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Arabian Medicinal Plants with Analgesic and Antipyretic Effects-Plant Based Review (Part 1)

Prof Dr Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, University of Thi qar, Iraq.
Corresponding Author: Prof Dr Ali Esmail Al-Sna

Abstract: Pain is an undesirable mental and emotional experience that is associated with damage of tissue. While, fever is a secondary impact of infection, tissue damage, inflammation, graft rejection, malignancy or other diseased states. The current review highlighted the medicinal plants possessed analgesic and antipyretic effects with special focus on their mode of action.

Keywords: Medicinal plants , Analgesic , Antipyretic, Pain, Fever, Mechanism

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I. INTRODUCTION

Pain is an undesirable mental and emotional experience that is associated with damage of tissue. It is mediated by many mediators (prostaglandins, cytokines, histamine, serotonin, substance P, capsaicin, and nitric oxide) an created by different reasons (harmful heat, stretch, electrical flow, necrosis, inflammation, laceration and spasm)[1-2]. Many medicinal plants possessed analgesic activities [3-4] by different mechanisms included: inhibiting release of acid arachidonic[5] inhibiting NO and COX synthesis [6], inhibition of activity of cyclooxigenase and subsequent inhibition of the synthesis of prostaglandins[7-9], potentiating of central nervous system endogenous opioid transmitters [10], GABA A receptors agonistic effect[11], Binding to pain receptors, affecting ligand-sensitive channels, decreasing sodium entrance and inhibiting releasing of many mediators [8, 12].

On the other hand, fever is a secondary impact of infection, tissue damage, inflammation, graft rejection, malignancy or other diseased states. The infected or damaged tissue initiates the enhanced formation of proinflammatory mediators (cytokines like interleukin 1β, α, β and TNF-α), which increase the synthesis of prostaglandin E2 near preoptic hypothalamus area and trigger the hypothalamus to elevate the body temperature[13]. Many medicinal plants possessed antipyretic activity via inhibition of prostaglandin production or inhibiting the production and/ or activity of proinflammatory mediators[14-16]. The current review was designed to highlight the medicinal plants with analgesic and antipyretic effects.

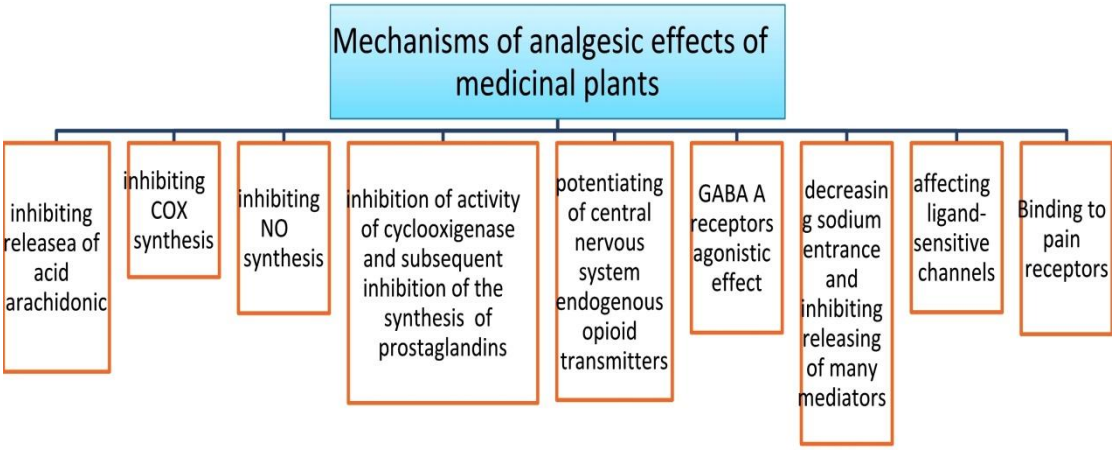

Fig 1: The mechanism of analgesic effects of medicinal plants

Althaea officinalis

Hypolaetin 8-glucoside has been tested for analgesic activity in rats. This flavonoid (30, 60 and 90 mg/kg ip) showed analgesic activity lower than the one of phenylbutazone**.** However, hypolaetin 8-glucoside was also more potent than flavonol, troxerutin (both at the doses of 100, 200, 300 and 400 mg/kg sc.)[17-18].

Adiantum capillus-veneris

The analgesic activity of the ethanolic extract of *Adiantum capillus-veneris* and its fraction was tested 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 [19-21].

Alhagi maurorum

The aqueous extract of *Alhagi maurorum* was evaluated in mice at doses of 125, 250 and 500µg/animal, for its analgesic effects. The analgesic effect of the aqueous extract of *Alhagi maurorum* at doses of 125, 250 and 500µg/animal and diclofenac sodium(1µg/animal. The extracts induced analgesic effects and the dose of 500µg/ animal, showed the most potent effect [22-23].

The antinociceptive effect of methanolic extracts (200 and 400 mg/ kg) of *Alhagi maurorum* was studied using acetic acid-induced writhing and tail-flick test in mice. Oral administration of methanolic extracts of *Alhagi maurorum* significantly inhibited the nociception to acetic acid-induced writhe even in low dose. In the tail-flick test, methanolic extracts of *Alhagi maurorum*in a dose of 400 mg/ kg produced significant increase in the latency to response of tail to thermal stimulation [24].

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 [25-26].

Allium cepa

Hot plate and formalin tests were used to study the analgesic effect of fresh onion juice (7.5 ml/kg) in mice during acute and chronic pain stages modeling. A significant analgesic property for fresh onion juice in both pain phases was recorded, the effect was similar to that of morphine (5 mg/kg). Fresh onion juice also decreased the hind paw thickness significantly. In the mean time, it also demonstrated better results than the standard treatment, diclofenac[27-28].

Alpinia galanga

A significant analgesic effect in formalin test was produced bytopical preparation containing methanolic extract of *Alpinia galanga* rhizome [29-30].

Ammannia baccifera

The ethanolic extract of the *Ammannia baccifera* (whole plant) at doses of 200, 400 and 600mg/kg ip produced an inhibition of 20.7%, 43.4% and 72.9%, respectively, of the abdominal writhes induced by acetic acid in mice. In the formalin test, the administration of 200,400 and 600mg/kg ip had no effects in the first phase (5 min) but produced a dose dependent analgesic effect on the second phase (1540 min) with inhibitions of the licking time of 27.3%, 47.7% and 57.4%, respectively [31-32].

The methanolic extract exhibited significant 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 [33].

Anethum graveolens

A 10% aqueous extract of the fruits and 5% aqueous solution of the essential oil had analgesic effects in mice pain induced by hot plate and acetic acid writhing models. The effect of the fruits (1.0 g/kg body weight) was comparable to 200 mg / Kg body weight of acetyl salicylic acid [43-35].

Arachis hypogaea

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 stilbenoids showed opioid recetor affinity . Combined use of this compound and analgesic agents resulted in lower amounts of the latter needed to block pain [36-37].

Asclepias curassavica

The analgesic (flick method on mice) and antipyretic (Brewer's yeast induced pyrexia in rats) effects of the alcoholic and aqueous extracts of the stem of the plant were studied. The aqueous and alcoholic extracts of stem of *Asclepias curassavica* showed significant anti-pyretic and analgesic activity[38-39].

Astragalus hamosus

The analgesic effects of chloroform, hexane, ethyl acetate and aqueous fractions were evaluated by the hot-plate method. The hydroalcoholic extract of *Astragalus hamosus* possessed significant anti-nociceptive effects on both animal models. The findings showed that the hydroalcoholic extract 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 [40-41].

Bidens tripartita

An aqueous infusion of aerial parts *Bidens tripartita* . was investigated analgesic effect.Infusion doses of 20ml/k bw exhibited significant analgesic properties in a hot-plate test and antipyretic properties in carrageenan-induced local hyperthermia in rats. The effects were dose-dependent [42-43].

Caesalpinia crista

The analgesic effect of the ethanolic seed extract of *Caesalpinia crista* was investigated by writhing reflexes and tail immersion method in mice. 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. On the other hand, *Caesalpinia crista* seed coat extracted by 95% ethanol was screened for analgesic activity using hot plate test and tail immersion method. It appeared that seed coat extract has the ability to increase the pain threshold of the animals, reduce the pain factor and induce analgesia [44-46].
The analgesic and antipyretic activity of *Caesalpinia crista* seed oil were determined in experimental animal model (hot plate and yeast-induced pyrexia) at a dose of 100, 200 and 400 mg/kg orally. Pyrexia and writhes were reduced significantly ($p < 0.05$) in *Caesalpinia crista* treated rats as compared to that of control [47-48].

Calendula officinalis

The analgesic effects of *Calendula officinalis* was evaluated in thermal pain threshold in male rats. *Calendula officinalis* extract significantly increased the tail flick latency compared to the control group ($P<0.05$), indicating that the extract reduced pain threshold [49-50].

Calotropis procera

The latex protein fraction administered intraperitoneally to male mice at doses of 12.5, 25 and 50 mg/kg showed a dose-dependent antinociceptive effect compared with the controls. Inhibition of the acetic acid induced abdominal constrictions was observed at doses of 12.5 mg/kg (67.9 %), 25 mg/kg (85 %) and 50 mg/kg (99.5 %) compared with controls. Latex protein at doses of 25 mg/kg (39.8 %; 42 %) and 50 mg/kg (66.6 %; 99.3 %) reduced the nociception produced by formalin in the 1st and 2nd phases, respectively, and this effect was not reversed by pretreatment with naloxone (1 mg/kg). In the hot plate test, an increase in the reaction time was observed only at 60 min after treatment with latex at doses of 25 mg/kg (79.5 %) and 50 mg/kg (76.9 %), compared with controls. Naloxone was unable to reverse this effect. The antinociceptive effects of protein fraction of the latex of *Calotropis procera* didn't depend of the opioid system [168]. A single oral dose of dry latex ranging (165 to 830 mg/kg bw) produced significant dose-dependent analgesic effect against acetic acid-induced writhing. The effect of a dose of 415 mg/kg was more pronounced than a 100 mg/kg oral dose of aspirin. Dry latex (830 mg/kg) produces marginal analgesia in a tail-flick model which was similar to that of aspirin [169]. The ethanol extract of *C. procera* produced significant reduction of yeast induced increase in body temperature. There was a significant increase in reaction time of the treated mice placed on hot plate confirming analgesic activity of the extract [170]. The ethanolic extract of the aerial parts also possessed antipyretic effect. Administration of yeast produced an increase in rectal temperature from 97.32 ± 0.19oF which reached to its maximum in 4 h (100.02 ± 0.27oF). Administration of dry latex (DL)-250 mg/kg and 500 mg/kg at 4 h produced a significant ($P <0.05$) decline in rectal temperature to 98.50 ± 0.29oF and 98.45 ± 0.60oF respectively. The antipyretic effect was compared with that of aspirin, which was found to be more potent and brought down the temperature to 96.9 ±0.38 oF ($P <0.001$) [51-52].

Canna indica

The effect of benzene and methanolextracts of various parts of C. indica on nociceptive response using writhing test and hot plate method in mice was examined. All the extracts of C. indica showed significant central and peripheral analgesic activity in hot plate method and acetic acid-induced writhing test, respectively, at the dose of 50 mg kg(-1) intraperitoneally. Methanolic extract of leaves of C. indica showed highest increase in reaction time in hot plate method while benzene extract of leaves of C. indica showed more inhibitory effect on writhing induced by acetic acid [53-54].

Capsicum annuum* and *Capsicum frutescens

Capsaicin reacts to transient receptor potential vanilloid 1 (TRPV1), previously known as the vanilloid receptor, which is mainly expressed in the sensory neurons. TRPV1 contained 838 amino acids and has a molecular weight of 95 kDa in both humans and rats, consisting of six transmembrane domains with a short pore-forming region between the fifth and sixth transmembrane domains. It was non-selective, ligand-operated cationic channel located primarily in the small fibers of nociceptive neurons. TRPV1 was also distributed in tissues of the brain, bladder, kidneys, intestines, liver, polymorphonuclear granulocytes, mast cells, keratinocytes, glial cells, and macrophages. It couples with a non-specific cation channel permeable to sodium and calcium ions, and is located in the plasma membrane and the endoplasmic reticulum where regulates intracellular calcium levels. Binding of capsaicin with TRPV1 increases intracellular calcium, triggering release of substance P and the calcium gene-related peptide (CGRP). Contact between capsaicin and sensory neurons produces pain, inflammation and a localized heat sensation. When applied locally to skin, it promotes an analgesic response due to desensitizing of the sensory neurons caused by substance P depletion [55-60]. Capsaicin and its analogues were used topically to treat chronic pain syndromes musculoskeletal pain, osteoarthritis, rheumatoid arthritis, post-herpetic neuralgia and diabetic neuropathy [61-63]. Topical application of capsaicin evokes burning pain, neurogenic inflammation (vasodilatation and plasma extravasation), and hyperalgesia to heat and mechanical stimuli [64-65]. The treated area becomes less sensitive to pain, after repeated applications, this effect made capsaicin a peripherally acting analgesic in chronic painful complains [66-67]. The sensory dysfunction after capsaicin application to the skin resulted from rapid degeneration of intracutaneous nerve fibers.The effect of intradermal injection of capsaicin on morphological changes in cutaneous nerve fibers that would account for its analgesic properties was studied by comparing cutaneous innervation in capsaicin-treated skin with psychophysical measures of sensation. At various times after capsaicin injection, nerve fibers were visualized immunohistochemically in skin biopsies and were quantified. In normal skin the epidermis is heavily innervated by nerve fibers immunoreactive for protein gene product (PGP) 9.5, whereas fibers immunoreactive for substance P (SP) and calcitonin gene-related peptide (CGRP) are typically associated with blood vessels. There was nearly complete degeneration of epidermal nerve fibers and the subepidermal neural plexus in capsaicin-treated skin, as indicated by the loss of immunoreactivity for PGP 9.5 and CGRP. The effect of capsaicin on dermal nerve fibers immunoreactive for SP was less obvious. Capsaicin decreased sensitivity to pain produced by sharp mechanical stimuli and nearly eliminated heat-evoked pain within the injected area. Limited reinnervation of the epidermis and partial return of sensation occurred 3 weeks after treatment; reinnervation of the epidermis was; 25% of normal, and sensation improved to 50–75% of normal [67-68].

Carum carvi

The analgesic effect of *Carum carvi* (CC) (100 and 500 mg/kg) was tested in acute and chronic pain in formalin test in mice. The results indicated that CC has analgesic effect in both doses in acute and chronic phases and the higher dose of the drug was more effective ($P<0.01$) [69].

Cassia occidentalis

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 [70-71].

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 [72-73].

Citrus medica

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 [74].

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 $1/4^{th}$. 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 [75-76].

Clerodendrum inerme

Clerodendrum inerme were investigated for analgesic effects at the dose 200 mg/kg body weight using acetic acid induced writhing methods. The extract produced significant ($P<0.01$) analgesic activity [77-78].
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 [79].

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 [80].

Clitoria ternatea

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 [81-82].

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 hole cross and open field test. The number of field crossed in open field test and hole crossed in hole cross test decreased as time approached [83]. 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 [84].

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 1st h of the study [85-86].

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 [87].

Cordia myxa

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 [88-89].

The analgesic activity 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 the most significant analgesic activity [90-92].

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 [93].

Coriandrum sativum

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 [94-95].

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 [96].

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 [97].

Cressa cretica

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 [98-99].

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 [100-101].

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 [102].

Cynodon dactylon

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 [103-104].

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. 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 [105].

Cyperus rotundus

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 [106-107].

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 [108].

Tail flick method was used for the determination of analgesic activity. The temperature and duration were 51 ± 1C° and 0, 1, 2, 3 and 4 hours respectively. *Cyperus routunds* ethanolic extract 300 and 500mg/kg orally showed significant analgesic activity [109].

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 [110].

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%) [111].

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 μM, 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 [112].

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 [113].

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 [114-115].

Dalbergia sissoo

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[116].

The alcoholic extract of *Dalbergia sissoo* seeds was evaluated for analgesic and antipyretic activities. The peripheral analgesic activity of seed extract (SSE) was studied using acetic acid-induced writhing in mice and by Randall-Selitto assay in rats. Furthermore, the central analgesic activity of SSE was studied by tail-clip test and hot plate method in mice. The antipyretic activity of SSE was studied in Brewer's yeast-induced pyrexia in rats. The alcoholic extract of *Dalbergia sissoo* seeds was significantly decreased writhing movements in mice by acetic acid-induced writhing test and significant increased in the pain threshold capacity in rats in Randall-Selitto assay and the reaction time in hot-plate test but not in tail-clip test. Moreover, it also showed significant antipyretic activity in Brewer's yeast-induced pyrexia in rats throughout the observation period of 6 h[117].

The analgesic activity of the ethanol extract of the bark of *D. sissoo* was investigated using the tail flick method in Wistar rats. The extract at the doses of 300, 500 and 1000 mg/kg was reported to possess significant and dose dependent, central analgesic activity, compared with the standard drug aspirin at the dose of 300 mg/kg. An ethanol extract of the leaves of *D. sissoo* showed both peripheral and central analgesic activity in a dose dependent manner. Peripheral analgesic activity was studied using the acetic acid-induced writhing reflex and Randall-Selitto assays in mice as well as central analgesic activity was studied using the hot-plate and tail-

clip tests in mice. In writhing test, the extract (100, 300 and 1000 mg/kg) moderately inhibited writhing in mice while aspirin (300 mg/kg) showed strong activity; in Randall-Selitto assay, the extract failed to increase pain threshold level at the doses of 100 and 300 mg/kg but exhibited significant (P<0.01) activity at the dose of 1000 mg/kg and comapared with the aspirin (300 mg/kg) which increased pain threshold throughout the observation period of 1 to 3 h; in hotplate test, the extract (1000 mg/kg) increased reaction time at 2 and 3 h while pathidine (5mg/kg) increased reaction time at 1 and 2 h; in tail-clip test, the extract failed to increase reaction time even at the higher dose of 1000 mg/kg.

The ethanol extract of the leaves of *D. sissoo* showed significant antipyretic activity in a Brewer's yeast-induced pyrexia assay in rats. The extract at the doses of 100 and 300 mg/kg showed significant antipyretic activity at 1 h after drug administration while at the 1000 mg/kg showed activity throughout the observation period up to 6 h and results were highly comparable with aspirin (300 mg/kg)[118-120].

The analgesic potential of the ethanolic bark extract of *Dalbergia sissoo* bark was measured by the Radiant Heat method (tail flick method). The bark extract showed significant analgesic activity as evidenced by the increase in reaction time to the pain stimulus. The extract 300 mg/ kg and 500 mg/kg failed to alter pain threshold capacity but increased significantly at the dose of 1000 mg/kg at 30 min[121].

The antinociceptive activity of ethanolic extract of the plant bark of *Dalbergia sissoo* (Roxb.) was investigated using tail flick method on Wistar rats. Three different dose levels (300, 500, and 1000 mg/kg) in 0.5% carboxyl methyl cellulose (CMC) were administered orally. At these doses, the extract exhibited significant and dose-dependent antinociceptive activity[122].

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 extrac[123-124].

Datisca cannabina

Ethanolic (50%) extract of seeds and flowers exhibited marked sedative, mild analgesic and antipyretic activity in rats[125].

Datura fastuosa

The aqueous extracts of *Datura fastuosa* leaves and seeds were evaluated for the analgesic effect on acetic acid-induced writhing and hot plate reaction in mice. The results revealed that *D. fastuosa* leaves and seeds extracts at doses of 400 and 800 mg/kg orally induced analgesic effects. The analgesic activity of leaf extract is reduced by naloxone but not that of seed extract[126-127].

Datura stramonium

The analgesic effect of alcoholic *Datura stramonium* seed extract was evaluated in acute and chronic pain using hot plate and formalin tests. The extract when intraperitonealy administered to the animals, they alleviated the pain dose dependently, and ED_{50} was equal to 25 and 50 mg/kg in hot plate and formalin tests, respectively[128].

Daucus carota

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[129].

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[130-131].

Desmostachya bipinnata

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 ($P<0.05$)[132].

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[133-134].

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, 1st hour, $p = 0.031$). However, a reliable analgesic effect was recorded with the using of 2 g/kg bw of the extract on the 2nd and 3rd 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 ($p = 0.024$, $p = 0.029$, $p = 0.021$)[135-136].

Echium italicum

The analgesic effect of the ethanol extracts from the roots and herbs of *E. italicum* L. E. vulgare L was investigated in mice using acetic acid-induced writhing and tail flick methods. The analgesic effect of root extracts of E. italicum (0.5 mg/g) was comparable with the standard drugs, Aspirin and Morphine. The findings imply the involvement of both peripheral and central antinociceptive mechanisms[137-138].

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[139-140].

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[141-142].

Eucalyptus camaldulentis

1,8-cineole (cineole) and beta-pinene, two monoterpenes isolated from the essential oil obtained from *Eucalyptus camaldulensis* leaves were tested for antinociceptive properties. Tail-flick and hot-plate methods, reflecting the spinal and supraspinal levels, respectively, were used in mice and/or rats using morphine and naloxone for comparison. Cineole exhibited an antinociceptive activity comparable to that of morphine, in

both algesic stimuli. A significant synergism between cineole and morphine was observed, but naloxone failed to antagonize the effect of cineole. Beta-pinene exerted supraspinal antinociceptive actions in rats only and it reversed the antinociceptive effect of morphine in a degree equivalent to naloxone, probably acting as a partial agonist through the mu opioid receptors[143-144].
Eucalyptus camaldulentis possessed an anti-nociceptive effect against both acetic acid-induced writhing and hot plate-induced thermal stimulation in mice[145].

Foeniculum vulgare

The analgesic and anti-inflammatory action of the ethanolic extracts *Foeniculum vulgare* (50,100 and 200mgm/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. 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[146].

The effects of *Foeniculum vulgare* extract in reduction of pain and other systemic symptoms accompanying primary dysmenorrhea were studied using double-blind clinical trial carried out on female students [90 (46 cases and 44 controls)] at Shahid Beheshti University, Iran. Five capsules containing 46 mg of *Foeniculum vulgare* and identical placebos were provided to be taken daily by the case and control groups respectively, during the first three days following the onset of dysmenorrheal pain whenever they needed the medications. The severity of pain in the treated group with *Foeniculum vulgare* extract, showed a significant difference ($p<0.001$) in comparison with the placebo group, in addition to significant differences in systemic symptoms [147]. The antinociceptive activities of some components of *Foeniculum vulgare* (alpha-pinene, limonene, fenchone, trans-anethol and alpha-copaene) were investigated for analgesic effects in mice using tail-flick tests. The drugs were injected intraperitoneally in doses of 0.05, 0.1 and 0.2 ml/kg. Alpha-pinene and fenchone caused significant reduction in the nociceptive threshold in the tail-flick test, while, other tested compounds showed no significant analgesic effects[148].

The methanolic extract of the aerial parts of *Foeniculum vulgare* subsp. *piperitum* exhibited the highest antinociceptive activity at a dose level of 2000 mg/kg, while the activity exhibited by the ethyl acetate extract was at (800 mg/kg). On the other hand, *n*-hexane extract (700 mg/kg) and methylene chloride extract (500 mg/kg) exhibited similar antinociceptive activities, being less than that of acetylsalicylic acid (200 mg/kg). The results also revealed that the extracts under investigation exhibited significant anti-inflammatory activity. The methanolic extract possessed the highest activity, where it significantly decreased the weight of edema induced by carrageenan in the rat paw at dose levels of 1500 and 2000 mg/kg, it exerted a protective effect of 28 and 47%, respectively, compared to the control value, while ibuprofen (35 mg/kg), used as a reference drug, exhibited a protective effect of 52.23 %[149].

Crude ethanolic extracts of *Foeniculum vulgare* seeds was investigated for antinociceptive activity. Results showed that the dosage of 298 mg/Kg, compared to the indomethacin pattern, led to a significant reduction in the number of abdominal writhings in the animals[150].

The hot plate method was used to determine the analgesic activity of the plant . *Foeniculum vulgare* ethanolic fruit extract (500 mg/kg, orally) showed a moderate analgesic activity that was significant after 90 ($p<0.5$) and 150 ($P<0.0l$) min of its administration. The observed analgesia was of higher magnitude at 150min than after 90min. The ethanolic fruit extract similarly showed an antipyretic activity that was evident at 30 and 90 rnin ($P<0.0l$) but not at 150min[151].

Fumaria officinalis

The analgesic effects of ethanol extract of arial parts of *Fumaria officinalis* were investigated using different models. The result of the effect of *Fumaria officinalis* extract on hot plate induced pain in mice showed that the extract 200 and 500 mg/kg significantly ($p < 0.001$, $p < 0.0001$ respectively) increased the post drug PRT. The tail withdrawal response or tail flick time was significantly ($p < 0.0001$) increased from 3.583±0.2386 seconds in the control group (10ml/ kg normal saline) to 13.75±0.2141seconds in the diclofenac sodium 10 mg/ kg and 12.42±0.2386 seconds in the highest dose of the extract (500 mg/kg). The percentage inhibition of writhing was also dose dependently increased from zero in the control group (normal saline) to 33% in the group that received 500mg/ kg of the extract. In acetic acid induced writhing method, there was significant analgesic effects produced by were given 200mg/ kg and those treated with the reference drug diclofenac 500 mg/ kg of extract[152-153].

Fumaria parviflora

The antipyretic activity of *Fumaria parviflora* was studied in rabbits. Pyresis was induced by subcutaneous yeast injections. Significant oral antipyretic activity in rabbits was exhibited by hexane-,

chloroform- and water-soluble extracts of *Fumaria parviflora* comparable with aspirin. The antipyretic activity was more prominent in the hexane-soluble extract [154-155].
The antinociceptive effects of the methanolic extract of *Fumaria parviflora* were evaluated in mice subjected to acute thermal [hot-plate] and persistent chemical [formalin] pain stimuli. Intra-peritoneal injection of the percolated extract evoked significant antinociceptive effects at a dose of 100 mg/kg in the second phase of formalin test. The maximum antinociceptive effect was induced by the dose of 300 mg/kg that was significant in both phases of formalin test. The results showed that only percolated extract had significant antinociceptive effect in hot-plate. Pretreatment of mice with naloxane, an opioid antagonist did not change antinociceptive effect of percolated extract in formalin test, but in hot-plate it increased extract's effect after the first 15 minutes [156].

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[157].

Hedera helix

The methanolic extract of the whole plant was partitioned with hexane, chloroform and ethyl acetate. The analgesic activity of the crude extract and subsequent solvent fractions of *H. helix* was carried in NMRI mice. In acetic acid induced writhing test, the crude extract provoked 33.33 and 55.90% pain reduction at 50 and 100 mg/kg ip respectively. When fractionated, the hexane fraction of plant did not produce significant reversal of induced pain. The chloroform fraction of the plant exhibited prominent pain inhibition: 48.71 and 65.70% at 50 and 100 mg/kg ip respectively. For ethyl acetate fraction, significant activity was observed with 40.76 and 59.76% at 50 and 100 mg/kg ip respectively, while, aqueous fraction elicited most profound effect 50.77 and 70.71% blockade of noxious stimulation at 50 and 100 mg/kg ip respectively[158].

Helianthus annuus

The analgesic effects of the ethanol extract of leaves of *Helianthus annus* (0.5 g/kg, 2 g/kg and 4 g/k) were investigated in rats. Treatment with the extract was 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[159-160].

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[161].

Hibiscus rosa-sinensis

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[162].

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[163].

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[164].

Hibiscus sabdariffa

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[165].

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 ($P<0.01$)[166].

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[167].

***Hyoscyamus* Species**

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[168-169].

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[170].

The analgesic effect of *Hyoscyamus niger* seeds alcoholic extract (500, 1000 and 2000 mg/kg bw, ip) was studied in acute and chronic pain in rats. The results revealed that injection of *Hyoscyamus niger* seeds alcoholic extract reduced the acute and chronic pain induced by formalin significantly ($P<0.001$) and significantly increased chronic pain threshold[171].

The antinociceptive effect of the metanolic extract of *Hyoscyamus reticulatus* was investigated in mice. Two models were used to study the effects of the extracts on nociception, acetic acid-induced writhing test and hot plate test in mice. The metanolic extract (50 mg/kg) possessed significant ($p<0.05$) analgesic activity comparable with diclophenac sodium, evidenced by increase in the reaction time by hot plate method and significant ($p<0.05$) reduction in acetic acid - induced writhings in mice with a maximum effect of 35.56 % reduction[172].

Hypericum triquetrifolium

The antinociceptive activity of *Hypericum triquetrifolium* lyophilized extract was investigated in mice. Formalin paw test and tail flick tests were used for the evaluation of the antinociceptive activity. The extract caused a significant dose-related inhibition of the first phase (50, 60 mg/kg, ip) and second phase (10, 25, 50 and 60 mg/kg, ip) of formalin induced hindpaw licking. Additionally, the extract administration (50, 60 mg/kg, ip) increased the tail flick latencies. No significant change was observed in any of the treatment groups in the sensorimotor performance test[173-174].

Inula graveolens

The antipyretic activities of the methanolic extract of *Inula graveolense* were examined in rats. The methanolic extract (400 mg/kg) showed a significant ($P < 0.01$) dose dependent anti- pyretic effect in yeast induced elevation of body temperature in rats. 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[175-176].

Jasminum sambac

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[177].

The analgesic activity of methanolic extract of root of Jasminum sambac (200 and 400 mg/kg) was evaluated in Wister albino rats and mice of using tail flick and acetic acid induced writhing method respectively. The results showed that the methanolic extract of Jasmine root possessed significant analgesic activity by both models, with a maximum effect for 400 mg/kg bw. The authors suggested central as well as peripheral mechanism of analgesic action[178].

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[179-180].

Juglans regia

The nociceptive effect of alcohol extract of juglans regia leave (0.5, 1 and 1.5 mg/kg) alone and in combination with morphine was tested in rats. Alcohol extract of walnut leave in dose of 1.5 mg/kg caused a significant nociception decrease in acute phase of formalin test and this effect was dose dependent. Moreover, rats received a combination of morphine and alcohol extract showed more nociception especially in acute phase of formalin test, in comparison to the groups that received each separately [181].

Juniperus communis

Methanolic extract of *J communis* (100mg/kg and 200mg/kg) was tested for analgesic activity by different tests like formalin test, acetic acid induced writhing, and tail flick tests. The extract showed significant (P < 0.01) and dose dependent analgesic activity. The blocking effect of naloxone (2mg/kg ip) to the analgesic activity of the extract of *J communis* confirmed the central analgesic activity[182-183].

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. Pretreatment with *Juniperus oxycedrus* extracts showed an analgesic effect on chemical stimulus test, they significantly reduced (P<0.001) the percentage of writhing movements induced by the intraperitoneal administration of 0.25 ml of **a** solution of 3% acetic acid. Methanol extract showed 63.6% inhibition, F1: 53.2%; F2: 80.2'%; F3: 41.3% and dichloromethanol extract: 40%. With the using of mechanical stimulus, pretreatment with methanol extract (200 mg/kg) possessed significant effects on mechanical pressure at 30 (p<0.001) and 60 min. (P<0.01). increasing the weight causing pain in 85 and 47% respectively. However, dichloroinethanol extract (200 mg/kg) did not show any activity on mechanical analgesia. In thermal mode**,** mice pretreated with methanol extract presented a significant (P<0.0.5) increase in the response time in both the jump (54%) and escape (42%) parameter evaluated in the hot plate test. Dichloromethanol (200 mg/ kg) extract gave no significant variation in the parameters evaluated in this test. Pretreatment with methanol and dichloromethanol extracts at a dose of 200 mg/kg induced a significant antiinflammatory throughout the 24 hr experimental period. Both extracts showed significant activity after I , 2. 3 and 24 hr[184-185].

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[186].

***Kochia scoparia* (*Bassia scoparia*)**

The 70% ethanol extract (KS-ext) from Kochiae Fructus at an oral administration of 500 mg/kg had an antinociceptive effect on writhing responses induced by acetic acid, but, it was ineffective in nociceptive response in the hot plate test. Oleanolic acid oligoglycoside, momordin Ic isolated from Kochiae Fructus significantly decreased the frequency of licking behavior within a unit of time at the late phase without affecting that of the early phase in the formalin test. KS-ext also inhibited the rise of vascular permeability induced by acetic acid, the increase of paw edema induced by carrageenin, histamine, serotonin or bradykinin and ear

swelling induced by arachidonic acid. Momordin Ic also possessed an inhibitory effect on carrageenin-induced edema[187-188].

II. CONCLUSION

The current review highlighted the medicinal plants possessed analgesic and antipyretic effects with special focus on their mode of action, as promising future drugs because of their safety and effectiveness.

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