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MANAGEMENT OF PAIN AND FEVER IN DIFFERENT MEDICINAL SYSTEM- A REVIEW

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ABSTRACT: Pain is a subjective, multidimensional and unpleasant experience allied with actual or potential tissue damage comprising sensory, affective and cognitive components. Pain signals interpretation is a complex process that entails excitation of peripheral nerves and further excitation of nociceptive inputs. Painkiller is member of diverse group of drugs used to relieve pain and to achieve analgesia. Fever is recognized as physiological response which is triggered by infectious stimuli or aseptic stimuli. Elevation in body temperature occur when concentrations of prostaglandin-E2 (PGE2) increases within certain areas of the brain. These elevations alter the firing rate of neurons that control thermoregulation in the hypothalamus. It is commonly suppressed with antipyretic medications. Several traditional medicinal systems are available for the treatment of pain & fever like Ayurveda, Unani, Chinese, homeopathic, physiotherapy & non- pharmacological procedures etc. Pain & fever treatment in allopathic system are frequently used but has many adverse effects like renal & liver dysfunction, ulceration, sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression, *etc.* This compilation addresses the different medicinal systems and therapies used for the treatment of pain and fever.

Keywords: Pain, Fever, Allopathic, Ayurvedic, Homeopathic, Unani

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INTRODUCTION: Pain is an ill-defined, unpleasant sensation which is evoked by external and internal noxious stimuli¹. Pain is useful in some situations that motivate individual to withdraw from damaging situations that may lead to many diseases such as a tumor, physical trauma, surgical procedures, noxious chemical stimulation, *etc.*² Thus, pain can be known as the protector as well as predictor³.

Pain Pathophysiology: A painful stimulus elicits activation of receptors in the periphery, which transduces the stimulus into an electrical impulse⁴. Pain signals is a complex process which results in local interactions within the spinal dorsal horn, and then activation of ascending and descending circuits that comprise a loop from the spinal cord to supraspinal structures and finally exciting nociceptive inputs at the spinal level⁵.

Numerous chemical substances play important role in generating nociceptive impulses (*e.g.*, prostaglandins, histamine, serotonin). Furthermore, the role of neuropeptides as calcitonin gene-related peptide and particularly substance P has been demonstrated in the activation of early neurogenic

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inflammation. Bradykinin and cytokines are also involved in prolonging the sensation of pain ⁶.

Nociceptive Pain Mechanism: Nociceptive pathway, consist of a three-neuron chain, is now understood to be a dual system at each level, and the sensation of pain is thought to arrive in the central nervous system with the discriminative component of pain ("first pain") carried separately from the affective-motivational component of pain ("second pain") ⁷. In addition to spinal control mechanisms of nociceptive transmission, descending pathways originates in three major areas that are cortex, thalamus, and brain stem and can modify functions at the spinal level. The nociceptive ending is stimulated by prostaglandins, bradykinin, and other neurotransmitter, metabolites and ions ⁸. Each of these factors sensitizes (lowers the threshold) or excite the terminals of the nociceptor by interacting with cell-surface receptors expressed by these neurons whereby release of substance P, neurotransmitters, and calcitonin gene-related peptide (CGRP), from the peripheral terminal, induces vasodilation and plasma extravasation ⁹.

Fever: Fever or pyresis is recognized as a complex, coordinated, autonomic, behavioral response, and

neuroendocrine, which occurs due to acute phase reaction to immune challenge ¹⁰.

Pathophysiology of Fever: Fever appears evolved in vertebrate hosts as an adaptive mechanism to control infection. This phenomenon is produced by some exogenous (largely microbial) stimuli that activated bone-marrow-derived phagocytes to release an endogenous pyrogen. That circulates to the thermoregulatory center of the brain (preoptic area of the anterior hypothalamus) where it causes an elevation in the "set-point" for normal body temperature ¹¹.

Molecular Mechanism of Fever: Distinct members of Toll receptors in macrophages receptor family recognize different and specific microbial components, but biosynthesis and releases same endogenous pyrogens, such as IL-1 β , TNF, and IL-6 ¹². These pyrogenic cytokines acts on organum vasculosum area of the brain known as laminae terminalis leading to activation of the enzyme cyclooxygenase-2 (COX-2) that results in release of prostaglandin E₂ (PGE₂), which binds to receptors in the hypothalamus leading to an increase in heat production and a decrease in heat loss until the temperature in the hypothalamus reaches an elevated set-point ¹³.

TABLE 1: ALLOPATHIC TREATMENT OF PAIN

For mild pain	For moderate pain	For severe pain
A non-narcotic analgesic or NSAIDs like Aspirin ¹⁴ , paracetamol ¹⁵ , ibuprofen ¹⁶ , acetaminophen ¹⁷ , diclofenac ¹⁸ , meloxicam ¹⁹ are used to treat mild pain if the pain is unable to recover then narcotic drugs is recommended Adverse effect- Renal & liver dysfunction, ulceration ²⁰	Narcotic (opioid) analgesics or low-efficacy opioids are codeine, dihydrocodeine ²¹ , dextropropoxyphene, pentazocine ²² , Alfentanil ²³ , Tramadol ²⁴ . NSAID, in combination with a low-efficacy opioid, can be used in case of acute pain but less convenient for chronic pain Adverse effect- respiratory depression, sedation, dependence, tolerance, dizziness, vomiting, constipation ²⁵	High-efficacy opioids are used in case of severe pain these are morphine ²⁶ , diamorphine ²⁷ , buprenorphine ²⁸ Adverse effect- Sedation, drowsiness, sleep disturbance, seizures, hyperalgesia and tolerance ²⁹ , constipation, hallucinations ³⁰

TABLE 2: CERTAIN CLINICAL PAIN AND THEIR TREATMENT

Clinical Pain Condition	Drug of Choice
Acute abdominal pain	Strong opioids ³¹
Acute migraine	Aspirin, acetaminophen, NSAID's, opioid analgesics ³²
Atypical facial pain	Ibuprofen, naproxen, procaine, lidocaine, sodium hyaluronate, cyclobenzaprine, amitriptyline, nortriptyline ³³
Fibromyalgia	Pregabalin, duloxetine, milnacipran, amitriptyline, cyclobenzaprine, gabapentin, tramadol, fluoxetine, sodium oxybate ³⁴
Burn injury	Opioids, NSAIDs, paracetamol and dipyron, gabapentin and pregabalin, ketamine, amitriptyline ³⁵
Neuropathic pain	First-line medications- nortriptyline or desipramine ³⁶

	Second-line medications- Tramadol ³⁷
	Third-line medications- antidepressant, antiepileptic medications, capsaicin, dextromethorphan, memantine, mexiletine ³⁸
Inflammatory arthritis	NSAID's, Paracetamol ³⁹ , capsaicin, cannabinoids, antidepressant, strong opioid ⁴⁰
Postoperative cancer pain	Strong opioids ⁴¹ , capsaicin ⁴²
Osteoarthritis	Strong opioids, weak arthritis, NSAID's ⁴³

Targets of New Analgesics: Ion channels are integral membrane proteins that contain pathways through which ions can flow⁴⁴. They are considered likely targets in the treatment of pain⁴⁵. Members of Voltage-gated calcium channels family contain $\alpha_2\delta$, β and γ subunits, and play a role in neuronal excitation. The $\alpha_2\delta$ subunit of L-type calcium channels is the target of the established co-treatments for neuropathic pain⁴⁶. These calcium channels also play key role in chronic pain⁴⁷. They are coded by the CACNA1B gene and expressed at the presynaptic terminals of primary afferent neurons that end in the dorsal horn of the spinal cord⁴⁸. Potassium channel $K_{IR}3.2$, a two-transmembrane-one pathway potassium channel, is involved in opioid signaling on postsynaptic inhibition⁴⁹ and mediates a significant component of analgesia⁵⁰. Cerebral endocannabinoid signaling is involved in antinociception⁵¹.

5-HT receptors are expressed in the central and peripheral nervous systems where they mediate both excitatory and inhibitory neurotransmission⁵². Several 5-HT receptor subtypes are involved in nociception⁵³. Currently, only the 5-HT_{1A} receptor is being studied as the target of an analgesic. trkA is a catalytic receptor being approached as an analgesics target⁵⁴.

Allopathic Treatment of Fever: For the treatment of fever it is necessary to know the fever's

underlying cause. Different over the counter are used in reducing body temperature to a normal level as well as to treat the underlying cause. OTC antipyretic that are used normally includes nonsteroidal anti-inflammatory drugs like aspirin⁵⁵, nimesulide⁵⁶, paracetamol⁵⁷, ketoprofen⁵⁸, ibuprofen⁵⁹, meloxicam⁶⁰, celecoxib⁶¹, rofecoxib⁶².

The Target of Antipyretic: Cyclooxygenase (COX), also known as prostaglandin endoperoxide synthase, is the key enzyme required for the conversion of arachidonic acid to prostaglandins. Two COX isoforms have been identified, COX-1 and COX-2. In many situations, the COX-1 protein is produced constitutively (*e.g.*, in gastric mucosa), whereas COX-2 is highly inducible (*e.g.*, at sites of inflammation and cancer). Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both enzymes, and a new class of COX-2 selective inhibitors (COXIBs) preferentially inhibits the COX-2 enzyme⁶³.

Herbal Treatment of Pain: Many medicines of plant origin had been used since ages without any adverse effects. There is much importance of pain relief from these analgesic herbs; some are the best-loved and most popular remedies. Some uses for Analgesic herbs are mostly common in neuralgia, toothaches, sore muscles lower back pain and headaches⁶⁴.

TABLE 3: SOME OF the HERBS WITH ANALGESIC ACTIVITY

Plant name	Family	Part used	Chemical Constituent	Activity may be due to
<i>Cleome rutidosperma</i> (Purple Cleome)	Capparidaceae	Ariel part	Tannins, steroids, flavonoids, terpenoids	Inhibition of cyclooxygenase, a prostaglandin derivative ⁶⁵
<i>Psidium Cattleianum</i> (araça-rosa)	Myrtaceae	Leaves	Phenolic compounds such as gallic acid and epicatechin	Its antioxidant effect ⁶⁶
<i>Caralluma dalzielii</i> (mosque stalk)	Asclepiadaceae	Whole plant	Saponins, alkaloids, glycosides, tannins, terpenoids, flavonoid	Inhibition of either synthesis, release or action of PGE ₂ , PGF ₂ α , serotonin, and histamine ⁶⁷
<i>Urtica circularis</i> (ortiga)	Urticaceae	Ariel part	Caffeic acid, chlorogenic acid, and vitexin	Increased cGMP concentration which will lead to hyperpolarization thereby inducing analgesia ⁶⁸
<i>Artemisia scoparia</i> (Jhahoo)	Asteraceae	Whole plant	Chlorogenic acid, coumarin, capillariasis,	An inhibitory effect on the production or action of inflammatory

<i>Indigofera cassioides</i> (Cassia Indigo)	Fabaceae	Leaves	butyl ester, magnolioside, and b- sitosterol Phenols, quercetin, flavonoids	mediators ⁶⁹ Inhibition of both cyclooxygenase and 5-lipoxygenase pathways ⁷⁰
<i>Cyathula prostrate</i> (Prostrate pasture weed)	Amaranthaceae	Leaves	Flavonoids	Inhibition of cyclooxygenase and 5- lipoxygenase pathways ⁷¹
<i>Impatiens balsamina</i> (Dopati)	Balsaminaceae	Flower	Phenols, flavonoids, and tannins	Decreased cAMP level, potassium ion efflux, and subsequent hyperpolarization of the nerves which give the anti-nociceptive effect ⁷²
<i>Alpinia calcarata</i> (Heen-araththa)	Zingiberaceae	Rhizome	Phenol, flavonoids	Inhibition of the production of prostaglandins (E ₂ & F ⁷³)

Herbal Treatment of Fever: Traditional systems of medicine or care by herbals are used throughout the world and from century's herbs have been the

source for most of the drugs. Numerous medicinal plants are available today for treating fever⁷⁴.

TABLE 4: SOME OF THE HERBS WITH ANTIPYRETIC ACTIVITY

S. no.	Botanical/ Common name	Family	Part used	Chemical constituent	Activity may be due to
1	<i>Magnolia obovate</i> (inha-do-brejo)	Magnoliaceae	Trunk bark	Costunolide and related sesquiterpene lactones	Inhibition of COX-2 ⁷⁵
2	<i>Vernonia cinerea</i>	Asteraceae	Leaf	Terpenoid, alkaloid, flavonoid	CNS depression which is due to decreased excitatory activities of the monoamines ⁷⁶
3	<i>Artemisia scoparia</i> (Worm wood)	Asteraceae	Whole plant	Chlorogenic acid butyl ester, Magnoliopsida	Inhibitory influence on prostaglandin biosynthesis or release ⁷⁷
4	<i>Bauhinia racemosa</i> (Mountain ebony)	Caesalpinaceae	Stem bark	Flavonoids, coumarins, triterpenoids, stilbenes, steroids, and tannin	Unknown ⁷⁸
5	<i>Clitoria ternatea</i> (Butterfly pea)	Fabaceae	Root	Flavonoids	Unknown ⁷⁹
6	<i>Phrygilanthus acutifolius</i> (corpo)	Loranthaceae	Flowers	-	Inhibition of prostaglandin synthesis ⁸⁰
7	<i>Mallotus peltatus</i> (Pataque)	Euphorbiaceae	Leaves	Sitosterol	Inhibition of prostaglandin synthesis ⁸¹
8	<i>Hyoscyamus niger</i> (henbane)	Solanaceae	Seed	Cleomiscosin A	Unknown ⁸²
9	<i>Diospyros mespiliformis</i> (Jackal berry tree)	Ebenaceae	Stem bark	Alkaloids, quinones, saponins, sterol, tannins	Inhibition of sensitization of pain receptors by prostaglandin at the inflammatory site ⁸³
10	<i>Caesalpinia bonducella</i> (Yellow nicker)	Caesalpinaceae	Leaves	Flavonoids, alkaloids, saponins, triterpenes, tannins, and steroids	Inhibition of prostaglandin synthesis ⁸⁴

Homeopathy Treatment of Pain: Homeopathic Remedies have an essential role in body pains and aches treatment. Homeopathic treatment does not have side effect and can be obtained from naturally occurring plant and substance⁸⁵.

Unani Treatment of Pain: In the *Unani* literature, Arabic word *Waja* is used for pain. Unani medicine system uses naturally the treatment of different alignment. These drugs treat the disease and have no side effect⁸⁷.

TABLE 5: HOMEOPATHIC REMEDIES FOR PAIN⁸⁵

Homeopathic Remedies	Treatment
<i>Rhus toxicodendron</i>	Essential in treatment of pain and aches at resting position and are of a better choice in overstraining and overstretching
<i>Arnica montana</i>	It is effective in sore body pain and joint pain
<i>Bryonia alba</i>	It is of use in pain and aches resulting from muscle and joint
<i>Magnesium phosphorica</i>	It is useful in pains and aches of wide varieties (shooting, cutting or stitching in nature)
<i>Ruta graveolens</i>	Useful when pain is associated with weakness
<i>Gelsemium sempervirens</i>	Useful in pain associated with drowsiness
<i>Eupatorium perfoliatum</i>	It is useful in pains that are associated with fever
<i>Bryonia alba</i>	It is useful in joint pain due to Rheumatoid arthritis.

TABLE 6: HOMEOPATHY TREATMENT OF FEVER⁸⁶

Homeopathic Remedies	Treatment
<i>Aconite</i>	When skin is dry and restless
<i>Belladonna</i>	When there is delirium with the fever
<i>Bryonia</i>	When the patient is restlessness and wants to rest
<i>Gelsemium</i>	When the patient is drowsy and sleepy
<i>Mercurius Vivus</i>	When there are chill and sweating
<i>Nux Vomica</i>	When the body is hot
<i>Pulsatilla</i>	When there is constant chillness
<i>Pyrogenium</i>	When the temperature is high and low in an alternating way
<i>Rhus Toxicodendron</i>	When fever is caused by getting wet

TABLE 7: UNANI DRUGS FOR PAIN

Plant	Family	Part used
<i>Zingiber officinale</i>	Zingiberaceae	Rhizome ⁸⁸
<i>Piper nigrum</i>	Piperaceae	Fruits ⁸⁹
<i>Bambusa arundinaceae</i>	Bambusaceae	Leaves ⁸⁹
<i>Curcuma longa</i>	Zingiberaceae	Rhizome ⁹⁰
<i>Saussurea lappa</i>	Asteraceae	Roots ⁹¹

TABLE 8: UNANI TREATMENT OF FEVER

Plant	Family	Part used
<i>Piper longum</i> Linn.	Piperaceae	Fruits, root ⁹²
<i>Cassia fistula</i> Linn.	Leguminosae	Resin ⁹³
<i>Eugenia jambolana</i> Lam.	Myrtaceae	Seed, bark, leaf ⁹⁴
<i>Plumbago zeylanica</i> Linn	Plumbaginaceae	Root, root bark ⁹⁵
<i>Zingiber officinale</i> Rosc.	Zingiberaceae	Rhizome ⁹⁶ .

Home Remedies for the Treatment of Fever:

When there is mild fever home remedy is sufficient to treat it, mainly when there is a mild infection like flu and cold. Some of the remedies are

- Fluid intake should be increased.
- If the fever is high then bath to reduce it and not to eliminate it, the room should be well ventilated.
- If the fever raises continuously then sponging with lukewarm water can be useful.
- Any type of stress should be avoided.
- Herbs and other cooking ingredient are also used to reduce fever.
- Boiled filtrate of basil leaves in the water on drinking once a day reduces the temperature.
- When fever is present, then a half teaspoon of saffron is taken with warm water.
- Grapefruit juice with water is useful in reducing fever.

- Honey mixed with ginger is useful in fighting fever⁹⁷.

Non-Pharmacological Treatment of Pain:

Physiotherapy: Physiotherapy modalities are commonly used in the treatment of pain, especially in rheumatoid arthritis. These consist of heat & cold applications, hydrotherapy, electrical stimulation, *etc.* By applying heat, muscle spasm is relieved, analgesia is accomplished and elasticity of periarticular structures obtained. The intra-articular temperature increased by superficial heat application⁹⁸. In cold application opposite of hot application occurs. Effects of heat application change between normal healthy subjects and patients with inflamed joints⁹⁹. Electrostimulation is used in patients with rheumatoid arthritis. Transcutaneous electrical nerve stimulation (TENS) therapy is the most commonly used method in which analgesia is persisted up to 18 hours¹⁰⁰. Massage is a commonly used treatment tool that enhances a feeling of connection with other treatment modalities, improves flexibility, general well being, and useful in inflamed joints¹⁰¹. Massage is found to be effective on depression, anxiety, mood, and pain¹⁰². Maintenance of normal muscle strength can be maintained by exercise therapy has beneficial effects on increasing physical capacity¹⁰³.

Magnetic Therapy: Magnetic therapy is a simple, non-invasive, and safe technique, usually administered over the site of a painful injury or inflammation. It has analgesic efficacy¹⁰⁴.

Psychological Therapy: Pain is also related to underlying physiological processes; there is evidence that indicates that psychological and social factors also play an important role in the experience and impact of pain¹⁰⁵.

Acupuncture: Acupuncture is used in eastern medicine. In these endogenous analgesics is released within the spinal cord¹⁰⁶. Acupuncture is reported to be effective in treating many conditions including, fibromyalgia¹⁰⁷, chronic low back pain¹⁰⁸, as well as chronic pain caused by osteoarthritis¹⁰⁹. Due to its analgesic effects, acupuncture is widely used, cost-effective¹¹⁰ and a relatively safe non-pharmacological treatment of musculoskeletal pain¹¹¹.

CONCLUSION: Allopathic treatment is the most frequently used system, potent and beneficial in emergencies like postoperative pain, burn pain, and acute abdominal pain. Thus in chronic conditions of pain and fever, allopathic medicine system is the preferred as the choice of treatment but has many adverse effects like renal & liver dysfunction, ulceration, sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, respiratory depression, angioneurotic edema, and GI hemorrhage, *etc.*

Herbal medicines make an enormous contribution to primary health care and have shown great potential in modern phytomedicine against pain and fever. Several plants have been described in Ayurveda, Unani, homeopathy and another traditional medicinal system for the management and prevention of pain and fever according to the perceived needs of the patient and based upon the individual herb's constituents. Disease with pain and fever are widespread and required more attention; a large number of people these days are looking for herbal remedies and relief for their ailments.

Besides these other non-pharmacological treatments such as physiotherapy, acupuncture, magnetic therapy is used to alleviate pain. Ayurvedic, homeopathic, Siddha, Unani, physiotherapy offers a wide range of preventive and curative treatments that are both cost effective and efficacious. Therefore, our efforts should be directed towards the review of different medicinal system with their target for the treatment of pain and fever with major drugs.

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