African Journal of Biotechnology Vol. 6 (25), pp. 2868-2885, 28 December, 2007
Available online at http://www.academicjournals.org/AJB
ISSN 1684–5315 © 2007 Academic Journals

Review

Inflammation: the foundation of diseases and disorders. A review of phytomedicines of South African origin used to treat pain and inflammatory conditions.

E. O. Iwalewa[1,2], L. J. McGaw[1], V. Naidoo[1] and J. N. Eloff [1]*

[1]Phytomedicine Programme, Department of Paraclinical Sciences, Faculty of Veterinary Science, University of Pretoria, Onderstepoort 0110, South Africa.
[2]Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife. Nigeria.

Accepted 13 November, 2007

Great interest in herbal medicine as a potential source of phytopharmaceuticals has created the need to review common factors responsible for major diseases and body disorders. This review shows one such common factor in inflammation and the role herbal medicine can play. Traditional medicinal herbal remedies in the southern African region have long been used to treat various pain- or inflammation-related symptoms. Although the precise mechanisms of action of many herbal drugs have yet to be determined, some of them have been shown to exert anti-inflammatory and/or antioxidant effects in a variety of cells in the human and animal bodies. There is increasing evidence to indicate that both peripheral and central nervous system cells play a prominent role in the chronic inflammatory responses in the body system and anti-inflammatory herbal medicine and its constituents are being proved to be a potent protector against various pro-inflammatory mediators in diseases and disorders. These mediators have therefore been suspected of being the functional basis of diseases and disorders. The structural diversity of these medicinal herbs makes them a valuable source of novel lead compounds against the therapeutic molecular targets, cytokines and mediators, that have been newly discovered by the platforms of genomics, proteomics, metabolomics and high-throughput technologies. This article reviews the basic mechanisms of inflammation and the potential of 123 southern African plant species to be effective as chronic inflammatory disease preventive agents. With one third of these species there are no indications of the chemical composition, indicating possible subjects for further research.

Key words: Medicinal plant, NO, NF kappa B, cytokines, reactive oxygen species.

INTRODUCTION

The molecular mechanism of chronic inflammation, its prevention and mitigation with phytomedicines have been intensively evaluated by our group over the past ten years (McGaw et al., 1997; Eloff et al., 2001; McGaw et al., 2001; Iwalewa et al., 2003; Omisore et al., 2004; Iwalewa and Agbani, 2004; Iwalewa et al., 2005; Omisore et al., 2005; Iwalewa et al., 2006; Idowu et al., 2006; Naidoo et al., 2006; Angeh et al., 2007). Epidemiological data suggest that lower incidences of certain chronic diseases such as atherosclerosis, arthritis, diabetes, acquired immune deficiency syndrome (AIDS) mediated by the Human Immunovirus, asthma, neoplasia, degenerative and cardiovascular diseases are associated with frequent intake of fruits and vegetables (Ames et al., 1993; Chu et al., 2002; Choi et al., 2002). Animal studies have also shown biological effects of several naturally occurring substances from foods, herbs and other natural sources being implicated in chronic diseases. Some of these naturally occurring bioactive substances with antioxidant properties, such as plant phenols, vitamins, carotenoids, phytoestrogens and terpernoids also have been shown to have anti-inflammatory activity and may play an important

*Corresponding author. E-mail:kobus.eloff@up.ac.za.

role in disease prevention and immune promotion, especially in chronic inflammatory diseases (Weisburger, 2002).

Inflammation is a complex process initiated by several factors ranging from bacterial infection and chemical injury to environmental pollution that result in cell injury or death (O'Byrne and Dalgleish, 2001; O'Byrne et al., 2000). Tissue injury induced by this trauma results in the release of inflammatory mediators including the cytokines and tumor necrosis factor (TNF-α), interleukin-1 (IL-1) from leukocytes, monocytes and macrophages (Paterson et al., 2003). Saklatvala et al. (2003) reported that the cytokines further trigger the up-regulation of other pro-inflammatory cytokines and chemokines, immunoglobulins, as well as increase the expression of many cellular adhesion molecules (CAMs). In other settings the phagocytosis of bacteria or foreign particles is associated with an increase in oxygen uptake by neutrophils, during which large amounts of reactive oxygen species ($ROS^{\cdot}$) such as superoxide anion ($O_2^{\cdot}$), hydroxyl radical ($HO\cdot$), and hydrogen peroxide (H_2O_2) are produced (Colin and Monteil, 2003). Also, there is an increase in the expression of phospholipase A_2, 5-lipoxygenase (5-LOX), and cyclooxygenase- 2 (COX-2) inducible nitric oxide synthase (iNOS) (Nakamura et al., 2003; Okamoto et al., 2004). $ROS^{\cdot}$ generating enzymes such as NADPH oxidase, xanthine oxidase, and myeloperoxidase are observed, along with the activation of the transcription factor and the nuclear factor kappa B (NFκB). Ultimately, the activation of the transcription factor NFκB appears to play a pivotal role in the regulation of inducible enzymes, inflammatory cytokines, CAMs, and other substances that are initiators or enhancers of the inflammatory process.

Phytomedicine constituents that inhibit any of the above-mentioned molecular targets have the potential to inhibit or reduce the inflammatory process, via the mechanisms highlighted and reviewed below. Based on these observations, several species of medicinal flora of South African origin were surveyed and reviewed; their chemical composition noted and related to their ethnomedical uses in the treatment of pain and inflammatory disorders.

It appears that there is growing interest in anti-inflammatory activity of plant extracts by Pharmaceutical companies as well as the herbal industry. A high proportion of the plant species listed here has not been examined in detail.

A REVIEW OF THE INFLAMMATORY PROCESS

Inflammation is a localized protective reaction of cells/ tissues of the body to allergic or chemical irritation, injury and/or infections. The symptoms of inflammation are characterized by pain, heat, redness, swelling and loss of function that result from dilation of the blood vessels leading to an increased blood supply and from increased intercellular spaces resulting in the movement of leukocytes, protein and fluids into the inflamed regions (Parham, 2000). Diseases and disorders are manifested through inflammatory responses as the body recognises the injury and prepare to repair the damage. To appreciate the inflammatory process it is important to understand the role of chemical mediators. These mediators are the substances released as plasma proteins, or that come from cells like mast cells, platelets, neutrophils and monocytes/macrophages. They are triggered by allergic or chemical irritation, injury and infections. These mediators, depending on the duration of injury determine the severity of inflammation and are termed pro-inflammatory fundamental factors. These substances bind to specific target receptors on the cells and may increase vascular permeability, promote neutrophil chemotaxis, stimulate smooth muscle contraction, increase direct enzymatic activity, induce pain and/or mediate oxidative damage (Coleman, 2002). Examples of chemical mediators include: nitric oxide (NO), prostaglandins (PG), leukotrienes (LK), vasoactive amines (histamine, serotonin), and cytokines (tumor necrosis factor and interleukins–1, 12). Although some of the cytokines (IL-3 -4,-5,-6,-10,-13) released are beneficial by acting as anti-inflammatory mediator within the cells (Esch and Stefano, 2002), these proinflammatory mediators present pathways through which disorders in the body may be eradicated or ameriolated (Esch and Stefano, 2002).

Even though the innate cascade process of inflammation is complex, it is mainly divided into two parts i.e. acute and chronic which could either be beneficial or detrimental.

- Acute inflammation is characterized by rapid onset and is of short duration. It is characterised by the exudation of fluids and plasma proteins; and the migration of leukocytes, most notably neutrophils into the injured area. This acute inflammatory response is believed to be a defense mechanism aimed at killing of bacteria, virus and parasites while still facilitating wound repairs.
- Chronic inflammation is of a more prolonged duration and manifests histologically by the presence of lymphocytes and macrophages, resulting in fibrosis and tissue necrosis. The persistent chronic inflammation increases the development of the degenerative diseases such as rheumatoid arthritis, atherosclerosis, heart disease, Alzheimer, asthma, acquired immunodeficiency disorder(AIDS), cancer, congestive heart failure (CHF), multiple sclerosis (MS), diabetes, infections (bacteria, fungi, parasites), gout, IBD-inflammatory bowel disease, aging and other neurodegenerative CNS depression, all of which are associated with immunopathological that appears to play a key role in the onset of the condition (O'Byrne and Dalgleish 2001; Dalgleish and O'Byrne 2002).

These various diseases and disorders have been linked to increased expression of pro-inflammatory mediators which activates inflammatory cells by increasing

the expression of pro-inflammatory cytokines, up-regulating genes that produce NF kappa B, NADPH oxidase, phospholipase A_2, COX-1 and -2, 5-LOX, myeloperoxidase, iNOS, increasing oxygen consumption and producing many oxygen-free radicals that can finally lead to certain degenerative diseases (Giacosa and Filiberti, 1996; Vicenzi et al., 1997; Charles et al., 1999; Locati and Murphy, 1999). Nitric oxide (NO) is an example of reactive species that participates in normal physiological processes such as vasodilation and neurotransmission; however, overexpression may result in disease as observed in inflammation, asthma, cardiovascular disorders and organ transplant rejection (Coleman, 2002). Many other factors such as chronic lung and liver inflammation caused by tobacco smoking and alcohol consumption may lead to lung cancer and liver cirrhosis respectively, while the persistent inflammation of the stomach is caused by the bacterium, *Helicobacter pylori* which may lead to ulcers and ultimately to stomach cancer (Farinati et al., 2003).

In summary, the followings are the main culprits that play prominent roles in inflammatory processes:

1. Leukocyte migration (Albelda et al., 1994; Ley, 1996),
2. NO and Arachidonic acid metabolism (Bennett, 1986; Balsinde et al., 2002; Bazan et al., 2002),
3. Reactive oxygen species (ROS) (Weitzman and Gordon 1990, Schreck et al., 1991, DiGiovanni 1992, Rosin et al., 1994, Gupta et al., 1999, Schoonbroodt and Piette 2000),
4. NF kappa B (Baldwin 1996, Pahl 1999) and
5. Pro-inflammatory cytokines (Le and Vilcek, 1987; Duff and Durum, 1982; Hirano, 1994; Tracey, 1994; Zhao et al., 2003).

Table 1 gives a brief description of the involvement and roles of pro-inflammatory cytokines in various diseases and disorders.

EVIDENCE SHOWING THE INVOLVEMENT OF CYTOKINES IN DISEASES

The importance of cytokines in disease has been illustrated in studies by Iwalewa and Agbani (2004) and Iwalewa et al. (2007) (submitted paper). These studies were conducted to inhibit the autacoids released before and during malaria infection and diabetes disorders respectively. It was found that although indomethacin, p-chlorophenylalanine (p-CPA), and cyproheptadine all block the synthesis of PG, 5-HT, and histamine respectively during inflammation, they were only capable of mild reduction of the infection in suppressive and prophylactic mode of treatment, and had no suppressive effect in curative established malaria infection. Bowman and Rand (1980) have established that even chloroquine which is the most effective anti-malarial synthetic agent, apart from its anti-malarial property, possesses anti-inflammatory activity. Also, in an experiment where alloxan was used to induce diabetes in rats, the extract *Harungana madagascariensis* suppressed glucose non-significantly. From the specific mechanism of action, it became clearer that other mediators, more devastating than the autacoids are involved in inflammation, which has since been identified as the cytokines.

In another study on *Azadirachta indica* leaves that produced gedunin – a limonoid complemented its anti-malarial property by reducing inflammatory symptoms of pain, pyrexia and swellings and also increasing immunomodulatory activities (Bray et al., 1990; Iwalewa et al., 1999). In addition to being directory pro-inflammatory, the cytokines IL-1, 12 are known to induce iNOS and COX-2 in chronic diseases which further contribute to immune complications. The pro-inflammatory cytokines, therefore, have to be taken care of in order to overcome completely the effect of inflammatory responses.

INFLAMMATORY CELLS INVOLVED IN PAIN–INFLAMMATORY DISORDERS IN VARIOUS ORGANS

The modulations of the various functions of inflammatory cells in the body are regulated by pharmacological-physiological constituents present in herbal products. Their actions directly or indirectly affect the immune system. The immune system is a highly complex, intricately regulated group of cells whose integrated function is essential to defend the body from diseases. Cells of the immune system may interact in a cell-cell manner and may also respond to intercellular messages through the transfer of hormones, cytokines, and autacoids elaborated by various cells (Kulmatycki and Jamali, 2005). In the CNS, the cells that modulate inflammatory effects are the neurons, microglia, astrocytes and endothelial cells (Licinio and Wong, 1999) while in the peripheral sites, the function of lymphocytes (T cells, B cells, macrophages, NK cells) and leukocytes (basophils, monocytes, neutrophils, eosinophils), mast cells, and platelets are involved. These are described briefly below to expose the biochemical markers that constituents of phytomedicines might affect to inhibit inflammatory processes.

Platelets (Thrombocytes)

In addition to their role in hemostasis and thrombosis, considerable evidence implicates platelets as inflammatory cellular elements (Weksler, 1983; Metzger and Page, 1998). Several pro-inflammatory mediators are derived from platelets, including thromboxane A_2 and serotonin, as well as TGF-b, PDGF, and LOX metabolites, some of which are implicated in the pathogenesis of asthma and atherogenesis (Metzger and Page, 1998). Platelet activating factor (PAF) is a well recognized pro-inflammatory

Table 1. The role of Pro-inflammatory (cytokines) mediators as expressed in disease (Kulmatycki and Jamali, 2005).

Diverse disorders	Pro-inflammatory (cytokines) Mediator Expression	References
Acquired Immunodeficiency Syndrome (AIDS)	Increased secretion of TNF-α, IL-1 and IL-6 by macrophages and monocytes correlated well with viral load and increased capacity of dendritic cells exposed to HIV-1 to produce TNF-α and IL-1β, IL-10 overexpression contributes to B-cell hyperactivity and risk of AIDS.	(Emilie and Galanaud 1998, Locati and Murphy 1999, Lore et al., 1999, Lee and Montaner 1999)
Acute Infection	Elevated myeloperoxidase, ROS and IL-6 in severe infections served as an index in viral and bacterial causes	(Kulander et al., 2001)
Parasitic Infections	Increased TNF-α concentrations in patients with *Plasmodium falciparum* malaria is associated with pathogenesis of disease	(Odeh 2001).
Asthma	Promotion of eosinophilia and cytokines that regulate allergic states and production of IL-4, IL-5, IL-10 and IL-13 were associated with asthma; administration of IL-12, IFN-α/γ are suggested to alleviate asthma disease; increased NO in exhaled air reflected airway inflammation in asthma patients.	(Bellanti, 1998., Romagnani 2000, Silvestri et al., 2003).
Cancer	Increases IL-6 and IL-6sR are associated with progression and metastasis of prostate cancer	(Shariat et al., 2001).
Cardiovascular Disorders		
Atherosclerosis	CRP is a strong predictor for future coronary events in healthy individuals; increased endothelium concentrations of IL-1 and TNF-inducible adhesion molecules P-selectin, E-selectin, VCAM-1 and intracellular adhesion molecule (ICAM)-1 in atherosclerotic tissue; high density lipoproteins may protect against coronary artery disease by inhibition of adhesion molecules; high density lipoproteins are suggest to inhibit TNF-α and IL-1β from increasing expression of E-selectin, VCAM-1 and ICAM-1; endothelial dysfunction is associated with altered NO bioavailability due to either reduced formation or accelerated degradation; CRP levels predicted future risk of coronary heart disease in healthy middle-aged men; CRP suggested to have a fundamental role in atherogenesis .	(Cockerill et al., 1999., Libby et al., 2002, Rifai and Ridker 2002).
Congestive Heart Failure	Increased concentrations of TNF-α and IL-6 were associated with progression from asymptomatic to symptomatic left ventricular dysfunction and excessive TNF-α levels associated with mortality; IL-6 is a strong predictor of disease progression; patients without cachexia that experience acute decompensation have increased levels of TNF-α.	(Milani. et al., 1996, Tsutamoto et al 1998, Torre-Amione 2000, Mann 2002).
Elderly (Aging)	Elevated concentrations of IL-1, TNF-α, IL-6 and sTNFRII increased concentrations of TNF-α independent of atherosclerosis; elevated concentrations of IL-6 and CRP predicted disability onset; increased concentrations of CRP and IL-6 were associated with mortality; increased CRP concentrations in the elderly was associated with development of diabetes mellitus; after challenge with endotoxin aging was associated with more rapid increase in CRP and prolonged inflammatory response and fever compared to younger individuals; high levels of TNF-α were associated with high prevalence of atherosclerosis	(Liao et al., 1993, Bruunsgaard et al 1999, Barzilay et al., 2001, Krabbe et al., 2001).
Fever	In periphery and brain increased concentrations of IL-1α, 1β, TNF-α and IL-6; post-myocardial infarction patients with prolonged fever had increased inflammatory activity.	(Zetterstrom et al., 1998, Gabriel et al., 2000)
Gastrointestinal Disorders		
Crohn's Disease	High IL-1 and 12 activity increases pro-inflammatory state.	(van Hogezand et al., 1998).
Peptic Ulcer	High ulcerogenic potential of *Helicobacter pylori* is linked, in part, to increased activity of IL-8 and TNF-α; *Helicobacter pylori* and NSAIDs cause ulcer recurrence through production of IL-1 and TNF-α by macrophages accumulated at the ulcer scar.	(Lehmann and Stalder, 1998, Arakawa et al., 1998).

Table 1. Contd.

Neurological Diseases		
Alzheimer's Disease	Neuroinflammation due to inflammatory mediator overexpression is associated with behavioral disturbances; increased IL-1 expression in Alzheimer brain is directly related to plaque formation and progression and neuronal overexpression of acetylcholinesterase; TNF-α, IL-1β and IL-6 overexpression stimulated production of amyloid-β which is crucial for neurodegeneration in Alzheimer's patients.	(Griffin et al., 1998, Mrak and Griffin 2001, Eikelenboom et al., 2002, Blasko and Grubeck-Loebenstein 2003)
Down's Syndrome	Overexpression of IL-1 in middle-aged individuals that have concurrent Alzheimer-type changes and in young and fetal Down's patients.	(Griffin et al., 1998)
Multiple Sclerosis	Elevated TNF-α concentrations in serum and cerebral spinal fluid; brain endothelium and astrocytes increased expression of ICAM-1.	(Ledeen and Chakraborty 1998, Lenercept 1999, Munoz-Fernandez and Fresno 1998)
Diabetes	Th-1 and Th-2 cells and their respective mediators participate and cooperate in inducing and sustaining pancreatic islet cell β-cell destruction in insulin dependent diabetes; inflammation important factor in pathogenesis of diabetes and metabolic disorders in women; increased CRP levels suggested to predict development of type 2 diabetes; obesity and diabetes inflammatory states in which mediators of inflammation contribute to insulin resistance.	(Almawi et al., 1998, Han et al., 2002, Dandona et al., 2004, Sjöholm and Nyström 2005)
Pain	TNF-α, IL-1 and IL-6 pathway is associated with altered pain perception; hyperalgesia induced by TNF-α via stimulating release of IL-1; hyperalgesia induced by peripheral inflammation is associated with IL-1 overexpression; spinal cord glia and glially derived proinflammatory cytokines suggested to be powerful modulators of pain; interleukin-1β mediated induction of cyclooxygenase-2 in neurons of the central nervous system contributes to inflammatory pain hypersensitivity; bradykinin B_2 receptors are suggested to be involved with the acute phase of the inflammatory and pain response; TNF-α expression is suggested to be upregulated in Schwann cells influencing central in painful neuropathies.	(Watkins and Maier, 1995, Watkins et al., 1999, Samad et al 2001, Couture et al 2001, Empl et al., 2001, Rutowski and DeLeo 2002, De Jongh et al., 2003, Wieseler-Frank et al., 2005)
Psychiatric Disorders		
Depression	Increased expression of IL-1β, IL-6 and IFN-γ, IL-1ra, sIL-6r and TNF-α; increased IL-1β concentrations in cerebrospinal fluid; increased concentrations of IL-6, sIL-6r, sIL-2r and transferrin receptor in major depression.	(Maes et al., 1995, Connor and Leonard, 1998, Levine et al., 1999)
Schizophrenia	Increased concentrations of IL-6 and TNF-α increased IL-1β polymorphism; drug-naïve schizophernic patients had increased IL-2 and IFN-γ production compared to controls.	(Naudin et al., 1996, Monteleone et al., 1997, Frommberger et al.,1997, Katila et al., 1999, Cazzullo et al., 2001).
Sleep disorders	TNF-α and IL-6 suggested to play an important role in mediating sleepiness and fatigue in disorders of excessive daytime sleepiness; systemic inflammatory response and reduced plasma availability of tryptophan was related to primary sleep disorders and major depression.	(Vgontzas et al., 1997, Song et al., 1998).
Stress	Psychological stress is associated with increased production of TNF-α, IL-1, IL-1ra, IFN-γ and lower production of IL-4 and IL-10; increased expression of neutrophils, monocytes, $CD8^+$, $CD2^+CD26^+$ and $CD2^+$HLA-DR^+ T cells and $CD19^+$ B cells; post traumatic stress disorder was associated with increased IL-6 signaling .	(Maes et al., 1998, 1999a 1999b)
Rheumatoid Arthritis	Increased concentrations of TNF-α as a central proinflammatory mediator increased concentrations of IL-1, IL-6, TNF-α, GM-CSF, and chemokines IL-8.	(Odeh 1997, Feldman et al., 1996, 1998, Charles et al., 1999)
Sepsis	Systemic inflammatory response syndrome due to pro-inflammatory mediator excess is associated with severe inflammatory responses then excessive anti-inflammatory responses possibly leading to increased susceptibility to infection; septic shock is caused at least in part by excessive or deregulated host inflammatory responses.	(van der Poll and van Deventer 1999, Marik and Varon 2001, Hotchkiss and Karl 2003).

mediator derived from membrane phospholipids by the enzymatic activity of phospholipase A_2 and an acetyl transferase in mast cells, basophils, eosinophils, and endothelial cells. PAF receptor-coupled activation of phosphoinositide-specific phospholipase C and phosphorylation of several cellular proteins has been reported.

Neutrophils/ macrophages/monocytes

Oxygen free radicals and non-radical reactive oxygen intermediates released by neutrophils and other phagocytes have been increasingly implicated in inflammatory/ immune disorders (Fantone and Ward, 1982; Ward et al., 1991). This may be accomplished by interference with NADPH oxidase, a powerful oxidant- producing enzyme localized on the surface membrane of neutrophils (Tauber et al., 1984).

Mast cells and basophils

Mast cells play a central role in the pathogenesis of diseases such as allergic asthma, rhino-conjunctivitis, urticaria, anaphylaxis, and systemic mastocytosis; they may also be important players in other chronic inflammatory disorders such as inflammatory bowel disease and rheumatoid arthritis (Galli, 1993; Theoharides, 1996). Mast cells may also participate in sterile inflammatory conditions exacerbated by stress, such as atopic dermatitis, interstitial cystitis, irritable bowel syndrome, migraines, and multiple sclerosis (Theoharides, 1996). Basophils, the circulating “equivalent” of the tissue mast cells, are now considered as important cells in the pathogenesis of late phase allergic reactions (Lemanske and Kaliner, 1988; Grant and Li, 1998). Both cells are known to produce histamine.

NF-kappa B, TNF-alpha, IFN-gamma

NF kappaB (NFκB) is a (complex of proteins) transcription factor that binds to DNA and activates gene transcription (Baldwin, 1996). The expression of many proteins, including all pro-inflammatory cytokines, chemokines, and enzymes of the arachidonic acid cascade, are regulated by the transcription factor NFκB (Pahl, 1999). In normal cells, NFκB is bound to an inhibitory protein IκB, and the complex IkappaB is present in the cytoplasm. A variety of inflammatory stimuli, such as bacterial infections, lipopolysaccharide (LPS), injury, TPA, UV irradiation, ROS, and inflammatory cytokines (TNFα and IL-1), activate NFκB by phosphorylating I-kappaB with IκB kinase and subsequently degrading the IκB complex. Released NFκB is then translocated into the nucleus and binds to DNA and activates the transcription of many genes, including pro-inflammatory cytokines, chemokines, TNFα, IL-1, adhesion molecules, phospholipids A_2, lipoxygenase, COX-2, iNOS, and myeloperoxidase (Baldwin, 1996; Pahl, 1999). Abnormal activation of the NFκB pathway is involved in degenerative chronic inflammatory diseases, such as asthma, rheumatoid arthritis, inflammatory bowel disease, artherosclerosis, and Alzheimer’s disease (Podolsky, 1991; Ross, 1993; Tak and Firestein, 2001; Collins and Cybulsky, 2001).

Lymphocytes (T and B cells)

T lymphocyte stimulation through the antigen receptor causes early activation of a tyrosine kinase (Samelson et al., 1986; Patel et al., 1987; Trevillyan et al., 1990) and the generation of phosphatidylinositol (PI) biphosphate (PIP_2)-derived second messengers, namely inositol triphosphare (IP_3) and diacyl glycerol (DAG), via activation of phospholipase C (Koretzky et al., 1990; Ledbetter et al., 1991). Several cellular substrates are phosphorylated through the activation of protein kinase PTK, this eventually lead to the expression of IL-1. It is now understood that the proliferative signal is generated by members of a family of PTKs that catalyze the phosphorylation of cellular substrates, which in turn leads to T cell proliferation (Rudd, 1990). B lymphocyte activation, like T cell activation, is accompanied by phosphorylation of tyrosine on particular B cell proteins (Campbell and Sefton, 1990; Gold et al., 1990; Lane et al., 1991; Yamanashi et al., 1991). Uckun et al., (1991) in human B cell studies, showed that IL-7 receptor ligation with recombinant human IL-7 caused increased phosphorylation on tyrosine of multiple substrate proteins, stimulated phosphatidylinositol turnover with increased IP_3 generation (PLC activation), and also DNA synthesis.

INVOLVEMENT AND INTERACTION BETWEEN NITRIC OXIDE AND PROSTAGLANDIN BIOSYNTHESIS IN INFLAMMATORY DISORDERS

The biosynthesis and release of nitric oxide (NO) and prostaglandins (PGs) share a number of similarities. Three major forms of nitric-oxide synthase (constitutive, inducible and endothelial NOS) and cyclooxygenase (COX) enzymes have been identified to date. Under normal circumstances, the constitutive isoforms of these enzymes (NOS and COX-1) are found in virtually all organs. Their presence accounts for the regulation of several important physiological effects (e.g. antiplatelet activity, vasodilation, and cytoprotection). On the other hand, in an inflammatory setting, the more inducible isoforms of these enzymes (inducible NOS and COX-2) are detected in a variety of cells, resulting in the production of large amounts of pro-inflammatory and cytotoxic NO and PGs. These substances play an important role in injured tissues by enhancing the blood flow to the area to promote healing. Unfortunately, the release of NO and PGs by the inducible isoforms of NOs

and COX has been associated with the pathological roles of these mediators in disease states as evidenced by the use of selective inhibitors. An important link between the NOS and COX pathways has been identified. Salvemini et al. (1993) demonstrated that the enhanced release of PGs, which follows inflammatory mechanisms, was nearly entirely driven by NO. Such studies raised the possibility that COX enzymes represent important endogenous "receptor" targets for modulating the multifaceted roles of NO. Furthermore, other studies have highlighted the importance of such interaction in physiology as well as in the mechanism of action of drugs such as organic nitrates. More importantly, mechanistic studies of how NO switches on/off the PG/COX pathway have been undertaken and additional pathways through which NO modulates prostaglandin production unraveled. On the other hand, NO donors conjugated with COX inhibitors have recently found new interest in the understanding of NO/COX reciprocal interaction and potential clinical use (Mollace et al., 2005).

PHYTOMEDICINES (HERBAL MEDICINE) AGAINST PAIN-INFLAMMATORY DISORDERS IN VARIOUS ORGANS

Based on the molecular events that lead to inflammation, we therefore suggest that the process of sustained inflammation that accompanies chronic diseases can be ameliorated and possibly even prevented by phytomedicines. The anti-inflammatory properties of several phytomedicines origin, that contain substances like phytoestrogens, flavonoids and its derivatives, phytosterol, tocopherol, ascorbic acid, curcumin, genistein, and others can be the inhibitors of the molecular targets of pro-inflammatory mediators in inflammatory responses. There are other plants that contain alkaloids, tannin, saponins, anthraquinones, triterpenoids and other constituents which have been reported to possess a diverse range of bioactivities including anticancer, immunostimulatory, antibacterial, antimalarial and antituberculosis activities bearing in mind that some of the causative organisms and factors responsible for the initiating and promoting inflammation could be remove or neutralised to suppress the expression of pro-inflammatory agents. All these are reviewed and discussed below.

The ancient African healers possessed numerous recipes in the form of herbs, minerals and animal parts used as remedies in disease conditions. The list was however, dominated by food plants with the belief that “food is medicine and medicine is food” (Etkins and Ross, 1983; Iwu 1993). Incidentally, some of the recipes cited for inflammatory and pain disorders in South African flora were also cited by Iwu (1993) with similar indications. This is pointing to the fact that African traditional medicine is the same in some respects despite cultural differences.

The southern African floral heritage has been described as among the most diverse in the world (Arnold and De Wet, 1993; Germishuizen and Meyer, 2003). The flora potential and the remarkable cultural systems pertaining to the use of herbal remedies to treat both animals and human diseases provides the information and opportunities for a scientific validation of acclaimed efficacy of these medicinal plants. The treatment of livestock diseases using traditional remedies is widely practiced in the rural communities. In the Eastern Cape Province, it is estimated that more than 75% of small scale farmers and dwellers use herbal remedies for their livestock (Masika et al., 2000). However, for medicinal plants used in the treatment of inflammatory-pain disorders, more than 115 plant species of 60 families are used as sources of therapies (Table 2). The evidence pointing to the fact that these flora are used for pain-inflammatory disorders arose from the various indications that emanated from ethnomedicinal surveys and the diverse arrays of chemical constituents found in these plants.

Some of the plants are employed to treat diabetes, tumors, stomach pain, rheumatism and many other indications (Watts and Breyer-Brandwijk, 1962; Hutchings et al., 1996). Jäger et al. (1996) also screened 39 Zulu medicinal plants for prostaglandin-synthesis inhibitors out of which two-thirds of the plants possessed high prostaglandin inhibitory activity. Another interesting feature of herbal remedies is the wide variety of conditions that is said to be treatable with a single plant or group of plants. The reasons why some remedies from plants are used for so many indications could be that they affect a common (denominator) factor responsible for the diseases and disorders as shown in Table 1. For example, a decoction from the stem bark extract of a plant could relief pain symptoms, abdominal cramp, fever, swelling, induce sleep, treat dysentery and diarrhoea, alleviate respiratory discomfort, cold and infections of various kinds. If one considers that the body reaction to all this diseases is standard - inflammatory, a plant effective against a variety of non–related diseases could just be inflammatory. This leads to speculation that inflammation may be the basis underlining many diseases and bodily disorders.

The changes observed in various functions of inflammatory cells in the body are regulated by pharmacological/physiological constituents present in herbal products. Therefore, the biochemical markers in inflammatory processes help to expose the pathways involved in diseases, which the constituents of phytomedicines might inhibit (Figure 1). In South Africa however, the choice of a plant material being used for pain – inflammatory disorder among the Zulus, Sotho and Xhosa is based on the name given to the plant, its frequency of usage of the same plant and for the same biological activities (Watts and Breyer-Brandwijk, 1962; Hutchings et al., 1996).

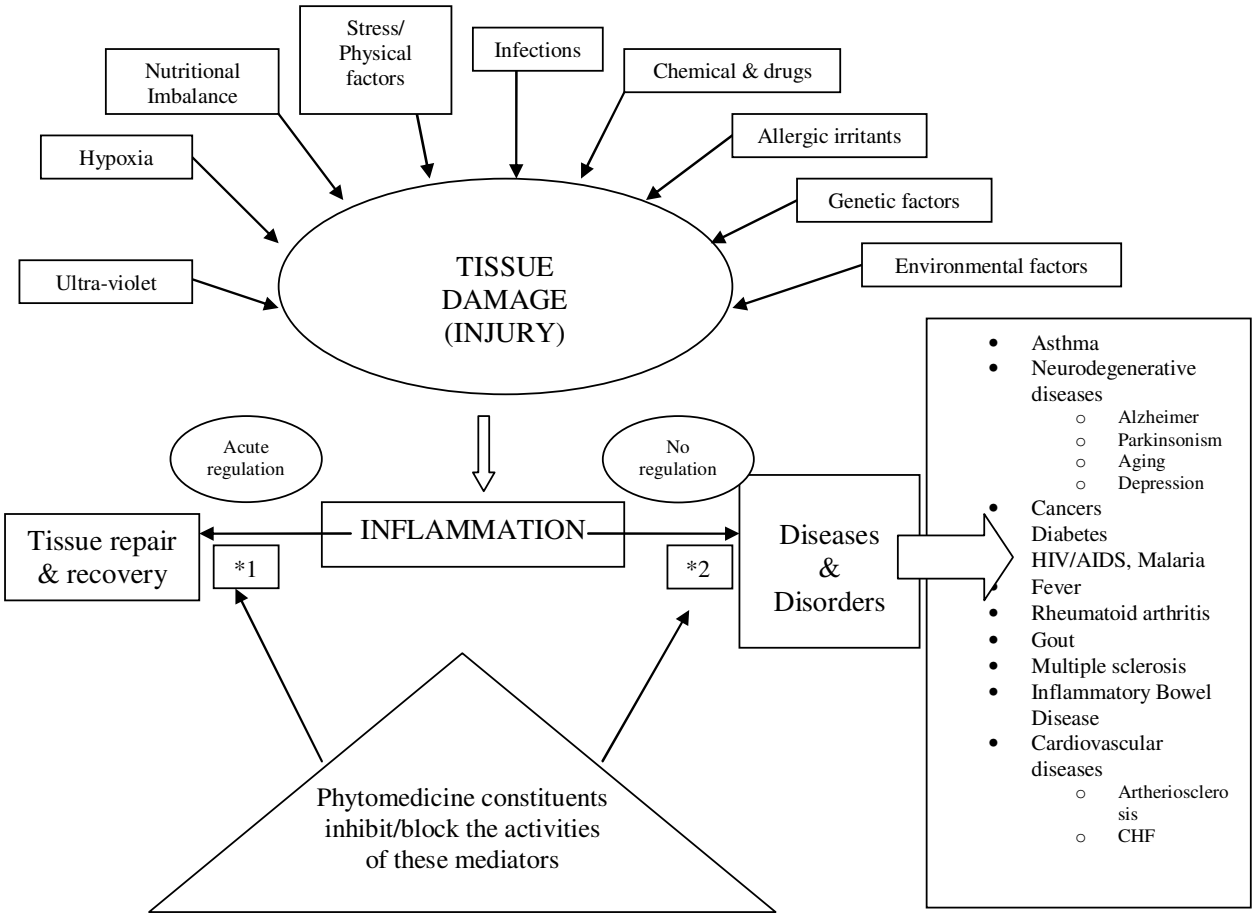

Figure 1. The sketch diagram shows the pathways of tissue damage and inflammatory diseases and disorders. Site *1 indicate the presence of mast cells, leukocytes (basophils, monocytes, neutrophils, eosinophils) and platelets that release 5-HT, histamine, PG- especially the COX-1, ROS in acute inflammatory stage. Site *2 shows the presence of platelets, lymphocytes (T cells, B cells, macrophages, NK cells), that release more devastating pro-inflammatory cytokines like IL-1, 12, NF-kappa B, TNF-alpha, IFN-gamma, COX-2, LOX, NO, ROS in chronic inflammatory stage.

Knowledge has been built for decades on the use of herbal medicinal products and extracts in the treatment of human diseases. We believe that parallel knowledge can be used for treating animal diseases and in fact there is a parallel body of knowledge on the use of medicinal plants in treating various animal diseases. This is applied to increase the quality of life of livestock and rural dwellers. One of the main factors militating against animal production in the rural communities in Southern Africa is infection of their livestock and infections from bacteria (including tuberculosis), fungi, viruses, worms and other parasites are sources of inflammatory disease. Some of the plants used by the Zulus, Sotho and Xhosa for pain – inflammatory disorder include *Terminalia* (Combretaceae) of different species, *Athrixia phylicoides* (Asteraceae), *Peltophorum africanum* (Fabaceae), *Sclerocarya birrea* (Anacardiaceae), *Acacia sieberiana* (Fabaceae) and some of these have been evaluated for their antibacterial, antifungal, anthelmintic, antioxidant and anti-inflammatory activities (Martini and Eloff, 1998; Eloff ,1999; McGaw et al., 2001; Eloff, 2001; Eloff et al, 2001; Kotze and Eloff, 2002; Martini et al., 2004a, b; Katerere and Eloff, 2004; Naidoo et al., 2004). These are some of the factors/ mechanisms through which inflammatory disorders are expressed in both animals and humans where these plant species are used. These factors that could trigger the release of mediators in inflammatory responses, we believe must be removed to ensure healthy conditions for both humans and animals. Other mechanisms are highlighted below.

Other prominent plants of southern African origin include *Sutherlandia frutescens* (Fabaceae), which contains canavanine non-protein free amino acids from the leaves, seeds, stem, flowers and fruits (Van Wyk et al., 1997; Katerere and Eloff, 2005), *Cyrtanthus suaveolens, Gethyllis ciliaris* and other species that belong to the family, Amaryllidaceae. These are known to contain alkaloids (Elgorashi and van Staden, 2004), which are of great importance in CNS inflammation in their neuroprotective activity (Suk, 2005). Other groups of

plants that affect the immune system (immunomodulatory /immunoprotective) are *Pelargonium sidoides,* and *Picrorhiza scrophularriflora* (Scrophulariaceae) (Van der Walt and Vorster, 1988). Table 2, however, show the list of other prominent South African floras employed in pain-inflammatory disorders.

CONSTITUENTS IN MEDICINAL PLANTS CAPABLE OF INHIBITING PRO-INFLAMMATORY MEDIATORS

The following plant secondary metabolites are capable of modifying the activities of inflammatory cells: flavonoids, triterpenoids, sterols (phytosterols), tannins, alkaloids, chalcone, anthraquinone, sesquitertepenoids, curcumin, coumarins, polyphenolic compounds, carotenes, vitamins A, E and C, limonoids, essential and volatile oils.

General inhibitory pathways of inflammation by phytomedicinal constituents

The general mechanism of actions of phytomedicines are classified into 4 basic groups:

1. Immunoprotective/immunomodulatory properties,
2. Inhibition of NFκB, NO, COX and ROS generation,
3. Inhibition of enzymes- tyrosine, and
4. Preventing the entry of microorganism (membrane stabilizing properties).

The immune system can be modified by diet, pharmacological agents, and naturally occurring food chemicals, such as vitamins and flavonoids. Plants contain a wide variety of natural compounds mainly plant secondary compounds. Among the secondary compounds are the flavonoids (Martins et al., 2007). Flavonoids are among the most common constituents in plants. They are present in high concentrations in flowers, seeds, leaves, herbs, fruits, stems, bulbs, tea, wine, vegetables and other food sources (Middleton et al., 2000). Over 4000 structural unique flavonoids have been identified in plants (Harborne et al., 1975; Harborne, 1986). They are non-steroidal natural phenolic compounds that exhibit likely or similar activities related to synthetic non-steroidal anti-inflammatory drugs (NSAID) used in inflammatory-pain disorders. It is evident that the flavonoids display, to a variable extent, a remarkable array of biochemical and pharmacological actions which suggest that certain members of this group of compounds significantly affect the function of the immune system and inflammatory cells (Middleton and Kandaswami, 1992). Several flavonoids specifically affect the function of enzyme systems critically involved in the generation of inflammatory processes, especially tyrosine (Nishizuka, 1988; Hunter, 1995) and serine-threonine protein kinases. Recently, it has become evident that these enzymes are intimately involved in signal transduction and cell activation processes involving cells of the immune system, as well as other cells activated by hormones, autocoids, neurotransmitters, and growth factors (Dangoria et al., 1996; Querbes et al., 2004). In addition, some constituents are free radical scavengers (Cos et al., 1998) and are therefore able to reduce tissue damage caused by oxidation stress of superoxide, hydroxyl and lipid peroxidation products. Green tea polyphenols, curcumin, and resveratrol inhibit the activation of NFκB and also have antioxidant activity (Nakamura et al., 1998; Shishodia et al., 2003). They are considered as moderate anti-inflammatory agents and could be used for preventive therapy and perhaps as therapeutics for the treatment of inflammation related diseases (Yamamoto and Gaynor, 2001). This particular action prevents microorganisms from gaining entry into cells especially during infections. Cell membrane stabilizing properties of the constituents would however come into play.

In another dimension, NFκB plays a critical role in the regulation of genes involved in the expression of pro-inflammatory enzymes (iNOS, COX-1 and 2, TNF-α), suppression of NFκB in its binding capacity to DNA by constituents of phytomedicine are likely to reduced the expression of nitric oxide and prostaglandin enzymes (Kim et al., 2005). As mentioned in Table 2, several herbal extracts of South African origin contain complicated mixtures of organic chemicals, including fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, and terpenes. Flavonoids are not the only component possessing anti-inflammatory effects, alkaloids detected in Amaryllidaceous species and other plants have been well demonstrated to significantly improve the impairment of learning, short-term and spatial memory through the inhibition of acetylcholinesterase in the CNS (Woodruff-Pak et al., 2001; Sweeney et al., 1990). Some of the plants found in this region for inflammatory conditions contain high concentrations of saponins, which has antioxidant activity (Metodiewa and Koska, 2000).

The role of pro-inflammatory cytokines in inflammation cannot be over-emphasized. Through the immunomodulatory and immunoprotective effects immune systems can be stimulated (up-regulation), suppressed (down-regulated) or restored by plant products and this is the most logical intervention in inflammatory therapies. This is because the cytokines and NFκB are the devastating products from cells that generate all other factors in inflammatory process. For example *Pelargonium sidoides,* and the *Picrorhiza scrophularriflora* (Scrophulariaceae) (Van der Walt and Vorster ,1988) are native of the coastal regions of South Africa are used for acute bronchitis and tonsillopharyngitis, and contain coumarins phenolic compounds and tannins. Immunomodulatory properties were demonstrated by tannins and coumarins which were mediated through NO, TNF-α, IL, and NK-cells inhibition (Koch et al., 2002). Several plant-derived natural products that possess immunomodulatory effects

Table 2. List of plant species and their families, constituents/isolated compounds, various indications and parts used in pain-inflammatory disorders (Watts and Breyer-Brandwijk, 1962; Hutchings et al., 1996).

Plant species (family)	Parts used	Constituents	Indications
Acacia burkei (Fabaceae)	stem bark / root	not known	painful back and eye
Acacia sieberiana (Fabaceae)	stem bark	not known	fever, genitals and back pains and aches
Achyranthes aspera (Amaranthaceae)	whole plant: root, leaves and aerial parts	achyranthine and glycosides	chest pain, coughs, menstrual bleeding, boils, abscesses and stomach complaints.
Acokanthera oppositifolia (Apocynaceae)	leaves and root	amorphous acokantherin	painful feet, rheumatism, toothache, abnormal menstrual period, and swellings
Alepidea amatymbica (Apiaceae)	root/rhizome	terpenoid kaurene	cold, cough, diarrhoea, headache and rheumatism
Aptenia cordifolia (Mesembryanthemaceae)	leaves and stem	alkaloids	painful joints.
Asclepias fruiticosa (Asclepiadaceae)	leaf, stem and root	aardenolide glycoside	diarrhoea and stomach pain, facilitate child-birth, asthma and diabetes.
Athrixia phylicoides (Asteraceae)	root and leaves	diterpenoids	cough , sores and boils
Barleria ovata (Acanthaceae)	root	not known	painful nodule swellings under the skin
Berchemia zeyheri (Rhamnaceae)	stem bark	pentahydroxychachones	backache and rectal ulcer
Berkheya speciosa (Asteraceae)	root and leaves	sesquiterpenoids, socomene	abdominal pains
Bidens pilosa (Asteraceae)	root and leaves	chalchones and polyacetylenes	jaundice, eye, colic, bronchial problems, and rheumatism
Boophane disticha (Amaryllidaceae)	bulb	alkaloids	headache, chest and bladder pain, boils wounds and swelling.
Bowiea volubilis (Liliaceae)	bulb	cardiac glycosides	facilitate child-birth, bladder pains, sore eyes and skin diseases.
Brachylaena elliptica (Asteraceae)	leaves	mucilage, tannins and onopordopicrin.	facilitate child-birth, back and stomach pain, pneumonia.
Bridelia micrantha (Euphorbiaceae)	root, stem bark and leaf	friedelin, epi-friedelin, gallic acid, anthocyanidin, taraxerol, taraxerone and caffeic acid	lung pain, cough, diabetes, epigastric pain, toothache and fever.
Bulbine alooides (Liliaceae)	tuber	not known	anti-syphilis and rheumatism
Bulbine asphodeloides (Liliaceae)	tuber and leaves	not known	rashes, sores wounds, dysentery and diarrhoea
Bulbine latifolia (Liliaceae)	leaves	not known	dysentery and diarrhoea
Capparis tomentosa (Capparaceae)	root bark	sulphur oil	swellingsand fever
Cavacoa aurea (Euphorbiaceae)	root	not known	pain and fever
Cenchrus ciliaris (Poaceae)	rhizome	not known	body pain, menstrual disorders and urinary infections in women
Cephalaria zeyheriana (Dipsaceae)	root decoction	not known	swellings andpain
Chaetacme aristata (Ulmaceae)	bark and root	not known	swellings in haemorrhoids and dental anodynes
Clausena anisata (Rutaceae)	leaves, stem and root	terpenoids, alkaloids, coumarins and limonoids	abdominal pain toothache fever and rheumatism

Table 2. Contd.

Clerodendrum glabrum (Verbenaceae)	Leaves and root	not known	intestinal worms, cough, fever, painful sore throat, fracture joints, and rheumatism
Clutia spp (Euphorbiaceae)	leaf	not known	painful joints, back and rheumatism
Colocasia antiquorum (Aracae)	tuber	sapotoxin and goitrogenic agent	tumor, stomach pain, rheumatism and stop bleeding
Commelina benghalensis (Commnlinaceae)	whole plant	hydrocyanic acid	sore eye and throat ailment, malaria, sooth urethral pains.
Cotyledon orbiculata (Crassulaceae)	leaf and sap	tyledoside and bufanolides	earache, toothache and boil
Crabbea nana (Acanthaceae)	leaves	not known	cancer and toothache
Crinum bulbispermum (Amaryllidaceae)	bulb and leaves	alkaloids, stigmasterol, triterpenoids and flavonoids.	painful joints, backache, rheumatism, sores and swellings
Crinum moorei (Amaryllidaceae)	bulb and leaves	lycorine, cheryrilline, crinamidine	swellings and growth
Croton gratissimus (Euphorbiaceae)	stem bark	not known	inhaled to relieve pain.
Croton steenkampianus (Euphorbiaceae)	leaf	not known	painful joints, back and rheumatism
Croton sylvaticus (Euphorbiaceae)	stem bark	tannin	abdominal and uterine disorders and fever
Cryptocarya lantifolia (Lauraceae)	stem bark	not known	internal and uterine pains, muscular cramps
Cucumis africanus (Cucurbitaceae)	fruits and leaf	curcumin	relieve of lumbago
Cycnium racemosum (Scrophulariaceae)	root	not known	painful eposodes in pregnancy.
Cyrtanthus suaveolens + spp (Amaryllidaceae)	bulb, root and leaves	alkaloids, triterpenoids and flavonoids.	chronic cough, headache, cystitis and facilitate child-birth.
Datura stramonium (Solanaceae)	leaves and flower	alkaloids, flavonoids	swellings and tumour growth, headache , asthma,
Dichrostachys cinerea (Fabaceae)	root	triterpenoids β-amyrim, β-sitosterol, alkaloids and saponin	abdominal pains, diarrhea, coughs, bacterial infections.
Diospyros villosa (Ebenaceae)	root and leaf	not known	painful fractures and intestinal complaints.
Dovyalis rhamnoides (Flacourtiaceae)	root and bark	not known	painful joints, and rheumatism
Ekebergia capensis (Meliaceae)	root	not known	coughs and chest pains ,headache and dysentry
Erythrina lysistemon (Fabaceae)	stem bark	alkaloids and protease inhibitors	swellings, abscesses and growth
Erythrophleum lasianthum (Fabaceae)	stem bark	erythrophleine	persistent body pain and intestinal spasm.
Euclea natalensis (Ebenaceae)	root bark	pentacyclic terpenoids	swellings and growth
Eucomis autumnalis (Liliaceae)	bulb	homoisoflavones, nortriterpenes, eucosterol	fever, cough and respiratory ailment, facilitate child-birth,
Eucomis comosa (Hyacinthaceae)	bulb and root	homoisoflavones, nortriterpenes, eucosterol	rheumatism and teething baby
Euphorbia bupleurifolia (Euphorbiaceae)	root	not known	swellings on the lower limbs and cancer.
Euphorbia ingens (Euphorbiaceae)	latex/bark	steroids, tetracyclic diterpenes	chronic ulcer and cancer, asthma and bronchitis
Euphorbia puginformis (Euphorbiaceae)	latex/root	resin	swellings on the lower limbs
Foeniculum vulgare (Apiaceae)	leaves and stem	quercetin derivatives, volatile oil	menstrual pains, jaundice, diarrhoea, cramp and diuretics

Table 2. Contd.

Gethyllis ciliaris (Amaryllidaceae)	fruit pods, leaves and flower	not known	colic, flatulent, indigestion, stomach disorders, and toothache.
Gnida kraussiana (Thymelaeceae)	root and flower parts	flavone,	painful joints, backache, bronchitis, coughs, boil, fever and rheumatism
Graderia scabra (Scrophulariaceae)	leaves and root	not known	fever and stomach trouble
Gunnera perpensa (Gunneraceae)	root	bitter principles	cancerous sores, facilitates child-birth, painful joints, rheumatism and swellings
Harpephyllum caffrum (Anacardiaceae)	root and stem bark	not known,	acne, skin problems and fractures
Helichrysum nudifolium (Asteraceae)	leaves	isocomene, sesquiterpenoids	swellings, chest pain cough, cold andfever.
Helinus intergrifolius (Rhamnaceae)	root	scyllitol, tannins, saponin.	painful joints and backache
Heteromorpha trifoliata (Apiaceae)	leaves and root	falcarindiol and sarisan	mental disturbances, headache, asthma, coughs, painful joints and backache.
Hibiscus aethiopicus (Malvaceae)	root	not known	painful swollen joints, and heart burn
Ilex mitis (Aquifoliaceae)	stem bark	not known	fever, rashes and sores and rheumatism
Kalanchoe crenata (Crassulaceae)	leaf	not known	swellings and growth
Kigelia africana (Bignoniaceae)	dried fruit/bark	luteolin, flavonoids isocoumarins, sterols and iridoid glycosides.	painful joints, back and rheumatism
Ledebouria ovatifolia (Liliaceae)	bulb	not known	gastro-enteritis, backache
Ledebouria revoluta (Liliaceae)	bulb	not known	skin irritation, wounds and sores
Leonotis leonurus (Laminaceae)	leaves and stem bark	phenolic compounds, resins and carotenoid	feverish headache, dysentery, coughs and colds and haemorrhoids.
Linum thunbergii (Linaceae)	root	not known	pain
Lippia javanica (Verbenaceae)	leaf, stem and root	pentacyclic triterpenoids, essential oil, amino acids, stearic and other acids	painful cough and cold, fever, chest pain, weak joints, back and rheumatism
Manilkara concolor (Sapotaceae)	root	not known	painful joints, back and rheumatism
Melia azadirach (Meliaceae)	leaves, stem root seed and friut	triterpenoids and steroids, limonoids, gedunin, coumarins, flavonoids	abdominal pains, malaria, swellings and growth
Melianthus comosus (Melianthaceae)	root and leaves	triterpenoids, bufadinolides	rheumatism, painful feet, wounds and dyspepsia.
Mesembryanthenum spp (Mesembryanthemaceae)	leaves	not known	swollen feet , stomach ailment
Ochna serrulata (Ochnaceae)	root	not known	gangrenous rectitis
Ocotea bullata (Lauraceae)	bark	tannins	urinary pains and headache
Peltophorum africanum (Fabaceae)	root and stem bark	flavonoids, gallic and chlorogenic acid	colic, cough, painful tooth, joints, backaches and fever
Pentanisia prunelloides (Rubiaceae)	root, leaves	not known	haemorroids, rheumatism, abdominal and chest-pains, in child-birth delivery and fever.
Phytolacca americana (Phytolaccaceae)	fruit root and leaves	triterpenoids, saponin	wound, fibroids growth, swellings and rheumatism
Pittosporum viridiflorum (Pittosporaceae)	stem bark	saponins	painful back, fever, stomach, chest and abdominal pains.

Table 2. Contd.

Plumbago auriculata (Plumbaginaceae)	root and leaves	naphthoquinone, plumbagin	painful joints, and fractures, headache and malaria.
Polygala fructicosa (Polygalaceae)	root	chromocoumarins and fritinone	facilitates child-birth, chronic ulcer, gonorrhoea.
Printzia pyrifolia (Asteraceae)	root	coumarate	abortion and stomach ache.
Protorhus longifolia (Anacardiaceae)	bark	tannins	heart burn and stomach bleeding
Prunus africana (Rosaceae)	bark and fruits	amygdalin, friedelin, hydrocyanic , ursolic acids, sterols	intercostal-pain, prostrate hypertropy.
Ptaeroxylon obliqum (Ptaeroxylaceae)	bark and root	essential oil, resin, saponin, pyrogallol, tannins flavone and alkaloids.	rheumatism and arthritis, headache, and fever
Pterocelastrus rosratus (Celastraceae)	root	tannin	spinal painful joints and respiratory ailments.
Pulicaria scabra (Asteraceae)	leaves/ whole part	terpenoids derivatives and flavonoids	cold and vagina tumor
Rapanea melanophloeos (Myrsinaceae)	bark and root	tannin, triterpenoids saponin	ulcer, stomach pain and fever
Raphinonacme spp (Periplocaceae)	root	not known	chronic ulcer, backache and uterine pain
Rhus chirindensis (Anacardiaceae)	stem bark	not known	heart and mental complaints, and rheumatism
Rothmannia capensis (Rubiaceae)	fruit and root	not known	painful burns, wounds and rheumatism
Rubus rigidus + spp (Rosaceae)	root	tannins, pyragallol	diarrhoea and dysentery, toothache, coughs and colds.
Sarcophyte sanguinea (Balanophoraceae)	whole plant	exocarpic acid , naringenin,	amenorrhoea, dysentery,and diarrhoea and swellings growth
Scilla natalensis (Liliaceae)	bulb	saponin	facilitate child-birth, sprains and fractures.
Scilla nervosa (Liliaceae)	bulb	digitalis	dysentery and rheumatism fever
Sclerocarya birrea (Anacardiaceae)	root, leaves and stem bark	tannins, trace alkaloids, vitamin c, flavonoids	malaria fever, diarrhoea, painful joints, backache, menorrhagia and stomach disorders.
Secamone gerardii (Asclepiadaceae)	root	not known	painful chest, and spinal disorders
Senecio speciosus (Asteraceae)	stem and leaves	not known	chest pain and headache
Solanum spp (Solanaceae)	root, fruits leaves and stem bark.	alkaloids, vitamin c, carotene	painful abdominal upset, toothache, ulcers, coughs asthma, rheumatism and swellings
Stapelia gigantea (Asclepiadaceae)	stem bark	anthraquinones	painful body and limbs
Strychnos henningsii (Loganiaceae)	root and bark	alkaloids, triterpenoids	dysmenorrhea, painful rheumatism fever and
Sutherlandia frutescens (Fabaceae)	seed, leaf, stem, flower and fruit.	canavanine and free amino-acids	cancer, gastric ailment, gynaecological problem, backache, rheumatism, swellings and fever.
Tecomaria capensis (Bignoniaceae)	bark	flavonols, alkaloids and tannins	fever, diarrhea and dysentery, pains sleeplessness, stomach and chest pains
Terminalia phanerophlebia (Combretaceae)	root bark	triterpenoids, tannin, nerifolin and sericoside	diarrhoea and colic
Terminalia sericae (Combretaceae)	root bark	triterpenoids, tannin, nerifolin and sericoside	diarrhoea and colic

Table 2. Contd.

Tetradenia riparia (Laminaceae)	leaves	diterpenoids	coughs and sore throat, malaria fever.
Trichilia emetica + spp (Meliaceae)	bark, leaves and seeds	tannin and resins	rheumatism, stomach andintestinal pains
Tulbaghia violacea (Alliaceae)	tuber	alkyl cystine sulfoxides, flavones, flavonols, steroidal saponin	fever, headache, painful joints, back and rheumatism
Turbina oblongata (Convolvulaceae)	root and leaves	not known	gout and arthritis, painful joints, rheumatism and swellings.
Turraea floribunda (Meliaceae)	root	limonoids	painful joints, rheumatism and swellings
Vernonia adoensis (Asteraceae)	stem and leaves	glaucolides	fever. painful joints, back and chest, and rheumatism
Viscum spp (Viscaceae)	whole plant or milk infusion	mistletoe lectin i	painful menstruation, asthma, bronchitis, stomach ailment and tumor swellings (watt and breyer-brandwijk 1962)
Vitex wilmsii (Verbenaceae)	leaf infusion	not known	body pains and as tonic
Warburgia salutaris (Canellaceae)	bark	tannins, sesquitertepenoids	malaria, painful chest/back and rheumatism
Withania somnifera (Solanaceae)	root and leaves	tropanol, steroidal lactones, alkaloids	swellings, painful joints, rheumatism, fever, haemorrhoids, sore and skin infections
Zanthoxylum capense (Rutaceae)	leaves and roots	resins essential oil and tannins	painful stomach, toothache joints and fever.
Ziziphus mucronata (Rhamnaceae)	leaves, stem bark and root	tannins and alkaloids	chronic cough, boil, toothache, rheumatism and swellings

have been reviewed (Wagner, 1990). These plants especially the Echinaceae species contain alkaloids, quinones, terpenoids, phenolcarboxylic acid, polysaccharides and glycoproteins. Apart from these constituents, β-sitosterols have been revealed to also possess immunomodulatory activity (Bouic et al., 1996).

CONCLUSION

Rheumatoid arthritis, asthma and diabetes (just to mention a few) are chronic diseases generally associated with immunological chaos. The introduction of molecular biological models and new target-directed pharmacological screening procedures (Wagner, 1999) in phytomedicine, research is a way to supply new information and to reveal the underlying mechanism of action of herbal medicinal products. The understanding of how chronic inflammation is responsible for various disease states supports studies to provide therapeutic remedies with target sites the cytokines, induced iNOS, COX-2, NFκB, and other enzymes.

The molecular mechanism of anti-inflammatory phytomedicine shares common molecular targets with nonsteroidal anti-inflammatory drugs, as well as steroidal drugs. Both nonsteroidal anti-inflammatory drugs and phytomedicine constituents such as sterols, alkaloids, flavonoids, glycosides, saponins, tannins, and terpenes α-tocopherol, ascorbic acid, curcumin, [salicylic acid derivatives] etc. are able to inhibit processes that lead to inflammation, such as (1) the activation of NFκB (2) induction and up-regulation of pro-inflammatory cytokines, (3) up-regulation and activation of CAMs by pro-inflammatory cytokine TNF-α and inflammatory mediators, (4) up-regulation of arachidonic acid metabolites by increasing its metabolism, and (5) production of ROS. Because inflammation is a complex, innate response that is triggered by tissue insult due to infection, toxin, trauma, post-ischemia, and autoimmune injury, the recovery from this process normally occurs during healing. However, if tissue destruction and assisted repair are not properly directed, inflammation can lead to persistent tissue damage in the CNS, through the neurons, microglia, astrocytes and endothelia cells, while in the peripheral sites, the function of lymphocytes (T cells, B cells, macrophages, NK cells) and leukocytes (basophils, monocytes, neutrophils, eosinophils), mast cells, platelets and collagen are involved. Such persistent inflammation may lead to certain chronic diseases and the inhibition of one or more of the complex chain reactions noted above may arrest this inflammatory process, thereby preventing chronic diseases. Therefore, it is worth evaluating the use of phytomedicines that have an effect on NFκB as potential agents of preventing inflammation and thus chronic diseases.

In approximately one third of the plant species listed in

Table 2 there is no indication of the chemical compounds present. In many other cases the chemicals present are based on group tests and only on rare cases have the active compounds been isolated and characterized. This opens up an important field for the application of phytochemistry and pharmacology to treating many diseases.

ACKNOWLEDGEMENTS

This work was made possible by the financial support given through the National Research Foundation Grant (NRF-2007) in South Africa. This work was also supported by the Obafemi Awolowo University, Ile – Ife, Nigeria.

REFERENCES

Albelda SM, Smith CW, Ward PA (1994). Adhesion molecules and inflammation injury. FASEB J. 8: 504-12.

Almawi WY, Tamim H, Azar ST (1999). T helper type 1 and 2 cytokines mediate the onset and progression of type I (insulin-dependent) diabetes. J. Clin. Endocrinol. Metab. 84: 1497-1502.

Ames BN, Shigenaga MK, Hagen TM (1993). Oxidants, antioxidants and the degenerative diseases of aging. Proceed. Nat. Acad. Sci. 90: 7915-7922.

Angeh JE, Huang X, Sattler I, Swan GE, Dahse H, Hartl A, Eloff JN (2007). Antimicrobial and anti-inflammatory activity of four known and one new triterpenoid from C*ombretum imberbe* (Combretaceae) J. Ethnopharmacol. 110: 56-60

Arakawa T, Watanabe T, Fukuda T, Higuchi K, Fujiwara Y, Kobayashi K, Tarnawski (1998). Ulcer recurrence cytokines and inflammatory response-dependent process. Dig. Dis. Sci. 43: 61S-66S.

Arnold TH, De Wet BC (1993). Plants of Southern Africa: Names and Distribution National Botanical Institute, Pretoria 0001, South Africa.

Baldwin AS (1996). The NF-_B and I_B proteins: new discoveries and insights. Ann. Rev. Immunol. 14: 649-681.

Balsinde J, Winstead MV, Dennis EA (2002). Phospholipase A_2 regulation of arachidonic acid mobilization. FEBS Lett. 531: 2-6.

Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP (2001).The relation of markers of inflammation to the development of glucose disorders in the elderly. Diabetes 50: 384-2389.

Bazan NG, Colangelo V, Lukiw WJ (2002). Prostaglandins and other lipid mediators in Alzheimer's disease. Prostaglandins Other Lipid Mediat. 68/69: 197-210.

Bellanti JA (1998). Cytokines and allergic diseases: clinical aspects. Allergy Asthma Proc. 19: 337-341.

Bennett A (1986). The production of prostanoids in human cancers, and their implications for tumor progression. Prog. Lipid Res. 25: 539-542.

Blasko I, Grubeck-Loebenstein B (2003). Role of immune system in the pathogenesis, prevention and treatment of Alzheimer's disease. Drugs Aging 20: 101-113.

Bouic PJD, Etserbeth S, Liebenberg RW, Albrecht CF, Pegel K, Van Jaarsveld PP (1996). β- sitosterols and β-sitosterol glucoside stimulate human peripheral blood lymphocytes proliferation: Implication for their use as a immunomodulatory vitamin combination. Int. J. Immunopharmacol. 18(12): 693-700.

Bowman W, Rand MJ (1980). Textbook of Pharmacology 2nd Edition Blackwell Publisher. London.

Bruunsgaard H, Anderson-Ranberg K, Juene B, Pedersen AN, Skinhoj P, Pedersen BK (1999). A high plasma concentration of TNF-α is associated with dementia in centenarians. J. Gerentol. A. Biol. Sci. Med. Sci. 54A: M357-M364.

Campbell MA, Sefton CM (1990). Protein tyrosine phosphorylation is induced in murine B lymphocytes in response to stimulation with anti-immunoglobulin. *EMBO* J. 9: 2125–2131.

Cazzullo CL, Sacchetti E, Galluzzo A, Pararielllo A, Colombo F, Zagliani A, Clerici M (2001). Cytokine profiles in drug-naïve schizophrenic patients. Schizophr. Res. 47: 293-298.

Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, Breedveld FC, Smolen JS, Ebrel G, deWoody K, Feldmann M, Maini RN (1999). Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-α therapy in rheumatoid arthritis. J. Immunol. 163: 1521-1528 17.

Choi CW, Kim SC, Hwang SS, Choi BK, Ahn HJ, Lee MY, Park SH, Kim SK (2002). Antioxidant activity and free radical scavenging capacity between Korean medicinal plants and flavonoids by assay-guided comparison. Plant Sci. 163: 1161-1168.

Chu YF, SunJ, Wu X, Liu RH (2002). Antioxidant and antiproliferative activities of common vegetables. J. Agric. Food Chem. 50: 6910-6916.

Cockerill GW, Saklatvala J, Ridley SH, Yarwood H, Miller NE, Oral B, Nithyanathan S, Taylor G, Haskard DO (1999). High-density lipoproteins differentially modulate cytokine-induced expression of E-selectin and cyclooxygenase-2. Arterioscler Thromb. Vasc. Biol. 19: 910-917.

Coleman JW (2002). Nitric oxide: a regulator of mast cell activation and mast cell-mediated inflammation. Clin. Exp. Immunol. 129: 4-10.

Colin DA, Monteil H (2003). Control of the oxidative burst of human neutrophils by staphylococcal leukotoxins. Infect. Immun. 71: 3724-3729.

Collins T, Cybulsky MI (2001). NF-_B: pivoral mediator or innocent bystander in artherognesis? J. Clin. Invest. 107: 255-264.

Connor TJ, Leonard (1998). Depression, stress and immunological activation: the role of cytokines in depressive disorders. Life Sci. 62: 583-606.

Cos P, Ying L, Calomme M, Hu JP, Cimanga K, Van Poel B, Pieters L, Vlietinck AJ, Vanden Berge D (1998). Structure–activity relationship and classification of flavonoids as inhibitors of xanthine oxidase and superoxide scavengers. J. Nat. Prod. 61: 71-76.

Couture R, Harrison M, Vianna RM, Cloutier F (2001). Kinnin receptors in pain and inflammation. Eur. J. Pharmacol. 429: 161-176.

Dalgleish AG, O'Byrne KJ (2002). Chronic immune activation and inflammation in the pathogenesis of AIDS and cancer. Adv. Cancer Res. 84: 231-276.

Dandona P, Aljada A, Bandyopadhyay A (2004). Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol. 25: 4-7.

Dangoria NS, Breau WC, Anderson HA, Cishek DM, Norkin LC (1996). Extracellular simian virus 40 induces an ERK/MAP kinase-independent signaling pathway that activates primary response genes and promotes virus entry. J. Gen. Virol. 77: 2173-2182.

De Jongh RF, Vissers KC, Meert TF, Booij LHDJ, De Deyne CS, Heylen RJ (2003). The role of interleukin-6 in nociceptin and pain. Anesth. Analg. 96: 1096-1103.

DiGiovanni J (1992). Multistage carcinogenesis in mouse skin. Pharmacol. Ther. 54: 63-128.

Duff GW, Durum SK (1982). Fever and pathogenesis of AIDS and cancer. Adv. Cancer Res. 84: 231-276.

Eikelenboom P, Hoogendijk WJG, Jonker C, van Tilburg W (2002). Immunological mechanisms and the spectrum of psychiatric syndromes in Alzheimer's disease. J. Psychiatr. Res. 36: 269-280.

Elgorashi EE, van Staden J (2004). Pharmacological screening of six Amaryllidaceae species. J. Ethnopharmacol. 90(1): 27-32.

Eloff JN (1999). The antibacterial activity of 27 South African members of the Combretaceae. S. Afr. J. Sci. 95: 148-152.

Eloff JN (2001). Antibacterial activity of Marula (*Sclerocarya birrea* (A. rich.) Hochst. subsp. caffra (Sond.) Kokwaro) (Anacardiaceae) bark and leaves J. Ethnopharmacol. 76(3): 305-308.

Eloff JN, Jager AK, van Staden J (2001). The stability and relationship between anti-inflammatory activity and antibacterial activity of southern African *Combretum* species. S. Afr. J. Sci. 97: 291-293.

Emilie D, Galanaud P (1998). Cytokines and chemokines in HIV infection: implications for therapy. Int. Rev. Immunol. 16: 705-726.

Empl M, Renaud S, Erne B, Fuhr P, Straube A, Schaeren-Wiemers N,

Steck AJ (2001). TNF-alpha expression in painful and nonpainful neuropathies. Neurology 56: 1371-1377.
Esch T, Stefano GB (2002). Proinflammation: A common denominator or initiator of different pathophysiological disease processes. Med. Sci. Monit. 8(5): HY1-9.
Etkins NL, Ross PJ (1983). Malaria, Medicine and Meals: Plants use Among the Hausa and its impact on Diseases, In: The anthropology of medicine, Romanucclros L, Moerman PE, Tancredi LR (Editors) New York., pp. 231-259.
Fantone JC, Ward PA (1982). Role of oxygen-derived free-radicals and metabolites in leukocyte-dependent inflammatory reactions. Am. J. Pathol. 107: 395-418.
Feldmann M, Brennan FM, Maini RN (1996). Role of cytokines in rheumatoid arthritis. Ann. Rev. Immunol. 14: 397-440.
Frommberger UH, Bauer J, Haselbauer P, Fraulin A, Riemann D, Berger M (1997). Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. Eur. Arch. Psychiatr. Clin. Neurosci. 247: 228-233.
Gabriel AS, Ahnve S, Wretlind B, Martinsson A (2000). IL-6 and IL-1 receptor antagonist in stable angina pectoris and relation of IL-6 to clinical findings in acute myocardial infarction. J. Int. Med. 248: 61-66.
Germishuizen G, Meyer NL (2003). Plants of southern Africa: an annotated checklist. National Botanical Institute, Pretoria.
Gold MR, Law DA, DeFranco AL (1990). Stimulation of protein tyrosine phosphorylation by the B-lymphocyte antigen receptor. Nature (London*)* 345: 810-813.
Grant JA, Li H (1998). Biology of Basophils, in *Allergy: Principles and Practice* (Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, BusseWWeds) Mosby, St. Louis., pp. 65-79.
Griffin WST, Sheng JG, Royston MC, Gentleman SM, McKenzie JE, Graham DI, Roberts GW, Mrak RE (1998). Glial-neuronal interactions in Alzheimer's disease: the potential role of a 'cytokine cycle' in disease progression. Brain Path 8: 65-72.
Gupta A, Rosenberger SF, Bowden GT (1999). Increased ROS levels contribute to elevated transcription factor and MAP kinase activities in malignantly progressed mouse keratinocyte cell lines. Carcinogenesis 20: 2063–2073.
Han TS, Sattar N, Williams K (2002). Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City diabetes study. Diabetes Care 25: 2016-2021.
Harborne JB (1986). Nature, distribution, and function of plant flavonoids, in Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological, and Structure- Activity Relationships (Cody V, Middleton E Jr., Harborne JB eds), Alan R Liss, Inc., New York. pp. 15-24,
Harborne JB, Mabry TJ, Mabry H (1975). The Flavonoids. Academic Press, New York.
Hirano T (1994). Tumor necrosis factor-alpha. In: Thomson A.W, editor. The cytokine handbook, 2nd edition. New York: Academic Press, pp. 145-168.
Hotchkiss RS, Karl IE (2003). The pathophysiology and treatment of sepsis. N. Engl. J. Med. 348(2): 138-150.
Hunter T (1995) Protein kinases and phosphatases: The yin and yang of protein phosphorylation and signaling. Cell 80: 225-236.
Hutchings A, Scott AH, Lewis G, Cunningham AB (1996). Zulu Medicinal Plants. An Inventory. University of Natal Press, Pietermaritzburg, pp. 53-54.
Idowu TO, Iwalewa EO, Aderogba MA, Akinpelu B, Ogundaini AO (2006). Antinociceptive Anti-inflammatory and Antioxidant activities of Eleagnine: An alkaloid Isolated from C*hrysophyllum albidum* seed cotyledons J. Biol. Sci. 6(6): 1029 – 1034.
Iwalewa EO, Adewale IO, Taiwo BJ, Arogundade T, Osinowo A, Daniyan OM, Adetogun GE (2007) Effects of *Harungana madagascariensis* stem-bark extracts on the anti-oxidant markers in alloxan-induced diabetics and carrageenan induced inflammatory disorders in rats. Submitted to J. Compliment. Int. Med. In press.
Iwalewa EO, Adewunmi CO, Omisore NOA, Adebanji OA, Azike CK, Adigun AO, Adesina OA, Olowoyo OG (2005). Pro- and Antioxidant effects and Cytoprotective potentials of Nine Edible Vegetables in South West Nigeria. J. Med. Foods 8(4): 539-544.
Iwalewa EO, Agbani EO (2004). Effect of autacoid inhibitors and of an antagonist on malaria infection in mice. Braz. J. Med. Biol. Res. 37(8): 1199-1204.
Iwalewa EO, Daniyan OM, Omisore NO (2006). Methanolic leaf extract of *Senna occidentalis* in the treatment of Malaria. J. Trop. Med. Plants. 7(1): 11-16.
Iwalewa EO, Iwalewa OJ, Adeboye JO (2003). Analgesic, Antipyretic, Anti-Inflammatory Activities of the Chloroform, Methanolic and Ether Extracts of *Vernonia cinerea* leaf. J. Ethnopharmacol. 86(2-3): 229 – 234.
Iwalewa EO, Mohammed K, Omotola OIF (1999). Contributory Pharmacological Effects of *Azadirachta indica* leaf in the treatment of malaria. Niger. J. Nat. Prod. Med. 3: 40-45.
Iwu MM (1993). Handbook of African Medicinal Plants CRC Press, Inc.
Jäger AK, Hutchings A, van Staden J (1996). Screening of Zulu medicinal plants for prostaglandin-synthesis inhibitors. J. Ethnopharmacol. 52: 95-111.
Katerere DR, Eloff JN (2004). Variation in the chemical composition, antibacterial and anti-oxidant activity of fresh and dried *Acacia* leaf extracts. S. Afr. J. Bot. 70: 303-305.
Katila H, Hanninen K, Hurme M (1999). Polymorphisms of the interleukin-1 gene complex in schizophrenia. Mol. Psychiatr. 4: 179-181.
Kim IT, Park YM, Won JH, Jung HJ, Park HJ, Choi JW, Lee KT (2005). Methanol Extract of *Xanthium strumarium* L. Possesses Anti-inflammatory and Anti-nociceptive Activities. Biol. Pharm. Bull. 28(10): 94-100.
Koch E, Lanzendorf-Goossens H, Wohn C (2002). Stimulation of interferon (INF) b-synthesis and natural killer (NK) cell activity by an aqueous-ethanolic extracts from the root of *Pelargonium sidoides.* Naunyn-Schmeideberg Arch. Pharmacol. 365(1): R75 (Abstr.288).
Koretzky GA, Picus I, Thomas ML, Weiss A (1990). Tyrosine phosphatase CD45 is essential for coupling T-cell antigen receptor to the phosphatidyl inositol pathway. Nature (London) 346**:** 66-63.
Kotze M, Eloff JN (2002). Extraction of antibacterial compounds from *Combretum erythrophyllum* (Combretaceae). S. Afr. J. Bot., 68: 62-67.
Krabbe SK, Bruunsgaard H, Hansen CM, Moller K, Fonsmark L, Qvist J, Madsen PL, Kronborg G, Andersen HO, Skinhoj P, Pedersen BK (2001). Ageing is associated with a prolonged fever response in human endotoxemia. Clin. Diag Lab. Immunol. 8: 333-338.
Kulander L, Pauksens K, Venge P (2001). Soluble adhesion molecules, cytokines and cellular markers in serum in patients with acute infections. Scand. J. Infect. Dis. 33: 290-300.
Lane PJL, Ledbetter JA, McConnell FN, Draves K, Deans J, Schieven GL, Clark EA (1991). The role of tyrosine phosphorylation in signal transduction through surface Ig in human B cells: Inhibition of tyrosine phosphorylation prevents intracellular calcium release. J. Immunol. 146: 715-722.
Le J, Vilcek J (1987). Biology of disease: tumor necrosis factor and interleukin 1: Cytokines with multiple overlapping biological activities. Lab. Invest. 56: 234-248.
Ledbetter JA, Schieven GL, Uckun GM, Imboden JB (1991). CD45 cross-linking regulates phospholipase C activation and tyrosine phosphorylation of specific substrates in CD3/Ti stimulated T cells. J. Immunol. 146: 1577-1583.
Ledeen RW, Chakraborty G (1998). Cytokines signal transduction, and inflammatory demyelination: review and hypothesis. Neurochem. Res. 23: 277-289.
Lee B, Montaner LJ (1999). Chemokine immunobiology in HIV-1 pathogenesis. J. Leukoc. Biol. 65: 552-565.
Lehmann FS, Stalder GAN (1998). Hypothesis on the role of cytokines in peptic ulcer disease. Eur. J. Clin. Invest. 28: 511-519.
Lemanske RF, Kaliner M (1988). Late-phase IgE-mediated reactions. J. Clin. Immunol. 8: 1-13.
Lenercept Multiple Sclerosis Study Group (1999). TNF neutralization in MS results of a randomized, placebo-controlled multicenter study. Neurology 53: 457-465.
Levine J, Barak Y, Chengappa KNR, Rapoport A, Rebey M, Barak V (1999). Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology 40: 171-176.
Ley K (1996). Molecular mechanism of leukocyte recruitment in the

inflammatory process. Cardiovasc. Res. 32: 733-742
Liao Z, Tu JH, Small CB, Schnipper SM, Rosenstreich DL (1993). Increased urine interleukin-1 levels in aging. Geronotology 39: 19-27.
Libby P, Ridker PM, Maseri A (2002). Inflammation and atherosclerosis. Circulation 105: 1135-1143.
Locati M, Murphy PM (1999). Chemokines and chemokine receptors: biology and clinical relevance in inflammation and AIDS. Annu. Rev. Med. 50: 425-440.
Lore K, Sonnerborg A, Olsson J, Patterson BK, Fehniger TE, Perbeck L, Andersson J (1999). HIV-1 exposed dentritic cells show increased pro-inflammatory cytokine production but reduced IL-1ra following lipopolysaccharide stimulation. AIDS, 13: 2013-2021.
Maes M, Lin Ah, Delmeire L, Van Gastel A, Kenis G, De Jongh R, Bosmans E (1998). Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following assidental man-made traumatic events. Biol. Psychiatry 45: 833-839.
Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, Desnyder R (1995). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J. Affect. Disord. 34: 301-309.
Maes M, Song C, Lin A, De Jongh RD, Gastel AV, Kenis G, Bosmans E, De Meester I, Benoy I, Neels H, Demedts P, Janca A, Scharpe S, Smith RS (1999a). The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. Cytokine 10: 313-318.
Maes M, Van Bockstaele DR, Van Gastel A, Song C, Schotte C, Neels H, DeMeester I, Scharpe S, Janca A (1999b). The effects of psychological stress on leukocyte subset distribution in humans: evidence of immune activation. Neuropsychobiology 39: 1-9.
Mann DL (2000). Inflammatory mediators and the failing heart past, present, and the foreseeable future. Circ. Res. 9: 988-998.
Marik PE, Varon J (2001). Sepsis: state of the art. Dis. Monit. 47(10): 465-532,
Martin JHJ, Crotty S, Warren P, Nelson PN (2007). Does an apple a day keep the doctor away because a phytoestrogen a day keeps the virus at bay? A review of the anti-viral properties of phytoestrogens Phytochemistry 68: 266-274.
Martini N, Eloff JN (1998). The preliminary isolation of several antibacterial compounds from *Combretum erythrophyllum* (Combretaceae) J. Ethnopharmacol. 62(3): 255-263.
Martini ND, Katerere DR, Eloff JN (2004a). Seven flavonoids with antibacterial activity isolated from *Combretum erythrophyllum*. S. Afr. J. Bot. 70: 310-312.
Martini ND, Katerere DR, Eloff JN (2004b). Biological activity of five antibacterial flavonoids isolated from *Combretum erythrophyllum* (Combretaceae). J. Ethnopharmacol. 93: 207-212.
Masika PJ, Van Averbeke W, Sonandi A (2000). Use of herbal remedies by small scale farmers to treat livestock diseases in the central Eastern Cape Province, South Africa. J. S. Afr. Vet. Ass. 71(2): 87-91.
McGaw LJ, Jäger AK, van Staden J (1997). Prostanglandin synthesis inhibitory activity in Zulu, Xhosa and Sotho medicinal plants. Phytother. Res. 11: 113-117.
McGaw LJ, Rabe T, Sparg SG, Jäger AK, Eloff JN, van Staden J (2001). An investigation on the biological activity of Combretum species J. Ethnopharmacol.75(1): 45-50.
Metodiewa D, Koska C (2000). Reactive oxygen species and reactive nitrogen species: Relevance to cyto(neuro)toxic events and neurologic disorders: An overview. Neurotox Res. 1: 197-233.
Metzger WJ, Page CP (1998). Biology of Platelets, in Allergy: Principles and *Practice* (Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW) Mosby, St. Louis, pp. 99-117.
Middleton E, Kandaswami C (1992). Effects of flavonoids on immune and inflammatory cell function. Biochem. Pharmacol. 43: 1167–1179.
Middleton E, Kandaswami C, Theoharides TC (2000). The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer. Pharmacol. Rev., 52: 673-751.
Milani RV, Mehr MR, Endres S, Eigler A, Cooper S, Lavie CJ (1996). Ventura HO. The clinical relevence of circulating tumor necrosis factor-α in acute decompensated chronic heart failure without cachexia. Chest 110: 992-995.
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: 217-252.
Monteleone P, Fabrazzo M, Tortorella A, Maj M (1997). Plasma levels of interleukin-6 and tumor necrosis factor alpha in chronic schizophrenia: effects of clozapine treatment. Psychiatr. Res. 71: 11-17.
Mrak RE, Griffin WST (2001). Interleukin-1, neuroinflammation and Alzheimer's disease. Neurobiol. Aging 22: 903-908.
Munoz-Fernandez MA, Fresno M (1998). The role of tumor necrosis factor, interleukin 6, interferon-γ and inducible nitric oxide synthase in the development and pathology of the nervous system. Prog. Neurobiol. 56: 307-340.
Naidoo V, Chikoto H, Bekker LC, Eloff JN (2006). Antioxidant compounds in *Rhoicissus tridentata* extracts may explain their antibabesial activity. S. Afr. J. Sci. 102: 198-200.
Naidoo VR, Katerere DR, McGaw LJ, Eloff JN (2004). Pre-treatment of bulb of Urginea sanguinense used in Ethnoveterinary medicine influences chemical composition and biological activity. Pharm. Biol. 42: 529-533.
Nakamura T, Goto M, Matsumoto A, Tanaka I (1998). Inhibition of NF_B transcriptional activity by _-tocopheryl succinate. Biofactors 7: 21-30.
Nakamura Y, Kozuka M, Naniwa K, Takabayashi S, Torikai K, Hayashi R, Sato T, Ohigashi H, Osawa T (2003). Arachidonic acid cascade inhibitors modulate phorbols ester-induced oxidative stress in female ICR mouse skin: differential roles of 5-lipoxygenase and cyclooxygenase-2 in leukocyte infiltration and activation. Free Radic. Biol. Med. 35: 997-1007.
Naudin J, Mege JL, Azorin JM, Dassa D (1996). Elevated circulating levels of IL-6 in schizophrenia. Schizophr Res. 20: 269-273.
Nishizuka Y (1988). The molecular heterogeneity of protein kinase C and its implications for cellular regulation. Nature (London) 334: 661-665.
O'Byrne KJ, Dalgleish AG (2001). Chronic immune activation and inflammation as the cause of malignancy. Br. J. Cancer 85: 473-483.
O'Byrne KJ, Dalgleish AG, Browning MJ, Steward WP, Harris AL (2000). The relationship between angiogenesis and the immune response in carcinogenesis and the progression of malignant disease. Eur. J. Cancer 36: 151-169.
Odeh M (1997). New insights into the pathogenesis and treatment of rheumatoid arthritis. Clin. Immunol. 83: 103-116.
Odeh M (2001). The role of tumor necrosis factor-α in the pathogenensis of complicated Falciparum malaria. Cytokine 14(1): 11-18.
Okamoto T, Gohil K, Finkelstein EI, Bove P, Akaike T, Van Der Vliet A (2004). Multiple contributing roles for NOS2 in LPS-induced acute airway inflammation in mice. Am. J. Physiol. Lung Cell Mol. Physiol. 286: L198-L209.
Omisore NOA, Adewunmi CO, Iwalewa EO, Ngadjui BT, Abegaz BM, Watchueng J, Ojewole JAO (2004). Antinociceptive and anti-inflammatory effects of Dorstenia barteri (leaves and twigs) extracts in mice. J. Ethnopharmacol. 95(1): 7-12.
Omisore NOA, Adewunmi CO, Iwalewa EO, Ngadjui BT, Adenowo TK, Abegaz BM, Watchueng J, Ojewole JAO (2005). Anti-trichomonas and antioxidant Activities of Dorstenia barteri and D. convexa Extracts. Braz. J. Med. Biol. Res. 38(7): 1087–1094.
Pahl HL (1999). Activators and target genes of Rel/NF-_B transcription factors. Oncogene 18: 6853-6866.
Parham P (2000). The immune system, Chapter 1. Elements of the immune systems and their roles in defense. New York: Garland Publishing., pp. 1-31.
Patel MD, Samelson LE, Klausner RD (1987). Multiple kinases and signal transduction: Phosphorylation of the T cell antigen receptor complex. J. Biol. Chem. 262: 5831-5838.
Paterson HM, Murphy TJ, Purcell EJ, Shelley O, Kriynovich SJ, Lien E, Mannick JA, Lederer JA (2003). Injury primes the innate immune system for enhanced Toll-like receptor reactivity. J Immunol. 171: 1473-1483.
Podolsky DK (1991). Inflammatory bowel disease (1). N. Engl. J. Med. 325: 928-9237.

Querbes W, Benmerah A, Tosoni D, Di Fiore PP, Atwood WJ (2004). A JC virus-induced signal is required for infection of glial cells by a clathrin- and eps15-dependent pathway. J. Virol. 78: 250-256.
Rifai N, Ridker PM (2002). Inflammatory markers and coronary heart disease. Curr. Opin. Lipidol. 13: 383-389.
Romagnani S (2000). T-cell subsets (Th1 versus Th2). Ann. Allergy Asthma. Immunol. 85: 9-21.
Rosin AP, Anwar AW, Ward AJ (1994). Inflammation, chromosomal instability, and cancer: the schistosomiasis model. Cancer Res. 54: 1929s–1933s.
Ross R (1993). Atherosclerosis: current understanding of mechanisms and future strategies in therapy. Transplant Proc. 25: 2041–2043.
Rudd CE (1990). CD4, CD8 and the TCR-CD3 complex: A novel class of proteintyrosine kinase receptor. Immunol. Today 11: 400-406.
Rutowski MD, DeLeo JA (2002). The role of cytokines in the initiation and maintenance of chronic pain. Drug News Perspect. 15: 626-632.
Saklatvala J, Dean J, Clark A (2003). Control of the expression of inflammatory response genes. Biochem. Soc. Symp. 70: 95-106.
Salvemini D, Misko TP, Masferrer JL, Seibert K, Currie MG, Needleman P (1993). Nitric oxide activates cyclooxygenase enzymes. Proc. Natl. Acad. Sci. 90: 7240-7244.
Samad TA, Moore KA, Sapirstein A, Billet S, Allchrone A, Poole S, Bonventre JV, Woolf CJ (2001). Interleukin-1β-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 410: 471-475.
Samelson LE, Patel MD, Weissman AM, Harford JB, Klausner RD (1986). Antigen activation of murine T cells Induces tyrosine phosphorylation of a polypeptide associated with the T cell antigen receptor. Cell 46: 1083-1090.
Schoonbroodt S, Piette J (2000). Oxidative stress interference with the nuclear factor- κB activation pathways. Biochem. Pharmacol. 60: 1075-1083.
Shariat SF, Andrews B, Kattan MW, Kim J, Wheeler TM, Slawin KM (2001). Plasma levels of interleukin-6 and its soluble receptor are associated with prostate cancer progression and metastasis. Urology 58: 1008-1015.
Shishodia S, Potdar P, Gairola CG, Aggarwal BB (2003). Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF_B activation through inhibition of IκB_ kinase in human lung epithelial cells: correlation with suppression of COX-2, MMP-9 and cyclin D1. Carcinogenesis 24: 1269-1279.
Silvestri M, Sabatini F, Defilippi AC, Ghiro L, Baraldi E, Rossi GA (2003). A marker of asthma inflammation: orally exhaled nitric oxide. ACI Int. 15: 37-43.
Sjöholm A, Nyström T (2005). Endothelial inflammation in insulin resistance. Lancet 365: 610-612.
Song C, Lin A, Bonaccorso S, Heide C, Vererk R, Kenis G, Bosmans E, Scharpe S, Whelan A, Cosyns P, de Jongh R, Maes M (1998). The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. J Affect. Disord. 49: 211-219.
Suk K (2005). Regulation of Neuroinfl ammation by Herbal Medicine and Its Implications for Neurodegenerative Diseases A Focus on Traditional Medicines and Flavonoids. Neurosignals, 14: 23-33.
Sweeney JE, Bachman ES, Coyle JT (1990). Effects of different doses of galanthamine, a long-acting acetylcholinesterase inhibitor, on memory in mice. Psychopharmacology (Berl). 102: 191–200.
Tak PP, Firestein GS (2001). NF_B: a key role in inflammatory diseases. J. Clin. Invest. 107: 7–11.
Tauber AI, Fay JR, Marletta MA (1984). Flavonoid inhibition of the human neutrophil NADPH-oxidase. Biochem. Pharmacol. 33: 1367-1369.
Theoharides TC (1996). Mast cell: A neuroimmunoendocrine master player. Int. J. Tissue React. 18: 1-21.
Torre-Amione G, Vooletich MT, Farmer JA (2000). Role of tumor necrosis factor-α in the progression of heart failure. Drugs 59(4): 745-751.
Tracey KJ (1994). Chapter 8. Interleukin-6. In: Thomson A.W, editor. The cytokine handbook, 2nd edition. New York: Academic Press, pp. 289-304.
Trevillyan JM, Lu Y, Atluru D, Phillips CA, Bjorndahl JM (1990). Differential inhibition of T cell receptor signal transduction and early activation events by a selective inhibitor of protein-tyrosine kinase. J. Immunol. 145: 3223-3230.
Tsutamoto T, Hisanaga T, Atsuyuki W, Maeda K, Ohnishi M, Fukai D, Mabuchi N, Sawaki M, Kinoshita M (1998). Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J. Am. Coll. Cardiol. 31: 391-398.
Uckun FM, Dibirdik I, Smith R, Tuel-Ahigren L, Chandan-Langlie M, Schieven GL, Waddick KG, Hanson M, Ledbetter JA (1991a). Interleukin 7 receptor ligation stimulates tyrosine phosphorylation, inositol phospholipid turnover, and clonal proliferation of human B-cell precursors. Proc. Natl. Acad. Sci. USA 88: 6323-6327.
van der Poll T, van Deventer SJH (1999). Cytokines and anticytokines in the pathogenesis of sepsis. Infect. Dis. Clin. N. Am. 13(2): 413-427.
Van der Walt JJA, Vorster PJ (1988). Pelargoniums of South Africa, Natural Botanical Gardens: Kirstenbosch. vol.3.
van Hogezand RA, Verspaget HW (1998). The future role of anti-tumor necrosis factor-α products in the treatment of Crohn's disease. Drugs 56: 299-305.
Van Wyk B, van Oudtshoorn B, Gericke N (1997). Medicinal Plants of South Africa. Briza, Pretoria.
Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP (1997). Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J. Clin. Endocrinol. Metab. 82: 1313-1316.
Wagner H (1990). Search for plant derived natural products with immunostimulatory activity (recent advances). Pure Appl. Chem., 62: 1217-1222.
Wagner H (1999). New approaches in phytopharmacological research. Pure Appl. Chem., 71(9): 1649-1654.
Ward PA, Warren JS, Varani J, Johnson KJ (1991). PAF, cytokines, toxic oxygen products and cell injury. Mol. Aspects Med. 12: 169-174.
Watkins LR, Maier SF (1999). Implications of immune-to-brain communication for sickness and pain. Proc. Natl. Acad. Sci. 96: 7710-7713.
Watkins LR, Maier SF, Goehler LE (1995). Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain 63: 289-302.
Watt JM, Breyer-Brandwijk MG (1962). The Medicinal and Poisonous Plants of Southern and Eastern Africa. E and S Livingston Ltd., Edinburgh-London.
Weisburger JH (2002). Lifestyle, health and disease prevention: the underlying mechanisms. Eur. J. Cancer Prev. 11(2): S1–S7.
Weitzman SA, Gordon LI (1990). Inflammation and Cancer: Role of phage-generation oxidants in carcinogenesis. Blood 76: 655–663.
Weksler BB (1983). Platelets and the inflammatory response. Clin. Lab. Med. 3: 667-677.
Wieseler-Frank J, Maier SF, Watkins LR (2005). Immune-to-brain communication dynamically modulates pain: physiological and pathological consequences. Brain. Behav. Immun. 19: 104-111.
Woodruff-Pak DS, Vogel RW, Wenk GL (2001). Galantamine: Effect on nicotinic receptor binding, acetylcholinesterase inhibition, and learning. Proc. Natl. Acad. Sci. USA 98: 2089-2094.
Yamamoto Y, Gaynor RB (2001). Role of the NF-kappaB pathway in the pathogenesis of human disease states. Curr. Mol. Med. 1: 287-296.
Yamanashi Y, Kakiuchi T, Milizuguchi J, Yamamoto T, Toyoshima K (1991). Association of B cell antigen receptor with protein tyrosine kinase Lyn. Science 251: 192-194.
Zetterstrom M, Sundgren-Andersson AK, Ostlund P, Bartfai T (1998). Delineation of the proinflammatory cytokine cascade in fever induction. Ann. N. Y. Acad. Sci. 856: 48-52.
Zhao B, Stavchansky SA, Bowden RA, Bowman PD (2003). Effect of interleukin-1_ and tumor necrosis factor-on gene expression in human endothelial cells. Am. J. Physiol. Cell Physiol. 284: C1577-1583.