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### A Review on advantages of Natural Analgesics over Conventional Synthetic Analgesics

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#### Abstract

Analgesic is a drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness. Pain is a warning signal, primarily protective in nature, but causes discomfort and suffering; may even be unbearable and incapacitating. There are various synthetic drugs like aspirin, ibuprofen, ketoprofen, diclofenac, aceclofenac, indomethacin, phenylbutazon, nimesulide, and cox-2 inhibitors (celecoxib, etoricoxib) are used as analgesics. Synthetic analgesics produce various serious adverse effects like stomach pain, nausea, vomiting, epigastric discomfort, ulceration, respiratory depression, cold extremities, hypotension, cardiovascular depression like bradycardia, stupor, coma and death etc. Medicinal plants also the rich source of analgesics like as- morphine, white willow bark, curcumine (turmeric), green tea, pycnogenol (maritime pine bark), boswellia serrata resin (*frankincense*), resveratrol, uncaria tomentosa (*cat's claw*), capsaicin (chili pepper), ginger, salmon etc. There is various plant and animal derived nutraceutical preparations have been used for hundreds and even thousands of years to obtain effective pain relief. Herbal medications are becoming increasingly popular because of their relatively few side effects.

Key-Words: Natural Analgesics, *Boswellia serrata*, White willow bark, Curcumine

#### Introduction

Algesia (pain) is an ill-defined, unpleasant sensation, usually evoked by an external or internal noxious stimulus. Analgesic-A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.<sup>2</sup> Pain is a warning signal, primarily protective in nature, but causes discomfort and suffering; may even be unbearable and incapacitating. It is the most important symptom that brings the patient to the physician. Excessive pain may produce other effects-sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in BP, tachypnoea. Analgesics relieve pain as a symptom, without affecting its cause. They are used when the noxious stimulus (evoking the pain) cannot be removed or as adjuvants to more etiological approach to pain.<sup>1</sup>

#### Phenomenon of pain

An understanding of the phenomenon of pain ought to accommodate the following points: Pain can occur without tissue injury or evident disease and can persist after injury has healed. Serious tissue injury can occur without pain.

Emotion (anxiety, fear, depression) is an inseparable concomitant of pain and can modify both its intensity and the victim's behavioural response.<sup>2</sup>

There is important processing of afferent nociceptive (see below) and other impulses in the spinal cord and brain.

**Analgesic drug:** a drug that relieves pain due to multiple causes, e.g. paracetamol, morphine. Drugs that relieve pain due to a single cause or specific pain syndrome only, e.g. ergotamine (migraine), carbamazepine (neuralgias), glyceryl trinitrate (angina pectoris), are not classed as analgesics; nor are adrenocortical steroids that suppress pain of inflammation of any cause.

**Analgesics** are classed as narcotic (which act in the central nervous system and cause drowsiness, i.e. opioids) and non-narcotic (which act chiefly peripherally, e.g. diclofenac).<sup>1</sup>

#### Types of Pain

Acute **pain** (defined as of < 3 months duration) is 7 *Neuralgia* is pain felt in the distribution of a peripheral nerve, transmitted principally by fast conducting A-delta fibres (but to a lesser extent involves slow conducting type C fibres) and has major nociceptive input (physical trauma, pleurisy, myocardial infarct,

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perforated peptic ulcer). Patients perceive it as a transient, though sometimes severe threat and they react accordingly.

**Neuropathic pain** follows damage to the nervous system. Acute pain without nociceptive (afferent) input (some neuralgias) is less susceptible to drugs unless consciousness is also depressed, and any frequently recurrent acute pain, e.g. trigeminal neuralgia, poses management problems that are more akin to chronic pain.

**Chronic pain** is transmitted principally by slow conducting type C fibres (but to a lesser extent by fast conducting A-delta fibres). It is better regarded as a syndrome rather than as a symptom (see above) for it is a collection of disparate pains of long duration, often sharing common emotional and behavioural aspects. It presents a depressing future to the victim who sees no prospect of release from suffering, and poses for that reason long-term management problems that differ from acute pain.<sup>2</sup>

#### Causes of pain

Pain is caused by the stimulation of pain receptors which are free nerve endings. Nociceptors 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.<sup>1</sup>

#### Mechanisms of Analgesia

Endogenous opioid neurotransmitters in the spinal cord and brain constitute a *pain inhibitory system*; they are activated by nociceptive and other inputs (including treatments such as transcutaneous nerve stimulation, and acupuncture) and mediate their effects through specific receptors. Activation of opioid receptors prevents the release of substance P (a neurotransmitter and local hormone involved in pain transmission) with the result that pain transmission is inhibited. Several types of receptor have been recognised, principally:  $\mu$  (mu),  $\delta$  (delta) and  $\kappa$  (kappa) receptors for which the endogenous ligands respectively are: endomorphins, etencephalin and dynorphins. *Synthetic* opioids produce analgesia by simulating the body's natural opioids and the existence of different types of receptor explains their varying patterns of actions. Definition of these receptors and their subdivisions offers hope for the design of new selective high-efficacy analgesics free from the disadvantages of the existing opioids.<sup>2</sup>

#### Sources of Analgesic Drugs

There are various sources of analgesic drugs; they are classified into following two types:

a) Synthetic Drugs b) Natural sources

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

#### Adverse Effects of Synthetic Analgesics<sup>1,2</sup>

GIT - stomach pain, heart burn, nausea, vomiting, epigastric discomfort, ulceration.

Effects on hearing – tinnitus (very common), vertigo, mild hearing loss.

Hypersensitivity – angioedema, skin eruptions, paroxysmal bronchospasm.

Haematological – iron deficiency anaemia, prolongation of bleeding time, may cause haemolytic anaemia in G6PD deficiency patients.

Liver – hepatotoxicity (usually reversible), fluid retention.

Kidney – Analgesic nephropathy – especially if combinations of NSAIDs are used.

Reye's syndrome (aspirin) – acute encephalopathy and hepatic injury in children, when used for antipyretic effects in viral infections such as flu or chicken pox.

Interstitial nephritis, papillary necrosis when used in combination with other analgesics.

Haemolytic anemia, methaemoglobinemia, thrombocytopenia, leucopenia may occur.

Dizziness, headache, tinnitus, depression..

Dependency and drug abuse.

CVS – tachycardia, hypertension.

Constipation.

Respiratory depression, apnoea, mydriasis ( unlike other opioids), extreme somnolence, muscle flaccidity, cold extremities, cold clammy skin, hypotension, cardiovascular depression like bradycardia, stupor, coma and death.

Steven Johnson's syndrome (**Indomethacin**).

Loss of libido

Disruptions in menstruation

#### Life-threatening side effects of selective COX-2 NSAIDs

In December 1998, celecoxib (Celebrex) was approved by the Food and Drug Administration (FDA) as the first selective COX-2 inhibitor for treatment of arthritis pain. Rofecoxib (Vioxx) was approved several months later, followed by valdecoxib (Bextra). These NSAIDs were designed to allow continued production of the gastrointestinally protective prostaglandins produced through the COX-1 enzyme system while blocking the

COX-2 enzyme that produces the inflammatory prostaglandins.<sup>1</sup>

Celebrex, Vioxx, and Bextra quickly became the mainstay for the treatment of chronic pain conditions related to inflammation. Within a few years, an estimated 15–20 million people in the US were using selective COX-2-inhibiting NSAIDs on a long-term basis. These drugs became the most commonly used pharmaceutical agent with more than 70 million NSAID prescriptions written each year and 30 billion over-the-counter NSAID tablets sold annually. It was estimated that 5–10% of the adult population used NSAIDs, and among the elderly (a group at higher risk of nonselective NSAID-induced gastrointestinal complications), the use of these drugs was as high as 15%. The general acceptance of these drugs was due to the perceived lack of serious gastrointestinal side effects that had been associated with the nonselective class of NSAIDs.<sup>2</sup>

## II) Analgesics from Natural Sources

Plant- and animal-derived nutraceutical preparations have been used for hundreds and even thousands of years to obtain effective pain relief. Herbal medications are becoming increasingly popular because of their relatively few side effects. Nevertheless, there are problems associated with these dietary supplements, and their use requires knowledge of their biological action, clinical studies (both affirmative and negative), and potential interactions with other nutraceutical products and prescription medications.

The evaluation of nutraceutical preparations with appropriately designed controlled studies has exploded in recent years. There is now a greater degree of confidence based on controlled study design and improved quality of the investigators that has strengthened positive findings found using natural compounds to treat diseases. It is important for healthcare practitioners to learn about these scientific studies to counsel patients who are taking various dietary supplements, herbs minerals and vitamins for both disease treatment and prevention.

There are various medicinal plants available in nature which shows analgesic activity, these are as follow:

### Morphine

Morphine exerts a narcotic action manifested by analgesia, drowsiness, changes in mood, and mental clouding. The major medical action of morphine sought in the CNS is analgesia.<sup>1</sup>

Opiates suppress the "cough center" which is also located in the brainstem, the medulla. Such an action is thought to underlie the use of opiate narcotics as cough suppressants. Codeine appears to be particularly

effective in this action and is widely used for this purpose.<sup>3</sup>

Morphine and codeine are contained in opium from the poppy (*Papaver Somniferum*) plant found in Turkey, Mexico, Southeast Asia, China, and India. This plant is 3-4 feet tall with 5-8 egg shaped capsules on top. Ten days after the poppy blooms in June, incisions are made in the capsules permitting a milky fluid to ooze out. The following day the gummy mass (now brown) is carefully scraped off and pressed into cakes of raw opium to dry.<sup>5</sup>

### White willow bark

Bark from the white willow tree is one of the oldest herbal remedies for pain and inflammation, dating back to ancient Egyptian, Roman, Greek, and Indian civilizations, as an analgesic and antipyretic agent. Because of the gastric side effects of aspirin, there has been a resurgence in the use of white willow bark for the treatment of inflammatory syndromes. The mechanism of action of white willow bark is similar to that of aspirin which is a nonselective inhibitor of COX-1 and COX-2, used to block inflammatory prostaglandins.<sup>4</sup>

Various randomized, placebo-controlled studies comparing white willow bark with nonsteroidal agents have shown an efficacy comparable to these agents and aspirin. Salicin from white willow bark is converted to salicylic acid by the liver and is considered to have fewer side effects than aspirin. However, it is costlier than aspirin, and should not be used in children (to avoid the risk of Reye's syndrome), or in patients with peptic ulcer disease, poorly controlled diabetes, hepatic or renal disorders, or other conditions in which aspirin would be contraindicated. The usual dose of white willow bark is 240 mg/day.<sup>3</sup>

### Curcumin (turmeric)

Curcumin is a naturally occurring yellow pigment derived from turmeric (*Curcuma longa*), a flowering plant of the ginger family. It has traditionally been used as a coloring and flavoring spice in food products. Curcumin has long been used in both Ayurvedic and Chinese medicines as an anti-inflammatory agent, a treatment for digestive disorders, and to enhance wound healing. Several clinical trials have demonstrated curcumin's antioxidant, anti-inflammatory, and antineoplastic effects. Results of a study by Zandi and Karin suggested that curcumin might be efficacious in the treatment of cystic fibrosis because of its anti-inflammatory effect. Curcumin is known to inhibit inflammation by suppressing NF-kB, restricting various activators of NF-kB as well as stemming its expression.<sup>5</sup>

Curcumin has also been suggested as a treatment for colitis, chronic neurodegenerative diseases, arthritis, and cancer. In addition, it regulates the activity of several enzymes and cytokines by inhibiting both COX-1 and COX-2. Most studies to date have been performed in animals, but given the centuries of use of curcumin, as well as its now demonstrated activity in the NF- $\kappa$ B, COX-1, and COX-2 inflammatory pathways, it may be considered a viable natural alternative to nonsteroidal agents for the treatment of inflammation. The usual dosage of standardized turmeric powder is 400–600 mg taken three times per day.<sup>6</sup>

#### Green tea

Green tea has long been recognized to have cardiovascular and cancer preventative characteristics due to its antioxidant properties. Its use in the treatment of arthritic disease as an anti-inflammatory agent has been recognized more recently. The constituents of green tea are polyphenolic compounds called catechins, and epigallocatechin-3 galate is the most abundant catechin in green tea.

Epigallocatechin-3 galate inhibits IL-1–induced proteoglycan release and type 2 collagen degradation in cartilage explants. In human *in vitro* models, it also suppresses IL-1 $\beta$  and attenuates activation of the transcription factor NF- $\kappa$ B. Green tea also inhibits the aggrecanases which degrade cartilage.<sup>5</sup>

#### Pycnogenol (maritime pine bark)

Pycnogenol, like white willow bark, is a nutraceutical material that has been used since ancient times. Pycnogenol is derived from the bark of the maritime pine tree (*Pinus maritima*) and has been used for more than 2000 years. It has been considered helpful for wound healing, treating scurvy, healing of ulcers, and reducing vascular inflammation. It contains a potent blend of active polyphenols, which includes catechin, taxifolin, procyanidins, and phenolic acids. It is one of the most potent antioxidant compounds currently known.<sup>4</sup>

#### Boswellia serrata resin (Frankincense)

The *Boswellia* species are trees located in India, Ethiopia, Somalia, and the Arabian Peninsula, and they produce a gum resin called olibanum, better known in the western world as frankincense. This resin possesses anti-inflammatory, anti-arthritic, and analgesic properties. *Boswellia* can inhibit the leukotriene biosynthesis in neutrophilic granulocytes by inhibiting 5-LOX, thus affecting various inflammatory diseases that are perpetuated by leukotrienes. Clinically, the substance is used in the treatment of degenerative and inflammatory joint disorders. It reduces the total white

blood cell count in joint fluid, and it also inhibits leukocyte elastase, which is released in rheumatoid arthritis. In one recent study, a statistically significant improvement in arthritis of the knee was shown after 8 weeks of treatment with 333 mg *B. serrata* extract taken three times a day. The treatment improved function, but radiographically there was no change in the affected joints.<sup>3</sup>

A combination of *Boswellia* and curcumin showed superior efficacy and tolerability compared with nonsteroidal diclofenac for treating active osteoarthritis. *Boswellia* typically is given as an extract standardized to contain 30-40% boswellic acids (300-500 mg two or three times/day). *Boswellia* has been well tolerated in most studies, although some people may experience stomach discomfort, including nausea, acid reflux, or diarrhea.

#### Resveratrol

Resveratrol is a plant-based polyphenol molecule that is found in various concentrations of many different plant sources. The plant is called Japanese Knot weed or *Polygonum cuspidatum*, and the skins of red wine grapes are believed to have the most concentrated amounts of resveratrol. In plants, resveratrol is generally found in the plant skin and acts as a phytoalexin to protect the plant from infection, excessive UV radiation and aide in general plant defense. Resveratrol has also been found to have significant anti-mutation, anti-inflammatory, antioxidant and DNA protective actions, when consumed by animals and humans.<sup>4</sup>

#### Uncaria tomentosa (cat's claw)

*Uncaria tomentosa* and *Uncaria guianensis* are Peruvian herbs derived from woody vines with small claw-like thorns (hence the vernacular name, cat's claw) at the base of the leaf, which allow the plant to climb to heights of up to 100 ft. Traditionally, the bark of cat's claw is used to treat arthritis, bursitis, and intestinal disorders. The active ingredients appear to be polyphenols (flavonoids, proanthocyanidins, and tannins), alkaloids, and sterols. Various studies indicate that this Peruvian herb induces a generalized reduction in proinflammatory mediators.<sup>3</sup>

#### Capsaicin (chili pepper)

*Capsicum annum* is a small spreading shrub which was originally cultivated in the tropical regions of the Americas but is now grown throughout the world, including the US. The small red fruit commonly used to accentuate chili owes its stinging pungency to the chemical, capsaicin. This was isolated by chemists more than a century ago and constitutes approximately 12% of the chili pepper. This fruit has been used for

various medicinal purposes by the native peoples of the American tropics for hundreds of years.

**Ginger**

Ginger is basically a wonder root. It combats nausea and motion sickness, and fights off pain with its anti-inflammatory properties. Some especially great news for the ladies: One study showed that ginger (specifically in the form of a 250g or 500g capsule of powdered ginger) was as effective as ibuprofen in relieving menstrual pain. Plus, ginger can be ingested a variety of ways, from supplements, to tea and cookies, to stir fry.<sup>4</sup>

**Salmon**

Not only is salmon tasty and a healthy protein, but it's full of omega-3 fatty acids, which have been shown to reduce arthritic pain (especially in the neck and back). In one study, the relief experienced from consuming omega-3s in the form of a fish oil supplement was comparable to the relief experienced from taking ibuprofen. Chow down on some of those omega-3s with this baked salmon with avocado yogurt sauce tonight.

**Coffee**

Just one more excuse to grab that second cup of Joe! Research suggests caffeine can reduce pain in those suffering from exercise-induced muscular injury and pain. Not only that, when taken with a standard dose of pain reliever (ibuprofen, for example), one study found that a 100mg to 130mg caffeine supplement — equal to about the amount of caffeine in one cup of coffee — increased pain relief.<sup>5</sup>

**Echinacea and Sage**

Some research shows that throat sprays containing sage or echinacea can help provide relief from that nasty sore throat, though there have been few other studies on this benefit, so the evidence isn't hulk strong. Another survey looking at 14 different studies found that echinacea can decrease the number of cold infections caught, and reduce their durations. Sage is easy to find at most grocery stores and is also especially tasty in any of these recipes, while echinacea is more commonly found in pill and ointment form. When choosing to take a supplement like echinacea, be aware: Supplements aren't regulated by the FDA, so manufacturers can often get away with making unproven claims about both the contents of the pills and the benefits of those contents.<sup>6</sup>

**Tart Cherries**

Turns out tart cherries are good for more than causing a pucker face. Studies have found they can help treat gout (a painful form of arthritis that causes

swollen, hot, red joints caused by a buildup of uric acid in the blood). But it's not just for gout — athletes can benefit, too. In one study, those who drank tart cherry juice for seven days prior to an intense running event showed reduced muscle-pain after the race.<sup>3</sup>

**Whiskey**

No, we do not recommend whiskey for a broken heart or curing any sort of emotional pain. But, it turns out adding a spoonful of warm water may just do the trick to kick that pesky sore throat.

**Oranges**

While vitamin C has been linked to helping prevent the onset of colds and respiratory infections, an antioxidant called beta-cryptoxanthin, found in oranges and other orange fruits and veggies such as sweet potato and cantaloupe, has been found to help reduce the risk of anti-inflammatory conditions like rheumatoid arthritis. Another reason to get out that juicer and start making fresh OJ each day. (Or, you know, just eat an orange.)<sup>5</sup>

**Evening Primrose**

Usually found as oil, this flower's powers have been linked to treating atopic dermatitis (a chronic itchy skin condition), rheumatoid arthritis, and PMS symptoms. The gamma-linolenic acid in the oil has anti-coagulant effects that may help reduce the effects of cardiovascular illnesses.

**Cannabis**

*Cannabis sativa* not legal in most places but very effective as a pain reliever. It is immediate relief in all forms but the tea and tincture is a very great way to use cannabis for pain relief and is a bit longer lasting than smoking. Not to mention better for your lungs! It is often used by those who are terminally ill and those suffering from chronic pain. 16% of cannabis users use it solely for pain relief.<sup>4</sup>

**Kava Kava**

Very effective for treating joint pain, migraines, muscle spasms, back pain, and the neuralgia related to cystic fibrosis. It should be avoided by pregnant women and those with liver problems. It is taken through tincture or a tea. You can also get it in capsule form but that is less effective. It is a sedative so be sure to take that into account before using.

**Arnica**

*Arnica Montana* arnica is used topically in a salve or an infused oil. It is a grief remedy for strains, sprains, bruising and arthritic or inflamed joints. It works almost immediately and is used by many in sports therapy and massage therapy.<sup>6</sup>

**Angelica**

(angelica sinensis) also known as dong quai. It is a Chinese herb and is an anti-inflammatory. Used as a

tincture it is effective for treating pain associated with the respiratory system.

#### Valerian

(*valeriana officinalis*) remedy for headaches. Both tension and migraines respond well to valerian. Also is good for minor aches and pains. Taken as a tea, tincture or capsule.

#### Other Natural Analgesics<sup>3,4,5,6</sup>

##### Gamma-linolenic acid

One of the good fats known to reduce inflammation and stiffness, help migraines and mild diabetic nerve damage.

##### Clove oil

A popular home remedy for toothache.

##### Fennel

Seeds have 16 analgesic and 27 antispasmodic chemicals.

##### Feverfew

Popular for headaches and migraines.

##### Licorice root

Recommended for sore throats. Not for those with high blood pressure, heart issues and other conditions. Research before using.

##### Rosemary, thyme

All used regularly in cooking and have analgesic, antispasmodic and anti-inflammatory properties.

##### Lavender, peppermint, chamomile and damask rose oil

Essential oils commonly used in aromatherapy for pain relief and relaxation.

#### Conclusion

For centuries, natural Analgesic compounds have been used to mediate the Analgesic effect and often with minimum side effects over conventional synthetic analgesics. We have briefly reviewed several of the most commonly used plant and animal derived natural compounds that may possess similar effectiveness in treating the pain reaction. Discovery of natural product chemistry to identify potential novel drugs candidates which will assist in sustaining health and the fight against disease and illness. Thus, it is worthwhile to

explore the applications of those natural compounds in drug discovery.

Through the present reviewed, it has found that the drugs of ayurvedic origin can be utilized in a better form with enhanced efficacy by incorporating in modern dosage forms with higher safety margins and minimal side-effect.

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