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ANTI-INFLAMMATORY MEDICINAL PLANTS AND THE MOLECULAR MECHANISMS UNDERLYING THEIR ACTIVITIES

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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-κB). 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 (Wiart, 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).

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Quercetin was repeatedly found to inhibit PLA2 from several sources. It inhibited PLA2 from rabbit peritoneal neutrophils with an $_{IC50}$ of 57100 µM (Lanni and Becker, 1985). It was also demonstrated that quercetin selectively inhibited group II sPLA2 from *Vipera russelli* with less inhibition of PLA2 from porcine pancreas, PLA2-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 PLA2, 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 PLA2. Extract of *Trichilia catigua* (Meliaceae) completely inhibited PLA2 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 A2 (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- PLA2 activity with an IC_{50} = 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 cPLA2 activation (Zhao *et al*., 2011). In a study to evaluate the effects of the flavonoid, quercetin, on *Crotalus durissus terrificus* secretory phospholipase A2 (sPLA2), 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 sPLA2, 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 cPLA2 among other molecular mechanisms of action (Kang *et al*., 2009).

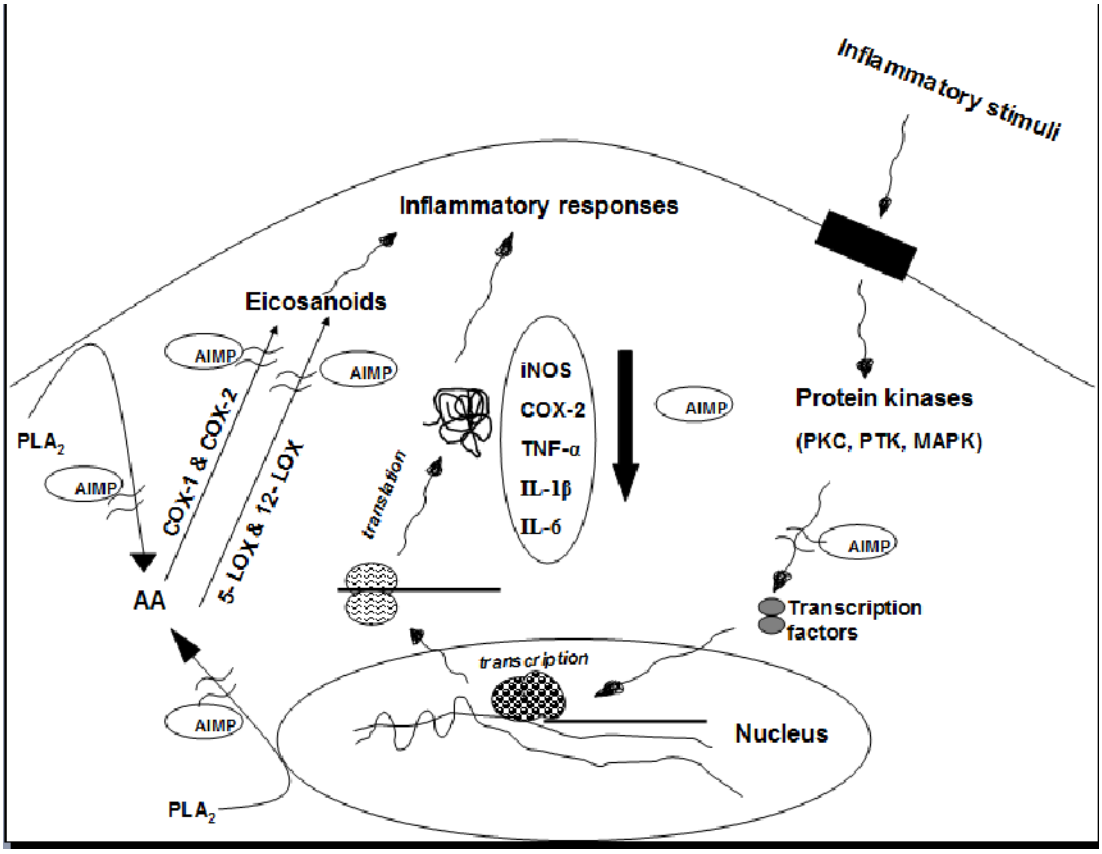

Figure 1: The proposed mechanism of action of anti-inflammatory medicinal plants (AIMP). "≈" and "↓" denote enzyme inhibition and down-regulation of the expression, respectively.

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).

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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-B arrera and Cuca-Suarez, 2011). Ethyl acetate-soluble extract of the stems of *Macrococculus 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'-dihyroxyflavone, 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_{50} values of flavones such as cirsiliol, 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 lipooxygenases (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. Lipooxygenases (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 artherosclerosis.

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

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A potential source for new 5-lipoxygenase inhibitors is undoubtedly provided by medicinal plants used in traditional medicine. The Arisia species and other Myrsinacea 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; Fuuishi *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_{50} 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_{50} of 35.8µM (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 lipophylic, 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-1f3 (IL-1f3), 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 sequiterpene 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 synthethase. For example, ambrosanolides-type sequiterpene known as cumanin isolated from *Ambrosia psilostachya* inhibited NO activity with an IC_{50} 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_{50} 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_{50} 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 f3), 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-f3), granulocyte macrophage colony-stimulating factor (GM-C SF), 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 antiinflammatory 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-ƙB (NF-ƙB) or activator protein-1 (AP-1) is

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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 sythethase (iNOS) expression by inhibiting p38 MAPK (Wadsworth and Koop, 2001) and inhibited TNF-α -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-α. It has been shown that quercetin inhibited NF--ƙB 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-KB 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
IL-1	*Curcuma longa*	*In vitro*, Human	Chan, 1995
	Polygala tenuifolia	*In vitro*, Murine	Kim et al, 998
	Smilax glabra	*Ex vivo*, Human	Jiang and Xu, 2003
	Uncaria tomentosa	*In vitro*, Murine	Lemaire et al, 1999
IL-1α	*Allium sativum*	*In vitro*, Human	Hodge et al, 2002
IL-1β	*Ampelopsis brevipedunculata*	*In vitro*, Human	Kuo et al, 1999
	Harpagophytum procumbens	*In vitro*, Human	Fiebich et al, 2001
	Ludwigia octovalvis	*In vitro*, Human	Kuo et al, 1999
	Pinus maritima	*In vitro*, Murine	Cho et al, 2001
	Rhus semialata	*In vitro*, Human	Kuo et al, 1999
	Tabernaemontana divaricata	*In vitro*, Human	Kuo et al, 1999
IL-6	*Allium sativum*	*In vitro*, Human	Hodge et al, 2002
	Astragalus membranaceus	*In vitro*, Human	Shon et al, 2002
	Coptis spp.	*In vivo*, Murine	Iizuka et al, 2000
	Harpagophytum procumbens	*In vitro*, Human	Fiebich et al, 2001
TNF	*Acanthopanax senticosus*	*In vitro*, Murine	Yi et al, 2002
	Acer nikoense	*In vitro*, Murine	Fujiki et al, 2003
	Allium sativum	*In vitro*, Human	Hodge et al, 2002
	Ampelopsis	*In vitro*, Human	Kuo et al, 1999
	Curcuma longa	*In vitro*, Human	Chan, 1995
	Dichroa febrifuga	*In vitro*, Murine	Kim et al, 2000
	Harpagophytum procumbens	*In vitro*, Human	Fiebich et al, 2001
	Ludwigia octovalvis	*In vitro*, Human	Kuo et al, 1999
	Perilla frutescens	*In vivo*, Murine	Ueda and Yamazaki, 1997
	Polygala tenuifolia	*In vitro*, Murine	Hong et al, 2002
	Polygala tenuifolia	*In vitro*, Murine	Kim et al, 1998
	Rhus semialata	*In vitro*, Human	Kuo et al, 1999
	Rosa davurica	*In vitro*, Murine	Kim et al, 1999
	Scutellaria baicalensis	*In vitro*, Murine	Kim et al, 2001
	Sinomenium acutum	*In vitro*, Murine	Kim et al, 1999
	Smilax glabra	*In vivo*, Murine	Jiang and Xu, 2003
	Tabernaemontana divaricata	*In vitro*, Murine	Kuo et al, 1999
	Tinospora cordifolia	*In vivo*, Murine	Dhuley, 1997
	Uncaria tomentosa	*In vitro*, Murine	Sandoval et al, 2002
	Withania somnifera	*In vivo*, Murine	Davis and Kuttan, 999
IL-8	*Coriolus versicolor*	*In vitro*, Human	Hsieh et al, 2002
	Curcuma longa (Curcumin)	*In vitro*, Human	Hidaka et al, 2002
	Paeonia suffruticosa	*In vitro*, Bovine	Oh et al, 2003
IL-12	*Allium sativum*	*In vitro*, 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,

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

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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-a (TNF-α), interleukins (ILs), cyclooxygenase (COX), and nitric oxide synthase (NO S). These genes of pro-inflammatory mediators are strongly induced during inflammation and are responsible for its initiation and persistence. TNF- α and IL-1β 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 iNO synthetase expression is an important target through which many anti-inflammatory medicinal plants mediate their activities. It is established that nuclear factor-κB (NF-κB) and AP-1 play the most important roles in the immune system. NF-κB is reported to regulate the expression of nearly all inflammatory mediators involved in inflammation. Nuclear translocation of NF- κB 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.

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