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Brief review on analgesic and anti-inflammatory properties of *Moringa oleifera, Senna auriculata* & other useful medicinal plants to inhibit release of immune mediators

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Abstract
Analgesics are pain relievers. Analgesics are of two classes: opioids and non-opioids. NSAIDs and paracetamol come under non opioids class and are taken to relieve pain during inflammation by decreasing body's internal temperature. Certain lifelong pain conditions like rheumatoid arthritis, wisdom teeth pain, accidental pain, after surgery pain, back pain, frequent body pain needs dose of analgesics in a required time period. In such conditions person already know about duration of analgesics. Long term usage of allopathic analgesics has several adverse effects. Thus during such long term pain time consumption of medicinal plants and traditional ayurveda based product is more preferable. Present review focuses on few medicinally important plants having anti-inflammatory and analgesic properties such as: *Moringa oleifera* and *Senna auriculata* as a chief medicinal source. Other than these *Eucalyptus globules, Ricinus communis, Syzygium aromaticum* L. *Trachyspermum ammi, Zingiber officinale* and *Vitex negundo, Cinnamomum camphora* and *Plumbago zeylanica* are also reported to have these properties. This review is less based on botanical identity of mentioned medicinal plants and more based on their therapeutic and medicinal analgesic and anti-inflammatory properties to relieve pain.

Keywords: Analgesic, analgesia, anti-inflammatory, *moringa oleifera*, *senna auriculata*, anti-inflammatory, immune mediators

1. Introduction
People who suffer acute or chronic pain is due to some complications in their body are often prescribed to take Analgesics. Consumption of analgesics relieves pain on that particular part of body. These drugs produce analgesia and make person unable to feel pain during his/her recovery period. This pain can be because of headache, muscles pain, menstrual pain in women, joints pain or some accidental pain. These drugs are basically called as pain relievers or pain killer. Analgesics are of two types: opiod and non opiods. Opiods are narcotics and they are generally taken as orally or sometimes they are injected. Opiod binds on opiod receptors and gives morphine like effects by generating analgesia in affected parts. Opiod receptors are present in our brain and in our gastrointestinal tract. Unable to feel pain sensation and changes in level of perspiration are signs of getting relief from pain. Whereas, non opiods are non-narcotics and non-steroidal drugs. Well known Non-steroidal Anti-Inflammatory Drugs (NSAIDs) and paracetamol comes under this class. These nonsteroidal analgesics are on counter available and also are often prescribed for decrease in internal body temperature and as a pain reliever.
Paracetamol is also taken during inflammatory response. At time of normal wound healing swelling occurs. Thus pathogens can enter from site of wound healing. As pathogens enter our body's immune cells start responding. Due to complement activation, on nearby blood vessel dilation occur and therefore neutrophils and basophiles come out and start acting at the site of wound healing or inflammation. After this they start releasing histamine, bradykinin and prostaglandins like mediators. Presence of prostaglandins increases our internal body temperature. This phenomenon is called pyrogenic fever that occurs due to inflammatory response of immune mediators. During the fever time paracetamol is taken as an anti-inflammatory drug to decrease body temperature. But if person has some serious difficult pain and if pain killers are prescribed for longer time then they are not good for health because prolong use of painkillers increases level of dopamine.
Normally dopamine stimulates our neurons to act on pain relief. But increased level of dopamine may cause other effects like increase in blood pressure, nausea, headache and breathing difficulties.

Increased consumption of opiods leads bone loss. It is reported that opiods bind with opiod receptors known as μ receptors present on bone osteoblasts and inhibits their function. Osteoblasts are engaged with bone matrix formation and bone mineralization. Thus use of opiods causes thinning of bone and decreasing bone density and may increases risk of bone osteoporosis [1].

Certain long pain conditions like rheumatoid arthritis, wisdom teeth pain, accidental pain, after surgery pain, back pain, frequent body pain needs dose of analgesics in a required time period. In such conditions person already know about duration of analgesics. Thus during such long term pain time it is advisable to have consumption of medicinal plants and traditional Ayurveda based product as a pain reliever. Present review is about certain useful applications of medicinal plants as an analgesic and anti-inflammatory pain reliever.

2.1 *Moringa oleifera*

M. oleifera is commonly known as Shobhanjana. It is cultivated widely throughout in every region of India and also found in tropical regions of Asia and Africa [2]. Almost every part of Moringa is useful and it is also determined as "Natural Nutrition for the tropics". It is also known as horseradish tree. This is because it has highest nutritional values [3]. Leaves of Moringa are reported to have effective function against pain produced during inflammation and also during arthritis. Therefore leaf extract has anti-inflammatory and anti-arthritis activity. Other than this leaves are also reported to have diuretic, antispasmodic and hypotensive activity [3]. Moringa extract is found effective to decrease swelling and inflammation in carrageenan, cotton pellet and formaldehyde induced acute, sub-acute and chronic edema in adult wistar rats [4].

Basically Moringa is full of proteins, vitamins and antioxidants. These antioxidants help to delay process of cell damage due to inflammation and swelling. Well known Bovine mastitis is udder tissue inflammation that is occurred in mammary gland of cattle. Moringa leaf extract is also reported to have beneficial effect to decrease udder tissue inflammation. Generally leaf extract affects LPS (Lipopolysacchrides) induced signal transduction pathway of cells. Leaf extract inhibits binding of Nf-κβ transcription factor to p65 and p50 in presence of IL 10 and inhibits gene expressions of mastitis stimulating genes and thus stop mastitis causing cell growth and in turn inflammation.

During different stages of inflammation prostaglandins, bradykinin, histamine and serotonin are released. It is reported that 200mg/kg dose of Moringa leaf extract is found to be an effective to inhibit release of these mediators [4]. Saponines, flavanoides, alkaloids, sterols and sugars are present in leaf extract are reported to have effective function during infiltration of different immune cells. During acute and sub-acute inflammation proliferation of inflammatory cells increases and thus formation of benign tumor. These mentioned substances present in leaf extract inhibit activity of certain inflammatory cytokines like TNF-α, IL6, IL8 and thus inflammatory cell infiltration during granulation. This leaf extract (200 mg/kg) is also reported to have anti-arthritis activity [4].

Thus by stopping further production of immune mediators Moringa leaf extract helps to decrease body's internal temperature. Generally arthritis is a cause of long term inflammation. Inflammation for a longer time period may also leads to diabetes, cancer, arthritis and certain autoimmune disorders. Moreover Moringa leaf extract is reported to increase stimulation of anti-inflammatory cytokine IL10 and stimulates production of polymorph nuclear cells and macrophages [5-6]. Moringa leaf is full of vitamins. Among them vitamin E, B and C are found to be effective to decrease neural pain during diabetic and certain neurodegenerative diseases. Therefore to get relief from neural pain these vitamins mainly inhibits COX 2 (Also mentioned as COX-2) activity and decrease oxidative stress. Generally consumption of 2 to 3 grams of leaf extract for 1 to 2 weeks is sufficient to relieve inflammation pain.

Useful Ayurvedic preparations: It is available in single powdered as well as in capsule form.

2.2 *Senna auriculata*

S. auriculata is commonly known as Avartaki. Tree is found in forest area, on road side areas and in certain wastelands [7]. Roots and leaves of *S. auriculata* contain various secondary metabolites like alkaloids, flavanoides, several phenolic compounds, saponins, tannins and steroids [8]. Among them tannins and flavanoids are found to have anti- inflammatory and analgesic activity. It has been reported that steroids, flavanoids, alkaloids, terpenoids and tannins present in leaves and roots of S. auriculata inhibits activity of inflammatory mediators like prostaglandins, leukoterines and bradykinins [9].

Useful Ayurvedic preparations: Avarai Panchaga Chooram, Kalpa herbal Tea is available in the market.

2.3 *Eucalyptus globules*

E. globule is a tall and an endemic to only southern part of India. It is reported that essential oil obtained from leaves of *E. globules* is useful for relieving headache pain. For this oil is directly inhaled or else it is rubbed over surface of forehead. Oil is available in highly concentrated form in market. For its direct use it should be diluted necessarily. Oil is also useful to get relief from joint pains in person suffering from rheumatoid arthritis. Other than this oil is also applied during frequent back pain and small muscles pain. Eucalyptus oil is generally obtained from three different species of Eucalyptus like *E. globule*, *E. citriodora* and *E. tereticornis*.

Eucalyptus oil contains cineole and limonene which may act as pain relievers. It has been reported that three days clinical trial on approximately 52 people who have recently gone for knee replacement treatment indicated that inhalation of Eucalyptus oil mixed with almond oil for 30 to 45 minutes significantly decreased pain and level of blood pressure down rather than use of single almond oil [10]. Whereas it has no beneficiary effect reported among cancer patients [11].

Leaf extract of Eucalyptus is also reported to decrease carrageenan and dextran induced edema (Swelling) effect among wistar rats. Basically extract inhibited neutrophil migration at site of selling and thus decrease effect of edema [12].

Useful Ayurvedic preparations: Generally oil obtained from Eucalyptus species is used in preparation of various ayurvedic pain balms. Oil is also an essential component of Viks Vaporub. Oil is useful in joint pain, muscles pain and headache. During severe coughing our nasal cavity is full of mucous and at thistime few drops of Eucalyptus oil helps to get relief from nasaldeco gestation. Well known oils like Joint care oil and Panchgun Oil and Chatur Bhuj Oil are available in market.

2.4 *Ricinus communis*

R. communis which is commonly known as castor is most widely cultivated economically and medicinally important crop in India. It is mostly found in many states in India like

Rajasthan, Gujarat and Andhra Pradesh in India. Among these Gujarat is largest caster producing state of India. Seeds of castor has economically and medicinally important value. Essential oil obtained from castor is reported to have analgesic and anti-inflammatory properties to relieve pain.

People who are suffering from Rheumatoid arthritis and other pains may get big relief from castor oil. Ricinoleic acid is primary constituent present in castor oil and it is reported to have analgesic and anti-inflammatory effect. Generally it decreases pain and swelling [13].

Useful Ayurvedic preparations: Available directly as castor oil in the market and also present as ingredient oil in some Pidantak oils available in the market.

2.5 *Syzygium aromaticum*

S. aromaticum which is commonly known as clove and it is most widely found in Southern part of India. Euginol is derivative of phenolic groups found in clover leaf. It is reported as an effective analgesic during tooth pain and anal fissure pain [14]. Euginol is reported to inhibit activity of prostaglandins and leukotriens [15]. Analgesic activity of clove which is because of euginol. Generally in our body pain receptors are present and they are distributed widely especially in muscles and joints and they have special nerve endings. For this our central nervous system contains different opiod receptors like μ, κ and δ receptor which take part in neurotransmission and receives pain signals.

It is reported that Euginol blocks this pain receptors and thus relieves pain especially muscle pain and joints pain [16]. It is also reported in Carrageenan-induced paw edema that jumping of front paws of experimental animal indicates analgesic effect on sensory receptors present on central nervous system of experimental animal(mostly rat).They got stimulated by application of clove oil. It is reported that clove oil prolonged reaction time. Thus analgesic effect of clove oil is central nervous system (CNS) dependent [17].

Generally opiod receptors present in our CNS receives pain signals. They are first stimulated and then they start releasing pain producing neurotransmitters like Substance P, Glutamate and GABA. Release of these pain inducing neurotransmitters further stimulates release of serotonin at site of synapse. Serotonin binds to its receptors (HT1A) and leads to depolarization of neurons. There is large influx of Na+ ions inside neurons and thus highly positive charge inside neurons. To maintain balance of charges Cl- ion channels are opened and Ca2+ ion channels are blocked. Therefore inside neurons there is balance between + and – charges. To further decrease intensity of depolarization K+ ion channels are opened and K+ ion comes out from neurons. To decrease effect and release of serotonin other pain relievers obtained from plant extracts may target these HT1A receptors. First during time of pain, serotonin release is increased to decrease effect of pain inducing neurotransmitters (GABA) and thus more and more HT1A receptors are activated and thus intensity of pain decreases. Euginol mainly blocks activity of opiod receptors.

Useful Ayurvedic preparations: Available directly as clove oil and as a separate ingredient of other Pidantak oil and clove seed powder is also used in Dantmanjan to get relief from toothache.

2.6 *Trachyspermum ammi*/*Carum copticum*

T. ammi is commonly known as ajwain and it is basically widely grown in Egypt therefore it is native to Egypt and also in many other countries around Mediterranean and Southwest Asia [18]. In India ajwain is mostly cultivated in Rajasthan. As a household cooking condiment, ajwain seeds are also reported to have analgesic and anti-inflammatory properties to cure rheumatoid arthritis. As an ethanobotanical medicine ajwain seed is used mainly for edema, emphysema, enteritis, back pain, ophthalmic pain, toothache, and wounds [18].

Seeds are known for their antispasmodic, antiseptic and emergency restoration of drug induced or natural dyspnea and certain inflammatory disorders [19]. Ajwain seeds contains approximately 35% to 60% of Thymol as a main constituent present in Ajwain essential oil [20, 21]. Other than Thymol it contains Paracymene, Gamma-terpinene, Alpha-pinene, Beta-pinene, α-terpinene, Styrene, Delta-3-carene, Beta-phyllanderene, terpinene-4-ol and Carvacrol [22, 23].

Analgesic potential of ajwain was estimated *in vivo* by using a Tail- flick Analgesiometer [24]. Based on this estimation it was stated that Tail–flick latency was increased in presence of ethanolic extract of ajwain [25]. Effectiveness of total ajwain essential oil was also checked during late phage of formalin test [26]. Positive formalin test was because of presence of Thymol in ajwain seed essential oil. Ajwain essential oil was analyzed under randomized controlled placebo control clinical trial, for its analgesic potential in neuropathic feet burn. From results it was confirmed that compared to placebo ajwain essential oil decreased feet burn [27].

Naturally *C. copticum* is used to relieve rheumatic pain, joint pain, neuralgic pain and pain during headache. It was stated by Dashti-Rahmatabadi *Cyperus rotundus*. (2007) that analgesic effect of ethanolic extract of *C. copticum* was as effective as morphine. This is because of presence of parasympathomimetic class of agents which are going to become functional through descending pain modulatory pathway [24]. Analgesic effect of *C. copticum* was analyzed by formalin test and pain scores were recorded during one hour of incubation period at a time interval of every five minutes and from results it was stated that compared to morphine *C. copticum* essential oil influenced late onset pain. This late onset pain was not because of opiod receptors and their effect was not reversed by naloxone [28]. *C. copticum* was also reported to suppress morphine withdrawal in mice suffering from morphine withdrawal syndrome. This effect was due to increasing strength of nerve impulse during GABA neurotransmission and suppression of glutamate receptor and nitric oxide pathway [29].

Total aqueous extract and ethanolic extracts ajwain shown great anti-inflammatory potential in rat. These both extracts blocked effect of carrageenan-induced paw oedema in rat. After treatment of both extracts shown significant increase in adrenal gland weigh which were comparatively better than results collected after treatment by anti-inflammatory drugs like aspirin and phenyl butazone [30].

Useful Ayurvedic preparations: Available directly as ajwain oil in which single ajwain seeds are used and it is used for different household joint pains, back pains and applied over acute toothache.

2.7 *Zingiber officinale*

Z. officinale is commonly known as ginger which is mainly a native of tropical and subtropical forests of south Asia. In India it is most probably cultivated in Karnataka, Gujarat, Assam, Meghalaya and Arunachal Pradesh. Basically ginger is a household spice and it is having both culinary and medicinal properties. It is reported that ginger is good pain reliever for arthritis, toothache, muscle soreness, lower back pain, stomach and minor abdominal pain and menstrual pain

and therefore it is recommended as good anti-inflammatory substance for joint pain problem [31].

It is reported that ethanol extract of ginger is good in suppressing rat paw edema at both early and late onset of inflammatory pains [32]. Early onset of edema began just after 1hour of administration of ethanol extract by releasing early onset mediators like serotonin and histamine whereas late onset of edema began after 3 to 4 hour of administration of ethanolic extract by releasing late onset mediators like bradykinin, protease, prostaglandin and lysosome [32, 33]. 6-shogaol isolated from ginger extract was effective to reduce experimentally induced swelling of the hind paw in rats. This was because of direct action of 6-shogaol on inhibition of cyclooxygenase enzyme activity and thus by inhibiting release of inflammatory immune mediators [34]. 6-shogaol is reported as main bioactive compound isolated from ginger rhizomes. Cyclooxygenase generally catalyzes biosynthesis of immune mediators like prostaglandins.

It is reported that ginger rhizome is proven to be an effective in treatment of rheumatism. Approximately 7 patients who were diagnosed with rheumatoid arthritis (including male and females above 60 age) were orally administered 5 g of fresh or 0.5-1 g of dried ginger for a period of one to three months were resulted decrese in joint pain and less stiffness [35]. It is experimentally reported that 50 and 100 mg/kg dose of [6]-gingerol (obtained from ginger extract) is much effective to inhibit edema than indomethacin at the doses of 10 mg/kg (p<0.001). Results indicated that similar inhibitory activity was observed against carrageenan-induced rat paw edema that was observed in presence of [6] gingerol at the dose of 100 mg/kg and indomethacin at the dose of 10 mg/kg. Therefore anti- inflammatory potential of [6] gingerol is higher than administered drug [36].

Useful Ayurvedic preparations: Ginger oil is available containing ginger rhizomes as a single ingredient. Ginger chewing gums are also available and in some cases are orally administered to patients. Ginger dried rhizome extract is directly available in dried form in the market.

2.8 *Vitex negundo*

V. negundo is native to Sri Lanka, India, Pakistan, Malaysia, China and East Africa [37]. *V. negundo* is commonly known as five leaved chaste tree or Nirgundi and it is mostly found in part of Burma, eastern and southern part of India, Karnataka and Tamil Nadu. Generally its leaves, bark, roots, stems and flowers are used for various medicinal purposes. Leaves of Nirgundi are used to get relief from headache pain. Root barks and leaves are reported as good tonic for treatment of acute rheumatism and joint pains. As major substances it contains terpenoids, lignans, flavonoids, alkaloids and glycosides [38]. Water extract of fresh mature leaves of *V. negundo* is reported as anti-inflammatory, analgesic and anti-itching agents [39]. Chromone analogues isolated from crude extract of Nirgundi are reported to have anti-inflammatory activities [40-41].

Chromones like methyl 3-(2-(5-hydroxy-6-methoxy-4-oxo4H- chromen-2-yl) ethyl) benzoate, and 3-(1-hydroxy-2-(5-hydroxy-6-methoxy-4-oxo-4Hchromen-2-yl) ethyl) benzoic acid are isolated from ethyl acetate extract of V. negundo [42]. The analgesic activity of these compounds were reported to decrease in frequency of acetic acid induced abdominal writhing in mice model [42]. Acetic acid induced painful response in mouse is a result of release of prostaglandins and other immune mediators upon stimulation sensory pathways in mouse peritoneum that ultimately causes abdominal writhing [43]. Chromones are reported to interact with cyclooxgenases enzyme and thus by blocking catalyzing efficiency of cyclooxygenase and in turn blocking release of early and late onset pain immune mediators [44].

Nishindine is an alkaloid present in root and bark extract of Nirgundi is reported to have anti-inflammatory and analgesic properties and is helpful during joint pains and muscle spasms in patients suffering from arthritis.

Useful Ayurvedic preparations: Nirgundi kasayam is available in a market as compound herbal oil together with sesame oil and coconut oil which is applied over joint pain, ear and nose dropwise. Balnirgundayikawatha is also available in powder form in the market.

2.9 *Cinnamomum camphora*

C. camphora is an evergreen plant and it is generally known as Karpoor as local name. *C. camphora* is widely grown in tropical part of Eastern Asia, Korea, India, Vietnam, Taiwan and Southern Japan. In India climatic atmosphere of Assam, East India and Western Ghats are favorable for cultivation of *C. camphora*. Kapoor is used to get relief from pain and to decrease symptoms of itching by stimulating nerve endings. Upon FDA approval Camphor is used as natural painkiller in concentrations of 3% to 11%. Camphore use above than mentioned concentrations in any heath and edible products is prohibited due to its serious side effects. Camphor is widely used in its prescribed concentrations in topical creams containing glucosamine sulfate and chondroitin sulfate is used for multiple joint pains.

C. camphora leaf contains camphor as a main substance. Other than camphor it contains cineol, linalool, eugenol, limonene, safrole, α-pinene, β-pinene, β-myrecene, α-humulene, p-cymene, nerolidol, borneol, camphene and other compounds [45-48].

It is reported that camphor activates TRP (transient receptor potential) channels like TRAPV1, TRPV3,TRPM8 and inhibits plasma membrane channel named TRPA1 upon sensation, excitation and desensitization of sensory nerves and in turn giving relief from pain in applied skin areas [49, 50, 51].

Borneol isolated from leaves of camphora is reported to have analgesic and anti-inflammatory properties. Natural borneol (BEO) is reported to have a significant analgesic effect when it was examined in glacial acetic acid induced pain in mouse model. BEO was also found to be an effective in suppressing PGE2 and TRPM8 in mouse model [52].

Useful Ayurvedic preparations: *C. camphora* is used as topical medications especially in cream and pain balms. It is also present in Vicks vaporub. It is also used in Herbal sprays and pain relief oil which are readily available in the market.

2.10 *Plumbago zeylanica*

P. zeylanica commonly known as Chitrak is widely grown in South East Asia, Malaysia and Africa and almost in tropical Asia. In India P. zeylanica is mostly grown in West Bengal and Southern part of India. Basically root of *P. zeylanica* is used for therapeutic purposes. It contains useful secondary metabolites like naphthoquinones class flavonoids, alkaloids, glycosides, saponins, steroids, tannins, triterpenoids, coumarins, carbohydrates, phenolic compounds, fixed oils, fats and proteins [53, 54].

Roots of *P. zeylanica* contain plumbagin as a major component which is mainly used for various therapeutic purposes. Plumbagin is a napthoquinone class of compound which has analgesic, anti-inflammatory and anti-carcinogenic properties. Anti-inflammatory and analgesic activities of

plumbagin was analyzed from dosage forms of 5 to 20 mg/kg. and from these it was depicted that oral dose dependent administration of plumbagin suppressed caragennan induced paw edema in rats and also suppressed release of various pro inflammatory mediators like histamine, serotonin, bradykinin and prostaglandin E2 [55].

It also hampered activity of these proinflammatory mediators releasing enzymes nitric oxide synthase and cyclooxygenase 1 [55]. Methanol extract of *P. zeylanica* at an amount of 300 and 500 mg/kg produced 31.03 and 60.3% inhibition in inflammation in rat paw oedema induced by caragennan [56]. *P. zeylanica* is also reported to decrease in oedema comparatively more than aspirin [57].

Useful Ayurvedic preparations: Root power of P. zeylanica is directly available in the market. Roots are also used in compound liquid formulations such like Pidantak Tail available in the market.

At last purpose of this review is to generate information based applications of chief medicinal plants like *Moringa oleifera* and *Senna auriculata* and above mentioned other useful medicinal plants. This is resource based and literature based information focusing on reported important analgesic and anti- inflammatory activity of above mentioned medicinal plants with their targeted immune mediators. This information might be helpful to produce easily available ayurvedic preparations which may prove to be more potent than synthetic analgesics available in the market.

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