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REVIEW ARTICLE

A Review on Analgesic: From Natural Sources.

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ABSTRACT

Analgesics are the painkiller substances, which act by the absence of pain without losing consciousness. The word *analgesic* derives from Greek *an-* ("without") and *algos* ("pain"). Analgesic drugs act in various ways on the peripheral and central nervous systems. There are various sources of analgesic drugs, some synthetic drugs like- Peracetamol, cox2 inhibitor, NSAIDs, Ibuprofen, diclofenac etc. Medicinal plants also the rich source of analgesics like as- *Opoid analgesics, Aloevera Barbedensis, Andrographis Paniculata, Elettaria cardamomum, Punica granatum, Eugenia caryophyllus , mimosa, Curcuma alismatifolia, Phoenix sylvestris, Stachys schtscheglee, Cissus quadrangularis, menthol , Bunts longifolia, Buxus sempervirens, Burns sempervirens, Fumaira vaillantii, Rumex crispus, Urtica dioica, Morinda Citrifolia etc.* This review gives an idea for analgesics which obtained from different natural sources.

Key Words: Natural Analgesics, *Aloevera Barbedensis, Elettaria cardamomum, Menthol.*

INTRODUCTION

Pain & Pain Management: Pain can be defined as a somatic sensation of acute discomfort, a symptom of some physical hurt or disorder, or even emotional distress. Pain is a crucial aspect of the body's defense mechanisms & it is a part of a rapid warning relay instruction the motor neurons of the central nervous system to minimize physical harm. [1]

Pain can be classified into two types: a) Acute pain b) Chronic pain

a) Acute pain: Acute pain "is the body's warning of present damage to tissue or disease. It is often fast and sharp followed by aching pain**.** It is short-term pain or pain with easily identifiable causes.

b) Chronic Pain: Chronic pain is pain that last much longer than pain normally would with a particular injury. Chronic pain can be constant or intermittent and is generally harder to treat than acute pain. Pain can also be grouped by its source and related pain detecting neurons such as cutaneous pain, somatic pain, visceral pain, and neuropathic pain.

Causes of pain:

- Pain is caused by the stimulation of pain receptors which are free nerve endings.
- Nocireceptors are pain receptors that are located outside the spinal column in the dorsal root ganglion and are named based upon their appearance at their sensory ends. These sensory endings look like the branches of small bushes.
- The perception of pain is when these receptors are stimulated and they transmit signal to the central nervous system via sensory neurons in the spinal cord.

Analgesics:

Analgesia: Analgesia simply means the absence of pain without losing consciousness.

Mechanism of action of Analgesics: The analgesia system is mediated by 3 major components:

- The periaquaductal grey matter (in the midbrain)
- The nucleus raphe magnus (in the medulla)
- The pain inhibitory neurons within the dorsal horns of the spinal cord, which act to inhibit pain-transmitting neurons also located in the spinal dorsal horn.

2. Sources of Analgesic Drugs: There are various sources of analgesic drugs; they are classified into following two types: **a) Synthetic Drugs b) Natural sources**

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I) Synthetic Drugs: There are various synthetic drugs available in market which gives analgesic activity like Peracetamol, Ibuprofen, COX-2 inhibitors, NSAIDs, diclofenac etc.

II) Analgesics from Natural Sources: There are various medicinal plants available in nature which shows analgesic activity, these are as follow**:**

(A) Opoid Analgesics: Opioids are drugs derived from Opium.Opium are derived from the juice of the opium poppy, *Papaver somniferum.* Opioids are any medication which bind to opioid receptors in the central nervous system & used as analgesic activity. Opioids are used in medicine as strong analgesics, for relief of severe or chronic pain. These are classified into following types:

- Endogenous opioid peptides (produced in the body: endorphins, dynorphins, enkephalins)
- Opium alkaloids (morphine, codeine, thebaine)
- Semi-synthetic opioids (heroin, oxycodone, hydrocodone, dihydrocodeine, hydromorphone, oxymorphone, nicomorphine)
- Fully synthetic opioids (pethidine or Demerol, methadone, fentanyl, propoxyphene, pentazocine, buprenorphine, butorphanol, tramadol, etc.) [2]

(B) Other medicinal plants:

***Aloevera Barbedensis*:** Aloe Vera is used as gel is its pain healing or analgesic effect. The Aloe Vera gel is used in reducing pain during dental treatments. It can be effectively used in treatment of mouth ulcers, sores, blisters. It provides quick relief of pain after dental surgical procedures. Aloe Vera is also used for pain healing purposes in the treatment of piles and Hemorrhoids**.** [3]

***Andrographis Peniculata*:** Andrographis paniculata (AP), a popular medicine, is commonly used for treating infection, inflammation, fever, analgesic and diarrhoea. In this study, extracts prepared their active constituent andrographolide were evaluated for antioxidant, antioedema and analgesic activities. At a dosage of 100 mg/kg, AP-H(2)O and andrographolide, but not AP-EtOH, showed antioedema and analgesic activities.[4]

***Bunts longifolia* (Aerial)**: The results, with regard to the analgesic activity of the ethanolic extract showed a highly significant (P<0.01) effects at all the three doses tested in mouse tail immersion method. The potency of the effects was increased with the increase Screening of s 32 ome Turkish medicinal plants in dose of the drug i.e., dose-dependent manner. The analgesic effects of this plant extract were quite comparable or even better at the doses of 500 and 100 mg/kg than acetylsalicylic acid (standard drug) in terms of Analgesia TFLD. The onset and duration of action is much better than standard drug. [5]

***Burns sempervirens* (Roots):** In this study ethanolic extract of the roots of *Buxus sempervirens,* was when studied for its analgesic activity in intact mouse tail immersion method, showed highly significant analgesic effects in dose-dependent manner. Even though the drug has a quick onset of action but has less potent analgesic effects, even at 1000 mg/kg dose level, when compared with that of standard drug in this study. [5]

***Buxus sempervirens* (Aerial):** The extract of aerial parts of *Bums sempervirens* showed varying degree of analgesic effects in this study. The analgesic effects at 300 rng/kg dose were less potent, while at 500 and 1000 mg/kg doses the extract was moderately significant. [5]

Cissampelos pareira: 50% ethanolic extract of the aerial part of *Cissampelos pareira* Linn. var. Hirsuta (*Menispermaceae*) was tested for anti-inflammatory and analgesic activity (abdominal writhes and hot plate) in rats and mice, respectively. Oral administration of extract exhibited significant and dose dependent anti-inflammatory activity in the carrageenin test, which was based on interference with prostaglandin synthesis, as confirmed by the arachidonic acid test. In the abdominal writhing test induced by acetic acid, higher dose of the plant extract had the highest analgesic activity, whereas in the hot-plate test the best dose was 100 mg/kg ($P < 0.05$). The LD50 showed that *Cissampelos pareira* (2000 mg/kg) presented low toxicity. [6]

Cissus quadrangularis: This study was intended to evaluate the analgesic anti-inflammatory and antipyretic activity of ethanolic extract of *Cissus quadrangularis* in experimental standard modals i.e. albino rats following oral administration. On the analgesic property acetic acid induce writhing was significantly reduce in the formalin test; the extract also significantly decreases the painful stimulus in both phases of test which confirms central and peripheral effects of the drugs. [7]

Curcuma alismatifolia: The antioxidant and analgesic potential of the 80% methanol extract of the leaves of *Curcuma alismatifolia* was evaluated. The analgesic activity was evaluated for its central and peripheral pharmacological actions using tail immersion method and acetic

acid-induced writhing test in mice respectively. The extract, at the dose of 250 and 500 mg/kg, produced a significant ($p < 0.05$-0.001) increase in pain threshold in tail immersion methods in a dose dependent manner. In acetic acid-induced writhing test the extract, at a dose of 500 mg/kg, showed a maximum of 60.5% inhibition ($p < 0.001$) of writhing reaction compared to the reference drug diclofenac-sodium (75.0%). [8]

Dalbergia sissoo: The peripheral analgesic activity of Dalbergia sissoo leaves (SLE; 100, 300 and 1000 mg/kg) was studied using acetic acid-induced writhing in mice and by Randall-Selitto assay. The central analgesic activity of SLE was studied using hot-plate method and tail-clip test in mice. The antipyretic activity of SLE was studied in Brewer's yeast-induced pyrexia in rats. SLE significantly decreased the writhing movements in mice in acetic acid-induced writhing test. SLE (1000 mg/kg) significantly increased the pain threshold capacity in rats in Randall-Selitto assay and the reaction time in hot-plate test but not in tail-clip test. It also showed significant antipyretic activity in Brewer's yeast-induced pyrexia in rats throughout the observation period of 6 h. [9]

Daphne retusa: *Daphne retusa* Hemsl, belongs to the genus *Daphne*, a member of Thymelaeaceae family. The barks and stems of *Daphne retusa* are used as a folkloric medicine 'Zhu Shi Ma' in Western China because of its effects of detumescence and acesodyne. In this paper investigate the anti-inflammatory and analgesic effects of the 75% ethanol extract of the stems and barks of *Daphne retusa* and different fractions partitioned with petroleum ether, methylene chloride, ethyl acetate and *n*-butanol, respectively. The acetic acid-induced writhing test and hot-plate test as models for evaluating the centrally and peripherally analgesic activity. The results showed the plant has significant anti-inflammatory and analgesic effects ($P < 0.05$–0.01). Meanwhile, the result of the acute toxicity test at which the MTD was above 5 g/kg indicates that the plant extract is relatively safe in, and/or non-toxic to, mice. The findings of these experimental animal studies indicate that the *Daphne retusa* ethanol extract possesses anti-inflammatory and analgesic properties. [10]

Elettaria cardamonuum: An investigation of the analgesic activity of the oil extracted from commercial *Elettaria cardamomum* seeds using p-benzoquinone as a chemical stimulus proved that a dose of 233microL/kg of the oil produced 50% protection against the writhing (stretching syndrome) induced by intraperitoneal administration of a 0.02% solution of p-benzoquinone in mice [3]

Fragaria vesca: In this study to compare the analgesic activities of ethanolic extract of fruits and whole plant of *Fragaria vesca* in experimental animal models. The extracts were prepared by percolation method and oral toxicity testing was performed as per OECD guidelines. Analgesic activity was assessed by tail flick method (for central action) and acetic acid-induced writhing test (for peripheral action). Fruit extract, whole plant extract and aspirin showed significant analgesic activity, both central and peripheral, as compared to control ($p< 0.01$). Although fruit extract at dose of 500 mg/kg showed better activity than 250 mg/kg ($p<0.05$). Analgesic activities of fruit extract 250 mg/kg and whole plant extract 500 mg/kg were almost equivalent while aspirin was most potent among all with significantly greater activities as compared to all the extracts ($p<0.05$).[11]

***Fumaira vaillantii* (Aerial)**: *Fumaria vaillamii* is another very promising Turkish medicinal plant which showed highly significant analgesic effects in this study. Again the results were in dose-dependent manner. The extract of this plant was found to be better than the standard drug, as at higher doses the extract has a rapid onset of action and longer duration of action, the two factors which determine the efficacy of a drug Thus, the plant has good biological value, as far as the analgesic activity is concerned. [5]

Jasminum amplexicaule: *Jasminum amplexicaule* Buch.-Ham. (Oleaceae) has been commonly used in the traditional medicine in dysentery, diarrhoea and bellyache in China. In the present work, the methanol extract of *Jasminum amplexicaule* and different fractions of this extractwere studied for anti-diarrhoea and analgesic activities. The anti-diarrhoea activities were investigated using castor oil-induced, magnesium sulphate-induced diarrhoea models, antienteropooling assay and gastrointestinal motility models in mice. The analgesic activities were studied using hot-plate, writhing and formalin models in mice. At the doses of 100, 200 and 400 mg/kg, the methanol extract (ME) showed significant and dose-dependent anti-diarrhoea and analgesic activity in these models. The chloroform fraction (CHF), ethyl acetate fraction (EAF) and the residual methanol fraction (RMF) exhibited similar activity using a dose of 200 mg/kg in these models. The pharmacological activities of the *n*-

butanol fraction (BUF) were lesser than the ME extract and other fractions. These results may support the fact that this plant is traditionally used to cure diarrhoea and pain. [12]

Lactuca scariola* & *Artemisia absinthium: Seeds and samples of stems from the two medicinal plants, Lactuca scariola and Artemisia absinthium respectively were extracted in absolute methanol to determine their analgesic and anti-inflammatory activity. The analgesic activity was assessed on intact mice by tail flick latency in tail immersion method. The anti-inflammatory activity was estimated volumetrically by measuring the mean increase in hind paw volume of rat with the help of plethysmometer. Acetylsalicylic acid in the dose of 300 mg/kg is used as standard drug. Both plant extracts were given in the doses of 300, 500 and 1000 mg/kg. Control group received 0.9% NaCI (saline) solution. All the doses administered orally. Results showed that Lactuca had potent analgesic activity and Artemisia had significant analgesic and anti-inflammatory activity**.** [13]

Landolphia owariensis: The aqueous, methanol and chloroform extracts of Landolphia owariensis leaves (AELO, MELO & CELO respectively) was investigated for anti-inflammatory and analgesic activities. All the extracts (100mg/kg each) were found to significantly (P<0.05) Inhibit paw edema induced by carrageenan in rats and the nociception induced by Tail immersion in hot water (50.0 ± 1.00C) and acetic acid. The methanol extract produced the highest paw edema inhibition while in thermally induced nociception both the MELO and CELO show high and comparable analgesic activity with acetylsalicylic acid (150mg/kg). However in chemically induced pain (acetic acid) MELO produced the highest and comparable analgesic activity to acetylsalicylic acid (150mg/kg). We therefore conclude, that apart from the folklore uses of L. Owariensis leaves as antimalarial agents, the various extracts of the plant also possess anti-inflammatory and analgesic activities. Phytochemical analysis showed that the methanollic extract of L. Owerensis contain some secondary metabolites namely: alkaloids and some polyphenolic compounds. Also, this extract exhibits some antioxidative activities**.**

Ligularia fischeri: The ethanol extract (LF) of *Ligularia fischeri* var. *spiciformis* (leaf) has been evaluated for antinociceptive and anti-inflammatory activities in mice. Analgesic and anti-inflammatory activitieswere studied by measuring nociception induced by formalin, acetic acid and hot-plate, and inflammation induced by carrageenan, formalin, and marachidonic acid. The acute treatment of mice with LF at doses of 100 and 200 mg/kg, by oral administration, produced a significant antinociceptive effect in the acetic acid-induced writhing, formalin-induced pain licking and hot-plate-induced pain. Also, the LF significantly inhibited both carrageenan- and formalininduced inflammation as well as arachidonic acid-induced ear edema in mice. These inhibitions were statistically significant ($P < 0.05$). Thus, our investigation suggests a potential benefit of *Ligularia fischeri* in treating conditions associated with inflammatory pain.[15]

Menthol: Menthol, after topical application, causes a feeling of coolness due to stimulation of 'cold' receptors by inhibiting Ca++ currents of neuronal membranes. Since Ca++ channel blockers are endowed with analgesic properties, the aim of the present study was to investigate the potential antinociceptive effect of menthol. [16]

***Mimosa pudica*:** *Mimosa pudica* L. is a creeping annual or perennial herb. It has been identified as Lajjalu in Ayurveda and has been found to have antiasthmatic, aphrodisiac, analgesic and antidepressant. In the present study the active phytocomponents of *Mimosa pudica* were revealed using phytochemical analysis. [3]

Morinda Citrifolia: In this study, the team lead by French scientist Chafique Younos, tested the analgesic and sedative effects of extracts from the Morinda Citrifolia plant. They were aware of the traditional use of the plant as a general analgesic, and set out to determine. [17]

Phoenix sylvestris: The analgesic activity of the methanol extract of *Phoenix sylvestris* root on Swiss *albino* mice was observed. The extract showed significant ($p<0.001$) analgesic activity by reduction of percent inhibition of writhing induced by acetic acid (0.5% v/v) in 20.07% and 32.57% at a dose level of 150 mg/kg and 300-mg/kg body weights respectively. [18]

Pterocephalus hookeri: This study evaluates the anti-inflammatory and analgesic activities of the ethanol and aqueous extracts of a Tibetan herb *Pterocephalus hookeri* (C.B. Clarke) Höeck to provide experimental evidence for its traditional use such as cold, flu and rheumatism. [19]

Punica granatum (Flower): The extract of flower of *punica granatum* is used for analgesic activity by Hot plate Method**.** The various extract of *punica granatum* of flower shows significant analgesic activity at the dose of 50mg/kg**.** The maximum analgesic activity is shown was at 60

min. after administration of drug, which was equivalent to standard drug morphine sulphate**.** [20]

***Rumex crispus* (Aerial):** The analgesic effects of ethanolic extract of aerial parts of Rumex crispus and acetylsalicylic acid (as standard drug) are summarized in Table 2. The plant extract showed highly significant analgesic activity at all the three doses tested 300, 500 and 1000 mg/kg. The extract showed a rapid onset of analgesic effect as compared to that of standard drug but the analgesic activity remained less potent when compared with standard drug throughout the whole study. [5]

Stachys schtscheglee: Extracts of the flowering aerial parts of *Stachys schtschegleevii* Sosn. and *S. balansae* Boiss. And Kotschy ex Boiss have been used in Iranian folk medicine as remedy for rheumatic and other anti-inflammatory and analgesic effects of some species of *Stachys* e.g. *Stachys inflata* have been reported.[21]

Termitomyces albuminosus: The objectives of this study were to investigate the analgesic and anti-inflammatory effects of the dry matter of culture broth (DMCB) of *Termitomyces albuminosus* in submerged culture and its crude saponin extract (CSE) and crude polysaccharide extract (CPE). The analgesic effects of DMCB, CSE and CPE were evaluated with models of acetic acid-induced writhing response and formalin test in mouse. The anti-inflammatory effects of DMCB, CSE and CPE were evaluated by using models of xylene-induced mouse ear swelling and carrageen-induced mouse paw edema. [22]

***Urtica dioica* (Aerial)**: The extract of the aerial parts *of Urtica dioica* showed significant analgesic effects only at the dose level of 1000 mg/kg, otherwise the extract failed to exhibit any analgesic activity at any other dose level. [5]

Vicoa indica: In this study to evaluate the anti-inflammatory,analgesic property of the 4',5,6-trihydroxy-3',7-dimethoxyflavone from *Vicoa indica DC* using different agents and models. Antiinflammatory effects were produced by different inflammatory agents and after 4 hours the hind paw of the animals were sacrified and weighed in a torsion balance. Analgesic effects were assessed by using different models and by acetic acid. In the former the analgesic effect was noted for a stipulated period of time and in the latter the writhings was counted for 15 minutes.The drug 4',5,6-trihydroxy-3',7-dimethoxyflavone at 50 mg/kg body weight was very effective in producing inhibition in both antiinflammatory-analgesic models.[23]

CONCLUSION

Analgesic drugs which are currently in use are either narcotics or nonnarcotics which have proven side and toxic effects. To develop new synthetic compounds in this category is an expensive venture and again may have problems of side effects. On the contrary, many medicines of plant origin had been used and are in use successfully since long time without any serious effects. This review gives an idea about different Indian, Chinese & Turkish medicinal plants used for analgesic activity.

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