

## Review

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

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**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 dis-

eases 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 terpenoids also have been shown to have anti-inflammatory activity and may play an important

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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 Dalglish, 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- $\alpha$ ), 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) such as superoxide anion ( $O_2^-$ ), 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<sup>-</sup> 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 (NF $\kappa$ B). Ultimately, the activation of the transcription factor NF $\kappa$ B 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 ameliorated (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 Dalglish 2001; Dalglish 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<sub>2</sub>, 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<sub>2</sub> and serotonin, as well as TGF- $\beta$ , 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).

| <b>Diverse disorders</b>                  | <b>Pro-inflammatory (cytokines) Mediator Expression</b>  | <b>References</b>  |
|---|--|--|
| Acquired Immunodeficiency Syndrome (AIDS) | Increased secretion of TNF- $\alpha$ , 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- $\alpha$ and IL-1 $\beta$ , 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- $\alpha$ concentrations in patients with <i>Plasmodium falciparum</i> 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- $\alpha/\gamma$ 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).  |
| <b>Cardiovascular Disorders</b>           |  |  |
| 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- $\alpha$ and IL-1 $\beta$ 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- $\alpha$ and IL-6 were associated with progression from asymptomatic to symptomatic left ventricular dysfunction and excessive TNF- $\alpha$ 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- $\alpha$ .   | (Milani. et al., 1996, Tsutamoto et al 1998, Torre-Amione 2000, Mann 2002).                  |
| Elderly (Aging)                           | Elevated concentrations of IL-1, TNF- $\alpha$ , IL-6 and sTNFRII increased concentrations of TNF- $\alpha$ 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- $\alpha$ 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-1 $\alpha$ , 1 $\beta$ , TNF- $\alpha$ and IL-6; post-myocardial infarction patients with prolonged fever had increased inflammatory activity.   | (Zetterstrom et al., 1998, Gabriel et al., 2000)   |
| <b>Gastrointestinal Disorders</b>         |  |  |
| Crohn's Disease                           | High IL-1 and 12 activity increases pro-inflammatory state.  | (van Hogezaand et al., 1998).  |
| Peptic Ulcer                              | High ulcerogenic potential of <i>Helicobacter pylori</i> is linked, in part, to increased activity of IL-8 and TNF- $\alpha$ ; <i>Helicobacter pylori</i> and NSAIDs cause ulcer recurrence through production of IL-1 and TNF- $\alpha$ 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- $\alpha$ , IL-1 $\beta$ and IL-6 overexpression stimulated production of amyloid- $\beta$ which is crucial for neurodegeneration in Alzheimer's patients.   | (Griffin et al., 1998, Mrak and Griffin 2001, Eikelenboom et al., 2002, Blasko and Grubeck-Loebenstern 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- $\alpha$ 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 $\beta$ -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- $\alpha$ , IL-1 and IL-6 pathway is associated with altered pain perception; hyperalgesia induced by TNF- $\alpha$ 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-1 $\beta$ mediated induction of cyclooxygenase-2 in neurons of the central nervous system contributes to inflammatory pain hypersensitivity; bradykinin B <sub>2</sub> receptors are suggested to be involved with the acute phase of the inflammatory and pain response; TNF- $\alpha$ 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-1 $\beta$ , IL-6 and IFN- $\gamma$ , IL-1ra, sIL-6r and TNF- $\alpha$ ; increased IL-1 $\beta$ 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- $\alpha$ increased IL-1 $\beta$ polymorphism; drug-naïve schizophrenic patients had increased IL-2 and IFN- $\gamma$ 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- $\alpha$ 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- $\alpha$ , IL-1, IL-1ra, IFN- $\gamma$ and lower production of IL-4 and IL-10; increased expression of neutrophils, monocytes, CD8 <sup>+</sup> , CD2 <sup>+</sup> CD26 <sup>+</sup> and CD2 <sup>+</sup> HLA-DR <sup>+</sup> T cells and CD19 <sup>+</sup> 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- $\alpha$ as a central proinflammatory mediator increased concentrations of IL-1, IL-6, TNF- $\alpha$ , 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<sub>2</sub> 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 (NFkB) 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 NFkB (Pahl, 1999). In normal cells, NFkB is bound to an inhibitory protein Ikb, and the complex Ikbeta is present in the cytoplasm. A variety of inflammatory stimuli, such as bacterial infections, lipopolysaccharide (LPS), injury, TPA, UV irradiation, ROS, and inflammatory cytokines (TNF $\alpha$  and IL-1), activate NFkB by phosphorylating I-kappaB with Ikb kinase and subsequently degrading the Ikb complex. Released NFkB is then translocated into the nucleus and binds to DNA and activates the transcription of many genes, including pro-inflammatory cytokines, chemokines, TNF $\alpha$ , IL-1, adhesion molecules, phospholipids A<sub>2</sub>,

lipoxygenase, COX-2, iNOS, and myeloperoxidase (Baldwin, 1996; Pahl, 1999). Abnormal activation of the NFkB pathway is involved in degenerative chronic inflammatory diseases, such as asthma, rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, 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<sub>2</sub>)-derived second messengers, namely inositol triphosphate (IP<sub>3</sub>) 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<sub>3</sub> 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**

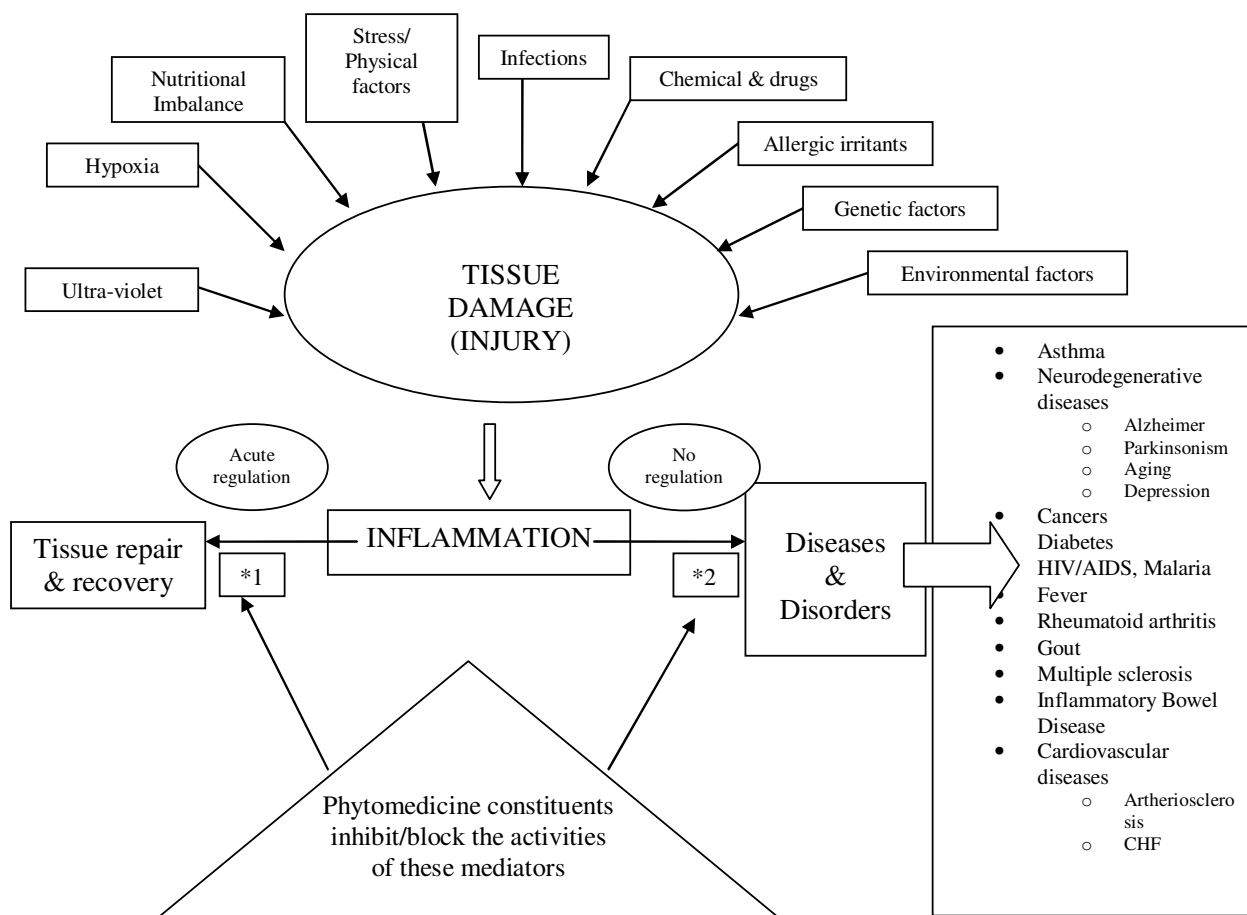
Based on the molecular events that lead to inflammation, we therefore suggest that the process of sustained inflammation that accompanies chronic diseases can be ameliorated and possibly even prevented by phytomedicines. The anti-inflammatory properties of several phytomedicines origin, that contain 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 removed 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 relieve 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 these 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 scrophulariflora* (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, sesquiterpenoids, 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 NF $\kappa$ B, 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 NF $\kappa$ B 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, NF $\kappa$ B plays a critical role in the regulation of genes involved in the expression of pro-inflammatory enzymes (iNOS, COX-1 and 2, TNF- $\alpha$ ), suppression of NF $\kappa$ B 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 NF $\kappa$ B are the devastating products from cells that generate all other factors in inflammatory process. For example *Pelargonium sidoides*, and the *Picrorhiza scrophulariflora* (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- $\alpha$ , 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  |
|---|--|--|--|
| <i>Acacia burkei</i> (Fabaceae)                 | stem bark / root                           | not known  | painful back and eye   |
| <i>Acacia sieberiana</i> (Fabaceae)             | stem bark                                  | not known  | fever, genitals and back pains and aches   |
| <i>Achyranthes aspera</i> (Amaranthaceae)       | whole plant: root, leaves and aerial parts | achyranthine and glycosides  | chest pain, coughs, menstrual bleeding, boils, abscesses and stomach complaints. |
| <i>Acokanthera oppositifolia</i> (Apocynaceae)  | leaves and root                            | amorphous acokantherin   | painful feet, rheumatism, toothache, abnormal menstrual period, and swellings    |
| <i>Alepidea amatymbica</i> (Apiaceae)           | root/rhizome                               | terpenoid kaurene  | cold, cough, diarrhoea, headache and rheumatism                                  |
| <i>Aptenia cordifolia</i> (Mesembryanthemaceae) | leaves and stem                            | alkaloids  | painful joints.  |
| <i>Asclepias fruiticosa</i> (Asclepiadaceae)    | leaf, stem and root                        | aardenolide glycoside  | diarrhoea and stomach pain, facilitate child-birth, asthma and diabetes.         |
| <i>Athrixia phylicoides</i> (Asteraceae)        | root and leaves                            | diterpenoids   | cough , sores and boils  |
| <i>Barleria ovata</i> (Acanthaceae)             | root                                       | not known  | painful nodule swellings under the skin  |
| <i>Berchemia zeyheri</i> (Rhamnaceae)           | stem bark                                  | pentahydroxychachones  | backache and rectal ulcer  |
| <i>Berkheya speciosa</i> (Asteraceae)           | root and leaves                            | sesquiterpenoids, socomene   | abdominal pains  |
| <i>Bidens pilosa</i> (Asteraceae)               | root and leaves                            | chalcones and polyacetylenes   | jaundice, eye, colic, bronchial problems, and rheumatism                         |
| <i>Boophane disticha</i> (Amaryllidaceae)       | bulb                                       | alkaloids  | headache, chest and bladder pain, boils wounds and swelling.                     |
| <i>Bowiea volubilis</i> (Liliaceae)             | bulb                                       | cardiac glycosides   | facilitate child-birth, bladder pains, sore eyes and skin diseases.              |
| <i>Brachylaena elliptica</i> (Asteraceae)       | leaves                                     | mucilage, tannins and onopordopicrin.  | facilitate child-birth, back and stomach pain, pneumonia.                        |
| <i>Bridelia micrantha</i> (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.                |
| <i>Bulbine alooides</i> (Liliaceae)             | tuber                                      | not known  | anti-syphilis and rheumatism   |
| <i>Bulbine asphodeloides</i> (Liliaceae)        | tuber and leaves                           | not known  | rashes, sores wounds, dysentery and diarrhoea                                    |
| <i>Bulbine latifolia</i> (Liliaceae)            | leaves                                     | not known  | dysentery and diarrhoea  |
| <i>Capparis tomentosa</i> (Capparaceae)         | root bark                                  | sulphur oil  | swellings and fever  |
| <i>Cavacoa aurea</i> (Euphorbiaceae)            | root                                       | not known  | pain and fever   |
| <i>Cenchrus ciliaris</i> (Poaceae)              | rhizome                                    | not known  | body pain, menstrual disorders and urinary infections in women                   |
| <i>Cephalaria zeyheriana</i> (Dipsaceae)        | root decoction                             | not known  | swellings and pain   |
| <i>Chaetacme aristata</i> (Ulmaceae)            | bark and root                              | not known  | swellings in haemorrhoids and dental anodynes                                    |
| <i>Clausena anisata</i> (Rutaceae)              | leaves, stem and root                      | terpenoids, alkaloids, coumarins and limonoids   | abdominal pain toothache fever and rheumatism                                    |

Table 2. Contd.

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

Table 2. Contd.

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

Table 2. Contd.

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

Table 2. Contd.

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

$\alpha$ -tocopherol, ascorbic acid, curcumin, [salicylic acid derivatives] etc. are able to inhibit processes that lead to inflammation, such as (1) the activation of NF $\kappa$ B (2) induction and up-regulation of pro-inflammatory cytokines, (3) up-regulation and activation of CAMs by pro-inflammatory cytokine TNF- $\alpha$  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 endothelial 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 NF $\kappa$ B 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.

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