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Arabian medicinal plants with antiinflammatory effects- plant based review (part 1)

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Abstract: The pharmacological studies showed that many medicinal plant possessed antiinflammatory activity. Biochemical and molecular investigations revealed that the anti-inflammatory activities of medicinal plants and plant-derived compounds were related to their interactions with several key enzymes, signaling cascades involving cytokines and regulatory transcription factors, and to their antioxidant effects. The current review highlighted the medicinal plants possessed antiinflammatory effects with special focus on their mode of action.

Keywords: Medicinal plants , Antiinflammatory, Therapeut,ic, Arthritis, Mechanism

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I. INTRODUCTION:

As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Two thirds of the new chemicals identified yearly were extracted from higher plants. 75% of the world's population used plants for therapy and prevention. In the US, where chemical synthesis dominates the pharmaceutical industry, 25% of the pharmaceuticals are based on plant-derived chemicals[1-2].

The pharmacological studies showed that many medicinal plant possessed antiinflammatory activity. Biochemical and molecular investigations revealed that the anti-inflammatory activities of medicinal plants and plant-derived compounds were related to their interactions with several key enzymes, signaling cascades involving cytokines and regulatory transcription factors, and to their antioxidant effects[3-5].

Some plants inhibited phospholipase A2 (PLA2), the enzyme catalyses the hydrolysis of the acyl group attached to the 2-position of intracellular membrane phosphoglycerides, and releases arachidonic acid from membrane phosphoglycerides. All drugs which inhibit PLA2 and decrease the availability of arachidonic acid to cyclooxygenase (COX) and lipooxygenase (LOX) pathways will inhibit the synthesis of prostaglandins (PGs), and leukotrienes as inflammatory mediators. Extracts of many plants such as *Ailanthus altissima, Cassia occidentalis, Trichilia catigua*, *Baccharis uncinella*, *Aloe vera* and *Ginkgo biloba*ia exerted their antiinflammatory effect via inhibition of PLA2. This inhibition could be occurred via lipocortine such as that possessed by plant triterpenoids, or via direct inhibition of PLA2 such as that exerted by flavonoids [6-13].

However, plant constituents such as luteolin, kaempferol, quercetin, apigenin, morin and galangin inhibited cyclooxygenases and subsequent prostaglandins production, while, quercetin and myricetin inhibited lipoxigenase and subsequent leukotrienes production. Crude plant extract may inhibited COX (such as *Ailanthus altissima, Arctium lappa Asparagus officinalis Betula, alba Brassica rapa, Calendula officinalis, Olea europaea* and *Urtica dioica*), LOX (such as *Ailanthus altissima,Calendula officinalis, Cuminum cyminum, Haplophyllum hispanicum*) or inhibited both arms of arachidonic acid metabolism (such as *Curcuma longa* and *Zingiber officinalis*)[14-17].

Some plant extracts possessed their antiinflammatory effects via inhibition of No generation (such as *Anthemis nobelis*, *Arctium lappa*, *Calotropis procera*, *Capsella bursa-pastoris*, *Carthamus tinctorius,* Citrus species, *Cuminum cyminum*, *Cyperus rotundus, Erigeron Canadensis, Hibiscus sabdariffa, Hypericum triquetrifolium and Kochia scoparia*) [(18-21)]. NO is a cellular mediators in physiological and pathological events. It was a toxic free radical that can cause tissue damage in high concentration. Three NOS [endothelial (eNOS), neuronal (nNOS), and inducible (iNOS)] were identified. The inducible enzyme is involved in overproduction of NO in response to pro-inflammatory mediators (interleukine-1β, tumor necrosis factor-α , and bacterial lipopolysaccharide) and participated in provoking inflammatory process with other inflammatory mediators[20-22].

Many medicinal plant inhibited the production and expression of the pro-inflammatory mediators: cytokines (*Adiantum capillus-veneris, Ailanthus altissima Althaea officinalis, Arctium lappa Capsella bursa-pastoris, Calotropis procera, Carthamus tinctorius, Cistanche tubulosa*, *Coriandrum sativum*, *Cydonia*

oblonga, *Eucalyptus* species, *Fumaria parviflora*, *Hibiscus sabdariffa*, *Hypericum triquetrifolium*, *Kochia scoparia*) and TNF-α (*Adiantum capillus-veneris*, *Allium cepa*, *Arctium lappa*, *Avena sativa*, *Calotropis procera*, *Calendula officinalis*, *Carthamus tinctorius*, *Cistanche tubulosa*, *Coriandrum sativum*, *Cydonia oblonga*, *Dianthus caryophyllus*, *Eucalyptus* species, *Fumaria parviflora*, *Helianthus annus*, *Hibiscus sabdariffa*, *Hypericum triquetrifolium*, *Juglans regia* and *Kochia scoparia*), in addition to medicinal plants possessed their effect on the production of IFN-γ (such as *Bauhinia variegata* and *Kochia scoparia*)[23-26].

Medicinal plants with antiinflammatory activity:

Achillea santolina

A. santolina ethanolic extract exerted anti-inflammatory activity[27]. Tekieh et al showed that methanolic extract of A. santolina caused significant reduction in the edema, hyperalgesia and serum IL-6 level in complete Freund's adjuvant induced inflammation in hind paw of rats[28]. Zaringhalam et al found that the methanolic extract of A. santolina exhibited significant antihyperalgesic and anti-inflammatory effects during pretreatment and short-term treatment at dose of 200 mg/kg and there was no significant difference between 200 and 400 mg/kg doses of this extract. Defatted extract of A. santolina did not show significant effect on CFA-induced inflammation during different stages of treatment ($P>0.05$). Short-term treatment with methanolic extract at dose of 200 mg/kg was found more effective than indomethacin in edema, hyperalgesia and serum IL-6 level reduction ($P<0.01$, $P<0.01$ and $P<0.05$ respectively)[29-30].

Althaea officinalis

Aqueous extracts of the roots ofAlthaea officinalis stimulated phagocytosis, and the release of oxygen radicals and leukotrienes from human neutrophils in vitro. The aqueous extract alsoinduced the release of cytokines, interleukin-6 and tumour necrosis factor from human monocytes in vitro, thereby exhibiting anti-inflammatory and immune stimulant activity[31]. A polysaccharide fraction (500mg/ml) isolated from a root extract had anticomplement activity in human serum in vitro. Marshmallow mucilage polysaccharides administered intraperitoneally to mice at a dose of 10 mg/kg produced a 2.2-fold increase in phagocytic activity of macrophages in the carbon-clearance test[32].However, with a dry 80% ethanolic extract administered orally (100 mg/kg b.w.), no inhibition of carrageenan induced rat paw oedema has been proved. Hypolaetin 8-glucoside has been tested for its anti-inflammatory, analgesic and anti-ulcer activity in rats. This flavonoid (30, 60 and 90 mg/kg i.p.) was more potent than phenylbutazone (30, 60 and 90 mg/kg ip) in suppressing the acute phase of adjuvant carrageenan-induced inflammation but had less effect in the prolonged inflammatory phase. In contrast to phenylbutazone, it did not cause gastric erosions. Analgesic activity of hypolaetin 8-glucosid has been found to be lower than the one of phenylbutazone**.** Hypolaetin 8-glucoside was also more potent than troxerutin (both at the doses of 100, 200, 300 and 400 mg/kg s.c.) in inhibiting histamine-induced capillary permeability in rats[33]. An ointment containing an aqueous marshmallow root extract (20%) applied topically to the external ear of rabbits reduced irritation induced by UV irradiation or by tetrahydrofurfuryl alcohol. The ointment has been compared to pure dexamethasone 0.05% ointment and a combined marshmallow and dexamethasone product. The anti-inflammatory effect of marshmallow ointment was lower than that of a dexamethasone ointment. The combined product had higher anti-inflammatory effect than the ointments with the individual ingredients.Scopoletin exert anti-inflammatory activity in croton oil induced mouse ear edema[34-35].

Adiantum capillus-veneris

Alcoholic extract of Adiantum capillus-veneris and its hexane fraction exerted significant anti-inflammatory activity against formalin induced inflammation. The hexane fraction showed topical anti-inflammatory activity after 6h and continued for 30h in croton oil- induced inflammation. The ethyl acetate fraction of the ethanolic extract of Adiantumcapillus-veneris showed significant inhibition of hind paw edema induced by carrageenan. The chronic anti-inflammatory activity of the ethanol extract was also evaluated by carrageen-induced paw edema method. The results, at the two dose levels tested in rats, indicate significant anti-inflammatory activity. The maximum inhibition of inflammation (71.15 %) was recorded with 100 mg/kg of plant extract. The analgesic activity of the ethanolic extract of Adiantumcapillus-veneris and its fraction carried out by tail flick method and writhing test, the result showed significant analgesic activity with insignificant gastric ulceration as compared to the standard anti-inflammatory analgesic antipyretic drugs[36-38]. The anti-inflammatory and anti-nociceptive activities of the crude ethanolic extract of Adiantum capillus veneris and its various fractions was studied using carrageenan induced hind paw edema, tail-flick method and writhing test at a dosage of 300 mg/kg po. Gastric ulceration studies have been further carried out for the ethanolic extract and its various fractions at dose of 900 mg/kg body weight. Amongst the tested fractions, the ethyl acetate fraction exhibited better anti-inflammatory effect (67.27%) at 300 mg/kg po dosage when compared to the standard

drug, indomethacin (63.63%) after 3h in the carrageenan induced hind paw edema. The anti-inflammatory activity of the ethanolic extract and its various fractions appear to be related to the inhibition of NO release, and the decreasing TNF-α level. The ethanolic extract and all its fractions especially the ethyl acetate ($p<0.01$) showed significant analgesic activity with insignificant ulceration as compared to the standard drug, ibuprofen. The histopathological study of the effect of ethanolic extract and its fractions in the stomach, reveals that none of them cause ulcer[37]. The anti-inflammatory effect of ethanolic extracts of Adiantum capillus-veneris and the involvement of NF-κB signaling in the regulation of inflammation was studied. The plant ethanolic extracts effectively suppressed PGE2, IL-6 and TNFα release with an IC_{50} less than 50 μg/ml. Moreover, luciferase expression could be specifically blocked in HepG2 cells, showing that the plant extracts displayed a cell-specific pattern on NF-κB gene transcription. The assayed biological activity also depended on the order of adding TNF-α and the plant extracts because the plant extracts could only block the NF-κB activation if added earlier but were unable to stop the signal when added after TNF-α. However, the plant extracts did not exert any effect on ubiquitination which regulates several steps in the NF-κB pathway. Additionally, the plant extracts down-regulated phosphorylation of IKKα/β at S176/180, p38 at T180/Y182 and p65 at S536, but not p65 at S276. This was confirmed by their ability to selectively abrogate the induction o IL-8 transcription, whereas the ICAM-1 gene, which is not transcribed selectively by an NF-κB complex containing a form of p65 phosphorylated on Ser536, did not change. Finally, the plant extracts at 200 μg/mg could normalize the LPS-induced elevation of spleen index as well as NF-κB and p38 activations in CD1 mice[39-41].

Alhagi maurorum

Pharmacological screening of extract of Alhagi maurorum has revealed that it possesses anti-inflammatory effect; the extract inhibited the release of pro-inflammatory mediators of acute inflammation such as histamine and prostaglandin[42]. The anti-inflammatory activity of an aqueous extract of Alhagi maurorum was examined in mice by formalin induced paw edema assay. The extract was also significantly reduce the thickness of paw edema induced by formalin at dose –dependent manner in both phase I, and phase II[43]. Zakaria et al. also found that Alhagi maurorum extract exerted significant anti-inflammatory activity in acutepaw edema and significant anti-inflammatory activity in sub-acute cotton pellet model[44-45].

Ailanthus altissima

Ailanthus altissima stem bark of Egyptian origin were evaluated for their analgesic, antipyretic and antiulcer activities. Analgesic and antipyretic activities were evaluated by hot plate test at doses of 50 mg/ kg and 100 mg/kg of the extracts. The extracts have similar analgesic activity and the ether extract showed good analgesic activity at 30min. Also extracts showed a decrease on rectal temperature that means an hypothermic activity of the plant extracts with longer effect for the ether extract. Ether extracts showed a gastric ulcer protection activity and cytoprotection activity in a doses of 100 mg/kg as well as 50 mg/kg in ethanol induced ulcer in mice[46]. Luteolin-7-O-glucoside (L7G), isolated from Ailanthus altissima, inhibited 5-lipoxygenase (5-LOX)-dependent leukotriene C_4 (LTC_4) production in bone marrow-derived mast cells (BMMCs) in a concentration-dependent manner with an IC_{50} of 3.0 μM. To determine the action mechanism of L7G, immunoblotting for cytosolic phospholipase A2 (cPLA2) and mitogen-activated protein kinases (MAPKs) following c-kit ligand (KL)-induced activation of BMMCs with or without L7G were performed. Inhibition of LTC_4 production by L7G was accompanied by a decrease in cPLA2 phosphorylation, which occurred via the extracellular signal-regulated protein kinase-1/2 (ERK1/2) and p38 and c-Jun N-terminal kinase (JNK) pathways. In addition, L7G also attenuated mast cell degranulation in a dose-dependent manner (IC_{50}, 22.8 μM) through inhibition of phospholipase Cγ1 (PLCγ1) phosphorylation. Accordingly, the authors suggested that the anti-asthmatic activity of L7G may be mediated in part via the inhibition of LTC_4 generation and mast cell degranulation[47]. The Antiinflammatory effect of an ethanol extract from the parts of Ailanthus altissima was evaluated in both in vitro and in in vivo system. The ethanol extract of Ailanthus altissima (EAa) inhibited generation of the cyclooxygenase-2 (COX-2) dependent phases of prostaglandin D2 in bone marrow-derived mast cells (BMMC) in a concentration-dependent manner with an IC_{50} value of 214.6 microg/ml. However, this compound did not inhibit COX-2 protein expression up to a concentration of 400 microg/ml in the BMMC, indicating that EAa directly inhibits COX-2 activity. In addition, EAa inhibited leukotriene C4 production with an IC_{50} value of 25.7 microg/ml. Furthermore, this compound inhibited degranulation reaction in a dose dependent manner, with an IC_{50} value of 27.3 microg/ml. When ovalbumin (OVA)-sensitized mice were orally pretreated with EAa before aerosol challenges. EAa reduced the eosinophil infiltration into the airway and the eotaxin, IL-4, and IL-13 mRNA expression levels[48]. The ethanol extract of Ailanthus altissima showed antiinflammatory activity in an ovalbumin (OVA)-sensitized murine asthmatic model. To determine the anti-inflammatory compounds in the plant, luteolin-7-O-glucoside (L7G) was isolated and its antiasthmatic activity was evaluated in an in vivo murine asthmatic model. L7G (10 to 100 mg/kg, po) reduced the amount of eosinophil infiltration in bronchoalveolar lavage (BAL) fluid in a dose-dependent manner. L7G inhibited both

the prostaglandin E2 (PGE2) and serum immunoglobulin E level in BAL fluid in a dose-dependent manner. In addition, L7G inhibited the transcript profiles of interleukin IL4, IL5, and IL13 mRNA expression levels in the murine asthma model[49-50].

Allium cepa

Ethanol (75%) extract of the fixed oil inhibited lipoxygenase in the polymorphonuclear leukocytes of guinea pigs[51]. The anti-inflammatory effect of an aqueous extract of Welsh onion green leaves (WOE) was investigated in mice. Administration of WOE, in the range of 0.25–1 g/kg, showed a concentration dependent inhibition on paw edema development after carrageenan treatment. The anti-inflammatory effects of WOE were closely attributed to decreased levels of tissue NO and tumor necrosis factor-α (TNF-α). Further evidence for WOE's protection is shown in the reduction of lipid oxidation and the increase of antioxidant enzyme activities, including catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPX) in vivo. WOE also decreased the number of acetic acid-induced writhing responses and formalin-induced pain in the late phase in mice. Overall, the results showed that WOE might serve as a natural source of anti-inflammatory compounds[52]. Seven different synthetic thiosulfinates, and cepaene-and/or thiosulfinate-rich onion extracts were found to inhibit in vitro the chemotaxis of human granulocytes induced by formyl-methionine-leucinephenylalanine in a dose-dependent manner at a concentration range of 0.1– 100 μM. Diphenylthiosulfinate showed the highest activity and was found to be more active than prednisolone. The anti-inflammatory properties of onion extracts are related, at least in part, to the inhibition of inflammatory cell influx by thiosulfinates and cepaenes[53]. In addition, ajoene inhibited the pain receptors at dorsal root of spinal cord, thus resulting in an inhibition of pain signal transduction[54-55].

Alpinia galanga

A polyherbal formulation (JointCare B) containing Alpinia galanga, exerteddose-dependent inhibition of inflammation in carrageenan induced paw and granuloma weight in croton oil-induced granuloma pouch model in rats[56]. In a randomized double-blind placebo controlled study,patients with osteoarthritisof the knee and moderate-to severe pain, the concentrated extract has been found significantly reduce symptoms of osteoarthritis[57-58].

Ammannia baccifera

Gopalakrishnan et al evaluated the anti-inflammatory and anti-arthritic activities of different extracts of Ammannia baccifera in acute inflammation induced by carrageenan in rat hind paw and in chronic inflammation induced by Freund's adjuvant induced arthritis models in comparison with indomethacin (10 mg/kg bw) as a standard drug. The ethanol extract of Ammannia baccifera exhibited significant dose dependent activity in acute inflammation and the doses of 100 mg/kg and 200 mg/kg bw produced 38.27% and 43.39% inhibition respectively after 3 h as compared with that of the standard drug which showed 48.52% inhibition. In Freund's adjuvant induced arthritis model, the doses of 100 mg/kg and 200 mg/kg bw of the ethanol extract produced (38.83%) and (44.08%) inhibition respectively after 19 days when compared with that of the standard drug (55.47%)[59]. The methanolic extract exhibited significant anti-inflammatory and analgesic activities at the dose of 100 and 200 mg/kg po. The analgesic effect of the higher dose of the extract (200 mg/kg) was comparable with the standard drugs aspirin and morphine[60].Tripathy et al found that ethanol extract of aerial parts of A. baccifera exhibited better anti arthritic activity than aqueous extract on cotton pallet induced granuloma and complete Freund'sadjuvant induced arthritis models in albino rats[61].

Ammi majus

Ammi majus coumarins were evaluated for anti-inflammatory activity by the carrageenan induced rat paw edema method. They possessed anti-inflammatory effects at a dose of 0.01 mg/100 g[62-64].

Anchusa italica

The anti-inflammatory activity of different extracts from the aerial parts and the roots of Anchusaitalicawas investigated in rats using carrageenan-induced acute inflammation. The methanolic extract from the aerial parts, its *n*-butanol fraction, and rosmarinic acid, which was isolated from the *n*-butanol fraction of the methanol extract, showed significant dose-dependent anti-inflammatory activity. During the acute phase of inflammation, the anti-inflammatory activity of rosmarinic acid was comparable to that of ibuprofen[65-66].

Anethum graveolens

The hydro alcoholic extract of the Anethum graveolens seed caused significant decrease in the inflammation and pain in rats[67]. Anethum graveolens oil and diclofenac-gel showed a significant ($p < 0.001$) decrease in the paw volume in rats compared to the blank group. Anethum graveolens oil showed even more

decrease in the paw volume compared to the diclofenac[68]. A single topical application of an ethanol extract of the fruits to the inner and outer surface of the ear of mice inhibited ear inflammation induced by 12-O-etradecanoylphorbol-13 acetate by 60%[69-70].

Anthemis nobelis

The volatile oil have been documented as having anti inflammatory activity (carrageenan rat paw odema test) and produced antidiuretic and sedative effects following intraperitoneal administration of doses up to 350 mg/kg to rats. The mechanism of antiallergic and anti inflammatory effects of azulenes is thought to involve inhibition of histamine release[71]. Two varieties of *Anthemis nobilis*, named (white-headed) or double flowered and (yellow-headed) yield essential oils with different composition. These essential oils proved to possess interesting anti-inflammatory and sedative properties, especially that derived from the (White-headed) variety. The oils caused 22.8 to 38.7% inhibition of the carrageenan induced increase in paw volume[72]. Six octulosonic acid derivatives were isolated from the flower heads of Roman chamomile (*Chamaemelum nobile*). The biological activity of the isolated compounds was evaluated toward multiple targets related to inflammation and metabolic disorder such as NAG-1, NF-κB, iNOS, ROS, PPARα, PPARγ, and LXR. Similar to the action of NSAIDs, all the six compounds increased NAG-1 activity 2-3-fold. They also decreased cellular oxidative stress by inhibiting ROS generation. Three of the compounds activated PPARγ 1.6-2.1-fold, while PPARα was activated 1.4-fold by compounds two compounds. None of the compounds showed significant activity against iNOS or NF-κB[73-74].

Apium graveolens

Apium graveolens exerted anti-inflammatory effects in the mouse ear test and against carageenan induced rat paw odema, Accordingly, Apium graveolens was recommended in arthritis and back pain[75-77].

Arachis hypogaea

The anti-inflammatory effects of proanthocyanidins isolated from peanut skin were tested on inflammatory cytokine production and melanin synthesis in cultured cell lines. Peanut skin extract (PSE, 200 μg/mL) decreased melanogenesis in cultured human melanoma HMV-II co-stimulated with phorbol-12-myristate-13-acetate. It also decreased production of inflammatory cytokines (PSE at 100 μg/mL), tumor necrosis factor-α and interleukin-6, in cultured human monocytic THP-1 cells in response to lipopolysaccharide. Proanthocyanidins of peanet showed suppressive activities against melanogenesis and cytokine production at concentrations ranging from 0.1-10 μg/mL. Among the tested compounds, the suppressive activities of proanthocyanidin dimers or trimers in two assay systems were stronger than those obtained with monomer or tetramers. These data indicate that proanthocyanidin oligomers from peanut skin have the potential to reduce dermatological conditions such as inflammation and melanogenesis[78-79]. Cho-K1 cells stably transfected with opioid receptor subtypes μ, Δ, and κ was used to assay the affinity of peanut constituents to opioid receptors. Compound GC-143-8 was run in competition binding against all three opioid subtypes (μ, κ, and Δ). One of peanet stilbenoidsshowed opioid recetor affinity . Combined use of this compound and analgesic agents may result in lower amounts of the latter needed to block pain . However, it is likely that the specific position and number ofhydroxy groups in the structure of the stilbenoid may be responsible for opioid receptor binding[80-81].

Arctium lappa

Arctium lappa decreased edema in the rat-paw model of carageenan-induced inflammation. Its extract was significantly reduce the release of inflammatory mediators through inhibition of degranulation and cys-leukotriene release[82-83]. Cultured macrophage RAW 264.7 was used to investigate the anti-inflammatory mechanism of arctigenin of A. lappa. Arctigenin suppressed lipopolysaccharide (LPS)-stimulated NO production and pro-inflammatory cytokines secretion, including TNF-a and IL-6 in a dose-dependent manner. Arctigenin also strongly inhibited the expression of iNOS and iNOS enzymatic activity, whereas the expression of COX-2 and COX-2 enzymatic activity were not affected by arctigenin[84]. Chlorogenic acid, as one of the constituents of A. lappa, inhibited lipopolysaccharide (LPS)-induced inflammatory response in RAW 264.7 cells, inhibited staphylococcal exotoxin-induced production of IL-1β, TNF, IL-6, INF-γ, monocyte chemotactic protein-l, macrophage inflammatory protein (MIP)-lα, and MIP-lβ in human peripheral blood mononuclear cells. Chlorogenic acid also inhibited lipopolysaccharide (LPS)-induced inflammatory response in RAW 264.7 cells, and decreased LPS-induced up-regulation of cyclooxygenase-2 at the protein and mRNA levels resulting in the inhibition of prostaglandin E2 release from LPS-treated RAW 264.7 cells[85-86]. Butanol extract of *A. lappa* caused significant inhibition of β-hexosaminidase release in RBL-2H3 cells and suppressed mRNA expression and protein secretion of IL-4 and IL-5 induced by ConA-treated primary murine splenocytes. 100 μg/ml of butanol extract of *A. lappa* suppressed not only the transcriptional activation of NF-κB, but also the

phosphorylation of MAPKs in ConA-treated primary splenocytes[87]. When BALB/C female mice were treated with *Arctium lappa* polysaccharide (ALP) at low, medium and high dose, the immunological analysis showed that the number of antibody-producing cells at all doses, the phagacytosis index at medium dose and the weight of spleen and thymus at all doses were significantly increased after 20 days[88].

Asclepias curassavica

Hydroalcoholic extract of the aerial part (95%) of plant showed anti-inflammatory activity. The aqueous and alcoholic extracts of stem of Asclepias curassavica also showed significant anti-pyretic and analgesic activity[89-90].

Asparagus officinalis

Jang et al., examined Asparagus officinalis for its inhibitory effects against both cyclooxygenase-1 and -2. They found that linoleic acid was the most active compound[91-92].

Astragalus hamosus

The anti-inflammatory effect of the hydro-alcoholic extract of the pods of Astragalus hamosus (HAAH) was evaluated by the rat paw edema induced by formalin. Also the analgesic effect was examined by the acetic-acid-induced writhing response and hot plate test. The analgesic effects of chloroform, hexane, ethyl acetate and aqueous fractions were evaluated by the hot-plate method. The hydroalcoholic extract of Astragalus hamosus could reduce the edema in a dose-dependent manner ($P<0.05$). In the acute phase, the result of 1000 mg/Kg and in the chronic phase, the result of 100 and 300 mg/Kg of the extract were more significant and comparable with the effect of sodium salicylate. Also application of different doses of HAAH had significant anti-nociceptive effects on both animal models. The findings showed that HAAH at doses of 700 and 1000 mg/Kg produced analgesic effects comparable to sodium salicylate. The hexane and ethyl acetate (but not the other fractions) showed significant analgesic activity in hot plate test, when compared to morphine [120].An aqueous and alcoholic extract of Astragalus hamosus (0.58 gm/kg) once a day for 13 days, orallyproduced highly significant anti-inflammatory effect in comparison to the control[93-94].

Avena sativa

The anti-inflammatory activities from whole oat groats of seven common varieties were evaluated. Oat variety CDC Dancer inhibited tumor necrosis factor-α induced nuclear factor-kappa B activation by 27.5% at 2 mg/ml, whereas, variety Deiter showed 13.7% inhibition at a comparable dose. Avenanthramide levels did not correlate with the observed anti-inflammatory activities[95].Avenanthramides have been reported to exhibit anti-inflammatory activity on the skin. At concentrations as low as 1 part per billion, it inhibited the degradation of inhibitor of nuclear factor kappa B-alpha (IkappaB-alpha) in keratinocytes which correlated with decreased phosphorylation of p65 subunit of nuclear factor kappa B (NF-kappaB). Furthermore, cells treated with avenanthramides showed a significant inhibition of tumor necrosis factor-alpha (TNF-alpha) induced NF-kappa B luciferase activity and subsequent reduction of interleukin-8 (IL-8) release. Additionally, topical application of 1-3 ppm avenanthramides mitigated inflammation in murine models of contact hypersensitivity and neurogenic inflammation and reduced pruritogen-induced scratching in a murine itch model[96-97].

Bacopa monnieri

Bacopa monniera effectively suppressed experimentally induced inflammatory reaction effect by inhibiting the prostaglandins synthesis and partly by stabilizing lyosomal membranes and didn't cause gastric irritation at anti-inflammatory doses[98].The ethanol extract of the whole plant of Bacopa monnieri produced significant writhing inhibition in acetic acid induced writhing in mice at the oral dose of 250 and 500 mg/kg ($P<0.001$) comparable to diclofenac sodium 25mg/kg[99]. The anti-inflammatory effects of the many extracts of Bacopa monnieri were investigated on carrageenan induced edema in rat's hind paws**.** The methanol extract and aqueous fractions (100 mg/kg) showed a significant reduction in the edema paw volume, while, petroleum ether and hexane extracts didn't reduced inflammation[100]. Human red blood cell (HRBC) membrane stabilization method was used to assay the in vitro anti-inflammatory activity of *Bacopa monnieri*. Methanolic extract and the callus (100, 200, 300 µg) produced membrane stabilization better than diclofenac sodium[101]. The anti-inflammatory activity of *Bacopa monnieri* is due to the triterpenoid and bacoside present in the plant. *Bacopa monniera* has the ability to inhibit inflammation through modulation of pro-inflammatory mediator release. The fractions containing triterpenoids and bacosides inhibited the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6[102-103].

Bauhinia variegata

Phytochemical analysis of non woody aerial parts of Bauhinia variegata yielded 6 flavonoids with one triterpene caffeate. These seven compounds showed anti- inflammatory activity, they inhibited the lipopolysaccharides and interferon γ induced nitric oxide (NO) and cytokines[104-105].

Bellis perennis

In two placebo-controlled studies, Traumeel injections, (which contains Bellis perennis) was used in patients with hemarthrosis. It showed that Traumeel injections improved joint and mobility, and decreased intensity of pain and effusion[106-108].

Benincasa hispida

The preliminary investigations of aqueous extract of Benincasa hispida showed that it exhibited anti-inflammatory properties. Petroleum ether and methanolic extract of Benincasa hispida fruit, at the dose of 300 mg/kg bw, produced dose dependent and significant inhibition of carrageenan- induced paw edema, histamine induced paw edema and cotton pellet induced granuloma in rat model. In carrageenan- induced paw edema model, petroleum ether and methanolic extracts showed maximum inhibition in inflammation (0.270 ± 0.063 and 0.307 ± 0.043 respectively) as compared to control group (1.27 ± 0.059) and standard valdecoxib (0.247 ± 0.033). In histamine-induced paw edema, both extracts showed (62.86% and 54.84% respectively) inhibition as compared to control. The effects were comparable with that of standard drug cetrizine (95.24%). Petroleum ether and methanolic extracts showed slight insignificant reduction in granuloma tissue formation in cotton pellet implanted rats[109]. The mechanism of anti-vascular inflammatory activity of an aqueous extract of B. hispida (ABH) in human umbilical vein endothelial cells (HUVECs) was investigated. ABH inhibited high glucose-induced cell adhesion molecules (CAMs) surface and protein expression, resulting in reduced adhesion of U937 monocytes. ABH also inhibited the mRNA expression level of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8). High glucose-induced ROS production was also inhibited by ABH. Pretreatment of HUVECs with ABH blocks NF-κB activation via blocking phosphorylation and degradation of its inhibitory protein, IκB-α . ABH also reduced NF-kB promoter activity[110]. The methanolic extract of Benincasa hispida at doses of 250 and 500 mg/kg bw, significantly ($P<0.05$) increased the antinociceptive effective (as determined by analgesiometer which exerts force at a constantly-increasing rate on the rat paw) in a dose dependent manner in rats. Similarly, at doses of 250 and 500 mg/kg bw, the extract significantly ($P<0.05$) decreased the Brewer'syeast induced pyrexia in rats[111-112].

Betula alba

Betulinic acid was found a moderate inhibitors of COX-1, COX-2 and Leukotriens formation in vitro with IC_{50} values of >125, >125 and 102.2 μM, respectively[113]. It also produced anti-inflammatory activity in the carrageenan and serotonin paw edema and TPA and EPP ear edema[114]. It was also produced an in vivo anti- inflammatory effect on TPA-induced model of inflammation in mice. Betulinic acid showed pronounced antinociceptive properties in the writhing test and formalin test in mice[115-116].

Bidens tripartita

The anti-inflammatory potential of three doses of an aqueous infusion of aerial parts Bidens tripartita L. was investigated against carrageenan-induced acute paw edema in rats. Infusion doses of 20ml/k bw exhibited significant anti-inflammatory activity in rats, as compared with indomethacin. In addition, the infusion showed analgesic properties in a hot-plate test and antipyretic properties in carrageenan-induced local hyperthermia in rats. The effects were dose-dependent[117-118].

Brassica nigra

The effect of Brassica nigra seed extracts on arthritic rats were assessed by the various models. In arthritic rats, inflammation reached maximum on day 3 and maintained till day 9. Paw maintained its inflammation till day 14. A significant reduction was recorded in the extracts treated group. Ankle diameter reached maximum on day 7 and maintained its inflammation till day 14. A non-significant reduction was observed in the extracts treated group[118]. In vivo and in vitro anti-inflammatory activity of the crude extract was evaluated using carrageenan induced rat paw edema and protease enzyme inhibition assay. In vivo anti-inflammatory test of the ethanolic extract of Brassica nigra (500 mg/kg) gave 17.9% inhibition whereas standard phenylbutazone (100mg/kg) gave 39.38%. In vitro anti-inflammatory test of Brassica nigra by protease inhibition method also gave 42.57% inhibition of trypsin at dose 250 μg/ml[119]. Volatile oil of mustard is an extremely diffusible and penetrating irritant, quickly exciting heat and burning pain through its dilating action upon the peripheral vessels and irritation of the sensory nerve endings. If too long applied it will blister, and cause inflammation, sloughing and deep ulceration; and not infrequently gangrene. To a degree local anesthesia is produced in some instances and the patient is then not aware of the possible destruction of tissue. When the

treatment removed in time only induration is caused, followed sometimes by desquamation. Mustard applied in the same manner acts similarly but more slowly and with gradually increased intensity[120-121].

Brassica rapa

Arvelexin also inhibited LPS-induced NO and prostaglandin E2 production through the suppression of iNOS and COX-2 at the level of gene transcription. In addition, arvelexin inhibited NF- κB dependent inflammatory responses by modulating a series of intracellular events of IκB kinase (IKK)-inhibitor κBα (IkBα)-NF- κB signaling. Moreover, arvelexin inhibited IKKβ -elicited NF- κB activation as well as iNOS and COX-2 expression. Serum levels of NO and inflammatory cytokines and mortality in mice challenged injected with LPS were significantly reduced by arvelexin[122].

Bryonia dioica

Bryonia dioica revealed interesting anti- inflammatory and antioxidant properties. Its anti-inflammatory effects provide the scientific evidence for its folk uses as anti-inflammatory[123]. The triterpene-glycosides, bryonioside B, C, E and G, cabenoside D and bryoamaride inhibited TPA-induced mouse ear oedema. The antiphlogistic activity of these triterpene glycosides (ID_{50} = 0.2–0.7 mg/ear) was stronger than the reference quercetin (ID50 = 1.6 mg/ear) and comparable to indomethacin (ID50 = 0.3 mg/ear[124].Triterpene glycosides were evaluated for their inhibitory effects on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation (1 μg/ear) in mice and on Epstein−Barr virus early antigen (EBV-EA) activation induced by TPA. All the tested compounds showed marked anti-inflammatory effects, with 50% inhibitory doses (ID_{50}) of 0.2−0.6 mg/ ear. In addition, all of the tested compounds ,except one, showed potent inhibitory effects on EBV-EA induction (100% inhibition at 1×10^3 mol ratio/TPA)[125].

Bryophyllum calycinum

The plant extract significantly inhibited fresh egg albumin-induced acute inflammation and significantly exhibited antinociceptive effectsagainst thermally- and chemically-induced nociceptive pain stimuli in mice. Stigmast-4, 20 (21), 23-trien-3-one, a steroidal derivative obtained from the leaves extract of the plant , also possessed anti-inflammatory effects[126-127].

Caesalpinia crista

The anti-inflammatory effects of the ethanolic seed extract of Caesalpinia crista was investigated by carrageenan induced paw edema and the analgesic activity by writhing reflexes and tail immersion method in mice. The extract showed maximum inhibition of 74.2% at 300 mg/kg by carrageenan induced paw edema method as compared to standard, diclofenac. Furthermore, the extract also showed potent analgesic activity 71% at 300 μg/ml by writhing reflexes in mice, and the tail withdrawal latency of mice was 5.30±0.05 sec at 300 μg/ml by tail immersion method. The anti-inflammatory activity was also studied in rats using the formalin arthritis and granuloma pouch methods. At a dose of 250 mg/kg, the extract was found to be effective in the granuloma pouch model. The seeds showed a 50% inhibitory activity against carrageenan-induced oedema in the rat hind paw, at an oral dose of 1000 mg/kg when given 24 hours and 1 hour prior to carrageenan injection. On the other hand, Caesalpinia crista seed coat extracted by 95% ethanol was screened for anti-inflammatory and analgesic activity using carrageenan-induced paw edema, egg albumin-induced paw edema, Eddy's hot plate test and tail immersion method. It appeared that seed coat extract has the ability to decrease the induced inflammation at varied doses in carrageenan and egg albumin model in rats. The antinociceptive results indicate that the extract has the ability to increase the pain threshold of the animals, reduce the pain factor and induce analgesia[128-130]. The analgesic and antipyretic activity of Caesalpinia crista seed oil on acute and chronic inflammation was determined in experimental animal model. Doses of 100, 200 and 400 mg/kg of the seed oil of Caesalpinia crista were given orally in carrageenan induced rat paw oedema, brewer's yeast-induced pyrexia, acetic acid-induced writhing and hot plate reaction time in experimental rats. The paw volumes, pyrexia and writhes were reduced significantly ($p < 0.05$) in Caesalpinia crista treated rats as compared to that of control[131-132].

Calendula officinalis

Calendula officinalis flower extract possessed significant anti-inflammatory activity against carrageenan and dextran-induced acute paw edema. Oral administration of 250 and 500 mg/kg body weight Calendula extract produced significant inhibition (50.6 and 65.9% respectively) in paw edema of animals induced by carrageenan and 41.9 and 42.4% respectively with inflammation produced by dextran. Administration of 250 and 500 mg/kg body weight Calendula extract produced an inhibition of 32.9 and 62.3% compared to controls, respectively in chronic anti-inflammatory model using formalin. TNF-alpha production by macrophage culture treated with lipopolysaccharide (LPS) was found to be significantly inhibited by

Calendula extract. Moreover, increased levels of proinflammatory cytokines IL- 1beta, IL-6, TNF-alpha and IFN-gamma and acute phase protein, C- reactive protein (CRP) in mice produced by LPS injection were inhibited significantly by the extract. LPS induced cyclooxygenase-2 (Cox-2) levels in mice spleen were also found to be inhibited by the extract treatment[133]. The hydroalcoholic plant extracts of Calendula officinalis suppressed the cell-free systems activities of 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2), the key enzymes in the formation of proinflammatory eicosanoids from arachidonic acid[134].

The inhibitory activity of nine oleanane-type triterpene glycosides isolated from Calendula officinalis was studied against 12-O-tetradecanoylphorbol-13-acetate (TPA) -induced inflammation (1 microg/ear) in mice, all of the compounds, except 1, exhibited marked anti-inflammatory activity, with ID_{50} values of 0.05-0.20 mg per ear[135]. The anti-inflammatory activity of the 3 main triterpendiol esters of marigold was tested against croton oil-induced edema of the ears in mice. Faradiol-3-myristic acid ester and faradiol-3-palmitic acid ester were found to have the same dose-dependent anti-inflammatory activity. The non-esterified faradiol was more active than the esters and had an equivalent effect on inflammation as an equimolar dose of indomethacin[136]. A dose of 1200 µg/ear of an aqueous-ethanol extract showed 20% inhibition in croton oil-induced mouse oedema. The activity was attributed to the presence of triterpenoids, the three most active compounds were the esters of faradiol-3-myristic acid, faradiol-3-palmitic acid and 4-taraxasterol[137-139].

Calotropis procera

The anti-inflammatory effect of the chloroform (CH) and hydroalcoholic extract (HE) of the stem bark of Calotropis procera against carrageenan-induced paw oedema has been studied by using two acute models, aspirin (100 mg/kg, po) and ethanol (96%) in albino rats. CH and HE extracts showed significant anti-inflammatory activity at 200 and 400 mg/kg. As part of investigations to obtain compounds with anti-inflammatory effects, a bioassay was carried out with fractions obtained from the CH extract with n-hexane (NF1), 1-butanol (BF1), ethyl acetate (EF1) and chloroform (CF1). The HE extract of the stem bark was fractionated with n-hexane (NF2), 1-butanol (BF2), ethyl acetate (EF2), chloroform (CF2) and water (WF2). The fractions were evaluated for their anti-inflammatory effects. Fractions NF1, CF1, BF2 and EF2 (20 mg/kg) showed significant anti-inflammatory activity[140]. The latex of Calotropis procera, ethanol extract of its flowers and the chloroform soluble fraction of its roots possessed significant anti-inflammatory activity[141]. The methanolic extract of plant Calotropis procera roots has been reported to exhibit potent anti-inflammatory activity against carrageenan induced paw oedema and cotton pellet induced granuloma in albino Wistar rats. The different extracts of the roots of C. procera and standard anti-inflammatory drugs were administered orally 1 hour before inducing of inflammation. The methanolic extracts (180mg/kg, po) of roots of C. Procera has potential to inhibit sub-acute inflammation by interruption of the arachidonic acid metabolism in both paw oedema as well as cotton pellet model and showed inhibition of inflammation ($p<0.01$ and $p<0.001$) very close to the inhibitory effect of diclofenac sodium (25 mg/kg, ip)[142]. The ethanolic extract of root bark of Calotropis procera was investigated for its anti-inflammatory activity at different dose in the different animal models. The experimental paradigms used were complete Freunds adjuvant (CFA) induced arthritis (chronic inflammation), acetic acid induced vascular permeability model in mice for anti-inflammatory activity. The extract of Calotropis procera (CPE) exhibited significant anti-inflammatory effect at the dose 100 and 200 mg/kg. The extract showed 21.6 and 71.6% inhibition against CFA induced arthritis at the dose of 100 and 200 mg/kg after drug treatment, as compared to standard drug dexamethasone which produced 99% inhibition. The extract also exhibited significant inhibition in polyarthritic index in rats caused by CFA induced arthritic inflammation. In the acetic acid induced vascular permeability the CPE (100 and 200 mg/kg), significantly reduced dye leaking by 45.4% and 61.5% ($p<0.001$) respectiviley as compared to standard drug dexamethasone and ibuprofen 23.7% and 67.4% respectively[143]. Laticifer proteins (LP) of Calotropis procera were fractionated by ion-exchange chromatography, and the influence of a sub-fraction LP(PI)) on the inflammatory response of Swiss mice challenged by Salmonella enterica Ser. Typhimurium was investigated. The survival rate reached 100 % in mice treated with LP(PI) (30 or 60 mg/kg as a single inoculum by the intraperitoneal route 24 h before infection), whereas, the phosphate-buffered saline treated group died 1-3 days after infection. The neutrophil infiltration into the peritoneal cavity of pretreated mice was enhanced and accompanied by high bacterial clearance from the bloodstream. Tumor necrosis factor-alpha mRNA transcripts, but not interferon-gamma, were detected early in spleen cells of pretreated mice after infection; however, the nitric oxide contents in the bloodstream were decreased in comparison to the phosphate-buffered saline treated group[144]. The protective effect of latex of Calotropis procera in complete Freund's adjuvant (FCA) induced monoarticular arthritis was evaluated in rats. Arthritis was induced by a single intra-articular injection of 0.1 ml of 0.1% FCA in the right ankle joint. The effect of dried latex (DL, 200 and 400 mg/kg) and its methanol extract (MeDL, 50 and 500 mg/kg) following oral administration was evaluated on joint inflammation, hyperalgesia, locomotor function and histology at the time of peak inflammation. The effects of DL and MeDL were compared with antiinflammatory drugs phenylbutazone (100 mg/kg), prednisolone (20 mg/kg), rofecoxib (20 and 100 mg/kg)

and immuno-suppressant methotrexate (0.3 mg/kg). Daily oral administration of DL and its methanol extract (MeDL) produced a significant reduction in joint inflammation (about 50% and 80% inhibition) and associated hyperalgesia. The antihyperalgesic effect of MeDL was comparable to that of rofecoxib. Both DL and MeDL produced a marked improvement in the motility and stair climbing ability of the rats. The histological analysis of the arthritic joint also revealed significant reduction in oedema and cellular infiltration by MeDL that was comparable to that of rofecoxib[145]. Oral mucositis is an important dose-limiting side effect of cancer chemotherapy. Soluble proteins of the latex of Calotropis procera, phytomodulatory laticifer proteins (LP) were challenged to regress the inflammatory events associated with 5-fluorouracil-induced oral mucositis. Oral mucositis was induced in hamsters by two injections of 5-fluorouracil (5-FU; 60 and 40 mg/kg, ip, on experimental days 1 and 2, respectively). LP (5 mg/kg, ip) was injected 24 h before and 24 h after mechanical trauma of the cheek pouches. The expression of pro-inflammatory cytokines and inducible enzymes, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) were studied. On day 10, the cheek pouches were excised for macroscopic and histopathological analysis and immunohistochemical assessment of tumor necrosis factor- (TNF-α), interleukin-1β (IL-1β), iNOS, and COX-2. Proteins of the latex of Calotropis procera were significantly inhibited macroscopic histopathological scores and myeloperoxidase activity compared with the 5-FU control group. 5-Fluorouracil also induced marked immunostaining of TNF-α, IL-1β, iNOS, and COX-2 on inflamed conjunctive and epithelial tissue compared with the normal control group. Such damage was also significantly inhibited ($p < 0.05$) by LP treatment compared with the 5-FU group[146]. The non-dialysable protein fraction isolated from the latex (LP) of Calotropis procera was evaluated for its efficacy against inflammation in rats where paw edema was induced by sub-plantar injection of carrageenin and monoarthritis was induced by intra-articular injection of Freund's complete adjuvant (FCA). The effect of LP was evaluated on edema volume in the paw model and on joint diameter, stair climbing ability, motility, dorsal flexion pain, levels of oxidative stress markers and joint histology in arthritis model. The protection afforded by LP was compared with that of standard antiinflammatory drug, diclofenac (5 mg/kg). LP exhibited a dose-dependent antiinflammatory effect and produced 32% and 60% inhibition of paw edema at 10 and 25 mg/kg doses and 12% and 36% inhibition of joint inflammation at 50 and 150 mg/kg doses. The protective effect of LP was associated with normalization of joint functions, histology and levels of oxidative stress markers in joint tissue[147]. The effect of non-dialyzable protein (LP) sub-fractions on neutrophil functions and nociception in rodent models (the rat peritonitis model and on nociception in the mouse model) was investigated. LP sub-fractions exhibit distinct protein profile and produce a significant decrease in the carrageenan and DF induced neutrophil influx and exhibit anti-nociceptive property. The LP and its sub-fractions produced a marked reduction in the number of rolling and adherent leukocytes in the mesenteric microvasculature as revealed by intravital microscopy. The anti-inflammatory effect of LP(PI), the most potent anti-inflammatory fraction of LP, was accompanied by an increase in the serum levels of NO[148-149].

Capparis spinosa

The anti-inflammatory effects of the flavonoids from caper fruits were evaluated by secreted placental alkaline phosphatase (SEAP) reporter assay, which was designed to measure nuclear factor-kappa B (NF-κB) activation. Isoginkgetin and ginkgetin showed inhibitory effects in initial screen at 20 μM, while the effect of ginkgetin was much greater than that of isoginkgetin. In a dose-response experiment, the IC_{50} value of ginkgetin was estimated at 7.5 μM, suggesting it could be a strong NF-κB inhibitor[150]. The anti-inflammatory activities of C. spinosa L. fruit (CSF) aqueous extract was studied mice. The CSF aqueous extract were separated into three fractions (CSF1-CSF3) by macroporous adsorption resins. The fractions CSF2 and CSF3 effectively inhibited the carrageenan-induced paw edema in mice[151]. The extracts of C. spinosa were found to possess marked anti-inflammatory activity but devoid of analgesic activity in animal models, cappaprenol-13 isolated from C. spinosa showed significant anti-inflammatory activity[152]. The anti- arthritic active fractions of Capparis spinosa fruits was evaluated by adjuvant arthritic rat model..The fraction eluted by ethanol-water (50:50v/v) had the most significant anti- arthritic activity. The chemical constituents of this fraction showed that it contained seven known compounds: P-hydroxybenzoicacid, 5-(hydroxymethyl)furfura,l bis(5-for- mylfurfuryl) ether, daucosterol, α-D-fructo furanosidesmethyl, uracil, and stachydrine.Ethanol and ethanol-water extracts of Capparis spinosa fruits showed anti-arthritic effects due to the presence of an important chemical constituents such as P-hydroxy benzoic acid, 5-(hydroxymethyl) furfural, bis (5-formylfurfuryl) ether, daucosterol, α-D-fructofuranosides methyl, uracil and stachydrine[153-154]. Plant extracts extracted with solvents of varying polarity were effective either in inhibiting the activity of xanthine oxidase or Cyt C. The IC_{50} ranges from 0.0226 ± 0.00019 to 4.32 ± 0.15g/[155-156].

Capsella bursa-pastoris

The plant induced anti-inflammatory activity in carrageenan-induced and dextran-induced rat paw oedema. It also reduced capillary permeability in guinea-pig induced by histamine and serotonin. It also

possessed anti-ulcer activity in rats following intraperitoneal injection. The extract did not affect gastric secretion, but accelerated recovery from stress-induced ulcers [178, 179]. The anti-inflammatory and antibacterial properties of a sulforaphane-containing solution (SCS) isolated from shepherd's purse (Capsella bursa-pastoris). SCS had significant anti-inflammatory activity indicated by the decreased levels of nitric oxide (NO), cytokines (interleukin 1β [IL-1β], IL-6, and IL-10), and prostaglandin E2 (PGE2) in lipopolysaccharide-stimulated RAW 264.7 murine macrophages. SCS also decreased the inducible NO synthase (iNOS) and cyclooxygenase 2 (COX-2) levels, which confirmed the anti-inflammatory activity of SCS[157-158].

Capsicum annuum* and *Capsicum frutescens

The potential effects of both topical capsaicinoids-containing patch and local subcutaneous capsaicin application on the anti-inflammatory action of NSAID were examined. Carrageenan-induced paw oedema of rats was used as the inflammation model. Topical capsaicinoids-containing patch application or local capsaicin injection (2, 10, 20 μg/paw) alone did not cause any effect on oedema volume and weight. However, the combination of diclofenac with topical capsaicinoids-containing patch significantly increased the effectiveness of diclofenac on inflammation. Evans blue content of the paws that represents plasma extravasation was decreased by capsaicinoids-containing patch with and without diclofenac[159]. The anti-inflammatory activity of Capsicum annuum was assessed by inhibiting Soyal lipoxygenase (LOX) enzyme. The results showed higher % of LOX inhibition by green capsicum (46.12 %) followed by yellow (44.09 %) and red capsicum (32.18 %)[160]. Carotenoids extracted from dried Capsicum annuum were evaluated for their analgesic activities. Carotenoids extracts exhibited significant peripheral analgesic activity at 5, 20, and 80 mg/kg and induced central analgesia at 80 mg/kg. The guajillo pepper carotenoids extract was also exerted anti-inflammatory activity, they significantly inhibited oedema formation and progression at a dose of 5 mg/kg compared to the control treatment at 1, 3, and 5 hours after carrageenan injection ($p<0.05$). A similar response was obtained with indomethacin compared to the control treatment. Interestingly, at higher doses (20 and 80 mg/kg), the guajillo pepper extract significantly reduced oedema generated by the carrageenan at the 5 h time point ($p<0.05$)[161]. The anti-inflammatory effects of ethyl acetate extract of Capsicum frutescens (CFE) was examined on rat hind paw inflammation induced by subplantar injections of fresh egg albumin (0.5 ml/kg).Ethyl acetate extract of Capsicum frutescensproduced anti-inflammatory effects that were comparable to diclofenac[162-163].

Carthamus tinctorius

Intragastric administration of 30 mg/kg bw of a 50% methanol extract of the flowers inhibited inflammation as measured by footpad oedema induced by carrageenan, serotonin, bradykinin, histamine or prostaglandin in mice. Intragastric administration of 30 g/kg bw of a 50% methanol extract of the flowers to mice also reduced writhing induced by acetic acid[164]. Subcutaneous administration of 10 g/kg bw of an aqueous or 50% methanol extract of the flowers inhibited carrageenan-induced footpad oedema in mice. Subcutaneous administration of 10.0 g/kg bw of an aqueous extract of the flowers to mice did not reduce pain perception as measured in the hot-plate test. Subcutaneous administration of 1.0–3.0 g/kg bw of a 50% methanol extract of the flowers to mice reduced writhing induced by acetic acid[165]. The effects of Hydroxysafflor yellow A (HSYA) on lipopolysaccharide (LPS)-induced inflammatory signal transduction in human alveolar epithelial A549 cells was studied. A549 cells stimulated with LPS were incubated with three doses of HSYA (1, 4 and 16μmol/l). HSYA suppressed the expression of TLR-4, Myd88, ICAM-1, TNFα, IL-1β and IL-6 at the mRNA and protein level, and inhibited the adhesion of leukocytes to A549 cells. HSYA treatment also decreased NF-κB p65 nuclear translocation and inhibited the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK)[166]. The effects of dried safflower petals aqueous extracts (SFA) and Carthamus yellow (CY) were investigated on lipopolysaccharide (LPS)-induced inflammation using RAW264.7 macrophages. Treatment with SFA (1-1000 microg/ml and CY (1-2000 microg/ml does not cause cytotoxicity. SFA and CY inhibited LPS-stimulated nitric oxide (NO), prostaglandin E_2 (PGE_2), and interleukin 1β (IL-1β) release, through attenuation of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) protein expression. Furthermore, SFA and CY suppressed the LPS-induced phosphorylation of nuclear factor-κB, which was associated with the inhibition of IκB-α degradation[167]. N-(p-Coumaroyl)serotonin (CS) inhibited proinflammatory cytokine generation from human monocytes in vitro. CS augmented the proliferation of normal human and mouse fibroblast cells. The cells continued to proliferate in the presence of CS and form a transformed cell-like focus without transformation. CS, however, does not augment the proliferation of other cell types, either normal or tumor cells. CS augmented the proliferation of fibroblasts in synergy with basic fibroblast growth factor (bFGF) or epidermal growth factor (EGF), but not with acidic FGF(aFGF) or platelet-derived growth factor (PDGF)[168]. The inhibitory effect of HSYA was studied on the inflammatory signal transduction pathway related factors which were induced by permanent cerebral ischemia in rats. The result showed that intravenous injection of HSYA (10 mg/kg) to rats after cerebral occlusion, the p65 translocation activity and the phosphorylation of IkappaB-alpha were significantly inhibited. At the same time, HSYA

suppressed p65 binding activity and the transcriptional level of pro-inflammatory cytokines including TNF-alpha, IL-1beta and IL-6, and promoted the mRNA expression of anti-inflammatory cytokine IL-10. The authors suggested that the anti-cerebral ischemic mechanism of HSYA may be due to its inhibition of NF-kappaB activity and the mRNA expression of cytokines in the inflammatory transduction pathway[169]. A new bioactive triterpenoid saponin 3beta-O-[beta-D-xylopyranosyl(1→3)-O-beta-D- galactopyranosyl]-lup-12-ene-28oic acid-28-O-alpha-L-rhamnopyranosyl ester, isolated from the methanolic fraction of the roots of Carthamus tinctorius, showed anti-inflammatory activity[170]. All the polyacetylene glucosides compounds isolated from the florets of Carthamus tinctorius (11 compounds) were also tested for antinflammatory and inhibitory activities against LPS-induced NO production in murine macrophages, they showed weak activities at concentrations of 1×10^{-5}M[171]. The mechanism of anti-inflammatory effect of the methanol extracts of Carthamus tinctorius (MEC) was investigated. The results showed that the expression of HO-1 protein by MEC in macrophages was increased in a concentration- and time dependent manner. Treatment with MEC significantly inhibited upregulation of both iNOS and COX-2 in LPS-activated macrophages and consequently reduced production of NO and PGE2. The reduced expression of iNOS and COX-2 by MEC was reversed by siHO-1 RNA transfection. In addition, NF-E2-related factor (Nrf2) was translocated from cytosol to nucleus by MEC. The binding of NF-$_k$B as well as NF-$_k$B luciferase activity was also significantly diminished by MEC. Tumor necrosis factor (TNF)-α-mediated VCAM-1 expression in endothelial cell was significantly inhibited by MEC[172-173].

Cassia occidentalis

The anti-inflammatory activity of Cassia occidentalis leaf powder was assayed in male albino rats using carrageenan-induced rat paw edema. C. occidentalis was maximally active at a dose of 2000 mg/kg. In the cotton pellet granuloma assay, Cassia occidentalis leaf powder was able to suppress the transudative, exudative and proliferative components of chronicinflammation.Furthermore,Cassia occidentalis leaf powder was able to lower the lipid peroxide content and gamma-glutamyl transpeptidase and phospholipase A2 activity in the exudate of cotton pellet granuloma. The increased alkaline phosphatase activity and decreased A/G ratio of plasma in cotton pellet granulomatous rats were normalized after treatment with Cassia occidentalis leaf powder. C. occidentalis powder was able to stabilize the human erythrocyte membrane against hypotonicity-induced lysis [214]. The ethanol and water extracts of Cassia occidentalis leaves were screened for antinociceptive activity using acetic acid induced writhing test, hot plate test and tail immersion test in mice. The antipyretic potential of the extract was evaluated using yeast induced pyrexia method in rats. The results showed that ethanol and water extracts had significant ($p<0.01$) dose dependent antinociceptive and antipyretic properties at a dose of 150 and 300 mg/kg. The inhibition produced by the highest dose (300 mg/kg) of the extracts was significantly ($P<0.01$) lower than that by acetylsalicylic acid (100 mg/kg). Both the ethanolic and water extracts of Cassia occidentalis showed significant ($P< 0.01$) effect on pyrexia induced by yeast[174-175].

Centaurea cyanus

Centaurea cyanus flower-heads had anti-inflammatory properties as shown by different pharmacological experiments including inhibition of carrageenan, zymosan and croton oil-induced edemas, inhibition of plasma hemolytic activity, and/or induction of anaphylatoxin activity [216]. Moschamine a safflomide-type phenylpropenoic acid amide found in Centaurea cyanus was a very potent COX-I inhibitor, it inhibited COX-I by 58% ($P< 0.012$) at the concentration of 0.1 μ mol /l[176-178].

Chenopodium album

The topical anti-inflammatory activity for Chenopodium album oil (5-0.625 mg) was evaluated by inhibition of the 12-O-tetradecanoylphorbol-13-acetate (TPA) induced ear edema in mice. The result revealed that the anti-inflammatory action of the oil is concentration dependent, the percentage reduction in the ear edema increases with increase in concentration of the oil. However, the oil caused significant reduction ($p < 0.05$) in the ear edema with all concentrations except at 0.625 mg[179]. The ethanolic extract from the fruits of Chenopodium album, 100-400 mg/kg orally, caused dose-dependently inhibition of scratching behavior induced by 5-HT (10 micro g per mouse, sc) or compound 48/80 (50 micro g per mouse, sc). But it failed to affect hind paw swelling induced by 5-HT or compound 48/80 in mice at doses of 100 and 200 mg/kg and only showed a relatively weak inhibition on the swelling at a higher dose of 400 mg/kg[180]. The role of NF kappa B (NFκB) in the antiarthritic potential of extracts of aerial parts of Chenopodium album was explored and evaluated. The result indicated that the acetone extract of Chenopodium album (ACCA) has shown significant reduction in rat paw edema (80.13%) at dose level of 200mg/kg orally in 21 days of the experiment. On 22nd day, it was observed that the altered hematological parameters (Hb, RBC, WBC and ESR), biochemical parameters (serum creatinine, total proteins and acute phase proteins) and loss in body weight in the arthritic rats were significantly brought back to near normal level by the ACCA extract. ACCA extract significantly decreased the NFκB

expression in paraventricular nucleus of hypothalamus and this effect is comparable with standard indomethacine[181-182].

Cicer arietinum

The anti-inflammatory potency of methanolic and ethanolic extracts of Cicer arietinum seeds at different doses (250 mg/kg and 500 mg/kg body weight) were investigated against carrageenan and histamine induced paw edema in rats. All doses of the extracts showed a significant ($p<0.001$) anti-inflammatory activity when compared to control groups and with standard drug (Indomethacin 10 mg/kg, orally). Both the methanolic and ethanolic extracts showed the dose dependant activity. Among these extracts, the methanolic 500 mg/kg and ethanolic 500 mg/kg extracts of Cicer arietinum showed maximum anti-inflammatory activity[183-184].

Cistanche tubulosa

The anti-inflammatory effects of fuciodan and Cistanche tubulosa extract were investigated in in vitro macrophage culture system and in vivo carrageenan-induced air pouch inflammation model. Although, fucoidan was inactive, but in vivo air pouch inflammation model, carrageenan-induced vascular exudation and increased nitric oxide and prostaglandin E_2 concentrations in the exudates were synergistically suppressed by co-administration of fucoidan and Cistanche tubulosa extract. Moreover, tissue inflammation was substantially attenuated by the combinational therapy. However, there was no synergistic effect against the inflammatory cell infiltration, although fucoidan and Cistanche tubulosa extract each markedly reduced the cell numbers. The authors concluded that fucoidan blocked infiltration of inflammatory cells, while Cistanche tubulosa extract inhibited activation of the cells, and that their combinational treatment could be a promising candidate for the relief of various types of inflammation[185].

The efficacy of echinacoside ECH-enriched extract of Cistanche tubulosa was evaluated in the treatment of dextran sulphate sodium (DSS)-induced colitis. Oral administration of ECH extract significantly suppressed the development of acute colitis, indicated by lowering disease activity index ($p<0.0001$) and preventing colonic damage ($p=0.0336$). Histological examinations showed that ECH extract treatment protected intestinal epithelium from inflammatory injury ($p = 0.0249$) but had less effect on inflammatory cellular infiltration ($p=0.1753$). The beneficial effect of ECH extract treatment was associated with upregulation of transforming growth factor (TGF)-β1, as well as an increase in the number of Ki67(+) proliferating cells in diseased colons ($p < 0.0001$). In cultured MODE-K cells, the addition of ECH extract enhanced in vitro wound healing that depended on TGF-β1 expression[186].

The effect of acteoside extracted from Cistanche tubulosa (Schrenk) R. Wight was studied on the basophilic cell-mediated allergic reaction. The effect of acteoside on β-hexosaminidase release and intracellular Ca^{2+}/l level from rat basophilic leukemia (RBL-2H3) cells was determined. Histamine, tumor necrosis factor (TNF)- α, and interleukin (IL)-4 on human basophilic (KU812) cells were also determined. The effect of acteoside on basophilic cell viability was studied using the 3-[4,5-dimethylthiazolyl]-2,5-diphenyltetrazolium bromide (MTT) assay. The results indicated that 0.1-10.0 μg/ml acteoside inhibited the release of β-hexosaminidase and Ca^{2+}/l influx from IgE-mediated RBL-2H3 cells. Moreover, acteoside inhibited histamine release, TNF- α, and IL-4 production in a dose-dependent manner from calcium ionophore A23187 plus phorbol 12-myristate 13-acetate (PMA) or compound 48/80-stimulated KU812 cells. The authors concluded that acteoside inhibited basophilic cell-derived immediate-type and delayed-type allergic reactions[187].

Citrullus colocynthis

The analgesic and anti-inflammatory activities of Tunisian Citrullus colocynthis immature fruit and seed organic extracts (petroleum ether, chloroform, ethyl acetate, acetone and methanol extract) were assessed in vivo. The acetic acid writhing test in mice and the carrageenan- induced paw edema assay in rats were used for evaluation. All extracts displayed an important analgesic and anti-inflammatory activities at different doses (0.5 and 1 mg/kg for anti-inflammatory and 0.05 and 1 mg/kg for analgesic effect) without inducing any side effects[188-189].

Methanol extract of Citrullus colocynthis significantly inhibited carrageenan, serotonin and prostaglandin E1-induced paw edema. Maximum inhibition was observed in prostaglandin E1-induced paw edema. In carrageenan air-pouch model, methanol extract of Citrullus colocynthis significantly reduced the volume of exudate and migration of neutrophils and monocytes. The extract significantly decreased formation of granuloma tissue in chronic inflammation model. Hence, this investigation established some pharmacological evidences to support the use of Citrullus colocynthis as anti-inflammatory agent[190].

***Citrus* species**

The inhibitory effect of pectin at different degrees of esterification (DEs) on the expressions of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in lipopolysaccharide (LPS)-activated

macrophages was investigated. Western blot and RT-PCR analyses demonstrated that 30% esterified pectin (DE30), DE60 pectin, and DE90 pectin significantly inhibited the protein and mRNA expressions of iNOS and COX-2 in LPS-activated macrophages, and DE90 pectin was the most-potent inhibitor. To clarify the mechanisms involved, DE90 pectin was found to inhibit the phosphorylation of MAPKs and IKK kinase activity. In addition, DE90 pectin inhibited the activation of NF-kB and AP-1 by electrophoretic mobility shift assay and transient transfection experiments. DE90 pectin bind with LPS, and might result in decreasing binding of LPS to its receptor[191-192].

The anti-inflammatory study of the stem and root barks of Citrus medica var. sarcodactylis Swingle has led to the isolation of new anti-inflammatory compounds. The new anti-inflammatory components included xanthyletin, nordentatin, atalantoflavon and lonchocarpol A, which displayed potent nitric oxide (NO)-reducing activity in microglial cells[193].

The anti-inflammatory and analgesic activities of ethyl acetate extract of Citrus medica peel (EtCM) (200, 300 and 400 mg/kg) were studied on carrageenan induced inflammatory pain in rats. Anti-inflammatory activity was assessed by measuring paw volume in rats. Analgesic activity was evaluated for its central and peripheral pharmacological actions by using hot plate, plantar, pin prick and mechanical allodynia tests in rats. EtCM (400 mg/kg) produced significant analgesic and anti-inflammatory effects[194].

Methanol extracts of peel of Citrus limetta fruits (MECL) were evaluated in two dose levels (200 and 400 mg/kg) in histamine, carrageenan and dextran induced acute rat paw oedema models for their anti-inflammatory potential. MECL was able to significantly ($p<0.001$) reduce the inflammatory potential produced by different inflammatory mediators in a dose dependant manner. MECL was able to produce significant anti-inflammatory activity better than the reference drug used (phenylbutazone 100 mg/kg bw po)[195].

Carotenoids, zeaxanthin and beta-cryptoxanthin, were the phytonutrients of Citrus sinensis which reduce remarkably the risk of rheumatoid arthritis. Persons consuming high amount of zeaxanthin and cryptoxanthin showed 52% less chances of developing rheumatoid arthritis[196].

Ultraviolet light (UV) induced an inflammatory response in the skin by cyclooxygenase (COX)-2 expression and prostaglandin PGE_2 production. Orange peel which contained polymethoxyflavonoids (PMFs) as a major ingredient, which have anti-inflammatory activity, has been used as a natural medicine. The extract suppressed UVB-induced COX-2 expression and PGE2 production in HaCaT cells. Furthermore, the extract acted as a peroxisome proliferator-activated receptor (PPAR)-γ agonist. The suppression of UVB-induced COX-2 expression by this extract was inhibited by GW 9662 and T0070907, which were both PPAR-γ antagonists. It was therefore suggested that orange peel extract, containing high levels of PMFs, suppresses UVB-induced COX-2 expression and PGE_2 production through PPAR-γ[197].

Clerodendrum inerme

The methanol extract of aerial part of Clerodendrum inerme were investigated for anti-inflammatory and analgesic effects at the dose 200 mg/kg body weight. The experimental models used were carrageenan, induced pedal edema for anti-inflammatory activity and acetic acid induced writhing methods to assess analgesic activity. In acute phase inflammation, a maximum inhibition 60.17% ($P<0.01$) was recorded at the dose of 200 mg/kg of treatment with methanol extract of Clerodendrum inerme (MECI) after 3 h in carrageenan, induced pedal edema. The extract also produced significant ($P<0.01$) analgesic activity in both models[198].

The total methanolic extract (TME) of the aerial parts, exhibited anti-inflammatory activity. Hind paw edema model was carried out by injection of 4% formalin (20 µl) solution into the subplanter region of the left hind paw of adult male albino rats. The total methanolic extract was administered as 50, 100, and 200 mg/kg subcutaneously. It showed anti-inflammatory activity more than indomethacin at a dose of 200 mg/kg after 4 hours[199-200]. The leaves of Clerodendron inerme were subjected to In vitro Anti-inflammatory activity by HRBC membrane stabilization method in various concentration 10, 50, 100, 200, 400, 800 and 1000µg/ml. All the extracts showed positive response as compared to standard Diclofenac sodium. The Ethyl acetate and ethanol extracts showed the maximum activity. The order of effect of different extracts were represented as follows Ethyl acetate> Ethanol >Water> Chloroform> Petroleum ether. The Petroleum ether, Chlorofrom, Ethyl acetate, Ethanol and water fractions of the leaves of Clerodendron inerme were subjected to in vitro anti-arthritic activity by protein denaturation method. All the extracts showed positive response. The effect was represented as follow: Ethyl acetate> Chloroform>Ethanol> Water> Petroleum ether[201].

Anti-inflammatory and analgesic effect of methanol extract of Clerodendrum inerme (MECI) was also evaluated in animal models. Pre-treatment with methanol extract of Clerodendrum inerme (MECI) (125, 250 and 400 mg/kg) prevented acetic acid induced writhing movements in mice. However, the inhibitory effect of diclofenac sodium (10 mg/kg) on acetic acid induced writhing was greater than MECI (500 mg/kg). In sub-chronic rat model of inflammation (cotton pellet granuloma), MECI inhibited the granulatory phase of inflammation in a dose related manner[202].

Adjuvant induced arthritic rats showed a significant decrease in body weights, organ weights, liver glycogen and serum ionic levels. But treatment with the effective fraction (apigenin, scutallarin and pectinolinergenin) of C. inerme for 15 days, produced a very good relief from the arthritic conditions by increasing the body weight by 18% and increasing serum ionic levels (copper 5.8%; zinc 49%, and iron 10%). Furthermore, increased liver glycogen content by 35% was noted after treatment with the effective fraction. Moreover, the X-ray analysis at the 30^{th} and 49^{th} days of untreated arthritic rats showed sever periostitis and other degenerative changes in the bone. Radiological scores of C. inerme treated rats showed little degenerative changes in the bones suggesting the long term effect of effective fraction. The authors concluded that the flavonoidal glycosides of the C. inerme may confer long term relief for arthritis without any side effects[203].

Clitoria ternatea

Clitoria ternatea roots methanol extract, 200-400 mg/kg orally, to rats was found to inhibit both the rat paw oedema caused by carrageenin and vascular permeability induced by acetic acid in rats. Moreover, the extract exhibited a significant inhibition in yeast-induced pyrexia in rats. In the acetic acid-induced writhing response, the extract markedly reduced the number of writhings at doses of 200 and 400 mg/kg po in mice[204]. The analgesic and anti-inflammatory activity of Clitoria ternatea flower extract were carried out in rats (carrageenan paw edema) and mice (hot plate). The petroleum ether (60-80◦C) extract possessed significant anti inflammatory and analgesic properties[205].

Conium maculatum

The alkaloidal fraction of Conium maculatum aerial parts was evaluated for analgesic and antiinflammatory activities. Test doses (100 or 200 mg/kg, po) of alkaloidal fraction were evaluated for analgesic activity using tail flick test and antiinflammatory activity using carrageenan-induced paw oedema test in rats. Morphine (5 mg/kg, po) and indomethacin (5 mg/kg, po) were used as standard analgesic and antiinflammatory drugs, respectively. Alkaloidal fraction of the plant exhibited significant analgesic activity at a dose of 200 mg/kg as it showed significant increase in tail flicking reaction time with respect to the control, during 2 h intervals of observation. It also exhibited significant antiinflammatory activity at a dose of 200 mg/kg as it inhibited paw oedema in rats to 71% and reduced the paw volume one-fourth to the control during 1^{st} h of the study[206-207].

Corchorus aestuans

The anti-inflammatory effect of methanol extract of aerial parts of Corchorus aestuans was evaluated using carrageenan induced rat paw edema. The increase in paw thickness was measured using digital vernier caliper after 1, 2, 3 and 4h of injection. Methanol fraction of aerial parts of the plant at dose of 200 mg/kg significantly inhibited acute phase of inflammation[208-209].

Corchorus capsularis

The antinociceptive and anti-inflammatory properties of Corchorus capsularis leaves chloroform extract were investigated in experimental animal models. The antinociceptive activity was measured using the writhing, hot plate and formalin tests, while the anti-inflammatory activity was measured using the carrageenan-induced paw edema test. The extract was used in the doses of 20, 100 and 200 mg/kg. It was administered subcutaneously, 30 min prior to subjection to the respective assays. The extract was found to exhibit significant ($p<0.05$) antinociceptive and anti-inflammatory activities[208, 210].

The antinociceptive, anti-inflammatory and antipyretic properties of an aqueous extract of Corchorus capsularis leaves were studied in experimental animals. The antinociceptive activity was measured using the abdominal constriction, hot plate and formalin tests, while, the anti-inflammatory and antipyretic activities were measured using the carrageenan-induced paw edema and brewer's yeast-induced pyrexia tests, respectively. The extract was used as 11.57, 57.85, and 115.7 mg/kg, it was administered subcutaneously, 30 min prior to subjection to the mentioned assays. The extract was found to exhibit significant antinociceptive, anti-inflammatory and anti-pyretic activities in a dosage-independent manner[211].

The analgesic and anti-inflammatory effect of the hydro-alcoholic extract of fruit of Cordia myxa was investigated in mice. Formalin test and acetic acid test were used for evaluation. Normal saline, oral indomethacin, intraperitoneal tramadol, 100 mg/ kg, oral hydro-alcoholic extract of fruit of Cordia myxa, 200 mg/ kg orally and 100 mg/ kg intraperitoneally were used for comparison. The duration of foot lickings were calculated in formalin- administered within 0 to 5 min (acute phase) and 15 to 25 (chronic phase). Acetic acid-induced writhings were counted within 10 min. The results showed that hydro-alcoholic extract of Cordia myxa fruit possessed analgesic and anti-inflammatory properties in both acute and chronic phases[212].

The anti-inflammatory effects of Cordia myxa fruit on experimentally induced colitis was investigated in rats. Colitis was induced by intrarectal administration of 4% acetic acid. All the animals were sacrificed 4

days after the fruit treatment. Colitis was monitored histologically and by activity of myeloperoxidase. Glutathione peroxidase, superoxide dismutase, as well as total antioxidant status and concentrations of zinc, copper, manganese, selenium, and iron were assayed in plasma, liver, and colon. Histology of the colon of colitic rats showed acute colitis that was confirmed by a significant increase in the myeloperoxidase activity. Colitis was associated with significant decreases in the tissue activities of glutathione peroxidase and superoxide dismutase and lower concentrations of trace elements. Histologic examination and myeloperoxidase activity showed that the fruit treatment reversed these findings in the inflamed colon, and in liver and plasma of colitic rats. The authors concluded that the antiinflammatory effect of the Cordia myxa may be attributed partly to its antioxidant property and to restoration of the levels of trace elements in the inflamed colon, liver, and plasma[213].

The analgesic, anti-inflammatory and anti-arthritic activities of different extracts of several species of Cordia was evaluated in rat. The results obtained showed that the petroleum ether and alcoholic extracts of Cordia myxa leaves exerted a significant analgesic, anti-inflammatory and anti-arthritic activity in rat[214-215].

The analgesic, anti-inflammatory and anti-arthritic activities of different extracts of Cordia myxa were studied in rat. The results obtained showed that the petroleum ether and alcoholic extracts of Cordia myxa leaves have a significant analgesic, anti-inflammatory and anti-arthritic activity[216].

Coriandrum sativum

The anti-inflammatory and anti-granuloma activities of Coriandrum sativum hydroalcoholic extract (CSHE) was studied in experimental models. The anti-inflammatory activity of CSHE was evaluated using carrageenan-induced paw edema model and the anti-granuloma activity of CSHE was evaluated using the subcutaneous cotton pellet implantation-induced granuloma formation and stimulation of peritoneal macrophages with complete Freund's adjuvant. Serum tumor necrosis factor-α (TNF-α), IL-6, IL-1 β levels, and peritoneal macrophage expression of TNF-R1 were evaluated as markers of global inflammation. CSHE at the highest dose (32 mg/kg) produced a significant reduction ($p<0.05$) in paw edema after carrageenan administration. CSHE treatment also reduced dry granuloma weight in all treated animals. Serum IL-6 and IL-1 β levels were significantly ($p<0.05$) lower in the CSHE (32 mg/kg)-treated group as compared to control. Although there was an increase in serum TNF-α level in the CSHE-treated group as compared to control, but TNF-R1 expression on peritoneal macrophages was reduced[217-218].

The anti-inflammatory and analgesic effects of Coriandrum sativum seeds were evaluatedin animal model. Carrageenan test was used for evaluation of anti-inflammatory effect, while, writhing and formalin tests were used for evaluation of analgesic effects. The results showed that coriander had no anti-inflammatory effect in carrageenan test. In writhing test, only the essential oil (4ml/100g, po) had a significant effect ($p<0.01$). Total extract, polyphenolic extract and essential oil of coriander, had significant effect in both phases of formalin test[219].

The anti-inflammatory activity of ethanolic extract of Coriandrum sativum was studied using carrageenan induced paw edema in albino rats. Ethanolic leaf extract of Coriandrum sativum was used as 200 and 400mg/kg. Oral administration of Coriandrum sativum ethanolic leaf extract of 400mg/kg/ip was more effective anti-inflammatory than 200mg/kg/ip[220].

The antiarthritic activity of Coriandrum sativum seed hydroalcoholic extract (CSHE) was evaluated in adult rats by using two experimental models (formaldehyde and complete Freund's adjuvant (CFA) induced arthritis). The expression of pro-inflammatory cytokines (predominantly contributed by macrophages) was also evaluated. TNF- α level was estimated in serum. TNF-R1, IL-1 β and IL-6 expression were also analysed in the synovium. CSHE produced a dose dependent inhibition of joint swelling as compared to control animals in both formaldehyde and CFA induced arthritis. Although there was a dose dependent increase in serum TNF-α levels in the CSHE treated groups as compared to control, the synovial expression of macrophage derived pro-inflammatory cytokines/cytokine receptor was found to be lower in the CSHE treated groups as compared to control[221].

The protective effects of Coriandrum sativum on acetic acid-induced colitis was investigated in rats. Treatment was carried out using three increasing doses of extract (250, 500, 1000 mg/kg) and essential oil (0.25, 0.5, 1 ml/kg) of coriander started 2 h before colitis induction and continued for a five-day period. Colon biopsies were taken for weighting, macroscopic scoring of injured tissue, histopathological examination and measuring myeloperoxidase (MPO) activity. Colon weight was decreased in the groups treated with extract (500 and 1000 mg/kg) and essential oil (0.5 ml/kg) compared to the control group. Regarding MPO levels, ulcer severity and area as well as the total colitis index, the results indicated that the treatment with extract and essential oil induced meaningful alleviation of colitis[222].

A polyherbal ayurvedic formulation from an ancient authentic classical text of ayurveda was evaluated for its activity against inflammatory bowel disease (IBD). The polyherbal formulation contained four different drugs viz., Bilwa (Aegle marmeloes), Dhanyak (Coriandrum sativum), Musta (Cyperus rotundus) and Vala

(Vetiveria zinzanioids). The formulation has been tried in clinical practice and was found to be useful in certain number of cases of IBD. Accordingly, the same form , decoction (aqueous extract) was evaluated in experimental animals. The formulation was tried on two different experimental animal models of inflammatory bowel disease (acetic acid-induced colitis in mice and indomethacin-induced enterocolitis in rats). Prednisolone was used as the standard drug for comparison. The formulation showed significant inhibitory activity against inflammatory bowel disease induced in these experimental animal models. The activity was comparable with the standard drug prednisolone. The results obtained established the efficacy of this polyherbal formulation against inflammatory bowel diseases[223].

The anti-inflammatory ability of the aerial parts (stem and leaf) of Coriandrum sativum was investigated on lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. The molecular mechanism underlying the pharmacological properties of Coriandrum sativum was also investigated. Ethanolic extracts from both stem and leaf of Coriandrum sativum (CSEE) significantly decreased LPS-induced nitric oxide and prostaglandin E_2 production as well as inducible nitric oxide synthase, cyclooxygenase-2, and pro-interleukin-1beta expression. Moreover, LPS-induced IkappaB-alpha phosphorylation and nuclear p65 protein expression as well as nuclear factor-kappaB (NF-kappaB) nuclear protein-DNA binding affinity and reporter gene activity were dramatically inhibited by aerial parts of CSEE. Exogenous addition of CSEE stem and leaf significantly reduced LPS-induced expression of phosphorylated mitogen-activated protein kinases (MAPKs). The authors concluded that CSEE had a strong anti-inflammatory property which inhibited pro-inflammatory mediator expression by suppressing NF-kappaB activation and MAPK signal transduction pathway in LPS-induced macrophages[224].

The anti-inflammatory potency of coriander oil was investigated in the ultraviolet (UV) erythema test in vivo. 40 volunteers were enrolled in this monocentric, randomized, placebo-controlled double-blind study. The test areas on the back were irradiated with the 1.5 fold minimal erythema dose UV-B. Subsequently, the test areas were treated under occlusion for 47 hours with a lipolotion containing 0.5% or 1.0% essential coriander oil. Hydrocortisone (1.0%) and betamethasone valerate (0.1%) in the vehicle were used as positive controls. The vehicle was used as placebo. The effect of the test substances on the UV-induced erythema was measured photometrically after 48 hours. Additionally, the skin tolerance of the test preparations was assessed on non-irradiated skin. Compared to placebo, the lipolotion with 0.5% coriander oil significantly reduced the UV-induced erythema, but it was not as effective as hydrocortisone. The skin tolerance of both coriander oil concentrations was excellent[225].

A randomized, placebo-controlled study was carried out on 40 healthy subjects to determine the anti-inflammatory effects of many plants. Test areas on the upper back were irradiated with the 1.5 fold UV-B minimal erythema dose (MED). Formulations of Aloe vera, Chamomilla recutita, Hamamelis virginiana, Melissa officinalis, Mentha arvensis, Melaleuca alternifolia, Coriandrum sativum, as well as 1% hydrocortisone acetate and 0.1% betamethasone valerate as positive controls and unguentum leniens as vehicle control were applied under occlusion on the irradiated areas and on non-irradiated area on the contralateral side. Photometric assessment of the erythema was performed before the application of the substances, at 24 h and at 48 h. Aloe vera, Chamomilla recutita, Melissa officinalis, Melaleuca alternifolia and Coriandrum sativum showed an antiinflammatory effect compared to UV-control and unguentum leniens[226].

Cressa cretica

The methanolic (Fr-Me) and ethyl acetate fraction (Fr-Et) obtained from the aerial parts of Cressa cretica exhibited inhibitory effect against acute and chronic models of inflammation (carrageenan-induced paw edema, cotton pellet granuloma, carrageenan air pouch inflammation, vascular permeability and Freuds complete adjuvant induced arthritis models). The fractions also inhibited arachidonic acid and other mediator (histamine, serotonin, prostaglandin E2)-induced paw edema in rats in a dose dependent manner. Moreover, Fr-Me and Fr-Et significantly increased plasma superoxide dismutase, catalase, glutathione and glutathione peroxidase activities. On the contrary, the malonaldehyde (as a measure of lipid peroxidation) level was significantly decreased in comparison with the control group. Also, it was found that Fr-Et reduced the inflammation and revealed the antioxidant activity more significantly than Fr-Me[227-228].

Crocus sativus

The preventive effect of the aqueous extract of saffron was studied against diazinon (DZN) -induced rise of several specific inflammation, oxidative stress and neuronal damage in rats. Vitamin E (200 IU/kg) and the aqueous extract of saffron at doses 50, 100 and 200 mg/kg were injected intraperitoneally three times per week alone or with DZN (20 mg/kg/day, orally) for 4 weeks. Red blood cell (RBC) cholinesterase activity was inhibited by DZN and this effect was not affected by vitamin E or saffron plus DZN. The levels of serum tumor necrosis factor-α (inflammation marker), direct 8-iso-prostaglandin F2α (oxidative stress marker) and soluble protein-100 β (S100β, neuronal damage marker) were increased significantly by DZN. The saffron

extract inhibited the effect of DZN on these biomarkers levels. However, vitamin E was able to only reduce 8-iso-prostaglandin F2α and S100β levels[229-230].

The antinociceptive and anti-inflammatory activity of saffron extracts were evaluated in mice using aqueous and ethanolic maceration extracts of Crocus sativus stigma and petals. Antinociceptive activity was examined using the hot plate and writhing tests. The effect of extracts against acute inflammation was studied using xylene induced ear edema in mice. The activity of the extracts against chronic inflammation was assessed by formalin-induced edema in the rat paw. In the hot plate tests, intraperitoneal injection of both extracts showed no significant antinociceptive activity in mice. The extracts exhibited antinociceptive activity against acetic acid induced writhing. Naloxone partially blocked only the antinociceptive activity of the stigma aqueous extract. Only the stigma extracts showed weak to moderate effect against acute inflammation. In chronic inflammation, both aqueous and ethanolic stigma extracts, as well as ethanolic petal extract, exerted anti-inflammatory effects[231].

Crotalaria juncea

Anti-inflammatory effect of the Crotalaria juncea seed oil (CJSPE) was assessed by its effect on NO radical production in isolated macrophages from rat peritoneal (in vitro method); and carragennan-induced paw edema rat model and cotton pellet-induced granuloma formation in rat model (in vivo method). The result showed a dose dependant reduction of carragennan-induced rat paw edema by the CJSPE. Moreover, significant ($p<0.001$) anti-inflammatory activity was displayed by CJSPE (200 mg/kg) in the late phase of inflammation; and the effect was comparable to that of diclofenac sodium. CJSPE was also found to be effective in the reduction of size ($48.55 \pm 0.244\%$) of granuloma formation and effect was nearly equal to that of diclofenac sodium[232-233].

The antiarthritic activity of ethanolic extract of the leaves of Crotalaria juncea (CJE) in complete Freund's adjuvant (CFA) induced arthritis model in rats, and also the anti-ulcerogenic activity of CJE was evaluated. Treatment with CJE at 200 and 400 mg/kg and standard indomethacin (0.3 mg/kg) was started on the same day and continued up to day 12. The paw volume was measured on day 1, 5, 12 and 21 for both the paws and antiarthritic activity. The drug CJE produced reduction in the inflammation of the paw produced by CFA. The antiarthritic action started on the day 5 and continued till day 12 and the activity was comparable to that of the standard on both days. In indomethacin treated animals, gastric ulcer was observed, while, CJE was found to protect the animals from ulcer formation. The authors concluded that CJE significantly inhibited adjuvant induced arthritis and has significant anti-inflammatory effect ($p<0.001$). It has anti-ulcerogenic property compared to indomethacin, which may be due to appetite suppressant activity[234].

Cuminum cyminum

Acetic-acid induced writhing, hot plate, Carrageenan-induced paw oedema and Cotton-pellet granuloma methods were used for evaluation of analgesic and anti-inflammatory effects of Cuminum cyminum extracts (200 and 500 mg/kg for aqueous and ethanolic extract). Both the aqueous and ethanolic extracts showed highly significant analgesic activity in Acetic-acid induced writhing, while the ethanolic extracts were effective in hot plate method. Both the aqueous and ethanolic extracts showed significant anti-inflammatory activity in Carrageenan-induced paw oedema and Cotton-pellet granuloma models when compared to the control group[235-236].

The anti-inflammatory effects of cumin essential oil (CuEO), in lipopolysaccharide- (LPS-) stimulated RAW 264.7 cells and the underlying mechanisms were investigated. Mitochondrial-respiration-dependent 3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyl tetrazolium (MTT) reduction assay demonstrated that CuEO did not exhibit any cytotoxic effect at the employed concentrations (0.0005–0.01%). Real-time PCR tests showed that CuEO significantly inhibited the mRNA expressions of inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), interleukin- (IL-) 1, and IL-6. Moreover, western blotting analysis revealed that CuEO blocked LPS-induced transcriptional activation of nuclear factor-kappa B (NF-κB) and inhibited the phosphorylation of extracellular signal regulated kinase (ERK) and c-Jun N-terminal kinase (JNK). The results revealed that CuEO exerted anti-inflammatory effects in LPS-stimulated RAW264.7 cells via inhibition of NF-κB and mitogen-activated protein kinases ERK and JNK signaling[237].

The potential anti-nociceptive and anti-inflammatory activities of the fruit essential oil of Cuminum cyminum has been evaluated in chemical (formalin test) and thermal (tail-flick test) models of nociception and formalin model of acute inflammation in rats and mice. The essential oil at the doses ranging between 0.0125 and 0.20 ml/kg exhibited a significant and dose-dependent analgesic effect in both model of chronic and inflammatory pain. However, the essential oil was devoid of anti-inflammatory activity. Moreover, the essential oil had no analgesic effect in tail flick test as a model of acute pain[238].

The antiinflammatory activity of cumin volatile oil was investigated in carrageenan-induced rat paw oedema. The volatile oil showed dose–dependent inhibition of rat paw oedema, at dose of 0.1ml/kg, ip, when compared to control group. The activity was comparable with that of the standard drug, diclofenac sodium[239].

The methanolic extract of Cuminum cyminum inhibited lipoxygenase (LOX) activity. Activity-guided screening of the Cuminum cyminum crude extracts helped the identification and isolation of cuminaldehyde as a 15-LOX inhibitor. The enzyme kinetics analysis suggested cuminaldehyde to be a competitive inhibitor and the IC_{50} value derived from LB plots is 1.370 μM[240].

Cydonia oblonga

The anti-inflammatory effect of polyphenolic extract from the Tunisian quince Cydonia oblonga Miller was investigated. Lipopolysaccharide (LPS) treatment of human THP-1-derived macrophages stimulated secretion of the pro-inflammatory cytokine TNF-α and the chemokine IL-8. Quince peel polyphenolic extract inhibited these changes in a dose-dependent manner. Concomitantly, quince polyphenols enhanced the level of the anti-inflammatory cytokine IL-10 as well as IL-6 secreted by LPS-treated macrophages. The increase in IL-6 secretion that occurred when quince polyphenols were associated with LPS treatment was partially responsible for the polyphenols-mediated inhibition of TNF-α secretion. Biochemical analysis showed that quince polyphenols extract inhibited the LPS-mediated activation of three major cellular pro-inflammatory effectors, nuclear factor-kappa B (NF-κB), p38MAPK and Akt[241-242].

Cynodon dactylon

The anti-inflammatory activity of aqueous extracts of Cynodon dactylon (200, 400, and 600 mg/kg of bw orally) was evaluated using the carrageenan, serotonin dextran and histamine induced rat paw edema. The results showed that all doses exerted significant anti-inflammatory activity in all models[243-244].

The 50% ethanolic extract of Cynodon dactylon at 300 and 600 mg/kg was investigated for possible anti-inflammatory and analgesic activity in several rodent model of inflammation and pain, including carrageenan-induced rat paw edema, cotton pellet granuloma method and biochemical parameters (Serum SGOT and SGPT levels) and lipid peroxide formation in experimental inflammation. The results revealed that the extract oral treatment for 7 days in albino rats, was significantly inhibited carrageenan-induced edema. It showed activity against granuloma formation and reduced enzymes activity (SGOT and SGPT), which were elevated in inflammation. The extract also elicited a pronounced inhibitory activity against increased output of peroxides found during the inflammation. Analgesic activity was studied using acetic acid-induced writhing and tail immersion method in albino mice. The extract significantly increased the pain threshold when evaluated for acetic acid induced writhes[245].

A significant increase in the levels of inflammatory mediators, myeloperoxidase, nitrite, C-reactive protein, ceruloplasmin was observed in rats with adjuvant- induced arthritis. This was associated with oxidative stress with a marked reduction in the activity of catalase, superoxide dismutase, glutathione peroxidase and the levels of glutathione, vitamins C and E and an increase in the lipid peroxidation as indicated by the higher levels of thiobarbituric acid reactive substances. Cynodon dactylon (20mg/kg/bw) orally administered to arthritic rats after adjuvant injection produced a significant attenuation in the inflammatory response, oxidative stress and ameliorated the arthritic changes to near normal conditions[246].

Cyperus rotuntdus

The alcoholic extract (70% alcohol) possessed antiinflammatory activity against carrageenan induced oedema and against formaldehyde induced arthritis in albino rats[247-248].

The anti-inflammatory activity of crude extract of *Cyperus rotundus* was studied in rats at a dose of (300mg/kg and 500mg/kg). Inflammation was produced by carrageenan in rats and compare with saline and aspirin treated groups. Plant extract exhibited significant anti inflammatory effect[249].

The Anti-inflammatory, anti-arthritic and analgesic of *Cyperus rotundus* essential oils were evaluated using anti-inflammatory (carrageenan induced), antiarthritic (formaldehyde induced) and analgesic (formalin induced writhing) in rats. The results showed dose dependent activity, indicated by reduction in paw edema in anti-inflammatory and antiarthritic activity. When compared with the control, treatment with Cyperus rotundus significantly ($p<0.01$) reduced the paw edema from 2^{nd} hr after carrageenan injection. Pretreatment with Cyperus rotundus at doses of 250 and 500 mg/kg showed a dose dependent effect. The assessment of anti-arthritic activity on the 10^{th} day showed that, treatment with Cyperus rotundus (500 mg/kg) significantly reduced ($p<0.01$) the swelling in the injected (left) hind paw as compared to Diclofenac sodium treated group. On the 10^{th} day the % inhibition of paw edema exhibited by Cyperus rotundus (500 mg/kg) was 75.54%. Analgesic effects was evaluated on both first (0–5 min) and second (15-30 min) phases of formalin induced pain. The phases corresponded to neurogenic and inflammatory pains, respectively. Essential oil inhibited both,

neurogenic and inflammatory pain ($p< 0.01$) at dose of 500mg/kg, whereas lower doses of essential oil significantly $p<0.05$ blocked the inflammatory pain[250].

Aqueous, ethyl acetate, methanol and TOF-enriched extracts of Cyperus rotundus (300, 150, and 50 µg/ml) were evaluated for their analgesic and anti-inflammatory activitiesin mice. The tested extracts were able to decrease the mouse ear oedema induced by xylene and reduced the number of abdominal contractions caused by acetic acid, revealing the peripheral analgesic activity of these extracts. No toxicity was recorded in mice treated with doses up to 300 mg/kg bw[251].

Two models of acute inflammation, carrageenan induced rat paw edema and acetic acid induced peritonitis in mice were used to investigate the anti-inflammatory effect of Cyperus rotundus. In the model of carrageenan induced paw edema Cyperus rotundus showed a trend to reduce the edema, whereas in a model of acetic acid induced peritonitis, Cyperus rotundus induced significant decrease in the protein content of the peritoneal exudates compared with the disease control group ($p < 0.05$)[252].

Clinical studies with 2% aqueous extract of Cyperus rotundus showed anti-inflammatory activity in conjunctivitis in human[253].

A double blind trial of crude powder of Cyperus rotundus, Withania somnifera and their combination (1:1) was carried out in 200 patients suffering from rheumatoid arthritis. Each patient received 500 mg capsule three times a day for three months. During this period biweekly general assessment based on global criteria (duration of morning stiffness, grip strength, articular index, consumption of escape analgesic, erythrocyte sedimentation rate, haemoglobin, rheumatoid factor titre, x-ray findings) was carried out. Cyperus rotundus was more effective than Withania somnifera, and when both drugs were combined, the response was better than the response of single drug[254].

The n-hexane fraction of the 80% ethanoic extract from the rhizomes of Cyperus rotundus was found to inhibit both NO and PGE_2 production in RAW 264.7 cells. α-Cyperone isolated from the n-hexane fraction significantly inhibited PGE_2 production by suppressing the LPS-induced expression of inducible COX-2 at both the mRNA and the protein levels. In contrast, α-cyperone had little effect on NO production and iNOS expression. Additionally, α-cyperone down regulated the production and mRNA expression of the inflammatory cytokine IL-6. Moreover, treatment with α-cyperone suppressed the transcriptional activity of NFκB and the nuclear translocation of the p65 NFκB subunit in LPS-induced RAW 264.7 cells[255].

The role of heme oxygenase HO^{-1} induction in anti-inflammatory effect of extract rhizomes of Cyperus rotundus was investigated. Induction of HO^{-1} and inhibition of inducible nitric oxide synthase (iNOS)/NO production by extract of rhizomes of Cyperus rotundus and its 12 constituents (3 monoterpenes, 5 sesquiterpenes, and 4 aromatic compounds) were investigated using RAW264.7 cells in vitro. In addition, anti-inflammatory action of extract of rhizomes of Cyperus rotundus and its two active ingredients (nookkatone, valencene) were confirmed in sepsis animal model in vivo. The extract of rhizomes of Cyperus rotundus increased HO^{-1} expression in a concentration-dependent manner, which was correlated with significant inhibition of iNOS/NO production in LPS-activated RAW264.7 cells. Among 12 compounds isolated from the extract of rhizomes of Cyperus rotundus, sesquiterpenes induced stronger HO^{-1} expression than monoterpenes in macrophage cells. Nootkatone and valencene (sesquiterpenes) significantly inhibited iNOS expression and NO production in LPS-simulated RAW264.7 cells. Inhibition of iNOS expression by nootkatone, valencene, and extract rhizomes of Cyperus rotundus were significantly reduced in si HO^{-1} RNA transfected cells. Furthermore, all three showed marked inhibition of high mobility group box-1 (HMGB1) in LPS-activated macrophages and increased survival rates in cecal ligation and puncture (CLP)-induced sepsis in mice[256].

Dalbergia sissoo

The anti-inflammatory activity of hexane extracts, methanol extracts of Dalbergia sisso Roxb and okanin was evaluated by carrageenan induced paw oedema in rats. The methanolic extract showed maximum activity[257].

The anti-inflammatory activity of a 90% ethanolic extract of Dalbergia sissoo bark was studied using a right hind paw oedema method in Wistar rats. One percent carrageenan in 0.5% sodium carboxymethyl cellulose. After oral administration of ethanolic extract at different doses (300, 500 and 1000 mg/kg), inhibition of right hind paw oedema was observed at 30, 60, and 120 min time intervals. The antiinflammatory effects increased with increasing doses. The ethanolic extract of Dalbergia sissoo bark at 1000 mg/kg showed the most potent anti-inflammatory activity compared to the other groups (300 and 500 mg/kg) throughout the observation period[258-259].

The analgesic and anti-inflammatory properties of the methanolic extract of leaves of Dalbergia sissoo were evaluated by using acetic acid induced writhing and hot plate tests (both in mice) and carrageenan- induced paw oedema in rats. Oral pretreatment with the leaves extracts of Dalbergia sissoo significantly decreased the writhing movements in mice in acetic acid-induced writhing test and significantly increase the mean pain latency time in mice placed on the hot plate at 50°C at dose dependant manner. In the carrageenan-induced paw

oedema model, the methanolic extract afforded 68.2% inhibition of hind paw oedema in rats at the highest dose (600 mg/kg) compared to 73.4% inhibition obtained with the reference drug, diclofenac (5 mg/kg) at the third hour after carrageenan administration[260].

Daphne mucronata

The analgesic and anti-inflammatory effects of ethyl acetate extract of aerial parts of Daphne mucronata and the possible involvement of opioid receptors were studied in mice using formalin test. Single doses of 2.5, 5.0 and 10.0 mg/kg bw of ethyl acetate extract of D. mucronata were intraperitoneally administered to the mice 30 min before carrying out the analgesic test. The results revealed that the extract (2.5, 5.0 and 10.0 mg/kg) increased the pain threshold of mice and induced analgesia in both phases of formalin test. Like morphine sulfate (5.0 mg/kg, ip), the extract also showed more effective analgesic effect on the late phase of formalin test. Pre-treatment of animals with naloxone (5.0 mg/kg ip) did not inhibit the effects of the extract[261-262].

Datisca cannabina

Extracts of the aerial parts of D. cannabina showed pronounced anti-inflammatory activity in rats and fairly good antipyretic activity in rabbits[263].

***Datura* species**

The anti-inflammatory activity of ethanolic and ethyl acetate extracts of root part of Datura fastuosa (50, 100, 150, 200 mg/kg orally) was evaluated using carrageenan induced rat paw edema. Indomethacin was used as a standard drug for measurement of anti-inflammatory activity. All extracts showed significant activity at 200 mg/kg dose as compared to indomethacin (10 mg/kg). The percentage inhibition was calculated for all doses of different extracts. Ethanolic extract possessed significant anti-inflammatory activity[264-265].
Dmetelins A–D, along with compound 7α,27-dihydroxy-1-oxo-witha-2,5,24-trienolide were isolated from the leaves of Datura metel . All the compounds were evaluated for their inhibitory effects on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW264.7 cells. Compounds, dmetelin A, D and 7α,27-dihydroxy-1-oxo-witha-2,5,24-trienolide**,** showed significant inhibitory activities, and compounds dmetelin B and C showed moderate inhibitory activities with IC50 values of 17.8, 11.6, 14.9, 33.3 and 28.6 μM, respectively[266].

Daucus carota

The anti-inflammatory effects of the aqueous and methanolic extracts of Daucus carota umbels was studied in acute and chronic inflammation in rats. In acute inflammation, the aqueous and methanolic extracts produced maximum anti-inflammatory activity at doses of 400 and 140 mg/kg body weight with 90.9 and 58.6 % inhibition, respectively. In chronic inflammation, the same doses showed maximum anti-inflammatory activity with 58 and 44.1 % inhibition, respectively[267-268].

The essential oil of Daucus carota subsp. carota from Portugal. exhibited some anti-inflammatory potential by decreasing nitric oxide production around 20% in LPS-stimulated macrophages, without decreasing macrophages viability[269].

The ethanolic extract of Daucus carota seeds (DCE) was investigated for anti-inflammatory and analgesic activity at the doses of 100, 200 and 400 mg/kg bw, orally. Carrageenan-, histamine- and serotonin-induced paw edema were used to study the effect of extract in acute inflammatory model, while, formaldehyde-induced arthritis was employed as a chronic model in rats. The acetic acid-induced writhing response and formalin-induced paw licking time in the early and late phases of mice were used to assess analgesic activity. The higher doses of DCE (200 and 400 mg/kg, po) inhibiting carrageenan, histamine and serotonin-induced paw edema as well as formaldehyde-induced arthritis successfully. DCE (200 and 400 mg/kg, po) also significantly attenuated the writhing responses induced by an intraperitoneal injection of acetic acid and late phase of pain response induced by an subplantar injection of formalin in mice[270].

Daucus carota seed extracts were investigated as Cyclooxygenase (COX) enzymes inhibitor. Compounds, 2,4,5-trimethoxybenzaldehyde, oleic acid, trans-asarone and geraniol were isolated from seed extract. They showed 3.32, 45.32, 46.15, and 3.15% of prostaglandin H endoperoxide synthase-I (COX-I) inhibitory activity and 52.69, 68.41, 64.39 and 0% prostaglandin H endoperoxide synthase-II (COX-II) inhibitory activity, respectively at 100 mg/ml. Compound 2,4,5-trimethoxy benzaldehyde showed selectivity towards COX-II enzyme inhibition at 100 μg/ml. The COX-II/COX-I ratio for this compound was 17.68 at 100 μg/ml compared to solvent control[271].

Desmostachia bipinnata

The anti-inflammatory activity was evaluated by using Digital plethysmometer. Inflammation in the hind paw of albino rat was induced by injection of 0.1 ml of 1% carrageenan suspension into sub-plantar surface of the right hind limb of each rat. The different extracts of Desmostachya bipinnata (300 mg/kg, orally) induced significant ($P<0.05$) reduction of rat paw edema. The maximum inhibition was shown by the ethanol extract 53.84% whereas the standard drug (Diclofenac sodium 100 mg/ kg ip) showed 32.30% inhibition. The tail immersion method was used to investigate the analgesic activity of petroleum ether, benzene, chloroform, ethanol and aqueous extract of the whole parts of Desmostachya bipinnata. Almost all the extracts possess a significant analgesic effect ($P<0.05$)[272-273].

The hydro-alcoholic extracts of D. bipinnata roots were investigated for their anti-inflammatory (carrageenan induced paw oedema) and analgesic potential (Hot plate method) on experimental model and compared to standard drugs (indomethacin for anti-inflammatory activity, analgin for analgesic activity). In the carrageenan-induced rat paw edema test for acute inflammation, the extract of D. bipinnata in doses of 200 mg, 300 mg and 400 mg/kg body weight showed 46%, 33.3% and 62.5% inhibition of edema, respectively, at the end of 3h. However, the analgesic effect of the extract (300 mg/kg) was comparable to that produced by 150 mg/kg of analgin[274].

Dianthus caryophyllus

Eugenol isolated from many plants possesses anti-inflammatory effects via inhibition of Nitric Oxide (NO) production , blocking the release of interleukin 1-β, TNF-α and PG E2 from stimulated macrophages[275-277].

Dodonaea viscose

The hydroalcoholic extract (HAE) of the leaves of Dodonaea viscosa, given by oral route at dose of 300 mg/kg, significantly inhibited the paw edema induced by carrageenin injection[278-279].

Hautriwaic acid (HA), a diterpene extracted from D. viscosa leaves, exhibited good anti-inflammatory activity in 12-O-tetradecanoylphorbol 13-acetate (TPA) mice ear edema models when applicated at doses of 0.25, 0.5 and 1.0 mg/ear (60.2, 70.2 and 87.1% inhibition, respectively); additionally Dodonaea viscose dichloro-methane extract (DvDE) displays a 97.8% anti-inflammatory effect at 3 mg/kg. Multiple applications of DvDE at doses of 100 mg/kg on TPA mice ear edema inhibited the edema-associated inflammation by 71.8%, while HA at doses of 15 mg/kg, reduced edema to 64% compared with indomethacin 40%[280].

Viscosine was isolated from Dodonaea viscosa, showed significant lipoxygenase inhibitory activity (IC_{50}: value 39 ± 0.17), the enzyme responsible for the metabolism of the fatty acids (FAs) and their metabolites eliciting inflammatory responses in the body. Molecular interactions of viscosine with catalytic triad (His523, His518, Ile875) inside active site of lipoxygenase via hydrogen bonding, seems to be the major factor involved in its significant lipoxygenase inhibitory activity[281].

Dolichos lablab

The anti-inflammatory effect of methanol extracts of two Bangladeshi bean pods namely Lablab purpureus L. sweet white and purple was studied using protease Inhibition. In in-vitro anti-inflammatory investigation there was a linear relation of % inhibition for the white bean pods which indicated positive anti-inflammatory property[282-283].

Mannose-specific legume lectin isolated from the seeds of Dolichos lablab (FRIL) evoked dose-dependent paw edema and increasing animal paw volumes. The edematogenic effect of FRIL was paralleled by an increase in vascular permeability, about 10-fold higher compared to control. FRIL also significantly raised the animals flinch reaction in the first, third and fifth hours in response to mechanical stimulation. The inflammatory elicited by FRIL was partly inhibited by α-d-methyl mannoside. The histopathological analysis of animal paws showed a characteristically acute inflammatory process that included severe infiltration of mixed leukocytes, changes in cytoarchitecture, edema and focal areas of hemorrhage. In addition, in silico assays confirmed that FRIL preferentially interacts with trimannoside that makes up the core N-glycans cell[284].

Erodium cicutarium

A 70% ethyl alcohol thick extract from equal amounts of the aerial parts of Geranium sanguineum, Astragalus glycyphyllos, Erodium cicutarium and Vincetoxicum officinalis was prepared to study of its anti-inflammatory and analgesic effects. The anti-inflammatory effect was conducted by the method of carageenan-induced paw edema, while analgesic effect was determined by hot/ cold plate and Randall & Selitto test (Analgesy-meter). Rats treated with the extract in (1 and 2 g/kg bw), showed no statistically significant anti-inflammatory effects. The extract also showed no reliable analgesic effect (excluding the dose of 1g/kg bw, 1^{st} hour, $p = 0.031$). However, a reliable analgesic effect was recorded with the using of 2 g/kg bw of the extract on the 2^{nd} and 3^{rd} hour ($p = 0.037$, $p = 0.022$). In repeated dose of the extract, the treated animalsshowed

statistically reliable analgesic effect at the dose of 1g/kg bw, on the 1st, 2nd and 3rd hour ($p = 0.024$, $p = 0.029$, $p = 0.021$)[285-287].

Equisetum arvense

The antinociceptive and anti-inflammatory effects of hydroalcoholic extract of stem from Equisetum arvense were studied in mice. The extract 10, 25, 50 and 100mg/kg, ip, reduced the writhing induced by acetic acid in 49, 57, 93 and 98%, respectively. In the formalin test, 50 and 100mg/kg, ip, reduced in 80 and 95% the licking activity in the first phase, but in the second phase only the latter dose diminished the licking time (35%). In both phases, naloxone failed to revert the analgesic effect of the extract. In the hot-plate test, the extract at 100 and 200mg/kg does not change the latency to licking or jumping. In the carrageenan-induced paw oedema, the extract at 50mg/kg, reduced the paw oedema 2h (25%) and 4h (30%) after carrageenan administration. The dose of 100mg/kg caused reduction of the paw oedema (29%) only 4h after carrageenan administration[288-289].

Erigeron canadensis

The petroleum ether and ethanolic extract from the epigean part of the plant exhibited a significant anti-inflammatory effect on rats with a carrageenin and formalin oedema. Eight sesquiterpenic hydrocarbons with the highest anti-inflammatory activity were found in the petroleum ether fraction (beta-santalene, beta-himachalene, cuparene, alpha-curcumene, gamma-cadinene and three other unidentified hydrocarbons)[290].

The anti-inflammatory activities and the underlying molecular mechanisms of the methanol extract from Erigeron Canadensis L. (ECM) was studied in LPS-stimulated RAW264.7 macrophage cells. ECM significantly inhibited inducible nitric oxide synthase (iNOS)-derived NO and cyclooxygenase-2 (COX-2) derived PGE2 production in LPS-stimulated RAW264.7 macrophages. These inhibitory effects of ECM were accompanied by decreases in LPS-induced nuclear translocations and transactivities of NFκB. Moreover, phosphorylation of mitogen-activated protein kinase (MAPKs) including extracellular signal-related kinase (ERK1/2), p38, and c-jun N-terminal kinase (JNK) was significantly suppressed by ECM in LPS-stimulated RAW264.7 macrophages[291-292].

Eryngium creticum

Ethanolic and aqueous extracts obtained from either aerial parts or roots of eight Eryngium species growing in Turkey, were evaluated for their in vivo anti-inflammatory and antinociceptive activities, using p-benzoquinone-induced writhing test for estimation of antinociceptive activity, and carrageenan-induced hind paw oedema and TPA-induced ear oedema tests for anti-inflammatory activity. Ethanolic extracts either from the aerial parts or roots of Eryngium creticum showed apparent anti-inflammatory and antinociceptive activity[293-294].

The anti-inflammatory activity of each of the extracts prepared using different solvents from leaves and stems of E. creticum was evaluated by measuring the viability of the RAW264.7 macrophage cells cell line after 24 hours treatment with increasing concentrations (5, 25, 50, 100, and 200 μg/ml) of these extracts. The cell viability XTT test shows that aqueous extracts of the leaves and stems of E. creticum increased the number of macrophages (RAW 264.7) with increasing concentrations of the extract from 5 to 200 μg/ml compared to control[295].

***Eucalyptus* species**

1,8-Cineole (cineole) possessed an inhibitory effect on some types of experimental inflammation in rats, i.e. paw oedema induced by carrageenan and cotton pellet-induced granuloma. Cineole also inhibits the acetic acid-induced increase in peritoneal capillary permeability and the chemical nociception induced by intraplantar formalin and intraperitoneal acetic acid in mice at an oral dose range of 100-400 mg/kg. In the formalin test, the antinociceptive effect of cineole was not reversed by pretreatment of mice with naloxone (1 mg/kg, sc), a mu-opioid receptor antagonist, suggesting the involvement of a non-opioid mechanism. Cineole demonstrated a significant inhibitory effect on locomotion and also potentiated the pentobarbital sleeping time in mice, indicating a plausible depressant effect on the central nervous system[296-297].

The effect of 1.8-cineole was evaluated on arachidonic acid (AA) metabolism in blood monocytes of patients with bronchial asthma. Patients with bronchial asthma and healthy test subjects were included in the study. Production of the representative AA-metabolites LTB4 and PGE2 from isolated monocytes stimulated with the calcium ionophore A23187 were measured ex vivo before therapy with 1.8-cineole (3 x 200 mg/day), after three days of treatment (day 4) and four days after discontinuation of 1. 8-cineole (day 8). The production of LTB4 and PGE2 from monocytes ex vivo was significantly inhibited on day 4 in patients with bronchial asthma (-40.3%, $n = 10$ and -31.3%, $p = 0.1$, $n = 3$ respectively) as well as in healthy volunteers (-57.9%, $n = 12$

and -42.7%, n = 8 respectively). In conclusion, 1.8-cineole was shown to inhibit LTB4 and PGE2, both pathways of AA-metabolism[298].

In studying the potential anti-inflammatory efficacy of 1,8-cineol (eucalyptol) in inhibiting polyclonal stimulated cytokine production by human unselected lymphocytes and LPS-stimulated monocytes, the therapeutic concentrations of 1,8-cineol (1.5 μg/ml=10−5 M) inhibited significantly (n=13–19, p=0.0001) cytokine production in lymphocytes of TNF-α > IL-1β> IL-4> IL-5 by 92, 84, 70, and 65%, respectively. Cytokine production in monocytes of TNF-α > IL-1β> IL-6> IL-8 was also significantly (n=7–16, p<0.001) inhibited by 99, 84, 76, and 65%, respectively. In the presence of 1,8-cineol (0.15 μg/ml=10−6 M), the production of TNF-α>IL-1β by monocytes and of IL-1β> TNF-α by lymphocytes was significantly inhibited by 77, 61 and 36, 16%, respectively[299].

The inhibitory effect of 1.8-cineole was studied on LPS-and IL1beta-stimulated mediator production by human monocytes in vitro. A dose-dependent and highly significant inhibition of production of tumor necrosis factor-alpha, interleukin-1beta, leukotriene B4 and thromboxane B2 were achieved by 1.8-cineole[300].

Eupatorium cannabinum

9-(3-Methylbutanoyl)-8,10-dehydrothymol; eupatobenzofuran; 9-isobutyryloxy-8,10-dehydrothymol; 10-acetoxy-8-hydroxy-9-O-angeloylthymol and 1-[2-hydroxy- 4-(hydroxymethyl)phenyl]ethan-1-one isolated from the aerial part of E. cannabinum inhibited fMLP/CB-induced elastase release with IC_{50} values e 18.3 μM). 9-Acetoxy-8,10-epoxythymol 3-O-tiglate; 9-acetoxy-8,10-dehydrothymol 3-O-tiglate (7), 9-acetoxythymol 3-O-tiglate; 8-methoxy-9-O-isobutyrylthymol; 10-acetoxy-8-hydroxy-9-O-angeloylthymol; and 1-[2-hydroxy-4-(hydroxymethyl)phenyl]ethan-1-one isolated from the aerial part of E. cannabinum exhibited potent inhibition (IC_{50} values e 18.4 μM) of superoxide anion (O^{2-}) generation by human neutrophils in response to fMLP/CB[301-302].

Foeniculum vulgare

The analgesic and anti-inflammatory action of the ethanolic extracts Foeniculum vulgare (50,100 and 200mg/kg, ip) was studied in Wistar rats and Swiss Albino mice. Analgesia was studied in albino rats using formalin test and in albino mice using writhing test[303]. Anti-inflammatory activity of the was investigated by carrageenan- induced hind paw edema. The ethanolic extract produced significant (p<0.001) dose-dependent inhibition of pain response elicited by acetic acid and formalin tests. It also exerted dose dependent inhibition of edema development in the carrgeenan induced inflammation[304].

The fennel oil and the main component of the fennel oil, anethole inhibited arachidonic acid-, collagen-, ADP- and U46619-induced aggregation (IC_{50}) from 4 to 147 microg/ml. Anethole also prevented thrombin-induced clot retraction at concentrations similar to fennel oil. The essential oil and anethole, tested in rat aorta with or without endothelium, displayed comparable NO-independent vasorelaxant activity at antiplatelet concentrations which have been proved to be free from cytotoxic effects in vitro. In vivo, both F. vulgare essential oil and anethole orally administered in a subacute treatment to mice (30 mg/kg/day for 5 days) showed significant antithrombotic activity preventing the paralysis induced by collagen-epinephrine intravenous injection (70% and 83% protection, respectively). At the antithrombotic dosage they were free from prohemorrhagic side effect at variance with acetylsalicylic acid used as reference drug[305].

The essential oil of Foeniculum vulgare L. was investigated using the model of carrageenan induced rat paw edema. It showed anti-inflammatory effect comparable to that of etodolac at 0.050 and 0.200 ml/kg doses[306].

Fraxinus ornus

The total ethanol extract of the stem bark of Fraxinus ornus and its constituent esculin inhibited classical pathway (CP) and alternative pathway (AP) of complement activation in mouse serum. Intraperitoneal administration the total ethanol extract displayed antiinflammatory activity in both zymosan- and carrageenan-induced paw oedema in mice. The antiinflammatory effects are at least partially due to coumarin constituents of Fraxinus ornus[307].

The anti-inflammatory effect of boiling 96% alcoholic extract of stem bark of Fraxinus ornus using odema induced in mice by Zymosan and carrageenan. After intraperitoneal administration the total extract displayed antiinflammatory activity in both zymosan- and carrageenan-induced paw oedema in mice. The effective dose of about 5-15 mg/kg is comparable to the data know for other lipoxygenase inhibitors like phenidone. The total ethanol extract from F. ornus bark contains substances of high potency capable of inhibiting classical pathway and alternative pathway complement activity. The comparison between the effects obtained with total ethanol extract and esculin in the haemolytic inhibitory assay indicates that the anticomplementary action of total extract is not due only to esculin[308-309].

Fumaria parviflora

The anti-inflammatory activity of leaves of Fumaria parviflora and underlying mechanisms was studied in rats by using in vivo models of inflammation. The anti-inflammatory activity was studied using carrageenan-induced paw edema method and cotton pellet granuloma method. Levels of cytokines such as TNF-α, IL-6 and IL-1 and activity of antioxidant enzymes including catalase (CAT) and glutathione peroxidase (GPx) were estimated. Leaves of F. parviflora possessed significant ($p<0.001$) decrease in paw edema in carrageenan-induced paw edema method. It diminished the serum tumour necrosis factor-α (TNF-α), IL-6 and IL-1 levels and also significantly attenuated the malondialdehyde (MDA) levels. The activity of CAT and GPx was increased in paw tissue. It also demonstrated significant decrease in granuloma formation in cotton pellet-induced granuloma method[310].

The anti-inflammatory effect of hydro alcoholic extract of Fumaria parviflora was investigated in rats at doses of 200, 400, 600, 800 or 1000 mg/kg using carageenan model. 200 and 400 mg/kg doses of extract had less effect on the paw's edema in comparison with animal group received aspirin ($p<0.05$). However, dose of 600, 800 and 1000 mg/kg of the extract possessed more antiinflammatory effects , and the difference between groups was not statistically significant ($p>0.05$)[311-312].

Geum urbanum

In a screening of Swedish traditional remedies Calluna vulgaris and Geum urbanum were reported to inhibit prostaglandin biosynthesis and platelet activating factor (PAF)-induced exocytosis in vitro[313].

The dried Geum urbanum herb was pulverized and extracted with many solvents. Extracts were tested (10 mg/Ml) on PPAR-α and PPAR-γ activation as well as on NF-κB inhibition , dichloromethane extract possessed moderate, moderate and strong effects, while dichloromethane extract without chlorophyll possessed strong, moderate and moderate effects respectively[314].

***Haplophyllum* Spp**

The essential oils from aerial parts and flowers of Haplophyllum tuberculatum exhibited a remarkable acute anti-inflammatory activity against carrageenan induced oedema in rats 9.52% and 8.56% which were found to be comparable to the standard drug, indomethacin[315].

The methanolic extract of Haplophyllum hispanicum was tested against two experimental models of acute inflammation, TPA-induced ear and carrageenan-induced paw edemas in mice. It possessed a 50% reduction of the ear edema when it was administered topically compared with indomethacin (86 %), when the extract was given orally it did not inhibit the paw edema to a significant degree in 5 h (inhibition = 37%). In a second stage, the extract was assayed against two other inflammatory conditions, oxazolone-induced delayed hypersensitivity and the multiple-dose TPA-induced response, which differ in their inflammation generating mechanism. The increase in ear thickness produced by oxazolone was magnified (+ 18%) by treatment with the plant extract, indicating that some constituents may cooperate with the sensitizing agent. Two topical anti-inflammatory aryl naphthalide lignans were isolated from the active fractions of the methanol extract. They were identified as diphyllin acetyl apioside and tuberculation. The former was the most active on acute TPA edema with a ID_{50} of 0.27 mumol/ear[315-316].

It appeared that the topical anti-inflammatory activity of Haplophyllum hispanicum was attributed to the presence of arylnaphthalene-type lignans acting as 5-lipoxygenase (5-LOX) inhibitors[317].

The methanol extract of H. linifolium (Haplophyllum hispanicum) was applied twice daily (15 µL, 1 mg/ml) during four days onto the left ears of Swiss mice in the morning immediately after TPA 2.5 µg/ear application and 6 h later. The extract has a potent topical anti-inflammatory activity with no apparent toxicity[318]**.**

Hedera helix

The ethanol Hedera helix plant extract was tested for antiinflammatory properties. Intraperitoneal injections of 7.5 ml/kg wt ethanol extract showed antiinflammatory activity (88.89% inhibition) in formalin-induced paw oedema, as compared to diclofenac which showed 94.44%. The effect of ethanol extract of Hedera helix was also investigated in arthritis. It possessed significant antiinflammatort effect manifested by visible reduction in arthritic symptoms[319].

The possible antiinflammatory effects of a crude saponin extract (CSE) and a saponin's purified extracts (SPE) of Hedera helix were studied in carrageenan- and cotton-pellet-induced acute and chronic inflammation models in rats. Both the CSE and SPE of Hedera helix possessed antiinflammatory effects. The most potent extract was the CSE of Hedera helix at 100 and 200 mg/kg bw doses with 77% acute antiinflammatory effects. The SPE of Hedera helix was more potent than the CSE in its chronic antiinflammatory effect (60% and 49%, respectively)[320].

Helianthus annuus

Three diterpene acids: grandiflorolic, kaurenoic and trachylobanoic acids were studied for potential anti-inflammatory activity on the generation of inflammatory mediators in lipopolysaccharide (LPS)-activated RAW 264.7 macrophages. At non-toxic concentrations, these compounds reduced, in a concentration-dependent manner nitric oxide (NO), prostaglandin E 2 (PGE 2) and tumor necrosis factor (TNF-α) production, as well as expression of inducible nitric oxide synthase (NOS-2) and cyclooxygenase-2 (COX-2). All diterpenoids displayed significant in vivo anti-inflammatory activity and suppressed the 12-O-tetradecanoylphorbol-13-acetate (TPA)-mouse ear edema. In addition, inhibition of myeloperoxidase (MPO) activity, an index of cellular infiltration, was observed[321].

The anti-inflammatory and analgesic effects of the ethanol extract of leaves of Helianthus annus L. (0.5 g/kg, 2 g/kg and 4 g/k) were investigated in rats using the albumin induced paw edema model of inflammation as well as both the hot plate and tail immersion analgesic test methods. The treatment with the tested doses of the extract effectively inhibited paw edema induced by egg albumin. This effect was comparable if not better than 10 mg/kg of indomethacin orally. Treatment with the extract was also significantly increased the mean tolerance time of rats to thermal noxious stimuli compared to control animals and appeared to be more effective than 10 mg/kg of indomethacin treatment[322].

The methanol extract of seeds of Helianthus annuus was evaluated for analgesic activity using acetic acid induced writhing and hot plate methods In acetic acid-induced writhing test, the extract showed significant ($P < 0.05$) analgesic potential at doses of 100 and 200 mg/kg bw (50.35 and 57.85% inhibition, respectively). In the hot plate method, increase ($p < 0.05$) of latency period was also observed in comparison to standard aspirin. At 60 minutes, the latency period of two different doses (100 and 200 mg/kg body weight) was found at 13 ± 0.91 and 16.5 ± 1.55 second[323-324].

Heliotropium bacciferum

The anti-inflammatory effect of plants' extracts of 17 genera were studied using the carrageenan induced inflammation in rats' paws. The plant extracts were obtained using methanol and dichloromethane as solvent and administered intraperitoneally at the concentration of 2g/kg body weight. Dichloromethane extract of the aerial parts of Heliotropium bacciferum caused 28.2±3.1% inhibition of oedema volume 2 hours after injection of Carrageenan[325].

Hibiscus rosa-sinensis

The antiinflammatory activity of ethanolic extract of Hibiscus rosa sinesis (125, 250 and 500 mg/kg) was evaluated using carrageenin induce paw edema, cotton pellet induce granuloma and xylene induce mice ear edema. The analgesic activities were analyzed using formalin test and writhing test; pyrexia induced by brewer's yeast in rats. The ethanolic extract showed significant anti-inflammatory, analgesic and anti-pyretic effect[326].

The anti- inflammatory activities of ethanol extract of flower and leaf of Hibiscus rosa-sinensis var alba (white Hibiscus) and Hibiscus rosa-sinensis L. (red Hibiscus) was determined using carrageena model. Carrageenan was injected subplantarly 30 min before administration of each extracts (5, 50 and 100 mg/kg). Dosing of 50 and 100 mg/kg of flower and leaf estracts of Hibiscus rosa-sinensis caused significant inhibition ($p<0.05$) of edema. Flower and leaf of Hibiscus rosa-sinensis var alba significantly inhibited ($p<0.05$) edema in all range of testing dose. The white hibiscus revealed more potent anti-inflammation. All extracts at various concentration caused significant reduction ($p<0.05$) in polymorphonuclear leukocytes infiltration with white Hibiscus also more potent than red hibiscus. All extracts showed significant reduction ($p<0.05$) in the duration of licking response, white Hibiscus was also more potent inhibitor[327].

The methanolic extract of Hibiscus rosa- sinensis leaves (250 and 500 mg/kg bw, orally) was studied for anti-nociceptive (acetic acid-induced writhing response and tail flick method) and anti-inflammatory (carrageenin and dextran induced rat paw edema) activities. The methanolic extract possessed significant anti-inflammatory activity and significant dose-dependent analgesic activity[328].

The antipyretic activity of the root extract of Hibiscus rosa sinesis, was evaluated in yeast induced pyrexia and the analgesic potentials was investigated in tail flicking method in rats at a dose of 250mg/kg body weight. The aqueous root extract showed significant antipyretic and analgesic activities[329].

The anti-pyretic activity of Hibiscus rosa-sinensis aqueous extracts was evaluated in fever induced by yeast suspension (intraperitoneally 0.1 g/kg bw in mice. The animals with fever were administered orally with aqueous extracts of H. rosa-sinensis (500 mg/kg of bw). The result of the study showed that H. rosa-sinensis aqueous extracts significantly ($p<0.05$) effective in combating fever[330].

Hibiscus sabdariffa

The essential oil of H. Sabdariffa exhibited excellent anti-inflammatory activity in lipopolysaccharide (LPS)-stimulated macrophage RAW 264.7 cells. The nitric oxide (NO) inhibition rate reached 67.46% when the concentration of the essential oil was 200 μg/ml. Further analysis showed that the anti-inflammatory activity of the essential oil extracted from H. Sabdariffa might be exerted through inhibiting the activation of NF-κB and MAPK (JNK and ERK1/2) signaling pathways to decrease NO and pro-inflammatory cytokine (IL-1, IL-6, TNF-α, COX-2, and iNOS) production[331].

The antiinflammatory effect of seed of H. sabdariffa was tested in rats. The oral administration of petroleum ether extract of H. sabdariffa seeds reduced the paw edema significantly that was induced by carrageenan in dose dependent manner. After 3 h of the treatment dosed at 4 and 8 ml/kg bt., paw edema was reduced by 27.9% ($p<0.05$) and 34.2% ($p<0.01$), respectively. In contrast, the ethanolic extract of H. sabdariffa seeds did not show significant reduction in paw edema (inhibition 0%) even at the test doses of maximum 400 mg/kg bw. In vascular permeability test, oral administration of diclofenac sodium dosed at 10 mg/kg bw, and petroleum ether extract of H. sabdariffa seeds (dosed at 4 and 8 mL/kg bw) significantly ($p<0.01$) inhibited the dye leakage induced by acetic acid as compared to control. In cotton pellet induced granuloma test, granuloma formation was inhibited significantly after administration of petroleum ether extract of H. sabdariffa seeds for 6 consecutive days as compared to control group. The test dose (4 and 8 ml/kg bw) showed 30.3% and 27.2% of inhibition ($p<0.01$) respectively as compared to the control group. The peripheral analgesic activity of petroleum ether extract was measured by acetic acid induced writhing test. H. sabdariffa seed petroleum ether extract exhibited a significant level of inhibition in abdominal writhes produced by acetic acid especially with high dose (8 ml/kg bwt, 45.0%, $p<0.001$) as compared to control group[332].

The anti-inflammatory activity of methanolic leaves extract of hibiscus sabdariffa (250 and 500 mg/kg bw) was investigated in adult wistar rat using carrageenan model. There was significant reduction ($p< 0.05$) in paw diameter in the group that received high dose (500 mg/kg bw) of methanolic extract of hibiscus sabdariffa from 0.566±0.023 to 0.414±0.009 as compared with the untreated group[333].

The effects of the extracts from Hibiscus sabdariffa calyces on nociceptive response were studied using writhing, hot plate and formalin test in mice, the antipyretic activity in yeast-induced fever in rats and anti-inflammatory activity on carrageenin-induced paw edema in rats. Oral administration of the ethanol extract at the dose of 800 mg/kg significantly decreased the number of contortions and stretchings induced by acetic acid in mice. Neither the ethanol nor aqueous extract had an effect in the formalin and hot plate tests in mice. The ethanol and the vacuum dried extract of H. sabdariffa calyces (200-800 mg/kg, po) decreased the yeast-induced fever in rats, while, H. sabdariffa extract had no effect on carrageenin induced paw edema in rats[334].

The antinociceptive and anti-inflammatory of the ethanolic calyx extract of Hibiscus sabdariffa were studied in mice. The antinociceptive activity of the extract was evaluated by using the acetic acid-induced writhing test. The anti-inflammatory effect of the extract was tested by using the xylene-induced ear edema model mice. In acetic acid-induced writhing test, the extract inhibited writhing in mice significantly compared with control ($P<0.01$). The extract showed significant inhibition of ear edema formation in xylene-induced ear edema model mice in a dose-related manner compared with control ($P<0.01$)[335].

The aqueous extracts of Hibiscus sabdariffa were tested for anti-inflammatory, analgesic and antipyretic activities in animal models. The extract had no effect on paw edema but had an inhibitory effect on yeast induced pyrexia and showed significant effect on the hot plate reaction time[336].

***Hyoscyamus* Spp**

The analgesic (acetic acid induced writhing response and the other formalin-induced paw licking in rats) and anti-pyretic properties (brewer's yeast induced fever in rats) of standardized Hyoscyamus albus methanolic extract were investigated experimentally. 100 and 200 mg/kg of Hyoscyamus albus methanolic extract decreased the acetic acid induced writhing responses and the licking time in the second phase of the formalin test. Moreover, it showed dose-dependent lowering of the body temperature up to 3h at both doses the effect was comparable to that of paracetamol[337-338].

The methanolic extract of seeds of H. niger was evaluated for analgesic, anti-inflammatory and antipyretic activities in experimental animal models at different doses. The methanolic extract of seeds of H. niger produced significant increase in hot plate reaction time, while decreasing writhing response in a dose-dependent manner indicating analgesic activity. It was also effective in both acute and chronic inflammation evaluated by carrageenin-induced paw oedema and cotton pellet granuloma methods. It also exhibited antipyretic activity in yeast-induced pyrexia model[339].

Hypericum triquetrifolium

The antiinflammatory effect of Hypericum triquetrifolium was evaluated in rat model of carrageenan induced inflammation. Male Wistar rats were treated intraperitoneally with 0.4% dimethylsulphoxide (DMSO) (as control group) and H. triquetrifolium extract (25, 50, 60 mg/kg), 30 min before 0.1 ml 1% carrageenan

injection. Paw volume was measured before and 1, 2, 3, 4, 5 and 6 h after the injection of carrageenan. Intraperitoneal administration of H. triquetrifolium extract (25, 50, 60 mg/kg) inhibited paw swelling dose-dependently at 2, 3, 4, 5 and 6 h after carrageenan injection ($P<0.05$). We can conclude that H. triquetrifolium extract may exert an antiinflammatory effect in rats. # 2002 Elsevier Science Ireland Ltd. All rights reserved[340].

The anti-inflammatory mechanism of Hypericum triquetrifolium was studied by measuring the expression and release of pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukine-6 (IL-6), and inducible nitric oxide synthase (iNOS) in human monocytic cells, THP-1. The effects were assessed by measuring the levels of secretory proteins and mRNA of TNF-α and IL-6, the levels of nitric oxide (NO) secretion and the expression of iNOS in THP-1 cells. Cells were treated with 5 μg lipopolysaccharide/ml (LPS) in the presence and absence of increasing concentrations of extracts from the aerial parts of H. triquetrifolium. During the entire experimental period, extract was used in a concentrations (up to 250 μg/ml) that had no cytotoxic effects, measured with MTT and LDH assays. Hypericum triquetrifolium extracts remarkably suppressed the LPS-induced NO release, significantly attenuated the LPS-induced transcription of iNOS and inhibited in a dose-dependent manner the expression and release of TNF-α. No significant effects were observed on the release of IL-6[341].

The anti-inflammatory activity of Hypericum triquetrifolium extracts (HT-extract) was evaluated on lipopolyssacharide -stimulated human monocytic (THP-1) cells and human peripheral blood mononuclear cells (PBMNCs). The expression and production of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), as well as the anti-inflammatory cytokine interleukin 10 (IL-10) were evaluated by assessing the levels of proteins and mRNA's of TNF-α, IL-6 and IL-10 in both cell types. Cells were exposed to 5 μg lipopolyssacharide (LPS) /ml in the absence and presence of increasing concentrations of 50% ethanol extracts from the aerial parts of Hypericum triquetrifolium. The anti-inflammatory efficacy experiments were performed with HT-extract concentrations up to 250 μg/ml that had no cytotoxic effects as assessed with MTT and LDH assays. HT-extract remarkably inhibited the expression and secretion of TNF-α and IL-6 at a concentration of 250 μg/ml. HT-extract remarkably elevated IL-10 secretion and mRNA levels at 125 μg/ml. Furthermore, HT-extract exhibited relatively high antioxidant activity (IC_{50} of 5 μg/ml) as measured with DPPH assay[342-343].

Inula graveolense

Anti-inflammatory and antinociceptive effects of the methanolic extract of Inula graveolense were studied in mice. The methanolic extract showed significant antiinflammatory and antinociceptive activity at the dose of 400 mg/kg ($P < 0.01$) as compared to diclofenac sodium (50 mg/kg). The extract inhibited paw and ear edema in a dose-related manner. A dose-dependent analgesic action was obtained against chemical (writhing test) and thermal (hot-plate test) stimuli. The effect of methanolic extract of Inula graveolense was evaluated against heat induced and anti-platelet aggregation of human blood activity. It was observed that the extract showed greater percentage of inhibition of BSA ($P < 0.01$) at the highest concentration (400 μg/ml). Denaturation of tissue proteins is one of the well documented causes of inflammatory and rheumatoid arthritis. This effect could be represented one of the mechanisms of antiinflammatory effects of the extract[344-345].

Jasminum sambac

The anti-inflammatory, analgesic and anti-pyretic activities of the ethanolic extract of the roots from Jasminum sambac (EJS) were investigated experimentally. Analgesic activity of EJS at 100, 200 and 400mg/kg orally was evaluated using writhing test on Swiss albino mice and tail-flick test on Charles Foster albino rats. Anti-inflammatory activity of EJS was assessed by carrageenan-induced rat paw edema, cotton pellet-induced granuloma and Freund′s adjuvant-induced arthritis models, while antipyretic activity was evaluated using Brewer′s yeast induced pyrexia. EJS at 400mg/kg orally, reduced writhing count up to 49.21%, whereas in tail-flick test, EJS in a dose dependent manner increased latency in flicking tail. EJS at 400mg/kg orally, showed significant anti-inflammatory activity after 2^{nd}, 3^{rd}, 4^{th} and 6^{th} h of treatment in carrageenan-induced edema, while a 33.58% inhibition in cotton pellet induced granuloma formation was observed at same dose level. EJS significantly ($p<0.001$) inhibited adjuvant-induced arthritis and also showed significant antipyretic activity[346].

The methanol extract (400 mg/kg bw) of Jasminum sambac flowers was investigated for antiinflammatory and analgesic activities using hot plate method, acetic acid induced writhing and carragenan induced paw odema in animal models. In the acetic acid-induced writhing model, the extract possessed significant analgesic and antiinflammatory effects compared to the control, These effects were comparable to that induced by Diclofenac sodium[347].

The ethanol extract of the dried leaves of Jasminum sambac produced significant ($P<0.001$) writhing inhibition in acetic acid-induced writhing in mice at an oral dose of 250 and 500 mg/kg of body weight comparable to the standard drug diclofenac sodium at the dose of 25 mg/kg of body weight[348].

The ethanol (50%) extract of the leaves of Jasminum sambac was investigated for anti-inflammatory activity using carrageenan induced hind paw oedema and cotton pellet induced granuloma models in rats. The extract (100, 200 and 400mg/kg bw) caused dose dependent significant decrease in paw oedema and weight of granuloma9. The extract at 400mg/kg bw, exhibited potential anti-inflammatory activity, comparable to dichlofenac[349].

The antiinflammatory property of the formulated topical gel from the extract of Jasminum sambac was evaluated against 1% diclofenac emugel as positive control in rats. The leaves of Jasminum sambac was extracted with 80% methanol. The extract was used for the formulation of the different concentration of topical gel. The extract possessed significant antiinflammatory activity[350].

Juglans regia

Methanol leaf extract produced statistically significant inhibition of edema induced by carrageenan at nearly all doses (250-1000 mg/kg ip) when compared to the control groups. The effect was dose-dependent. The highest activity showed at 1000 mg/kg ip that inhibited 77% of inflammation. The same activity was found for diclofenac at 100 mg /kg ip (73%) ($p>0.05$)[351].

The ethanolic extracts of J. regia leaves exhibited potent anti-inflammatory activity as potent as indomethacin against carrageenan-induced hind paw edema model in mice without inducing any gastric damage[352].

When BV-2 microglial cells were treated with walnut methanolic extract prior to LPS stimulation, production of nitric oxide and expression of inducible nitric oxide synthase were attenuated. Walnut extract also induced a decrease in tumor necrosis-alpha (TNFalpha) production. Walnut extract induced internalization of the LPS receptor, toll-like receptor 4, and that the anti-inflammatory effects of walnut were dependent on functional activation of phospholipase D2[353].

Juniperus oxycedrus

Methanol and dichloromethanol extracts of leaves and stems of Juniperus oxycedrus were tested for analgesic and antiinflammatory effects. The methanol extract exhibited an analgesic effect in models of chemical, mechanical and thermal stimulation whereas dichloromethanol extract showed only a significant effect in models of pain induced by chemical stimulation. Both extracts showed a significant antiinflammatory activity and inhibition of the rat paw oedema induced by carrageenan[354].

The antiinflammatory and antinociceptive activities of subextracts of J. oxycedrus subsp. oxycedrus berries and leaves were evaluated using p-benzoquinone-induced writhing test for antinociceptive activity and the carrageenan-induced hind paw edema model for antiinflammatory activity in mice. The n-butanol subextract of J. oxycedrus subsp. oxycedrus berry ethanol extract exhibited remarkable antiinflammatory effect at 100 mg/kg. The same subextract displayed significant antinociceptive activity without inducing any gastric damage or apparent acute toxicity[355-356].

Kochia scoparia

The effects of methanol extracts of K. scoparia dried fruit (MEKS) was investigated on ear swelling, histopathological changes (such as epidermal acanthosis, spongiosis and immune cell infiltration) and cytokine production in 1 fluoro 2,4-dinitrofluoro benzene (DNFB) induced contact dermatitis mice. Topical application of MEKS inhibited DNFB induced ear thickness and weight increases as well as DNFB induced epidermal acanthosis, spongiosis and immune cell infiltration. In addition, treatment with MEKS significantly decreased the levels of tumor necrosis factor α, interferon γ and monocyte chemotactic protein 1 in inflamed tissues[357].

The effects of the methanol extract of the fruits of Kochia scoparia was evaluated for antiinflammatory on lipopolysaccharide (LPS)-induced nitric oxide (NO), prostaglandin E_2, and tumor necrosis factor (TNF-α) release by the macrophage cell line RAW 264.7. The results indicated that the extract was a potent inhibitor of NO production and it also significantly decreased PGE_2 and TNF-α release. The protein and mRNA expression level of inducible NO synthase (iNOS) and cyclooxygenase-2 were inhibited by methanol extracts of Kochia scoparia in a dose-dependent manner. It also inhibited the LPS-induced DNA binding activity of nuclear factor-kappaB, which was associated with prevention of the inhibitor kappaB degradation[358].

The anti-inflammatory effects of externally applied Kochia scoparia water extract (KSW) was investigated in 2,4-dinitrochlorobenzene (DNCB)-induced contact dermatitis mouse model. 100 µl of 1% DNCB in acetone/olive oil (4:1) had been applied for three days on shaved dorsal skin. 1% KSW was topically applied to mice to develop atopic dermatitis-like skin lesions. After KSW treatment, histological analysis showed that hyperplasia of the epidermis and dermis in the KSW treated group was markedly decreased as

compared with the DNCB group. The expression levels of pro-inflammatory cytokine such as IL-1β, and TNF-α mRNA were significantly reduced by topical application of KSW, whereas these cytokines were increased in DNCB-induced dorsal skin. NF-κB expression was inhibited by KSW treatment in DNCB-induced mice. KSW treatment also significantly suppressed the expression of several MAP kinases, including ERK1/2, p38, and JNK compared to their expression in DNCB-induced mice[359].

The anti-inflammatory effect of methanol extracts of K. scoparia dried fruit (MEKS) was investigated on ear swelling, histopathological changes (such as epidermal acanthosis, spongiosis and immune cell infiltration) and cytokine production in 1-fluoro-2,4-dinitrofluorobenzene (DNFB)-induced contact dermatitis mice. Topical application of MEKS inhibited DNFB-induced ear thickness and weight increases, as well as DNFB-induced epidermal acanthosis, spongiosis and immune cell infiltration. Treatment with MEKS significantly decreased the levels of tumor necrosis factor-α, interferon-γ and monocyte chemotactic protein-1 in inflamed tissues[360].

Methanol extract of Kochia scoparia fruits and both ethyl acetate and Butanol fractions were active in the rheumatoidal rat induced Freund's complete adjuvant reagent whereas chloroform fraction was inactive. Oleanolic acid and momordin lc showed significant activities in the same assay. These effects were also observed in carrageenan-induced edema of the rat and in the antinociceptive activity tests undertaken in hot plate- and writhing methods. The results suggested that momordin lc and its aglycone, oleanolic acid, could be active principles for rheumatoid arthritis[361-362].

II. CONCLUSION:

The use of non steroidal anti-inflammatory drugs is associated with severe side effects. Therefore, medicinal plants with anti-inflammatory effects are preferred as a result of effectiveness and safety. The current review highlighted the medicinal plants possessed anti-inflammatory effects with special focus on their mode of action.

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