Targeting the production of monocytes/macrophages-derived cytokines by anti-inflammatory herbal drugs

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Abstract

Macrophages and their immature undifferentiated predecessors, monocytes, are part of the innate immune system with primary function in defense against infection, malignancy and in immunity. Of the various protein mediators produced by monocytes/macrophages are proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1β) and IL-6. The regulated release of these cytokines result in the initiation of inflammation through activation of immune cells and upregulation of expression of adhesion molecules that eventually lead to leucocyte infiltration to extravascular sites. Hence, one of the most attractive approaches of alleviating the severity of chronic inflammatory diseases is suppressing the production of monocytes/macrophages-derived TNF-α, IL-1β and IL-6. This review highlights some common targets of the monocytes/macrophage-derived cytokines expression, experimental models of proinflammatory cytokines release, and mechanism of action of some exemplary antiinflammatory herbal drugs. The effects of crude drug preparations on transcription factors (e.g. nuclear factor-κB), signalling pathways including the mitogen-activated protein kinase cascades and induction of immunosuppressive proteins (IL-10) are among the common targets discussed.

Keywords: Monocytes; macrophages; inflammation; herbal drugs; proinflammatory cytokines; TNF-α; IL-1β; IL-6; IL-8; IL-10; HMGB1

Introduction

Monocytes are members of the granulocytes (neutrophils, basophils, eosinophils, mast cells, natural killer cells and monocytes) cell populations that constitute the innate immune system (Papatriantafyllou, 2011). Being the first line of defense of the body, their primary function is that of cell mediated immunity against infection and malignancy. Monocytes are formed in the bone marrow from a common monocyte, macrophage and dendritic pluripotent stem cell precursors (Gordon and Taylor, 2011). Following the differentiation process that lasts less than 24 hours, mature monocytes leave the bone marrow and enter the bloodstream...
as quiescent cells. Circulating monocytes then migrate into tissues such as spleen, liver, central nervous system, lymph nodes, lungs, peritoneal cavity, and the subcutaneous tissue (Strauss-Ayali et al., 2007). The spleen is considered as a secondary reservoir where about half of the monocyte population in the body are stored.

Circulating monocytes are recruited to sites of inflammation, injury or antigen deposition where they are activated by a variety of stimuli. Once entered into tissues, monocytes differentiate into cells that express the macrophage phenotype and also into dendritic cells (Gordon and Taylor, 2011; Strauss-Ayali et al., 2007). In general, the macrophage population in tissues are classified as ‘resident’ when they are present in tissues at all times or ‘newly recruited’. Undoubtedly, the major function of the monocytes/macrophages is phagocytosis. They are equipped with an array of sensory recognition and removal mechanisms for invading pathogens as well as senescent, damaged or dead host cells. In addition to their routine phagocytosis role, monocytes/macrophages are further involved in specific immunity by presenting antigens to T-cells (Parkin and Cohen, 2001). They are also by far the most well known secretory cells which are capable of responding to a variety of stimuli. Of the various mediators produced by monocytes/macrophages are enzymes, enzyme inhibitors, cytokines, chemokines, complement components, coagulation factors, and arachidonic acid metabolites. They are also influenced by their own products in a paracrine and autocrine manner. The crucial role of monocytes/macrophages in physiological and pathological conditions, including chronic inflammatory disorders, have been reviewed in the various literatures (Gui et al., 2012; Lebre and Tak, 2012). The main focus of this communication is to review the monocyte/macrophone inflammatory cytokines production as a valued target for herbal drug preparations.

Major Monocytes/macrophages-derived proinflammatory cytokines

Tumour necrosis factor-α (TNF-α)

TNF-α is one of the major proinflamatory cytokenes secreted by monocytes/macrophages. The human TNF-α is known to be expressed as a 26-kDa precursor monomer protein which is anchored to a plasma membrane. Further proteolytic cleavage by TNFα-converting metalloprotease enzyme releases a mature 17-kDa soluble TNF-α protein. Both secreted and membrane-bound TNF-α are assembled in trimeric structural form that induce a range of biological activities (Aggarwal, 1992; Bazzoni & Beutler, 1995). It is now well established that TNF-α gene expression is primarily regulated at transcriptional level by nuclear factor κB (NFκB) and other transcription factors though regulation at translational level has also been reported (Pauli, 1994; Sariban et al., 1988).

The release of TNF-α from monocytes/macrophages is triggered by a variety of agents including physical trauma, infection, bacterial cell wall components and cytokines. TNF-α does also act on monocytes/macrophages in an autocrine fashion to induce a more sustained release of inflammatory mediators such as protein (cytokines including TNF-α) and lipid-borne mediators. Not surprisingly, TNF-α is now considered as a major target for chronic inflammatory diseases including rheumatoid and osteo arthritis, ankylosing spondylitis, Crohn’s disease and ulcerative colitis, psoriasis, etc. (Wong et al., 2008; Vinay and Kwon,
2012). Etanercept and infliximab are two examples of protein based clinically useful drugs that neutralise TNF-α. The therapeutic potential of these drugs in various chronic inflammatory conditions have been extensively reviewed in recent years (Hauwermeiren et al., 2011; Furst et al., 2007; Griffoul et al., 2009; Markham & Lamb 2000; Mortensen et al., 2011; Tracey, 2008; Weinberg et al., 2003).

**Interleukin-1β (IL-1β)**

The second most prominent proinflammatory cytokine of monocyte/macrophage origin is IL-1β (Gabay et al., 2010; Dinarello, 2011). As with TNFα, IL-1β is formed as a precursor protein that requires proteolytic processing by IL-1β converting enzyme (Dinarello, 1997). The role of IL-1β in the pathology of chronic inflammatory conditions is well established. An IL-1 receptor antagonist (e.g. anakinra) and protein that neutralize IL-1 (e.g. rilonacept) have been clinically used to treat various chronic inflammatory conditions (Llord et al., 2007; Furst, 2004; McDermott MF, 2009; Scott, Terkeltaub, 2010). Other approaches of targeting IL-1 family cytokines have also been reviewed recently (Dinarello et al., 2012).

**Interleukin-6 (IL-6)**

IL-6 is the late addition of proinflammatory cytokine of monocyte origin that gained some attention in recent years. In view of its possible therapeutic potential, receptor antagonist approaches have also been developed (Jalal et al., 2010). Some clinical studies demonstrated that a monoclonal antibody against IL-6 showed beneficial effect in treating rheumatoid arthritis (Alonso and Bilbao, 2009). The true potential of targeting IL-6 for inflammatory diseases however is yet to be fully assessed.

**The therapeutic approach of targeting monocytes/macrophages-derived proinflammatory cytokines**

Once released, TNF-α, IL-1β and IL-6 activate vascular endothelial cells and leucocytes leading to the expression of various adhesion molecules. The receptor-ligand type interaction by the various adhesion molecules on leucocyte and endothelial cell surface further mediate leucocytes arrest and infiltration to extravascular sites of injury and/or antigen deposition. As shown in Scheme 1, the regulated acute inflammatory process is part of the body’s defense mechanism and is necessary for the overall maintenance of tissue repair and architecture. Under chronic inflammatory condition however, over expression of inflammatory cytokines coupled with continuous leucocyte recruitment lead to a disease state. The various approaches of targeting cytokines-induced expression of adhesion molecules by natural products is reviewed recently (Habtemariam, 2010).

A decade ago, a comprehensive review article from this laboratory (Habtemariam, 2000) also outlined the potential role of natural products as inhibitors of by far the most potent inflammatory mediator, TNF-α. The present review is intended, to shade some light on advances in herbal medicine research since then with particular emphasis to monocyte/macrophage-derived proinflammatory cytokines release.
Inflammation is a necessary body defense mechanism against infection and injury. Among other granulocytes, monocytes contribute in phagocytosis and elimination of microbes and injured cell debris. As a major producers of proinflammatory cytokines (TNF-α, IL-1β and IL-6), monocytes orchestrate the inflammatory reaction through activation of endothelial and leucocytes leading to adhesion molecules expression and eventually leucocyte accumulation at extravascular sites. This acute normal physiological phenomenon (shown as 1) however became exaggerated under pathological condition (route 2) and lead to chronic inflammatory condition.

Experimental models of monocyte/macrophage-derived cytokines release

The use of human peripheral blood mononuclear cells (PBMC) as an in vitro method for studying monocyte immune functions has been extensively reviewed (Reddy et al., 2004). In this study protocol, whole blood from healthy donors is collected in sterile tubes containing anticoagulants such as heparin or EDTA. After dilution, PBMC can be isolated by density gradient centrifugation over leukocyte separation media (e.g. Ficoll-Hystopaque). PBMC often at a higher density (~ 10^6/ml) are cultured in RPMI-1640 medium containing 10% heat-inactivated foetal bovine serum. Various other literatures have also described cytokines release study from PBMS of rodent’s origin (Treffkorn et al., 2004).

The other common source of primary culture for cytokines release study is mice/rats-derived peritoneal macrophages. In this classical model of monocyte/macrophage in vitro cell culture, animals are sacrificed and surface sterilisation of the skin achieved by using 70% alcohol. Phosphate buffered saline can then be injected into the peritoneal cavity and residental macrophages collected after vigorous shaking. In order to increase the yield of peritoneal macrophages, mice/rats are often treated with thioglycollate (Ezeamuzie & Khan, 2007).
and macrophages recovered few days (3-4 days) later. Bronchoalveolar lavage fluid (Joubert et al., 2011) and bone marrow (dos Santos et al., 2011) from mice/rats have also been used as sources of primary monocyte/macrophages culture for cytokines studies. One could therefore adopt a primary culture-based cytokines release from either human or animal sources depending on availability of volunteers and available resources. In all cases, isolated cells can be seeded in a flat-bottomed 96-well culture plate at $10^5$-$10^6$ cells/well in a final volume of 100-200 μl. Cell culturing for 2-3 days in RPMI medium (supplemented with 10% serum) at 37 °C will then allow macrophages to adhere to the plate while other blood cells (e.g. lymphocytes) are still suspended in the culture medium. Non-adherent cells are removed by repeated washing with warm buffer (e.g. Hank's balanced salt solution). Macrophages can be distinguished by their morphology and expression of a marker lipopolysaccharide (LPS)-binding protein, CD14.

The vast majority of cytokine release studies from monocytes/macrophages came through the use of transformed cell lines. THP-1 and U937 are human leukaemia derived monocytic cells that are routinely used for in vitro cytokine release studies. These cells can be readily differentiated to macrophage phenotypes when stimulated by appropriate simply such as phorbol esters. Perhaps the most convenient method of cytokine release inhibition study is that based on the murine macrophage-like cell line, RAW 264.7 cells. These adherent cells can easily be maintained and activated by a variety of inflammatory stimuli including bacterial LPS or proinflammatory cytokines. Treatment of cultured macrophages results in the release of IL-1, IL-6 and TNF-α that can be quantified by ELISA or other bioassay methods. For further details of each bioassay model, readers are directed to the various literature cited in Table 1.

**Herbal drugs with inhibitory effect against targets in monocyte/macrophage-derived proinflammatory cytokines: progress in the last decade**

Cytokines expression in macrophages requires activation of specific genes that can be regulated at various levels. The promotor genes of these cytokines (e.g. TNF-α) have been shown to have specific binding sites for transcription factors, including NF-κB, AP-1 (activator protein-1), CRE, and CCAAT/enhancer binding protein β (C/EBPβ, also called NF-IL6) (Zagariya et al., 1998). Numerous studies suggest that the transcriptional control of proinflammatory cytokines is primarily mediated by NF-κB. It is now unequivocally established that NF-κB exists in macrophages as a heterodimeric inactive form in the cytosol by binding with an inhibitory IκB protein subunit. NF-κB activation thus requires phosphorylation, ubiquitination, and subsequent proteolytic degradation of IκB through the action of the IκB kinase (IKK) (Karin, 1999). The liberated NF-κB subsequently translocates into the nucleus and binds to the κB motif in the promoters region of target genes, leading to the induction of inflammatory cytokine (TNF-α, IL-1β and IL-6) genes. A number of inflammatory stimuli including reactive oxygen species are now known to trigger inflammatory response through the activation of NF-κB (Gloire et al., 2006). As shown in Table 1, the vast majority of anti-inflammatory herbal drugs have been shown to inhibit proinflammatory cytokines release through inhibition of NF-κB activation.

In addition to the NF-κB system, cytokine production from macrophages involves multiple signalling pathways, including the phosphatidylinositol-3 protein kinase/Akt, and the
mitogen-activated protein kinases (MAPKs) (Zhang & Ghosh, 2000; Ojaniemi et al., 2003; Yang et al., 2000). The MAPKs are a group of serine–threonine protein kinases that mediate signal transduction from the cell surface to the nucleus. Numerous recent reports highlighted the role of MAPK signaling cascade in cell survival and proliferation, differentiation, and apoptosis. In macrophages, the three well-defined MAPK cascades involved in proinflammatory cytokines expression are ERK (extracellular signal-related kinase), p38 MAPK, and JNK/SAPK (C-Jun N-terminal kinase), ERK1/2, JNK, and p38 MAP kinase (Morel and Barenbaum, 2004). Activation of the MAPK system is achieved by a variety of inflammatory stimuli, including mitogens, proinflammatory cytokines and reactive oxygen species, UV radiation and physical stress (Morel and Barenbaum, 2004; Raingeaud et al., 1995). It is also widely accepted that MAPK signalling is a prerequisite to transcription factors activation such as NF-κB. Non-receptor type protein tyrosine kinases including Syk and Src have also been shown to play a role in monocyte-derived proinflammatory cytokines release (Pan et al., 1999). Since all of these signalling events eventually lead inflammatory cytokines gene expression in macrophages, they are considered as valuable anti-inflammatory targets for new drugs (Kaminska 2005). As with the NF-κB, the MAPK system has been shown to be a validated target for a number of herbal medicines (Table 1). As described in section 2, both IL-1β and TNF-α are produced as inactive molecules and need processing by converting enzymes. It remains to be seen however if this mechanism is the primary target for crude anti-inflammatory herbal drug preparations.

IL-8 is a pleiotropic cytokine product of not only monocytes/macrophages but also a variety of other cell types including lymphocytes, neutrophils, vascular endothelial cells, fibroblasts, keratinocytes, airway epithelial cells and hepatocytes. The role of IL-8 in the pathogenesis of inflammatory diseases has now been well established and high level of this cytokine has been detected in patients suffering from psoriasis, rheumatoid arthritis, osteoarthritis, gout, respiratory distress syndrome or idiopathic pulmonary fibrosis (Aherne et al., 2009; Ferran et al., 2010; Mihailidou et al., 2010). The major pathological role of IL-8 that gained considerable attention in recent years was however in airway inflammation (e.g. asthma) where a good correlation between IL-8 level and severity of the disease was established (Mihailidou et al., 2010). As a potent leucocyte activator and chemotaxin product of airway epithelial cells, IL-8 is often used as a biological marker of environmentally induced pulmonary inflammation (Strieter, 2002; Tal et al., 2010). The selective recruitment of eosinophils to accumulate in the airways of asthmatic patients is also shown to be attributed to IL-8 (Nakagome & Nagata, 2011). Agents that inhibit the secretion of IL-8 are thus likely to benefit asthmatic and other patients suffering from airway inflammation. As shown in Table 1, some crude plant extract preparations have been shown to inhibit the release of IL-8 from monocytes in vitro, suggesting their potential use for the above mentioned disease conditions.

Interleukin-10 (IL-10) is another pleiotropic cytokine that is released from monocytes and other activated immune cells. IL-10 was initially named as cytokine-synthesis inhibitory factor due to its ability to reduce the production of cytokines including TNF-α (Mocellin, et al., 2004). This cytokine is thus regarded as immunosuppressive and its level of production is associated with susceptibility to infection that is common in diseases like AIDS (Clerici et al., 2000). Under chronic inflammatory conditions where overproduction of proinflammatory cytokines is the major pathological hallmark, however, administration of IL-10 could be seen as an attractive therapeutic approach. Hence, IL-10 administration benefits patients suffering
from psoriasis, Crohn's disease, rheumatoid arthritis and many other chronic inflammatory diseases (Mocellin et al., 2003). Agents that increase the production of IL-10 can also offer immunosuppressive effect and the identification of Cucumis melo (Vouldoukis et al., 2004) and Vitex trifolia (Matsui et al., 2009) as anti-inflammatory agents that act through this mechanism are interesting findings (Table 1).

High mobility group box 1 (HMGB1) is a highly conserved, ubiquitous protein present in the nuclei and cytoplasm of nearly all cell types. As a late-stage proinflammatory cytokine, HMGB1 is secreted by immune cells to induce the expression of adhesion molecules and production of pro-inflammatory cytokines (Park et al., 2004). High level of HMGB1 has been shown to be associated with sepsis and a number of chronic inflammatory diseases like atherosclerosis while blocking monoclonal antibodies against HMGB1 and other inhibitory drugs could ameliorate the severity of these disease conditions (de Souza et al., 2012; Schierbeck et al., 2011). Angelica sinensis (Table 1) appears to be one good example of an anti-inflammatory herbal drug that work through HMGB1 inhibition.

Table 1. Crude plant preparations with reported inhibitory activities towards monocyte/macrophage-derived proinflammatory cytokines.

<table>
<thead>
<tr>
<th>Plant Name (Family)</th>
<th>Plant Part (Extract)</th>
<th>Study model</th>
<th>Stimuli</th>
<th>Cytokines</th>
<th>Proposed mechanisms: Inhibition of -</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelica sinensis (Apiaceae)</td>
<td>Root (Aqueous)</td>
<td>RAW 264.7</td>
<td>LPS</td>
<td>HMGB1</td>
<td>cytokine cytoplasmic translocation</td>
<td>Wang et al., 2004; Wang et al., 2006</td>
</tr>
<tr>
<td>Artemisia vestita Wall (Asteraceae)</td>
<td>Herb (EtOH)</td>
<td>RAW 264.7</td>
<td>LPS</td>
<td>TNF-α, IL-1β</td>
<td>MAPKs (p38, ERK1/2, JNK); NFKB</td>
<td>Sun et al., 2006</td>
</tr>
<tr>
<td>Boerhaavia diffusa (Nyctaginaceae)</td>
<td>Herb (EtOH)</td>
<td>RAW 264.7; hPBMCs</td>
<td>LPS</td>
<td>TNF-α</td>
<td>Mehrotra et al., 2002</td>
<td></td>
</tr>
<tr>
<td>Boswellia serrata (Bruseraceae)</td>
<td>Resin (hexane, CH2Cl2, EtOAc, MeOH)</td>
<td>RAW 264.7</td>
<td>LPS</td>
<td>TNFα, IL-1β, IL-6</td>
<td>MAPKs (JNK, p38)</td>
<td>Gayathri et al., 2007</td>
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<tr>
<td>Centella asiatica (Umbelliferae)</td>
<td>Whole plant (80% EtOH or Aqueous)</td>
<td>J774.2</td>
<td>LPS</td>
<td>TNF-α</td>
<td>Gene expression</td>
<td>Punturee et al., 2004</td>
</tr>
<tr>
<td>Crinum asiaticum Linne var. Japonicum (Amaryllidaceae)</td>
<td>(95% EtOH)</td>
<td>RAW 264.7</td>
<td>LPS</td>
<td>IL-6, IL-8</td>
<td>Kim et al., 2008</td>
<td></td>
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<tr>
<td>Cryptolepis buchanani Roem. &amp; Schult. (Asclepiadaceae)</td>
<td>(50% EtOH)</td>
<td>THP-1</td>
<td>LPS</td>
<td>TNF-α</td>
<td>Laupattarakasem et al., 2006</td>
<td></td>
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<tr>
<td>Curcuma comosa Roxb. (Zingiberaceae)</td>
<td>Rhizome (Hexane or EtOH)</td>
<td>U937, hPBMC</td>
<td>PMA</td>
<td>TNF-α, IL-1β</td>
<td>Sodsai et al., 2007</td>
<td></td>
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<tr>
<td>Cucumis melo L.C., Cucurbitaceae)</td>
<td>Fruit (Aqueous)</td>
<td>Peritoneal macrophages (PM)</td>
<td>IFN-gamma and IgG1/anti-IgG1 immune</td>
<td>TNF-α; induction of IL-10</td>
<td>Vouldoukis et al., 2004</td>
<td></td>
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<tr>
<td>Plant Name</td>
<td>Part Used</td>
<td>Extractant</td>
<td>Method</td>
<td>LPS</td>
<td>TNF-α</td>
<td>IL-1β, TNF-α, IL-6, IL-8</td>
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<tr>
<td>Cymbopogon citrates (lemon grass; Poaceae)</td>
<td>Leaves (50% EtOH)</td>
<td>Alveolar macrophages (AM)</td>
<td>LPS</td>
<td></td>
<td></td>
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<tr>
<td>Daenomorops draco BL. (Palmae). (Areaceae)</td>
<td>Resin (EtOAc)</td>
<td>RAW 264.7</td>
<td>LPS</td>
<td>IL-1β, TNF-α, IL-6, IL-8</td>
<td>Possibly ROS production</td>
<td>Heo et al., 2010</td>
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<td>Daphne gnidium (Thymelaceae)</td>
<td>Leaves (EtOAc)</td>
<td>PM</td>
<td>LPS</td>
<td>IL-1β, TNF-α</td>
<td></td>
<td>Harizi et al., 2011</td>
</tr>
<tr>
<td>Dionysia termeana (Primulaceae)</td>
<td>Aerial parts (MeOH)</td>
<td>PM</td>
<td>LPS</td>
<td>IL-1β</td>
<td></td>
<td>Amirghofran et al., 2011</td>
</tr>
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<td>Dracocephalum kotschyi (Labiatae)</td>
<td>Aerial parts (MeOH)</td>
<td>PM</td>
<td>LPS</td>
<td>IL-1β</td>
<td></td>
<td>Amirghofran et al., 2011</td>
</tr>
<tr>
<td>Duchesnea indica (Andr) Focke</td>
<td>(EtOH)</td>
<td>RAW 264.7</td>
<td>LPS</td>
<td>TNF-α, NF-κB</td>
<td>Zhao et al., 2008</td>
<td></td>
</tr>
<tr>
<td>Eunicostema axillare (Lam.) A. Raynal (Gentianaceae)</td>
<td>Whole plant (MeOH)</td>
<td>PM</td>
<td>LPS</td>
<td>TNF-α, IL-1β</td>
<td></td>
<td>Saravanan et al., 2012</td>
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<tr>
<td>Eupatorium perfoliatum L. (Asteraceae)</td>
<td>Aerial parts (MeOH, EtOH, CH₂Cl₂)</td>
<td>hPBMC; RAW 264.7</td>
<td>LPS</td>
<td>TNF-α, IL-1β</td>
<td></td>
<td>Maas et al., 2011</td>
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<td>FAHF-2</td>
<td>Mixed herbal formula (Butanol)</td>
<td>RAW 264.7</td>
<td></td>
<td></td>
<td></td>
<td>Yang et al., 2009</td>
</tr>
<tr>
<td>Ferulago angulata (Apiaceae)</td>
<td>Aerial parts (MeOH)</td>
<td>PM</td>
<td>LPS</td>
<td>IL-1β</td>
<td></td>
<td>Amirghofran et al., 2011</td>
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<tr>
<td>Ginkgo biloba (Ginkgoaceae)</td>
<td>Standardised commercially available extract</td>
<td>RAW 264.7</td>
<td>LPS</td>
<td>TNF-α</td>
<td>NF-κB; MAPKs (ERK1/2, p38 MAPK)</td>
<td>Wadsworth et al., 2001</td>
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<tr>
<td>Glossogyne tenuifolia (Hsiang-Ju) (Asteraceae)</td>
<td>Aerial parts (EtOH)</td>
<td>hPBMC; RAW 264.7</td>
<td>LPS</td>
<td>TNF-α, IL-1β, IL-6, IL-12</td>
<td>NF-κB; IκB-α phosphorylation</td>
<td>Wu et al., 2005; Wu et al., 2004; Ha et al., 2006</td>
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<td>Glycyrrhiza glabra (Fabaceae)</td>
<td>Root (Aqueous (CH₃)₂CO)</td>
<td>J774A.1</td>
<td>LPS</td>
<td>IL-1β</td>
<td></td>
<td>Thiyagarajan et al., 2011</td>
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<tr>
<td>Harpagophyton procumbens (Pedaliaceae)</td>
<td>Root (50 or 60% EtOH; standardised extract (SteilHap 69; MeOH)</td>
<td>RAW 264.7;</td>
<td>LPS</td>
<td>TNFa, IL-6, IL-1β</td>
<td>Gene expression; No effect on NF-κB and MAPK.</td>
<td>Fiebich et al., 2012; 2010; 2001; Gvyrkovska et al., 2011; Inaba et al., 2010</td>
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<td>Hibiscus sabdariffa (Malvaceae)</td>
<td>Calyces (Aqueous)</td>
<td>U937</td>
<td>Cadmium</td>
<td>TNFa, IL-6, IL-1β</td>
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<td>Okoko and Ere, 2012</td>
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<td>Plant Name</td>
<td>Extract Type</td>
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<td>Stimulus</td>
<td>Translocation/Phosphorylation</td>
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<tr>
<td>Hippophae rhamnoides (Elaeagnaceae)</td>
<td>(Supercritical CO2 extract)</td>
<td>hPBMCs</td>
<td>LPS</td>
<td>IL-6; TNF-α; NF-κB translocation; p38 MAPK</td>
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<tr>
<td>HMC05</td>
<td>Comprises of eight different herbs (Aqueous)</td>
<td>RAW264.7</td>
<td>LPS</td>
<td>TNF-α, IL-1β</td>
<td></td>
<td></td>
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<tr>
<td>Hypericum triquetrifolium (Hypericaceae)</td>
<td>(Aqueous)</td>
<td>RAW 264.7; THP-1</td>
<td>LPS</td>
<td>TNF-α, IL-6</td>
<td></td>
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<tr>
<td>Inula japonica Asteraceae</td>
<td>Flowers (EtOH)</td>
<td>RAW264.7</td>
<td>LPS</td>
<td>TNF-α; IL-6</td>
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<tr>
<td>Justicia gendarussa Burm. F. (Acanthaceae)</td>
<td>Roots (MeOH, EtOAc)</td>
<td>hPBMCs</td>
<td>LPS</td>
<td>IL-6</td>
<td></td>
<td></td>
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<td>Kochia scoparia (L.) Chard (Chenopodiaceae)</td>
<td>Fruits (MeOH)</td>
<td>RAW264.7</td>
<td>LPS</td>
<td>TNF-α</td>
<td></td>
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<td>Mangifera indica L. (Anacardiaceae)</td>
<td>Stem bark (Aqueous)</td>
<td>RAW264.7</td>
<td>LPS</td>
<td>TNF-α</td>
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<td>Ligustrum lucidi Oleaceae</td>
<td>Fruit (EtOH)</td>
<td>PM; J774 cells</td>
<td>LPS</td>
<td>TNF-α</td>
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<td>Linum persicum (Linaceae)</td>
<td>Aerial parts (Aqueous)</td>
<td>PM *</td>
<td>LPS</td>
<td>TNF-α, IL-1β</td>
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<td>Paeonia suffruticosa (Paocniaceae)</td>
<td>Root (MeOH)</td>
<td>PM*; U937</td>
<td>LPS/rIFN-gamma</td>
<td>TNF-α; IL-8; NF-κB</td>
<td></td>
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</tr>
<tr>
<td>Panax notoginseng Burk. (Araliaceae)</td>
<td>Root (EtOH)</td>
<td>RAW264.7</td>
<td>LPS</td>
<td>TNF-α, IL-1β IL-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebodium decumanum (Polypodiaceae)</td>
<td>Fronds (aqueous)</td>
<td>hPBMC; J774; RAW</td>
<td>LPS</td>
<td>TNF-α; No effect on NF-κB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phyllanthus amarus (Euphorbiaceae)</td>
<td>(Standardised commercially available extract; Hexane, aqueous EtOH, Aqueous)</td>
<td>RAW 264.7; PM; BMDM*</td>
<td>LPS</td>
<td>TNF-α; NF-κB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platycladus orientalis Linn. (Cupressaceae)</td>
<td>Leaves (95% EtOH)</td>
<td>PM; RAW264.7</td>
<td>LPS</td>
<td>TNF-α</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polygononum hydropiper L. (Polygonaceae)</td>
<td>Leaves (MeOH)</td>
<td>RAW264.7; PM*</td>
<td>LPS</td>
<td>NF-κB activator protein (AP-1) and cAMP responsive element binding protein (CREB), Syk, Src, and IRAK1</td>
<td></td>
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</tbody>
</table>
Traditional herbal medicines have been used as a primary healthcare medicine by mankind for thousands of years. Numerous reports also claim that the vast majority of the world population today still rely on such crude drug preparations for treating various diseases (Habtemariam, 2010 and references there in). While scientific data are available to justify the claimed traditional uses of some medicinal plant, more research is needed to prove the quality, safety and efficacy of many herbal preparations. In this communication, the release of proinflammatory cytokines from monocytes/macrophages is evaluated as a target for anti-inflammatory crude herbal preparations. The use of in vitro monocyte/macrophage culture methods allows rapid screening and identification of plant extracts that inhibit cytokine production/release. Further validation of anti-inflammatory activity can be obtained by employing in vivo studies as secondary assays. For example, the popular Chinese herbal medicine,
Angelica sinensis, which has been shown to inhibit proinflammatory cytokines release (Table 1) can protect mice against lethal endotoximia and sepsis (Wang et al., 2006). Similarly, lemongrass extract has been shown to inhibit the LPS-induced IL-6 in vivo (Bachiega and Sforcin, 2011) while Mangifera indica demonstrated to have anti-inflammatory activity in a variety of in vivo inflammation models (Garrido et al., 2004a; b; Garrido et al., 2006).

**Conclusion**

The production and release of proinflammatory cytokines (TNF-α, IL-1β and IL-6) from monocytes/macrophages play critical role in the pathogenesis of chronic inflammatory diseases. The anti-inflammatory effect of many herbal drugs are now shown to be attributed to their potent suppressive effect of TNF-α, IL-1β and/or IL-6 release. Although the exact mechanism of action has not been studied for all of these crude herbal drugs, many have been shown to inhibit the activation of NF-κB and/or the MAPK signalling system that are crucial for cytokines gene expression in monocytes/macrophages. Few herbal preparations have been shown to enhance the production of an immunosuppressive cytokine, IL-10. Other interesting development in this field is the identification of HMGB-1 as a target for chronic inflammatory diseases.

**References**


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