

## **Review Article**

# **Medicinal plants possessed anti-inflammatory antipyretic and analgesic activities (part 2) - plant based review**

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**Abstract:** In a previous review, we mentioned that there were many plants possessed anti-inflammatory antipyretic and analgesic effects, these included *Achillea santolina*, *Althaea officinalis*, *Adiantum capillus-veneris*, *Alhagi maurorum*, *Ailanthus altissima*, *Allium cepa*, *Alpinia galanga*, *Ammannia baccifera*, *Ammi majus*, *Anchusa italica*, *Andrachne aspera*, *Anethum graveolens*, *Anthemis nobelis*, *Apium graveolens*, *Arachis hypogaea*, *Arctium lappa*, *Aristolochia maurorum*, *Asclepias curassavica*, *Asparagus officinalis*, *Astragalus hamosus*, *Avena sativa*, *Bacopa monnieri*, *Bauhinia variegata*, *Bellis perennis*, *Benincasa hispida*, *Betula alba*, *Bidens tripartita*, *Brassica nigra*, *Brassica rapa*, *Bryonia dioica*, *Bryophyllum calycinum*, *Caesalpinia crista*, *Calendula officinalis*, *Calotropis procera*, *Canna indica*, *Capparis spinosa*, *Capsella bursa-pastoris*, *Capsicum annum*, *Capsicum frutescens*, *Carthamus tinctorius*, *Carum carvi*, *Cassia occidentalis*, *Centaurea cyanus* and *Chenopodium album*. This review was designed as a second part of the previous one to cover the medicinal plants possessed anti-inflammatory antipyretic and analgesic effects.

**Keywords:** medicinal plants, herbs, anti-inflammatory antipyretic, analgesic.

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### **INTRODUCTION:**

Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. Plants have been used as drugs by humans since thousands of years ago. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives. In our previous reviews, we mentioned that many medicinal plants exerted anti-inflammatory antipyretic and analgesic effects [1-3]. These plants included *Achillea santolina* [4], *Althaea officinalis* [5], *Adiantum capillus-veneris* [6], *Alhagi maurorum* [7], *Ailanthus altissima* [8], *Allium cepa* [9], *Alpinia galanga* [10], *Ammannia baccifera* [11], *Ammi majus* [12], *Anchusa italica* [13], *Andrachne aspera* [1], *Anethum graveolens* [14], *Anthemis nobelis* [15], *Apium graveolens* [16], *Arachis hypogaea* [17], *Arctium lappa* [18], *Aristolochia maurorum* [1], *Asclepias curassavica* [19], *Asparagus species* [20], *Avena sativa* [21], *Bacopa monnieri* [22], *Bauhinia variegata* [23], *Bellis perennis* [24], *Benincasa hispida* [25], *Betula alba* [26], *Bidens tripartita* [27], *Brassica species* [28], *Bryonia dioica* [1], *Bryophyllum calycinum* [29], *Caesalpinia crista* [30], *Calendula officinalis* [31], *Calotropis procera* [32], *Canna indica* [33], *Capparis spinosa* [34], *Capsella bursa-pastoris* [35], *Capsicum species* [36], *Carthamus tinctorius* [37], *Carum carvi* [38], *Cassia occidentalis* [39], *Centaurea cyanus* [40], and *Chenopodium album*

[41]. This review is the second part of the previous one to cover the medicinal plants possessed anti-inflammatory antipyretic and analgesic effects.

### **Plants with anti-inflammatory, antipyretic and analgesic effects**

#### ***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 [42-43].

#### ***Cistanche tubulosa***

The anti-inflammatory effects of fuciodan and *Cistanche tubulosa* extract were investigated in vitro macrophage culture system and in vivo carrageenan-induced air pouch inflammation model. Although, fuciodan was inactive, but in vivo air pouch inflammation model, carrageenan-induced vascular exudation and increased nitric oxide and prostaglandin

E<sub>2</sub> 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 [44].

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)- $\beta$ 1, 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- $\beta$ 1 expression [45].

*Cistanche tubulosa* dialysate (CTD) prepared using a 3,500-Da molecular weight cut-off dialysis membrane, enhanced IgM production in B-cell line BALL-1 and IgG production in B-cell line HMy-2, induced cell proliferation in BALL-1 and T-cell line Jurkat, and oppositely inhibited cell proliferation in B-cell line Namalwa [46].

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  $\beta$ -hexosaminidase release and intracellular Ca<sup>2+</sup>/I level from rat basophilic leukemia (RBL-2H3) cells was determined. Histamine, tumor necrosis factor (TNF) -  $\alpha$ , 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  $\mu$ g/ml acteoside inhibited the release of  $\beta$ -hexosaminidase and Ca<sup>2+</sup>/I influx from IgE-mediated RBL-2H3 cells. Moreover, acteoside inhibited histamine release, TNF- $\alpha$ , 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 [47].

#### *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 [48-49].

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 [50].

#### 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- $\kappa$ B and AP-1 by electrophoretic mobility shift assay and transient transfection experiments. DE90 pectin binds with LPS, and might result in decreasing binding of LPS to its receptor [51].

Orally, Citrus Limon essential oil (EO) (50, 100, and 150 mg/kg) significantly reduced the number of writhes, and, at highest doses, reduced the number of paw licks. Naloxone antagonized the antinociceptive action of EO (highest doses), this suggested, at least, the participation of the opioid system<sup>(84)</sup>. The ethanolic extract of peels of Citrus Limon (Burm) fruit was screened for its anti-nociceptive property using both chemical and thermal methods of nociception in rats. The extract at doses 250 and 500 mg/kg po, showed

nociceptive property in both chemical and thermal methods. The activity exhibited by the extract was comparable to that of the standard drug, diclofenac sodium (15 mg/kg) [52].

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 [53].

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 [54].

The analgesic effect of fresh decoction of *Citrus medica* fruits was studied in rats. The decoction was prepared from fresh fruits in distilled water and the volume was reduced to 1/4<sup>th</sup>. Three doses of decoction (1, 2 and 4ml/kg po) were tested for analgesic activity using tail immersion method and hot plate method. Diclofenac sodium (10mg/kg ip) was used as standard. The decoction at doses (2 and 4ml/kg) showed significant increase in latency to flick compared to control in tail immersion method. Whereas the decoction of *Citrus medica* at all three doses showed significant increase in the mean basal reaction time in hot plate method. In both methods, analgesic effect of 4ml/kg decoction was observed comparable to the standard drug [55].

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) [56].

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 [57].

The effect of orange juice on cellular modifications induced by a fatty meal was investigated. 18 apparently healthy subjects consumed a fatty meal, during which they drank orange juice, either blond or red, or water, according to a randomized cross-over design. Two hours after the end of the fatty meal, both white blood cell (WBC) and platelet counts significantly increased (12.5 and 5%, respectively), while mean platelet volume decreased and a 25% release of myeloperoxidase (MPO) from polymorphonuclear leukocyte occurred. Both juices significantly prevented WBC increase and MPO degranulation, in respect to control. Triglycerides significantly increased (42%) after the fatty meal, but at a lower extent when red orange juice was consumed with the meal (20%), in respect to blond orange juice or control. This effect was statistically significant in the subgroup subjects with hypertriglyceridemia. Vascular stiffness (augmentation index), measured by Endo-PAT2000, significantly decreased after the meal only in conjunction with red orange juice. Accordingly, in healthy subjects the concomitant intake of orange juice may prevent the low-grade inflammatory reaction induced by a fatty meal, at cellular and possibly at vascular function levels [58].

Ultraviolet light (UV) induced an inflammatory response in the skin by cyclooxygenase (COX)-2 expression and prostaglandin PGE<sub>2</sub> 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 PGE<sub>2</sub> production in HaCaT cells. Furthermore, the extract acted as a peroxisome proliferator-activated receptor (PPAR)- $\gamma$  agonist. The suppression of UVB-induced COX-2 expression by this extract was inhibited by GW 9662 and T0070907, which were both PPAR- $\gamma$  antagonists. It was therefore suggested that orange peel extract, containing high levels of PMFs, suppresses UVB-induced COX-2 expression and PGE<sub>2</sub> production through PPAR- $\gamma$  [59].

#### *Clerodendrum inerme*

The alcoholic and aqueous extracts of the leaves of *C. inerme* showed significant antinociceptive activity in analgaesimeter tests [60]. 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 [61].

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 [62-63]. The leaves of *Clerodendron inerme* were subjected to In vitro Anti-inflammatory activity by HRBC membrane stabilization method in various concentrations 10, 50, 100, 200, 400, 800 and 1000 µg/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, Chloroform, Ethyl acetate, Ethanol and water fractions of the leaves of *Clerodendron inerme* were subjected to in vitro anti-arthritis activity by protein denaturation method. All the extracts showed positive response. The effect was represented as follow: Ethyl acetate > Chloroform > Ethanol > Water > Petroleum ether [64].

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 [65].

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, scutellarin and pectinolinigenin) 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<sup>th</sup> and 49<sup>th</sup> days of untreated arthritic rats showed severe 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 [66].

The petroleum ether, Chloroform, Ethyl acetate, Ethanol and water fractions of the leaves of *Clerodendron inerme* were subjected to in-vitro anti-arthritis activity by protein denaturation method. It appeared that all the extracts of *Clerodendron inerme* leaves are capable of controlling the production of autoantigen and thereby, they inhibited the denaturation of proteins, and their effects were comparable with the standard drug diclofenac sodium. The percentage protection was found to be 78.94% (Petroleum ether extract), 88.46% (Chloroform extract), 89.25% (Ethyl acetate extract), 87.10% (Ethanol extract), 82.31% (Water extract) and 92.20% (Diclofenac sodium). All the extracts showed dose dependant effect [64].

The analgesic and antipyretic effects of aqueous extract obtained from *Clerodendrum inerme* leaves (AECI) was investigated in rats and rabbits. Analgesic effect of AECI was evaluated by Hot plate, Tail Flick and Tail immersion methods in albino rats. Antipyretic activity of AECI was evaluated by milk-induced hyperpyrexia in rabbits. The AECI produced significant (P<0.001) analgesic activity in all models. Furthermore, the AECI potentiated the Diclofenac sodium-induced analgesic effect in albino rats. Treatment with AECI showed a significant (P<0.001) dose-dependent reduction of pyrexia in rabbits [67].

### *Clitoria ternatea*

Ethanol extract of *Clitoria ternatea* root (ECTR) at doses 100, 125 and 150 mg/kg ip were evaluated for antihistaminic activity using clonidine and haloperidol induced catalepsy in mice. Results showed that chlorpheniramine maleate (CPM) and ECTR inhibit clonidine induced catalepsy significantly (P<0.001) when compare to control group, while CPM and ECTR fail to inhibit haloperidol induced catalepsy [68-69].

The methanol extract of blue flowered variety of *Clitoria ternatea* root (MECTR), was evaluated for its anti-pyretic potential on normal body temperature and yeast-induced pyrexia in albino rats. Yeast suspension (10 ml/kg BW) increased rectal temperature after 19 hours of subcutaneous injection. The extract, at doses of (200, 300 and 400 mg/kg BW, po), produced significant reduction in normal body temperature and yeast-provoked elevated temperature in a dose-dependent manner. The effect extended up to 5 hours after the drug administration. The anti-pyretic effect of the extract was comparable to that of paracetamol (150 mg/kg BW, po) [70].

*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 [71].

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 [72].

The analgesic activities of the methanolic extract of *Clitoria ternatea* Linn. Leaves were examined at the doses of 200 and 400 mg/kg of body weight on mice. The analgesic activities were investigated using acetic acid induced writhing test. The plant extract's Central Nervous System (CNS) depressant activity was evaluated by using hole cross and open field tests. Acetic acid induced writhing test revealed that the extract at the lower dose inhibited 82.67% and at the higher dose produced a maximum of 87.87% inhibition of writhing that is comparable to the reference drug, diclofenac sodium. The results of CNS depressant activity showed that the extract decreased the dose dependent motor activity and exploratory behavior of mice in whole cross and open field test. The number of field crossed in open field test and hole crossed in whole cross test decreased as time approached [73]. On the other hand, the possible mechanism underlying the antinociceptive action of methanolic extracts of *Clitoria ternatea* leaf and root was studied using several antinociception models. The different antinociception models such as hot plate, tail-flick and formalin tests were used along with naloxone (a non-selective opioid antagonist) to establish the antinociceptive activity of both leaf and root extracts. Both *Clitoria ternatea* leaf and root extracts markedly demonstrated antinociceptive action in experimental animals. Results of formalin test showed that the antinociceptive activity of the extracts may be mediated at both central and peripheral level. Moreover, the results of hot plate and tail-flick tests further confirmed that *Clitoria ternatea* root extract mediated antinociceptive activity centrally at supraspinal and spinal levels whereas, the *Clitoria ternatea* leaf extract's antinociceptive activity is mediated centrally at supraspinal level only. The authors believe that the opioid receptors are probably involved in antinociceptive activity of both *Clitoria ternatea* root extract [74].

#### ***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<sup>st</sup> h of the study [75].

Conmaculatin (2-Pentylpiperidine), a novel volatile alkaloid related to coniine identified from *Conium maculatum* showed strong peripheral and central antinociceptive activity in mice, which observed in a narrow dose range (10–20 mg/kg). It was found to be lethal in doses higher than 20 mg/kg [76].

#### ***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 [77].

#### ***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 [77-78].

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 [79].

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 [80].

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 anti-inflammatory 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 [81].

The analgesic, anti-inflammatory and anti-arthritis 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-arthritis activity in rat [82-83].

The analgesic, anti-inflammatory and anti-arthritis 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-arthritis activity [84].

The ability of *Cordia myxa* extract in potentiating the analgesic effect of mefenamic acid (ponstan) was investigated in mice. Two tests were employed, hot plate test and formalin test. Mefenamic acid and *Cordia myxa* extract were given (each one alone) orally as aqueous solutions at a dose of 100mg and 600mg per kg BW. *Cordia myxa* extract alone increased the reactive time to the thermal stimuli. Simultaneous gavages of half of above mentioned doses

of *Cordia myxa* extract and mefenamic acid (ponstan) had significantly prolonged the reactive time to the thermal stimulus. This could be due to a synergistic action through a common mechanism of *Cordia myxa* extract and ponstan in producing analgesia and relieving pain by disrupting the chain of synthesis of prostaglandin. In formalin test, a combination of *Cordia myxa* extract at a dose of 300mg per kg bw and mefenamic acid (ponstan) at a dose of 50 mg per kg bw was given before the injection of diluted formalin solution, they were significantly showed antinociceptive effect at the early and late phases, which could be attributed to their inhibitory effect on the nociceptive system and inflammatory mediators [85].

#### *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- $\alpha$  (TNF- $\alpha$ ), IL-6, IL-1  $\beta$  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  $\beta$  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- $\alpha$  level in the CSHE-treated group as compared to control, but TNF-R1 expression on peritoneal macrophages was reduced [86].

The anti-inflammatory and analgesic effects of *Coriandrum sativum* seeds were evaluated in 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 [87].

The role of opiate system in the antinociceptive effects of *Coriandrum sativum* (CS) was studied in acute and chronic pain in mice using hot plate (HP), tail flick (TF) and formalin (FT) tests, and its effects were compared with dexamethasone (DEX) and stress (ST). CS (125, 250, 500 and 1000 mg/Kg IP), DEX (0.5, 1 and 2 mg/Kg IP), vehicle (VEH) or swim stress were used 30 min before the pain evaluation tests. Acute and chronic pain was assessed by HP, TF and FT

models. In addition, Naloxone (NAL, 2 mg/Kg, IP) was injected 15 min before the CS extract administration in order to assess the role of opiate system in the antinociception of CS. Results indicated that CS, DEX and ST have analgesic effects ( $p < 0.01$ ) in comparison with the control group and higher dose of CS was more effective ( $p < 0.001$ ). Pretreatment with NAL modulated the antinociceptive effects of CS in all models ( $p < 0.001$ ). The findings showed an interaction between antinociceptive effects of CS and opiate system [88].

The analgesic effects of the extract were assessed using hot plate method. Aqueous extract at 50, 100 and 200 mg/kg significantly produce analgesic activity compared to control group [89].

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 [90].

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- $\alpha$  level was estimated in serum. TNF-R1, IL-1  $\beta$  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- $\alpha$  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 [91].

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 [92].

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 zinzanoids*). 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 [93].

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<sub>2</sub> 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 [94].

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 [95].

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 anti-inflammatory effect compared to UV-control and unguentum leniens [96].

#### ***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 E<sub>2</sub>)-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 [97-98].

The analgesic and antipyretic activities of methanolic extract of *Cressa cretica* at different doses (100, 150 and 200 mg/kg) was studied using hot plate, acetic acid induced writhing and yeast induced hyperthermia methods. Methanolic extract of *Cressa cretica* showed significant analgesic and antipyretic activities at the dose of 200 mg/kg in all models studied [99].

#### ***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- $\alpha$  (inflammation marker), direct 8-iso-prostaglandin F<sub>2</sub> $\alpha$  (oxidative stress marker) and soluble protein-100  $\beta$  (S100 $\beta$ , 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 F<sub>2</sub> $\alpha$  and S100 $\beta$  levels [100-101].

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 [102].

#### ***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 carrageenan-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 carrageenan-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 [103].

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 [104].

#### ***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 [105-106].

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- $\kappa$ B) 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- $\kappa$ B and mitogen-activated protein kinases ERK and JNK signaling [107].

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 [108].

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 [109].

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<sub>50</sub> value derived from LB plots is 1.370  $\mu$ M [110].

#### ***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- $\alpha$  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- $\alpha$  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- $\kappa$ B), p38MAPK and Akt [111-112].

#### ***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 [113].

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 models 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 [114].

The analgesic and anti-pyretic activities of aqueous extract of *Cynodon dactylon* at different doses was studied using hot plate, acetic acid induced writhing and yeast induced hyperthermia in rats. *Cynodon dactylon* showed significant analgesic and anti-pyretic activities in all models studied [115].

The antipyretic effect of aqueous extract of *Cynodon dactylon* was studied in mice, it was found that at the dose of 600 mg/kg, the aqueous extract possessed significant decrease in rectal temperature of mice similar to that shown by paracetamol [115].

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 [116].

The effects of the aqueous extract prepared from the rhizomes of *Cynodon dactylon* was investigated on vascular endothelial growth factor (VEGF) expressions in human umbilical vein endothelial cells (HUVECs) and also on angiogenesis in carrageenan induced air-pouch model in rats. Oral administration of 400 mg/kg/day of the extract significantly increased angiogenesis ( $p < 0.05$ ) and markedly decreased neutrophil ( $p < 0.05$ ) and total leukocyte infiltration ( $p < 0.001$ ) into the granulation tissues. Moreover, the extract increased the expression of total VEGF in HUVECs at a concentration of (100  $\mu$ l/ml). Accordingly, the aqueous extract of *Cynodon dactylon* promotes angiogenesis probably through stimulating VEGF expression [117].

The ethanol extract of aerial parts of *Cynodon dactylon* significant reduced the number of writhes and stretches induced in mice by 1.2% acetic acid solution. It also potentiated analgesia induced by morphine and pethidine in mice [118].

### *Cyperus rotundus*

The alcoholic extract (70% alcohol) possessed anti-inflammatory activity against carrageenan induced oedema and against formaldehyde induced arthritis in albino rats [119].

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 [120].

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<sup>nd</sup> 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<sup>th</sup> 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<sup>th</sup> 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 [121].

Aqueous, ethyl acetate, methanol and TOF-enriched extracts of *Cyperus rotundus* (300, 150, and 50  $\mu$ g/ml) were evaluated for their analgesic and anti-inflammatory activities in 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 [122].

Tail flick method was used for the determination of analgesic activity. The temperature and duration were  $51 \pm 1^\circ\text{C}$  and 0, 1, 2, 3 and 4 hours respectively. *Cyperus rotundus* ethanolic extract 300 and 500mg/kg orally showed significant analgesic activity [123].

The ethanol extract of *Cyperus rotundus* showed significant analgesic properties as evidenced by

the significant reduction in the number of writhes and stretches induced in mice by 1.2% acetic acid solution. It also potentiated analgesia induced by morphine and pethidine in mice [124].

The antinociceptive activity of the extract of whole plant of *Cyperus rotundus* was investigated in thermal-induced (hot plate and tail immersion) and chemical-induced (formalin) nociception models in mice at three different doses (50, 100 and 200 mg/kg; po). Morphine sulphate (5 mg/kg, ip.) and diclofenac sodium (10 mg/kg, ip) were used as reference analgesic agents. In the hot-plate and tail-immersion tests, the extract significantly increased the latency period to the thermal stimuli at all the tested doses (50, 100 and 200 mg/kg) ( $p < 0.05$ ). The significant increase in latency was clear from the observations at 60 and 90 min. In formalin-induced paw licking test oral administration of extract of whole plant of *Cyperus rotundus* at 100 and 200 mg/kg doses decreased the licking of paw in early phase. All the tested doses (50, 100 and 200 mg/kg) significantly decreased the licking of paw in late phase of the test ( $p < 0.001$ ). The dose 200 mg/kg was most effective showing maximum percentage of inhibition of licking in both early (61.60%) and late phase (87.41%) [125].

The effect of *Cyperus rotundus* extract and its constituents was studied on the transient receptor potential vanilloid 1 channel (which was a nonselective cation channel that senses various noxious chemical and thermal stimuli, and involves in heat- and UV-induced skin aging). Ethylacetate and hexane fractions of the methanol extract were found to partially inhibit transient receptor potential vanilloid 1 channel activity, and at a concentration of 90  $\mu$ M, oleanolic acid, which was one of three constituents isolated from the ethylacetate fraction, inhibited this activity by  $61.4 \pm 8.0\%$ . The results highlight the potential therapeutic effects of *Cyperus rotundus* in the contexts of analgesia and UV-induced photo-aging [126].

The alcoholic extract of *Cyperus rotundus* showed significant ( $p < 0.001$ ) antipyretic activity against pyrexia induced in rats by the subcutaneous injection of suspension of dried Brewer's yeast in gum acacia in normal saline [127].

The alcoholic extract of *Cyperus rotundus* showed highly significant ( $p < 0.001$ ) antipyretic activity against pyrexia produced in albino rats by the subcutaneous injection of suspension of dried Brewer's yeast. However, a specific fraction obtained from the petroleum ether extract showed significant anti-pyretic effect similar to acetyl salicylic acid. The petroleum ether extract and essential oil of *Cyperus rotundus* possessed analgesic activity [128-129].

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 ( $p < 0.05$ ) [130].

Clinical studies with 2% aqueous extract of *Cyperus rotundus* showed anti-inflammatory activity in conjunctivitis in human [131].

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 [132].

A study was undertaken to investigate the effect of methanol extract of rhizomes of *Cyperus rotundus* on NO and  $O_2^-$  productions by murine macrophage cell line, RAW 264.7 cells. The methanolic extract of rhizomes of *Cyperus rotundus* inhibited NO production in a dose-dependent manner by RAW 264.7 cells stimulated with interferon-gamma plus lipopolysaccharide. The inhibition of NO production by the extract was due to the suppression of iNOS protein, as well as iNOS mRNA expression, determined by western and northern blotting analyses, respectively. In addition, the methanolic extract suppressed the production of  $O_2^-$  by phorbol ester-stimulated RAW 264.7 cells in dose- and time-dependent manners. Collectively, the results suggest that the methanolic extract of rhizomes of *Cyperus rotundus* could be developed as anti-inflammatory candidate for the treatment of inflammatory diseases mediated by overproduction of NO and  $O_2^-$  [133].

The n-hexane fraction of the 80% ethanoic extract from the rhizomes of *Cyperus rotundus* was found to inhibit both NO and PGE<sub>2</sub> production in RAW 264.7 cells.  $\alpha$ -Cyperone isolated from the n-hexane fraction significantly inhibited PGE<sub>2</sub> production by suppressing the LPS-induced expression of inducible COX-2 at both the mRNA and the protein levels. In contrast,  $\alpha$ -cyperone had little effect on NO production and iNOS expression. Additionally,  $\alpha$ -cyperone down regulated the production and mRNA expression of the inflammatory cytokine IL-6. Moreover, treatment with

$\alpha$ -cyperone suppressed the transcriptional activity of NF $\kappa$ B and the nuclear translocation of the p65 NF $\kappa$ B subunit in LPS-induced RAW 264.7 cells [134].

The role of heme oxygenase HO<sup>-1</sup> induction in anti-inflammatory effect of extract rhizomes of *Cyperus rotundus* was investigated. Induction of HO<sup>-1</sup> 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<sup>-1</sup> 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<sup>-1</sup> 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<sup>-1</sup> 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 [135].

#### CONCLUSION:

The paper reviewed the anti-inflammatory, antipyretic and analgesic effects of the medicinal plants to be utilize in medical applications as a result of effectiveness and safety.

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