Y, Damak M, Gargouri Y, Bezzine S (2011). *In vitro* study of the PLA2 inhibition and antioxidant activities of *Aloe vera* leaf skin extracts. *Lipids Health Dis.* 11:10:30.
  44. Kang JM, Kim N, Kim B, Kim JH, Lee BY, Park JH, Lee MK, Lee HS, Jang IJ, Kim JS, Jung HC, Song IS (2009). Gastroprotective action of *Cochinchina momordica* seed extract is mediated by activation of CGRP and inhibition of cPLA(2)/5-LOX pathway. *Dig Dis Sci.* 54(12):2549-2560.
  45. Khanapure SP, Garvey DS, Janero DR, Letts LG (2007). Eicosanoids in inflammation: biosynthesis, pharmacology, and therapeutic frontiers. *Curr Top Med Chem.* 7(3): 311-340.
  46. Kim HM, Lee EH, Na HJ, Lee SB, Shin TY, Lyu YS, Kim NS, Nomura S (1998). Effect of *Polygala tenuifolia* root extract on the tumor necrosis factor-alpha secretion from mouse astrocytes. *J Ethnopharmacol* 61:201-208.
  47. Kim HM, Park YA, Lee EJ, Shin TY (1999). Inhibition of immediate-type allergic reaction by *Rosa davurica* Pall. in a murine model. *J Ethnopharmacol.* 67:53-60.
  48. Kim HP, Son KH, Chang HW, Kang SS (2004). Anti-inflammatory Plant Flavonoids and Cellular Action Mechanisms. *J. Pharmacol. Sci.* 96: 229-245
  49. Kim YH, Ko WS, Ha MS, Lee CH, Choi BT, Kang HS, Kim HD (2000). The production of nitric oxide and TNF-alpha in peritoneal macrophages is inhibited by *Dichroa febrifuga* Lour. *J. Ethnopharmacol.* 69:35-43.
  50. Kim YO, Leem K, Park J, Lee P, Ahn DK, Lee BC, Park HK, Suk K, Kim SY, Kim H (2001). Cytoprotective effect of *Scutellaria baicalensis* in CA1 hippocampal neurons of rats after global cerebral ischemia. *J. Ethnopharmacol.* 77:183-188.



51. Krol W, Czuba ZP, Threadgill MD, Cunningham BD, Pietsch G (1995). Inhibition of nitric oxide (NO) production in murine macrophages by flavones. *Biochem. Pharmacol.* 50:1031–1035.
52. Kumar S, Zierys K, Wiegrebe W, Müller K (2000). Medicinal plants from Nepal: evaluation as inhibitors of leukotriene biosynthesis. *J Ethnopharmacol* 70: 191–195.
53. Kumari R, Meyyappan A, Selvamani P, Mukherjee J, Jaisankar P (2011). Lipoxygenase inhibitory activity of crude bark extracts and isolated compounds from *Commiphora berryi*. *J. Ethnopharmacol.* 31:138(1):256-259.
54. Kundu JK, Mossanda KS, Na HK, Surh YJ (2005). Inhibitory effects of the extracts of *Sutherlandia frutescens* (L.) R. Br. and *Harpagophytum procumbens* (Devil's Claw) on phorbol ester-induced COX-2 expression in mouse skin: AP-1 and CREB as potential upstream targets. *Cancer Lett.* 218(1):21-31.
55. Kuo YC, Sun CM, Tsai WJ, Ou JC, Chen WP, Lin CY (1999). Blocking of cell proliferation, cytokines production and genes expression following administration of Chinese herbs in the human mesangial cells. *Life Sci.* 64:2089-2099.
56. Lanni C, Becker EL (1985). Inhibition of neutrophil phospholipase A2 by p-bromophenylacetyl bromide, nordihydroguaiaretic acid, 5, 8, 11, 14-eicosatetraenoic acid and quercetin. *Int. Archs. Allergy Appl. Immun.* 76: 214– 217.
57. Loughton MJ, Evans PJ, Moroney MA, Houlst JRS, Halliwell B (1991). Inhibition of mammalian 5-lipoxygenase and cyclooxygenase by flavonoids and phenolic dietary additives. *Biochem. Pharmacol.* 42:1673–1681.
58. Lee HT, Yang SW, Kim KH, Seo EK, Mar W (2002). Pseudoguaianolides isolated from *Inula britannica* var. *chinensis* as inhibitory constituents against inducible nitric oxide synthase. *Arch. Pharmacol. Res.* 25: 151-153
59. Lee T-P, Matteliano ML, Middleton E (1982). Effect of quercetin on human polymorphonuclear leukocyte lysosomal enzyme release and phospholipid metabolism. *Life Sci.* 31:2765–2774.
60. Lemaire I, Assinewe V, Cano P, Awang DV, Arnason JT (1999). Stimulation of interleukin-1 and -6 production in alveolar macrophages by the neotropical liana, *Uncaria tomentosa* (una de gato). *J. Ethnopharmacol.* 64:109-115.
61. Lindahl M, Tagesson C (1993). Selective inhibition of group II phospholipase-A2 by quercetin. *Inflammation.* 17:573–582.
62. Matsunaga K, Takahashi A, Ohizumi Y (2000). Inhibitory action of Paraguayan medicinal plants on 5-lipoxygenase. *Nat Med* 54: 151–154.
63. McMurray RW, Hardy KJ (2002). COX-2 inhibitors: today and tomorrow. *Am. J. Med. Sci.* 323:181–189.
64. Momin RA, De Witt DL, Nair MG (2003). Inhibition of cyclooxygenase (COX) enzymes by compounds from *Daucus carota* L. *Seeds. Phytother. Res.* 17(8):976-979.
65. Moncada S, Palmer RMJ, Higgs EA (1991). Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol. Rev.* 43:109–142.
66. Mollace V, Muscoli C, Masini E, Cuzzocrea S, Salvemini D (2005). Modulation of prostaglandin biosynthesis by nitric oxide and nitric oxide donors. *Pharmacol Rev.* 57(2):217-252
67. Müller K, Zierys K, Paper DH. (1998). *Ilex aquifolium*: Protection against enzymatic and non-enzymatic lipid peroxidation. *Planta Med* 64: 536–540.
68. Müller-Jakic B, Breu W, Pröbstle A, Redl K, Greger H, Bauer R (1994). *In vitro* inhibition of cyclooxygenase and 5-lipoxygenase by alkaloids from Echinacea and Achillea species. *Planta Med* 60: 37–40.
69. Murakami M, Kudo I (2004). Recent advances in molecular biology and physiology of the prostaglandin E2-biosynthetic pathway. *Prog. Lipid Res.* 43:30–35.
70. Nathan C (1992). Nitric oxide as a secretory product of mammalian cells. *FASEB J.* 6:3051–3064.
71. Needleman P, Isakson P (1997). The discovery and function of COX-2. *J. Rheumatol.* 24 Suppl 49:6–8.
72. Newton R (2000). Molecular mechanisms of glucocorticoid action: what is important? *Thorax* 55 (7): 603–613
73. Nworu CS, Akah PA, Okoye FBC, Kamdem Toukam D, Udeh J, Esimone CO (2011). The leaf extract of *Spondias mombin* L. displays an anti-inflammatory effect and suppresses inducible formation of tumor necrosis factor- $\alpha$  and nitric oxide (NO). *J. Immunotoxicol* 8(01): 10-16.
74. Nworu CS, Akah PA, Okoye FBC, Esimone CO (2012). Inhibition of pro-inflammatory cytokines and inducible nitric oxide by extract of *Emilia sonchifolia* L. aerial parts. *Immunopharmacology and Immunotoxicology*, 34(6): 925–931.
75. Nworu CS, Nwuke HC, Akah PA, Okoye FBC, Esimone CO (2013). Extracts of *Ficus exasperata* leaf inhibit topical and systemic inflammation in rodents and suppress LPS-induced expression of mediators of inflammation in macrophages. *Journal of Immunotoxicol* 10 (3): 302-310.
76. Oh GS, Pae HO, Choi BM, Jeong S, Oh H, Oh CS, Rho YD, Kim DH, Shin MK, Chung HT (2003). Inhibitory effects of the root cortex of *Paeonia suffruticosa* on interleukin-8 and macrophage chemoattractant protein-1 secretions in U937 cells. *J. Ethnopharmacol* 84:85-89.
77. Ohadoma SC, Akah PA, Nkemmele CA, Nnatuanya I, Nwosu PJC (2011). Investigation of the analgesic and anti-inflammatory activities of methanol leaf extract of *Lupinus arboreus*. *J. Appl. Scs.*14: 10158-10169.
78. Okoli CO, Akah PA (2000). A pilot evaluation of the anti-inflammatory activity of *Culcasia scandens*, a traditional anti-rheumatic agent. *J. Altern. Compl. Med.* 6: 632-637.
79. Okoye FB C, Nworu CS, Akah PA, Esimone CO, Debbab A, Proksch P (2013). Inhibition of inflammatory mediators and reactive oxygen and nitrogen species by some depsidones and diaryl ether derivatives isolated from *Corynespora cassiicola*, an endophytic fungus of *Gongronema latifolium* leaves. *Immunopharmacol & Immunotoxicol* 35(06): 640–646.
80. Okoye NN, Ajaghaku DL, Okeke HN, Ilodigwe EE, Nworu CS, Okoye FBC (2014). Beta-amyrin and alpha-amyrin acetate isolated from the stem bark of *Alstonia boonei* displayed profound anti-inflammatory activity. *Pharm Biol* 52 (11): 1478 – 1486.
81. Perlmann P, Troye-Blomberg M (2000). Malaria blood-stage infection and its control by the immune system. *Folia biologica* 46 (6): 210–218.
82. Ryu SY, Oak MH, Yoon SK, Cho DI, Yoo GS, Kim TS, Kim KM (2000). Anti-allergic and anti-inflammatory triterpenes from the herb of *Prunella vulgaris*. *Planta Med.* 66: 358-360.
83. Sandoval M, Okuhama NN, Zhang XJ, Condezo LA, Lao J, Angeles' FM, Musah RA, Bobrowski P, Miller MJ (2002). Anti-inflammatory and antioxidant activities of cat's claw (*Uncaria tomentosa* and *Uncaria guianensis*) are independent of their alkaloid content. *Phytomedicine* 9: 325-337.

84. Schubert SY, Lansky EP, Neeman I (1999). Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids. *J. Ethnopharmacol.* 66: 11–17.
85. Sendl A, Elbl G, Steinke B, Redl K, Breu W, Wagner H (1992). Comparative pharmacological investigations of *Allium ursinum* and *Allium sativum*. *Planta Med* 58: 1–6.
86. Shah BN, Seth AK, Maheshwari KM (2011). A Review on Medicinal Plants as a Source of Anti-inflammatory Agents. *Res. J. Med. Plant*, 5: 101-115.
87. Shon YH, Kim JH, Nam KS (2002). Effect of *Astragali radix* extract on lipopolysaccharide-induced inflammation in human amnion. *Biol Pharm. Bull.* 25:77-80.
88. Spellman K (2006). Modulation of cytokine expression by traditional medicines: a review of herbal immunomodulators. *Altern. Med. Rev.* 11(12): 128-150.
89. Stavri M, Ford CH, Bucar F, Streit B, Hall ML (2005). Bioactive constituents of *Artemisia monosperma*. *Phytochemistry* 66: 233-239
90. Stuehr DJ (1999). Mammalian nitric oxide synthases. *Biochim. Biophys. Acta* 1411 (2–3): 217–230.
91. Su BN, Jones WP, Cuendet M, Kardono LB, Ismail R, Riswan S, Fong HH, Farnsworth NR, Pezzuto JM, Kinghorn AD (2004). Constituents of the stems of *Macrocarallium pomiferum* and their inhibitory activities against cyclooxygenases-1 and -2. *Phytochemistry*. 65(21):2861-2866.
92. Sunil Kumar KC, Müller K. (1998). Inhibition of leukotriene biosynthesis and lipid peroxidation in biological models by the extract of *Cassia fistula*. *Phytother Res* 12: 526–528.
93. Tornhamre S, Schmidt TJ, Näsman-Glaser B, Ericsson I, and Lindgreen JA (2001). Inhibitory effects of helenalin and related compounds on 5-Lipoxygenase and leukotriene C4 synthase in human blood cells. *Biochem. Pharmacol.* 62: 903-911
94. Venema RC, Ju H, Zou R, Ryan JW, Venema VJ (1997). Subunit Interactions of Endothelial Nitric-oxide Synthase. *J. Biol. Chem.* 272(2): 1276–1282
95. Vane J, Botting (1987). Inflammation and the mechanism of action of anti-inflammatory drugs, *The FASEB J.* 1:89-96
96. Wadsworth TL, Koop DR (2001). Effects of *Ginkgo biloba* extract (EGb 761) and quercetin on lipopolysaccharide-induced release of nitric oxide. *Chem. Biol. Interact.* 137:43–58.
97. Wadsworth TL, McDonald TL, Koop DR (2001). Effects of *Ginkgo biloba* extract (EGb 761) and quercetin on lipopolysaccharide-induced signaling pathways involved in the release of tumor necrosis factor- $\alpha$ . *Biochem. Pharmacol.* 62:963–974.
98. Wagner H (1989). Search for new plant constituents with potential antiphlogistic and antiallergic activity. *Planta Med.* 55: 235–241.
99. Wagner H, Dorsch W, Bayer Th, Breu W, Willer F (1990). Antiasthmatic effects of onions: inhibition of 5-lipoxygenase and cyclooxygenase in vitro by thiosulfonates and ‘cepaenes’. *Prostaglandins Leukot. Essent. Fatty Acids* 39: 59–62.
100. Weinstein SL, Sanghera JS, Lemke K, DeFranco AL, Pelech SL (1992). Bacterial lipopolysaccharide induces tyrosine phosphorylation and activation of mitogen-activated protein kinases in macrophages. *J Biol Chem.* 267:14955–14962.
101. Welton AF, Tobias LD, Fiedler-Nagy C, Anderson W, Hope W, Meyers K, Coffey JW (1986). Effect of flavonoids on arachidonic acid metabolism. In: Cody V, Middleton E, Harborne JB, editors. *Plant flavonoids in biology and medicine*. New York: Alan R. Liss; p. 231–242.
102. Werz O (2007). Inhibition of 5-Lipoxygenase Product Synthesis by Natural Compounds of Plant Origin. *Planta Med.* 73(13): 1331-1357
103. Yang LK, Khoo-Beattie, Goh KL (2001). Ardisiaquinones from *Ardisia teysmanniana*. *Phytochemistry* 58: 1235-1238
104. Zalewski CA, Passero LF, Melo AS, Corbett CE, Laurenti MD, Toyama MH, Toyama DO, Romoff P, Fávero OA, Lago JH (2011). Evaluation of anti-inflammatory activity of derivatives from aerial parts of *Baccharis uncinella*. *Pharm Biol.* 49(6):602-607.
105. Zhao Z, Liu N, Huang J, Lu PH, Xu XM (2011). Inhibition of cPLA2 activation by *Ginkgo biloba* extract protects spinal cord neurons from glutamate excitotoxicity and oxidative stress-induced cell death. *J Neurochem.* 116(6):1057-1065. doi: 10.1111/j.1471-4159.2010.07160.x.
106. Barnes PJ (1998). Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clinical Science* 94: 557–572
107. Wiart C (2006). Anti-inflammatory plants In: *Ethnopharmacology of Medicinal Plants: Asia and the Pacific*; Christopher Wiart (Ed.); Humana Press Inc., Totowa, NJ