Anti-inflammatory and Analgesic Agents from Indian Medicinal Plants

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Abstract

Inflammatory diseases including arthritis and rheumatism are major group of prevalent diseases. Most of the available non-steroidal anti-inflammatory drugs are effective in inflammatory conditions of the joints, but are devoid of gastro protective property. Many substances, interfering with the inflammatory response have been isolated from Indian medicinal plants (IMP). The review analyses formulations, extracts and phytochemicals (derived from IMP) evaluated for possible anti-inflammatory activity. Reputed databases and indexed journals dealing with medicinal plant were consulted for data generation.

Keywords: Alkaloids, anti-inflammatory activity, inflammation, experimental models.

INTRODUCTION

Inflammation is the complex biological response of vascular tissues to harmful stimuli including pathogens, irritants, or damaged cells. It is a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue (Denko, 1992). The process of inflammation is necessary in healing of wounds. Inflammation however, if runs unchecked, lead to onset of diseases like vasomotor rhinorrhea, rheumatoid arthritis and atherosclerosis (Henson and Murphy, 1989).

Acute inflammation is characterised by classical signs- edema, erythema, pain, heat, and above all, loss of function. The classical signs are triggered by the infiltration of the tissues by serum and white blood corpuscles (leucocytes). Chronic inflammation results in a progressive shift in type of cells, present at site of inflammation. It is characterized by simultaneous destruction and healing of the injured tissue from incidence of inflammation.

According to Evans (1992), the cellular processes of inflammation fall into four distinct categories: a) Changes in blood flow caused by changes in smooth muscle cell function causing vasodilatation. b) Alterations in vascular permeability engendered by cytoskeletal contraction in endothelial cells. c) Migration of phagocytic leukocytes to the site of inflammation. d) Phagocytosis.

Early inflammatory changes in damaged tissues are now known to involve the release of various biologically active materials from polymorph nuclear leukocytes, lysosomal enzymes and others. The vascular effects are primarily mediated by kinins, prostaglandins and vasoactive amines (histamine) released by mast cells. Vasoactive amines cause increased vascular permeability leading to plasma exudation. The inflammatory process involves a complex interplay between cells of the blood, the blood vessels themselves and the cells of the involved tissue. The process can be seen as a coordinated response of a large number of cells to an initial stimulus (Henson and Murphy, 1989).

Inflammation research involves a number of experimental models to study the anti-
inflammatory activity. According to Lewis, (1989), these models are of two types: Acute inflammatory models and Chronic inflammatory models.

Acute models are designed to test drugs that modulate erythema, changes in vascular permeability, leukocyte migration and chemotaxis, phagocytosis - polymorphonuclear leucocytes and other phagocytic cells, measurement of local pain, antipyretic activity, local analgesic action and rat paw edema (Barbosa-Filho et al. 2006).

Chronic models are designed to find drugs that may modulate the disease process and these include sponge and pellet implants and granuloma pouches which deposit granulation tissue, adjuvant induced arthritis and rabbit mono-articular arthritis which have an immune etiology (Lewis, 1989).

It is well known that several physiological changes play key role in initiating inflammation in disorders like arthritis and rheumatism. These responses to inflammation include hyperpyrexia, increased total leucocyte count (TLC) and differential leucocyte count (DLC), elevated erythrocytic sedimentation rate (ESR) and c-reactive proteins. These are referred to as markers of acute inflammation (Henson and Murphy, 1989).

Natural products have long been recognized as an important source of therapeutically effective medicines (Cragg et al. 1997). Different approaches used to analyze the anti-inflammatory potential of plant and plant-derived compounds have been developed in the past years (Handa et al., 1992). Further, traditional herbal medicines like Commiphora mukul, Boswellia serrata, Harpagophytm procumbens, and Pluchea indica have been used for analgesic effect with success (Vohora and Dandiya, 1992).

**Anti-inflammatory and analgesic phyto-products from Traditional Medicine**

Arthritis and rheumatism are well-defined diseases of the musculoskeletal system. Before the availability of synthetic drugs, man was completely dependent on medicinal plants for curing diseases. With synthesis of aspirin in 19th Century, a new era started in the history of anti-inflammatory and analgesic drugs (Vane, 1971). Hippocrates prescribed leaves and bark from willow tree to relieve fever and pain (Julkunen-Tuto and Tahvanainen, 1989). In 200 B.C, native people of North America learn to make salicylate pain remedies from birch bark (Schmid and Heide, 1995). Salicin, a glycoside, isolated from Salix alba L. (Salicaceae) attracted the researchers and it provided the modern science with acetyl-salicylic acid. Inside the human system, the salicin splits up into aglycone and salicylic acid. Salicin is devoid of inducing gastritis unlike acetyl salicylic acid (Rainsford and Whitehouse, 1980).

![Fig. 1: Structure of Salicin](image)

Practitioners of Traditional Indian Medicine (TIM), use formulations for anti-inflammatory, analgesic and anti-rheumatic action with considerable success (Chatterjee and Pal, 1984). Dashmool (combination of roots of ten plants) is standard Ayurvedic remedy for inflammatory diseases (Sharma et al., 1973). Scientific studies on traditional formulations like Rasonadi kvatha (Kishore and Banerjee, 1973), Maharasnadi quath (Thabrew, et al., 2003), Cheriya rasnadi kashayam (Valarmati et al. 2004) and Triphala (Rassol and Sabina, 2005) have justified there role in the treatment of arthritis.

Commiphora mukul (Hook. ex Stocks) Engl. (Burseaceae), traditionally known as guggul, has figured high in the treatment of arthritis. Animal models have demonstrated anti-inflammatory activity of crude drug and standardized extracts containing guggulsterones (Arora, 1972; Sharma, 1977). Clinical trials have justified the utilization of the drug in the treatment of rheumatoid arthritis (Vyas, 1987) and osteoarthritis (Singh et al., 2003). Recent works on poly-herbal formulations; Triphala Guggul and Yograja Guggul have reported the immunomodulator (Shukla et al., 1986) and cartilage-protective (Sumantran et al., 2007) activities.

The present review is dedicated to polyherbal formulations (used as anti-inflammatory and analgesic agents in Ayurveda), extracts and the bioactive or active constituents isolated and identified from the Indian medicinal plants, which have been previously reported to have an anti-inflammatory activity. Polyherbal formulations, extracts and the bio-actives have
been selected, and the data has been presented on basis of pharmacological activity in different experimental models.

Table 1: Summary on Ayurvedic formulations showing anti-inflammatory activity

<table>
<thead>
<tr>
<th>Formula</th>
<th>Activity</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Cheriya rasnadi kashayam</td>
<td>Anti arthritic</td>
<td>Valarmati et al., 2004</td>
</tr>
<tr>
<td>Maharasnadhi quath</td>
<td>Anti-inflammatory &amp; analgesic</td>
<td>Thabrew, Dharmasiri &amp; Senaratne, 2003</td>
</tr>
<tr>
<td>Narayan taila</td>
<td>Anti-inflammatory</td>
<td>Patil et al., 2001</td>
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<tr>
<td>Rasnadiguggulu</td>
<td>Anti-rheumatic</td>
<td>Shukla et al., 1985</td>
</tr>
<tr>
<td>Rasonadi kvatha</td>
<td>Anti-rheumatic</td>
<td>Kishore &amp; Banerjee, 1973</td>
</tr>
<tr>
<td>Sinhanad guggul</td>
<td>Anti-inflammatory</td>
<td>Patil et al., 2001</td>
</tr>
<tr>
<td>Suthi guggulu</td>
<td>Anti-rheumatic</td>
<td>Kishore et al., 1982</td>
</tr>
<tr>
<td>Suvarnamakshika di wati</td>
<td>Analgesic</td>
<td>Joshi &amp; Shrotri, 1995</td>
</tr>
<tr>
<td>Triphala</td>
<td>Anti-inflammatory</td>
<td>Rassol &amp; Sabina, 2005</td>
</tr>
<tr>
<td>Triphala guggul</td>
<td>Immunomodulator</td>
<td>Shukla et al., 1986, Sumantran et al., 2007</td>
</tr>
<tr>
<td>Vachadi guggulu</td>
<td>Anti-rheumatic</td>
<td>Chandrasekhara, 1966</td>
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<tr>
<td>Vyoshadi guggulu</td>
<td>Anti-rheumatic</td>
<td>Chandrasekhara, 1966</td>
</tr>
<tr>
<td>Yograja guggul</td>
<td>Cartilage-protective</td>
<td>Shukla et al., 1986</td>
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MATERIALS AND METHODS

The key words for the present preview were anti-inflammatory activity plus formulations and bioactive (active constituents) of Indian Medicinal Plants. Chemical Abstracts, Pub-Med, MAPPA (Medicinal and Aromatic Plants Program), ABIM (Annotated Bibliography of Indian Medicine) and data bank on Indian Medicinal Plants provided by Central Council of Research in Ayurveda and Siddha (CCRAS), were used for searching data, updated until May 2008 and updated.

Ayurvedic formulations with anti-inflammatory and analgesic activity

Summary on Ayurvedic formulations showing anti-inflammatory activity is shown in Table 1.

Indian medicinal plants with anti-inflammatory and analgesic activity

Acacia farnesiana (Linn.) Willd. (Fabaceae)

In previous studies, anti-inflammatory effect of glycosidal fraction of A. farnesiana was reported (Trivedi et al., 1986). In a study, the ethanolic extract of leaves of A. farnesiana was tested for the anti-inflammatory activity by carrageenan induced paw oedema for acute inflammation and cotton pellet induced granulation for chronic inflammatory model. The ethanolic extract showed significant anti-inflammatory activity in both the models studied (Hukkeri et al., 2002).

Adhatoda vasica Nees (Acanthaceae)

The anti-inflammatory activity of the methanol extract of the leaves, the non-alkaloid fraction, the saponins and the alkaloids was evaluated by the modified hen’s egg chorioallantoic membrane test. The alkaloid fraction showed potent activity at a dose of 50 microg/pellet equivalent to that of hydrocortisone while the MeOH extract and the other fractions showed less activity (Chakraborty and Brantner, 2001).

Aegle marmelos Corr. (Rutaceae)

Ethyl acetate and methanol extracts of leaves A. marmelos were screened for in vivo anti-inflammatory activity in albino rats. Methanol extract of A. marmelos showed significant anti-inflammatory activity at a dose of 100 mg/kg (Gurulingappa et al., 2002).

Alstonia macrophylla Wall. ex A.DC. (Apocynaceae)

Methanolic extract of dried leaves of A. macrophylla and its fractions were investigated for its anti-inflammatory activity. The extract at a concentration of 200 mg kg⁻¹ and 400 mg kg⁻¹, p.o. and its fractions at 25 mg kg⁻¹ and 50 mg kg⁻¹, p.o. showed the significant dose dependent anti-inflammatory activity in carrageenan and dextran-induced rats hind paw edema (acute models) as well as in cotton pellet-induced granuloma (chronic model) in rats. Anti-inflammatory activity of the tested extract and its fractions was comparable with that of the standard drug Indomethacin at a concentration of 10 mg kg⁻¹ (Arunachalam et al., 2002).

Ammania baccifera Linn.

The analgesic activity of the ethanol extract of roots of A. baccifera whole plant was investigated in chemical models of nociception in mice. A. baccifera at doses of 200, 400 and
600mg/kg i.p produced an inhibition of 20.7%, 43.4% and 72.9%, respectively, of the abdominal writhes induced by acetic acid in mice. In the formalin test, the administration of 200, 400 and 600mg/kg i.p had no effects in the first phase but produced a dose-dependent analgesic effect on the second phase with inhibitions of the licking time of 27.3%, 47.7% and 57.4%, respectively. These observations suggest that A. baccifera possesses some analgesic activity (Dhanapal et al., 2004).

**Anacardium occidentale** Linn. (Anacardiaceae)

Hydrolysable and non-hydrolysable tannins obtained from the bark of A. occidentale on i.p. injection, demonstrated apparent anti-inflammatory activity in carrageenan- and dextran-induced rat paw oedemas, cotton pellet granuloma test and adjuvant-induced polyarthritis in rats. At higher doses orally administered tannins also had activity in carrageenan paw oedema and adjuvant arthritis experiments. The tannins i.p. also inhibited acetic acid-induced "writhing responses" in mice and were found to antagonise the permeability-increasing effects in rats of certain mediators of inflammation and to inhibit the migration of leucocytes to an inflammatory site (Mota et al., 1985).

**Arnebia euchroma** (Royle) Johnston (Boraginaceae)

The petroleum ether, chloroform, alcoholic and aqueous extracts of A. euchroma roots (500 mg/kg, orally each) were found to exhibit maximal edema inhibition: 61.2%, 45%, 27.5% and 60%, respectively against carrageenan-induced rat-paw edema at 300 min interval. The activity shown by different extracts was comparable to that shown by the reference drug, ibuprofen: 50 mg/kg, p.o., 61.6% inhibition, 200 min (Kaith et al., 1996).

**Atalantia monophylla** Corr. (Rutaceae)

Ethyl acetate extract of A. monophylla were screened for in vivo anti-inflammatory activity in albino rats. The extract of A. monophylla showed significant anti-inflammatory activity at a dose of 100 mg/kg (Gurulingappa et al., 2002).

**Azadirachta indica** A Juss. (Meliaceae)

The water soluble part of alcoholic extract of A. indica leaves at a dose of 200 mg/kg, p.o., exerted significant anti-inflammatory activity in cotton pellet granuloma assay in rats. The extract also inhibited significantly the biochemical parameters (viz. DNA, RNA, lipid peroxide, acid phosphatase and alkaline phosphatase) studied in cotton pellet exudates (Chattopadhyay, 1998).

**Betula alnoides** Buch.-Ham. ex D.Don

The extract of B. alnoides was also evaluated for anti-inflammatory activity in sheep RBC induced sensitivity and in membrane stabilization models. Except for the sheep RBC induced sensitivity model, the extract showed significant anti-inflammatory activity (Sur et al., 2002).

**Bryonia laciniosa** Linn. (Cucurbitaceae)

The chloroform extract of roots of B. laciniosa exhibited significant anti-inflammatory effect at the dose 50, 100 and 200 mg/kg. Maximum inhibition (52.4%) was noted at the dose of 200 mg/kg after 3 h of drug treatment in carrageenan induced paw edema, whereas the indomethacin (standard drug) produced 62.1% of inhibition. The extract exhibited significant anti-inflammatory activity in dextran induced paw edema in a dose dependent manner. The extract also exhibited significant inhibition on the hind paw oedema in rats caused by histamine and serotonin respectively. In cotton pellet induced granuloma B. laciniosa (200 mg/kg) and standard drug (phenylbutazone) showed decreased formation of granuloma tissue by 50.1 and 57.3% (p<0.001) respectively. The extract also inhibited peritoneal leukocyte migration in mice (Gupta et al., 2003).

**Cassia fistula** Linn. (Fabaceae)

C. fistula leaves were tested for anti-inflammatory effects, as compared with phenylbutazone, using carrageenin, histamine, and dextran induced paw edema in rats. Potent anti-inflammatory activity against all phlogistic agents was noted (Bhakta et al., 2000).

**Cedrus deodara** (Roxb.) Loud. (Pinaceae)

The volatile oil extracted by steam distillation of the wood of C. deodara was examined for its oral anti-inflammatory and analgesic activity at the doses of 50 and 100 mg/kg body weight. It produced significant inhibition of carrageenan-induced rat paw edema and of both exudative-proliferative and chronic phases of inflammation in adjuvant arthritic rats at doses of 50 and 100 mg/kg body weight. The oil at both tested doses was found to possess analgesic activity against cotton pel
acetic acid-induced writhing and hot plate reaction in mice (Shinde et al., 1999).

**Cissampelos pareira**

In the present study, 50% ethanolic extract of C. pareira roots (CPE) in acute, subacute and chronic models of inflammation was assessed in rats. Per os (p.o.) administration of C. pareira at 200, 400 mg/kg exhibited significant anti-inflammatory activity. In acute inflammation as produced by carrageenin 59.55% and 64.04%, by histamine 15.38% and 30.77%, by 5-hydroxytryptamine 17.78% and 31.11% and by prostaglandin E-induced hind paw edema 19.23% and 30.77% protection was observed. While in subacute anti-inflammatory models using formalddehyde-induced hind paw edema (after 1.5 h) 38.36% and 47.95% and in chronic anti-inflammatory model using cotton pellet granuloma 15.02% and 19.19% protection from inflammation was observed. C. pareira did not show any sign of toxicity and mortality up to a dose level of 1000 mg/kg, p.o. in rats. Both acute as well as chronic administration of C. pareira (100, 200 and 400 mg/kg, p.o.) did not produce any gastric lesion in rats (Amresh et al., 2007).

In yet another study, 50% aqueous ethanolic extract of C. pareira at the dose levels of 100–400 mg/kg, once daily for 3 days exhibited significant (P < 0.001) resistance against mechanical pain after 30 min in analgesymeter induced pain in mice. In acetic acid (0.6%; i.p.) inducing writhing, C. pareira significantly (P < 0.05) decreased the writhing episodes; the degree of percent protection at 200 and 400 mg/kg was 22.73 and 51.63. The hot plate reaction time was increased by 2.07 (P < 0.05) and 2.70 (P < 0.001) folds respectively. Further C. pareira showed the dose dependent significant protective effect against complete Freund's adjuvant induced arthritis. The percentage protection on the 18th day was 40.54 (P < 0.01) and 71.52 (P < 0.001) at 200 and 400 mg/kg respectively. Lysosomal enzymes (acid phosphatase and N-acetyl glucosaminidase) were decreased by 50% (P < 0.01) and 26.26% (P < 0.05) by using C. pareira, dexamethasone decreased them 56.56% (P < 0.01) and 31.82% (P < 0.01) and the glycoprotein contents (total hexose and sialic acid) were increased by 1.55-folds (P < 0.01) and 1.51-folds (P < 0.05) by using C. pareira while dexamethasone increases them by 1.51-folds (P < 0.001) and 1.60-folds (P < 0.01) respectively in stomach homogenate with respect to arthritic group. The increased pain threshold and protective effect against carrageenan induced footpad edema by C. pareira vindicated its medicinal value in treatment of pain and arthritis (Amresh et al., 2007).

**Cissus quadrangularis Linn. (Vitaceae)**

The analgesic activity of alcoholic extract of whole plant of C. quadrangularis family vitaceae), was studied in mice by Haffner's Clip and Eddy's hot plate methods. The extract effective by both oral and i.p. routes significantly (P < 0.001) increased the reaction time by both methods. The duration of analgesic activity was from 2 to 4 h and optimum effect was observed at 1/20th -1/10th of LD50 dose. The extract compared well with acetylsalicylic acid (Singh et al., 1984).

**Clemone gynandra Linn. (Capparidaceae)**

The ethanolic extract of C. gynandra was administered orally at a dose of 150 mg/kg body weight for 30 days to the experimental rats after the induction of adjuvant arthritis. The anti-inflammatory activity of C. gynandra leaves was assessed by paw volume measurement, and its capacity to stabilize lysosomal enzyme activities in the plasma and liver of control and experimental rats. The activity of pathophysiological enzymes such as AST, ALT, ALP, cathepsin-D, β-glucuronidase, N-acetyl-β-glucosaminidase LDH and the levels of glycoproteins were also estimated in plasma and liver. The increased levels of both lysosomal enzymes and protein-bound carbohydrates in arthritic rats were significantly suppressed to near normal level by the administration of C. gynandra extract. Further, the significantly elevated plasma levels of TNF-α found in arthritic rats were found to be significantly restored back to near normal levels by the extract in experimental animals. The membrane stabilizing activity of the extract was further evidenced by histological observations made on the limb tissue (Narendhirakannan, et al., 2005).

**Clemone rutidosperma Linn. (Capparidaceae)**

Oral administration of the ethanolic extract (200 and 400 mg/kg, p.o) and its fractions (200 mg/kg each) of the aerial parts of C. rutidosperma produced significant analgesic activity in acetic acid-induced writhing and tail immersion tests, anti-inflammatory effect against carrageenin
induced inflammation and adjuvant induced polyarthritis and antipyretic activity against yeast-induced pyrexia. Fractionation of the ethanolic extract potentiated the activities (Bose et al., 2007).

**Curcuma amada Roxb. (Zingiberaceae)**

The extract of *C. amada* was screened for anti-inflammatory activity in albino rats using acute carrageenan paw oedema and chronic granuloma pouch model. The extract exhibited dose dependant anti-inflammatory activity in acute and chronic models (Mujumdar et al., 2000).

**Dalbergia lanceolaria** L.f. (Dalbergieae)

Topical anti-inflammatory activity of *D. lanceolaria* bark ethanol extract was demonstrated in albino mice using TPA-, EPP- and AA-induced ear edema models. The systemic activity of extract was confirmed using acute and sub-acute anti-inflammatory models in albino rats. The ethanol extract exhibited significant systemic anti-inflammatory activity in Carrageenan-induced rat paw edema, by inhibition of histamine and prostaglandin phases of acute inflammation. The extract also showed significant activity against turpentine-induced exudative changes and no activity against granular tissue formation in cotton pellet-induced granuloma in albino rats (Kale et al., 2007).

**Drymaria cordata** (Linn.) Willd. (Caryophyllaceae)

The anti-inflammatory effect of the methanol extract of *D. cordata* was investigated against carrageenin, histamine, serotonin, dextran and PGE$_1$ induced rat hind paw oedema. It exhibited significant anti-inflammatory activity against all these phlogestic agents except PGE$_1$. It exhibited significant anti-inflammatory activity against all these phlogestic agents except PGE 1. All these effects were compared with standard drug phenylbutazone in both the acute and chronic experimental models in albino rats. All these effects were compared with standard drug phenylbutazone in both the acute and chronic experimental models in albino rats (Mukerjee et al., 1998).

**Echinops echinatus** Roxb. (Asteraceae)

Anti-inflammatory studies were conducted on an ethanol extract of *E. echinatus* whole plant. Ethanol extract of *E. echinatus* inhibited the acute inflammation induced in rats by carrageenan, formaldehyde and adjuvant and the chronic arthritis induced by formaldehyde and adjuvant. The extract was more effective parenterally than orally (Singh et al., 1989).

**Eclipta alba** (Linn.) Hassk. (Asteraceae)

The present experimental research work was undertaken to determine the analgesic activity of the total ethanol extract of *E. alba*, and also the isolated alkaloids of *E.alba* in albino mice by using standard experimental models such as the tail clip method, the tail flick method and the acetic acid induced writhing response. The results from this study show that both the ethanol extract as well as the total alkaloids produce good analgesic activity in all the different models of analgesia used. The total alkaloidal fraction was the most efficacious in all models tested (Swant, et al., 2004).

**Emilica sonchifolia** Linn. (Asteraceae)

Fresh juice and methanolic extract of *Emilia sonchifolia* leaves were found to be potent inhibitors of hydroxyl radical formation and superoxide radical generation in vitro. The methanolic extract inhibited the carrageenan-induced oedema (Shylesh and Padikkala, 1999).

**Emicostemma littorale** Bl. (Gentianaceae)

The anti-inflammatory activity of whole plant extract of *E. littorale* was assessed by carrageenan-induced inflammation and cotton pellet granuloma method in rats. *E. littorale* exerted 54 % anti-inflammatory activity for a dose of 100 mg/100 g body wt, in carrageenan-induced acute inflammation. In chronic inflammation of cotton pellet granuloma, *E. littorale* exerted 30 % anti-inflammatory activity at the above dosage (Sadique et al., 2000).
**Ficus racemosa** Linn. (Moraceae)

The extract of bark of *F. racemosa* at doses of 200 and 400 mg/kg has been found to possess significant anti-inflammatory activity on the tested experimental models. The extract (400 mg/kg) exhibited maximum anti-inflammatory effect (30.4, 32.2, 33.9 and 32.0%) at the end of 3 h with carrageenin, serotonin, histamine, dextran-induced rat paw oedema, respectively. In a chronic test, the extract (400 mg/kg) showed 41.5% reduction in granuloma weight. The effect produced by the extract was comparable to that of phenylbutazone (Mandal et al., 2000).

**Hypericum perforatum** Linn. (Guttiferae)

A standardized 50% aqueous ethanolic extract of the Indian variety of *H. perforatum* was examined for its putative anti-inflammatory and analgesic activity at the doses of 100 and 200 mg/kg, po. The experimental paradigms used were carrageenan induced pedal edema and cotton pellet induced granuloma for anti-inflammatory activity, whereas the tail flick, hot plate and acetic acid induced writhing methods were used to assess analgesic activity. Indomethacin (20 mg/kg, ip) was used as the standard anti-inflammatory drug. Pentazocine (10 mg/kg, ip) and aspirin (25 mg/kg, ip), both clinically used analgesics, were used as standard analgesics for comparison. *H. perforatum* extract showed significant anti-inflammatory and analgesic activity at both dose levels, in all the paradigms used. Additionally, *H. perforatum* potentiated the anti-inflammatory activity of indomethacin and analgesic activities of pentazocine and aspirin (Kumar et al., 2001).

**Ixora brachiata** Roxb (Rubiaceae)

Methanolic extract of the flowers of *I. brachiata* was found to possess anti-inflammatory activity against cotton pellet granuloma in rats at a dose level of 100 mg/kg body weight, sc. *I. brachiata* reduced the protein content, acid phosphatase, glutamate pyruvate transaminase and glutamate oxalo-acetate transaminase activities in liver and serum. A significant reduction in the ascorbic acid content in adrenals was also observed in drug-treated animals (Vimala et al., 1997).

**Jatropha curcas** Linn. (Euphorbiaceae)

Anti-inflammatory activity of topical application of *J curcas* root powder in paste form in TPA-induced ear inflammation was confirmed in albino mice and the successive solvent extraction of these roots was carried out by ether and methanol. The methanol extract exhibited systemic and significant anti-inflammatory activity in acute carrageenan-induced rat paw edema. It also showed activity against formalin-induced rat paw edema, as well as, turpentine-induced exudative changes and cotton pellet-induced granular tissue formation after oral treatment for 7 days in albino rats. The ether extract failed to elicit anti-inflammatory activity (Mujumdar and Misar, 2004).

**Michelia champaca** Linn. (Magnoliaceae)

Methanolic extract of the flowers of *M. champaca* was found to possess anti-inflammatory activity against cotton pellet granuloma in rats at a dose level of 100 mg/kg body weight, sc. *M. champaca* reduced the protein content, acid phosphatase, glutamate pyruvate transaminase and glutamate oxalo-acetate transaminase activities in liver and serum. A significant reduction in the ascorbic acid content in adrenals was also observed in drug-treated animals (Vimala et al., 1997).

**Mollugo cerviana** (L.) Ser. Ex DC. (Molluginaceae)

The anti-inflammatory activity of *M. cerviana* was assessed by carrageenan-induced inflammation and cotton pellet granuloma method in rats. *M. cerviana* exerted 26% anti-inflammatory activity for a dose of 100 mg/100 g body wt, in carrageenan-induced acute inflammation. In chronic inflammation of cotton pellet granuloma, *M. cerviana* exerted 46% anti-inflammatory activity at the above dosage (Sadique et al., 2000).

**Morus indica** Linn. (Moraceae)

Anti-inflammatory activity of the ethanolic extract of the leaves of *M. indica* was studied in wistar rats using the carrageenan induced left hind paw edema, carrageenan induced pleurisy and cotton pellet induced granuloma model. The ethanolic extract (100 mg/kg, p.o.) inhibited carrageenan induced rat paw edema. It also showed an inhibitory effect on leukocyte migration and a reduction on the pleural exudates as well as reduction on the granuloma weight in the cotton pellet granuloma method (Balasubramanian et al., 2005).

**Nyctanthes arbor-tristis** Linn. (Verbenaceae)
The water soluble portion of the alcoholic extract of the leaves of *N. arbor tristis* was screened for the presence of anti-inflammatory activity. *N. arbor tristis* inhibited the acute inflammatory oedema produced by different phlogistic agents, viz. carrageenin, formalin, histamine, 5-hydroxytryptamine and hyaluronidase in the hindpaw of rats. The acute inflammatory swelling in the knee joint of rats induced by turpentine oil was also significantly reduced. In subacute models, *N. arbor tristis* was found to check granulation tissue formation significantly in the granuloma pouch and cotton pellet test. Acute and chronic phases of formaldehyde induced arthritis were significantly inhibited. *N. arbor tristis* was also found to inhibit the inflammation produced by Freund's adjuvant arthritis and PPD induced tuberculin reaction (Saxena *et al.*, 1984).

**Ocimum basilicum** Linn. (Lamiaceae)

A methanol extract and an aqueous suspension of *O. sanctum* inhibited acute as well as chronic inflammation in rats as tested by carrageenan-induced pedal edema and croton oil-induced granuloma and exudate, respectively. In both test procedures, the anti-inflammatory response of 500 mg/kg of methanol extract and aqueous suspension was comparable to the response observed with 300 mg/kg of sodium salicylate. Both the extract and suspension showed analgesic activity in the mouse hotplate procedure and the methanol extract caused an increase in the tail-withdrawal reaction time of a subanalgic dose of morphine. Both preparations reduced typhoid-paratyphoid A/B vaccine-induced pyrexia. The antipyretic action of the methanol extract and aqueous suspension was weaker and of shorter duration than that of 300 mg/kg sodium salicylate (Godhwani, Godhwani and Vyas, 1987).

**Piper longum** Linn. (Piperaceae)

An aqueous suspension of *P. longum* root powder is given orally to mice and rat in doses of 200, 400 and 800 mg/kg. The delay in reaction time for thermal stimulus in rats and the number of writhings to chemical stimulus in mice are determined in each group. The results are analysed statistically. The 400 and 800 mg/kg doses of *P. longum* show significant NSAID type of analgesia (P < 0.001). Both Ibuprofen (40 mg/kg) and *P. longum* (800 mg/kg) show 50% protection against writhing. The delay in reaction time to thermal stimulus was less than 6% for different doses of *P. longum* as against 100% for pentazocine (Vedhanayaki, *et al.*, 2003).

**Pluchea indica** Less. (Asteraceae)

A methanolic fraction of a chloroform extract of defatted *P. indica* roots was investigated for its anti-inflammatory potential against several models of inflammation. The extract showed significant inhibitory activity against carrageenin-, histamine-, serotonin-, hyaluronidase- and sodium urate-induced pedal inflammation. The extract inhibited protein exudation and leucocyte migration. The extract also inhibited carrageenin- and cotton pellet-induced granuloma formation as well as turpentine-induced joint oedema and adjuvant-induced polyarthritis (Sen, *et al.*, 1991).

**Pongamia pinnata** Linn. (Fabaceae)

A study, the anti-inflammatory activity of 70% ethanolic extract of *P. pinnata* leaves in acute, subacute and chronic models of inflammation was assessed in rats. Per os (p.o.) administration of PLE (300, 1000 mg/kg) exhibited significant anti-inflammatory activity in acute (carrageenin, histamine, 5-hydroxytryptamine and prostaglandin E2-induced hind paw edema), subacute (kaolin-carrageenin and formaldehyde-induced hind paw edema) and chronic (cotton pellet granuloma) models of inflammation. *P. pinnata* did not show any sign of toxicity and mortality up to a dose level of 10.125 g/kg, p.o. in mice. Both acute as well as chronic administration of *P. pinnata* (100, 300 and 1000 mg/kg, p.o.) did not produce any gastric lesion in rats (Srinivasan *et al.*, 2001).

**Rhododendron arboreum** Smith (Ericaceae)

50% ethanolic and methanolic extracts of flowers of *R. arboreum* were investigated against carrageenan. PG (E2), histamine and 5-HT induced rat's hind paw oedema. The extracts exhibited significant anti-inflammatory activity against all the four phlogistic agents. The aqueous extracts showed maximum anti-inflammatory activity followed by 50% ethanolic and methanolic extracts (Agarwal and Sharma, 1986).

**Rhynchosia cana** (Willd.) DC.

Methanolic extract of the flowers of *R. cana* was found to possess anti-inflammatory activity against cotton pellet granuloma in rats at a dose level of 100 mg/kg body weight, sc. *R. cana*
reduced the protein content, acid phosphatase, glutamate pyruvate transaminase and glutamate oxalo-acetate transaminase activities in liver and serum. A significant reduction in the ascorbic acid content in adrenals was also observed in drug-treated animals. R. cana was recorded to possess significant antipyretic activity from the first hour of administration (Vimala et al., 1997).

\textit{Ricinus communis} Linn. (Euphorbiaceae)

Petroleum ether extract of \textit{R. communis} exhibited significant anti-inflammatory activity against (Formaldehyde and adjuvant induced rat's paw arthritis). \textit{R. communis} (150 mg/kg po) exhibited no significant analgesic activity. \textit{R. communis} was safe upto a dose of 1 g/kg p.o. in rats (Banerjee et al., 1991).

\textit{Sida cordifolia} Linn. (Malvaceae)

The ethyl acetate extract of root of \textit{S. cordifolia} showed comparable anti-inflammatory activity with indomethacin and possessed significantly higher activity when compared with that of the methanol extract of the root part. The ethyl acetate extract of both root and aerial parts of \textit{S. cordifolia} showed very good central and peripheral analgesic activities at a dose of 600 mg/kg. The methanol extract of root (SCR-M) was found to possess significant hypoglycaemic activity (Kanth and Diwan, 1999).

\textit{Sida rhombifolia} Linn. (Malvaceae)

In an animal study, anti-inflammatory of the methanolic extract of the aerial parts of \textit{S. rhombifolia} was studied. Oedema was induced by carrageenan and the oedema suppressant activity was measured using a plethysmometer. The methanolic extract of the aerial parts showed significant anti-inflammatory activity in rats. The researchers concluded that the anti-inflammatory activity of \textit{S. rhombifolia} was due to the inhibitory effects on the release of histamine like substances (Rao and Mishra, 1997).

\textit{Spilanthes acemella} (Asteraceae)

\textit{S. acemella} was evaluated for anti-inflammatory action by carrageenan-induced rat paw edema. The analgesic activity was tested by acetic acid-induced writhing response in albino mice and tail flick method in albino rats. The aqueous extract of \textit{S. acemella} in doses of 100, 200 and 400 mg/kg showed 52.6, 54.4 and 56.1% inhibition of paw edema respectively at the end of three hours and the percentage of protection from writhing was 46.9, 51.0 and 65.6 respectively. In the tail flick model, the aqueous extract of \textit{S. acemella} in the above doses increased the pain threshold significantly after 30 min, 1, 2 and 4 h of administration. \textit{S. acemella} showed dose-dependent action in all the experimental models (Chakraborty et al., 2004).

\textit{Teramnus labialis} (L.) Spreng. (Fabaceae)

Bioassay-guided fractionation, based on anti-inflammatory activity of the methanolic extractives of \textit{T. labialis} led to the isolation and characterization of vitexin, bergenin, daidzin and 3-O-methyl-D-\textit{chiro}-inositol as active constituents. Vitexin exhibited a dose-dependent inhibitory activity on 5-lipoxygenase enzyme (Sridhar, et al., 2006).

\textit{Vernonia cinerea} Ness. (Asteraceae)

An alcoholic extract from the flower of \textit{V. cinerea} change was investigated for anti-inflammatory activity. Changes in paw volume, body and tissue weights and serum and tissue enzyme activities of ALT, AST, ACP and cathepsin-D in adjuvant rats were reversed by oral administration of 100 mg/kg body weight (BW) of the flower extract. 3. The extract also reversed the major histopathological changes in the hind paws of the arthritic rats (Latha, et al., 1998).

\textit{Vitex negundo} Linn. (Verbenaceae)

Analgesic activity of \textit{V. negundo} leaf extract (500 and 1000 mg/kg) was studied using acetic acid induced writhing test in mice for assessing peripheral analgesic effect and tail immersion test in mice for assessing central analgesic effect. The anti-inflammatory activity of VLE (500 and 1000 mg/kg) was studied by using the models of carrageenin-induced rat paw oedema and carrageenin-induced granuloma pouch in rats for assessing the effect on acute and sub acute inflammations, respectively. \textit{V. negundo} significantly increased the reaction time and decreased the writhing movements in mice in acetic acid-induced writhing test. There was a significant increase in the reaction time in tail immersion test. \textit{V. negundo} significantly decreased the rat paw oedema volume at higher dose. It also significantly decreased the formation of granuloma pouch in rats (Telang, et al., 1999).
Database search provided brief information on several medicinal plants which have been evaluated for anti-inflammatory and analgesic activities in animal models. These have been tabulated in Table 3 [Supplementary data].

Active constituents reported from Indian medicinal plants with anti-inflammatory and analgesic activity

(+-)pinitol
In the carrageenin-induced paw oedema in rats, (+)-pinitol at a dose of 2.5-10 mg/kg, i.p., isolated from Abies pindrow Royle. (Pinaceae) leaves, showed a significant anti-inflammatory effect, the highest dose being comparable to phenylbutazone at a dose of 100 mg/kg, i.p. (Singh et al., 2001).

Achyranthine
The water-soluble alkaloid, achyranthine isolated from Achyranthes aspera L. (Amaranthaceae) was screened for its anti-inflammatory and anti-arthritic activity against carrageenin-induced foot oedema, granuloma pouch, formalin induced arthritis and adjuvant arthritis in rats. It showed significant anti-inflammatory activity in all the four models employed but was less active than phenylbutazone and betamethasone. Incidence of gastric ulcers was maximum with betamethasone and minimum with achyranthine (Neogi et al., 1969).

Agnuside and pedunculariside
A new iridoid, pedunculariside, together with the known iridoid agnuside were isolated from the butanol extract of Vitex peduncularis Wall. ex Schauer (Verbenaceae) stem bark. Both pedunculariside and agnuside showed preferential inhibition of COX-2, with IC50 values of 0.15 +/- 0.21 mg/ml and 0.026 +/- 0.015 mg/ml respectively, while having only small inhibitory effects on COX-1 (Suksamrarn et al., 2002).

Andrographoholide
Andrographoholide, diterpene lactone from Andrographis paniculata (Burm.f.) Wall. ex Nees (Acanthaceae) exerts its anti-inflammatory effects by inhibiting NF-KB binding to DNA, and thus reducing the expression of COX-2 (Madhav et al., 1996).

Betulinic acid
Betulinic acid, a triterpene isolated from Nelumbo nucifera Linn. (Nymphaceae) demonstrated significant anti-inflammatory activity when tested in carrageenin and 5-hydroxytryptamine induced paw edema. The activity was comparable to betamethasone and phenylbutazone (Mukherjee et al. 1997).

Cerpegin
Cerpegin, a novel furopyridine alkaloid isolated from the plant Cerpegia juncea Roxb. (Asclepiadaceae) was subjected to various pharmacological investigations. A dose-related analgesic effect was observed in mice. Cerpegin did not produce any autonomic or behavioral changes up to a dose of 200 mg/kg but doses of more than 400 mg/kg produced excitation and later convulsions in mice (Sukumar, et al., 1966).

Crotalaburnine or anacrotine
Anti-inflammatory activity of crotalaburnine or anacrotine isolated from Crotalbria laburnifolia Linn. (Fabaceae) was investigated against several models of inflammation. The effect was compared with the activity of hydrocortisone, phenylbutazone, sodium salicylate and cyproheptadine against different types of inflammation. Crotalaburnine (40 mg/kg s.c. × 5 alternate days) had no significant inhibitory effect against formalin-induced arthritis, while hydrocortisone (40 mg/kg s.c. × 10 days) was effective from the fifth day onwards. Against carrageenin-induced oedema both crotalaburnine (10 mg/kg s.c.) and phenylbutazone (100 mg/kg oral) produced a similar degree of inhibition. Hydrocortisone (10 mg/kg s.c.) produced slightly greater inhibition (Ghosh and Singh, 1974).

Curcumin
Curcumin was found to inhibit arachidonic acid metabolism, cyclooxygenase, lipoxygenase, cytokines (Interleukins and tumour necrosis factor) Nuclear factor-kB and release of steroidal hormones. Curcumin was reported to stabilize lysosomal membrane and cause uncoupling of oxidative phosphorylation besides having strong oxygen radical scavenging activity, which was responsible for its antiinflammatory property. In various animal studies, a dose range of 100-200 mg/kg body weight exhibited good antiinflammatory activity and seemed to have negligible adverse effect on human systems (Kohli et al., 2005).
Gangetin
Gangetin, pterocarpene flavonoid, isolated from the hexane extract of the root of the Desmodium gangeticum (L.) DC. Var. maculatum (L.) Baker (Fabaceae) showed significant anti-inflammatory activity in the exudative and the proliferative phases of inflammation in the doses of 50 and 100 mg/kg orally. The compound showed significant analgesic activity (Ghosh and Anadakumar, 1981).

Gossypin
Gossypin, found in Hibiscus vitifolius Linn. (Malvaceae) was found to significantly reduce the rat paw, edema and the increased vascular permeability induced by various phlogistic agents. It produced significant inhibition of the accumulation of pouch fluid and granulation tissue formation in the carrageenin induced granuloma pouch in rats. Gossypin was also found effective against the adjuvant and formalin induced chronic arthritis in rats (Parmer and Ghosh, 1978).

Hedychenone
Pharmacological investigations on rhizomes of Hedychium spicatum Buch.-Ham. (Zingiberaceae) indicated anti-inflammatory and analgesic activities. The anti-inflammatory activity was localised mainly in the hexane fraction from which one of the pure active constituents, hedychenone, a terpene has been isolated. The analgesic activity was more prominent in the benzene fraction (Srimal et al., 1984).

Premnazole
Premnazole, an isoxazole alkaloid isolated from Premna integrifolia L. and Gmelina arborea L. (Verbenaceae) demonstrated significant anti-inflammatory activity in reducing cotton pellet-induced granuloma formation in rats. The anti-inflammatory activity was comparable to that of phenylbutazone (Barik et al., 1979).

Tylpohorine
Experiments conducted with tylpohorine, a phenanthroindalizidine alkaloid, present in Tyllophora asthmatica (L. f.) Wight and Arn. (Asclepiadaceae) in various animal models have shown significant anti-inflammatory, anti-anaphylactic and anti-spasmodic activities (Gopalakrishnan, et al., 1979).

Withaferin A
Withaferin-A, steroidal lactone from Withania somnifera Dunal. (Solanaceae) exhibited fairly potent anti-arthritic and anti-inflammatory activities. It was found to suppress arthritic syndrome without any toxic effect. Unlike hydrocortisone-treated animals which lost weight, the animals treated with withaferin A showed gain in weight in arthritic syndrome. It is interesting that withaferin A seems to be more potent than hydrocortisone in adjuvant-induced arthritis in rats, a close experimental approximation to human rheumatoid arthritis. In its oedema-inhibiting activity, the compound gave a good dose-response in the dose-range of 12-25 mg/kg. body-wt. of albino rats intraperitoneally and a single dose had a good duration of action, as it could effectively suppress the inflammation after four hours of its administration (Sethi et al., 1970). Database search provided brief information on several medicinal plants which have been evaluated for anti-inflammatory and analgesic activities in animal models (Table 3 [Supplementary data]).

DISCUSSION
Literature research afforded several plants (single or poly-herbal), extracts and active constituents with significant anti-inflammatory activity. Limited data accumulated for analgesic and anti-rheumatic activity. Among polyherbal formulations, guggul was the ‘principal medicinal drug’. They are active against several model of inflammation but carragenin induced pedal edema seems to be commonly employed method (Biren et al. 2006). In one study, the mild laxative formulation, Triphala was reported to have significant anti-inflammatory (Rassol and Sabina, 2005).

Majority of the active constituents, were identified as alkaloids, flavonoids and rarely xanthones and sterols. Guggulsteones, boswellic acid, curcumin, withaferin–A, and andrographolide have been reported to be promising anti-inflammatory agents in animal models. Experts are of the view that there is not acute shortage of leads for developing anti-inflammatory drugs. We need to initiate pending work on these phyto-constituents with emphasis on side-effect profile (Biren et al., 2006).

The studies are valuable for identifying lead compounds for anti-inflammatory drugs, keeping
in mind the side effects of non-steroidal anti-inflammatory drugs and corticosteroid (Majumdar1971; Singh, 1993). Animal data is valuable for developing cost effective and efficacious anti-inflammatory agents. This further supports the correlation of reverse pharmacology with Ayurvedic drug actions (Vaidya, 2006). The studies provide little data pertaining to side effect profile of phytto-drugs, keeping in mind the unpleasant effects of non-steroidal anti-inflammatory drugs (Biren et al., 2006). To add, clinical trials are warranted to justify the ancient and pre-clinical findings about anti-inflammatory agents.

References


Anti-inflammatory and Analgesic Agents from Indian Medicinal Plants


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