

## Natural anti-inflammatory agents for pain relief

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#### FROM ABSTRACT:

The use of both over-the-counter and prescription nonsteroidal medications is frequently recommended in a typical neurosurgical practice. But persistent long-term use safety concerns must be considered when prescribing these medications for chronic and degenerative pain conditions.

Although nonsteroidal medications can be effective, herbs and dietary supplements may offer a safer, and often an effective, alternative treatment for pain relief, especially for long-term use.

#### SIDE EFFECTS OF STEROID DRUGS:

Increased Infection	Dermatitis	Fluid retention	Hyperglycemia
Mood Changes	Hypertension	Stomach Ulcers	Osteoporosis
Cataracts	Increased Appetite	Weight Gain	Depression
Impaired Wound Healing	Adrenal Suppression	Fat Deposits Upper Back-Stomach	Fat Deposits Face-Chest

#### THESE AUTHORS ALSO NOTE:

“In most cases, the genesis of pain is inflammatory, regardless of the etiology.”

This inflammation has 2 primary causes:

- 1) Inflammatory hormones (PGE<sub>2</sub>, LTB<sub>4</sub>, etc.)  
[derived from the omega-6 fatty acid arachidonic acid]
- 2) Inflammatory cytokines (interleukin ((IL))-1a, IL-1b, IL-6 and tumor necrosis factor ((TNF-a)).  
[proteins that are derived form the immune system cells]

“The use of non-steroidal anti-inflammatory drug (NSAID) medication is still the mainstay of most classically taught clinicians for joint and spine related inflammatory pain, despite their commonly known side effects.”

The pro-inflammatory cytokines stimulate the production of the pro-inflammatory hormone prostaglandin E<sub>2</sub> (PGE<sub>2</sub>).

NSAIDs' ability to interfere with the production of prostaglandin E2 (PGE2) is the major mechanism for the anti-inflammatory success of these drugs.

## INFLAMMATORY PATHWAYS

"Prostaglandins act as short-lived localized hormones that can be released by any cell of the body during tissue, chemical, or traumatic injury, and can induce fever, inflammation, and pain, once they are present in the intercellular space."

Thromboxane hormones increase the inflammatory response.

"A major component of the inflammatory pathway is called the arachidonic acid pathway because arachidonic acid is immediately released from traumatized cellular membranes."

Cell membrane trauma releases arachidonic acid. Arachidonic acid is then transformed into the pro-inflammatory hormones prostaglandins and thromboxanes through the enzymatic action of cyclooxygenase.

"Nonselective NSAIDs' major side effects include significant gastrointestinal upset, gastritis, ulceration, hemorrhage, and even death. By blocking COX-1, which also normally acts to protect the gastrointestinal mucosa, nonselective NSAIDs and aspirin can cause significant gastric tissue damage."

"NSAIDs can delay muscle regeneration and may reduce ligament, tendon, and cartilage healing."

NSAIDs also have adverse effects on kidney function. "The National Kidney Foundation asserts that approximately 10% of kidney failures per year are directly correlated to substantial overuse of NSAIDs."

Selective COX-2 inhibiting NSAIDs were thought to reduce inflammatory pain without enhancing GI bleeding. Celebrex was FDA approved in 1998, followed by the approval of Vioxx and Bextra in 1999. These drugs "quickly became the mainstay for the treatment of chronic pain conditions related to inflammation."

On September 30, 2004, Vioxx was withdrawn because it "doubled the risk of serious thromboembolic events, including myocardial infarction."

## **Natural compounds for inflammation**

"Because of the significant side effect profiles of steroidal and NSAID medications, there is a greater interest in natural compounds, such as dietary supplement and herbal remedies, which have been used for centuries to reduce pain and inflammation."

Nuclear Factor kappa-B (Nf-kB) controls the transcription of DNA for the perpetuation of the inflammatory immune response. "It acts as a switch to turn inflammation on and off in the body."

"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."

"The US governmental agencies, through the FDA and others, routinely inspect the manufacture of vitamins or supplements made in this country, as they do for any other food product."

"Products such as omega-3 essential fatty acids (EFAs) (O3) do have strong scientific support to be considered as an alternative and/or complementary agent to NSAIDs. Published studies have shown the effectiveness of O3 to successfully treat spine-related pain."

### **Omega-3 EFAs (fish oil)**

The use of fish oil for the treatment of muscular, skeletal, and discogenic diseases, can be traced back to the late 18th century.

"Research has shown that the omega-3 polyunsaturated fatty acids are some of the most effective natural anti-inflammatory agents available." [7 references]

"With the discovery that vascular inflammation is the underlying cause of coronary artery disease, fish and fish oil supplements are now recommended by the American Heart Association for the prevention of this disease."

"Countries that have the highest fish consumption also have a lower incidence of neurodegenerative disease and depression."

"The biological basis for the effectiveness of fish oil in treating arthritis has been well documented with many positive clinical studies, when compared to traditional pharmaceutical anti-inflammatory agents."

"The active ingredients in fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), enhance the conversion of COX to prostaglandin E3. A natural anti-inflammatory agent, prostaglandin E3 competitively inhibits the effects of the arachidonic acid conversion to prostaglandin E2, a highly inflammatory substance."

"Prostaglandin E3 also inhibits the synthesis of TNF-a and IL1b, both of which are inflammatory cytokines."

“The EPA and DHA can inhibit the 5-LOX pathway, which converts arachidonic acid to inflammatory leukotrienes.”

When EPA and DHA are incorporated into articular cartilage chondrocyte cell membranes, there is a dose-dependent decrease in the expression and activity of the enzymes that degrade cartilage.

Omega-3 EFA, found in fish oil, can directly reduce the degenerative enzymes and reduce the inflammation in synovial cartilage.

Belching may occur if fish oil supplements are not taken with meals.

“Persons on a regimen of anticoagulant medications should not take omega-3 EFAs because of the possibility of increasing the bleeding potential.”

### **White willow bark**

Bark from the white willow tree has analgesic and antipyretic properties.

Salicin from white willow bark is converted to salicylic acid by the liver and is considered to have fewer side effects than aspirin.

White willow bark 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.”

### **Curcumin (turmeric)**

“Curcumin is a naturally occurring yellow pigment derived from turmeric, a flowering plant of the ginger family. It has traditionally been used as a coloring and flavoring spice in food products. Curcumin is an anti-inflammatory agent, and has antioxidant, anti-inflammatory, and antineoplastic effects.”

Curcumin is known to inhibit inflammation by suppressing NF-kB and COX enzymes, and “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.”

### **Green tea**

Green tea has cardiovascular and cancer preventative characteristics due to its antioxidant properties; its use in the treatment of arthritic disease as an anti-inflammatory agent is more recent.

The constituents of green tea include polyphenolic compounds called catechins; epigallocatechin-3 galate is the most abundant catechin in green tea.

Epigallocatechin-3 galate inhibits NF- $\kappa$ B and the production of pro-inflammatory cytokines.

Green tea inhibits the aggrecanases that degrade cartilage.

Green tea has both anti-inflammatory and chondroprotective effects.

Increased green tea consumption in Asia may lead to significant cardiovascular, neuroprotective and cancer prevention properties.

The recommendation for green tea consumption is 3–4 cups a day, or green tea extract dosage of 300–400 mg a day.

### **Pycnogenol (maritime pine bark)**

“Pycnogenol is derived from the bark of the maritime pine tree and has been used for more than 2000 years.”

Pycnogenol is helpful for wound healing, treating scurvy, healing of ulcers, and reducing vascular inflammation.

Pycnogenol 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.

Pycnogenol inhibits NF- $\kappa$ B production of pro-inflammatory cytokines.

“Studies have shown that pycnogenol is 50–100 times more potent than vitamin E in neutralizing free radicals and that it helps to recycle and prolong the activity of vitamins C and E.”

“Studies have shown pycnogenol to be effective in reducing blood pressure and reducing the risk of venous thrombosis by its effect on vascular endothelium. The usual dosage is 100–200 mg daily.”

Because pycnogenol enhances immune system function, it should not be taken by patients who are being treated with immunosuppressants or by those receiving corticosteroid drugs, both of which have the opposite effect on the immune system.

### **Boswellia serrata resin (Frankincense)**

Boswellia possesses anti-inflammatory, anti-arthritic, and analgesic properties.

Boswellia can inhibit the leukotriene biosynthesis, thus affecting various inflammatory diseases that are perpetuated by leukotrienes.

Clinically, Boswellia is used in the treatment of degenerative and inflammatory joint disorders.

“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).”

### **Resveratrol**

Resveratrol is a plant-based polyphenol molecule that is found in many different plant sources, but the skins of red wine grapes are believed to have the highest concentration.

In plants, resveratrol protects the plant from infection, excessive UV radiation and aids 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.”

“Most of the active research with resveratrol has been done in neuro and cardioprotection, but several studies are being reported on resveratrol’s use for arthritic joint pain.”

Resveratrol inhibits NFkB and the production of pro-inflammatory cytokines.

The typical dose for Resveratrol is 50 to 500 mg daily.

### **Uncaria tomentosa (cat’s claw)**

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.

Cat’s claw inhibits NFkB and the production of pro-inflammatory cytokines.

“Cat’s claw can be consumed as a tea (1000 mg root bark to 8 oz water), or as a dry, standardized extract in a capsule (20-60 mg daily).”

## Capsaicin (chili pepper)

Capsicum accentuates chili's stinging pungency.

"Capsaicin produces highly selective regional anesthesia by causing degeneration of capsaicin-sensitive nociceptive nerve endings which can produce significant and long-lasting increases in nociceptive thresholds."

Capsaicin inhibits NF-kB, thus producing an anti-inflammatory effect.

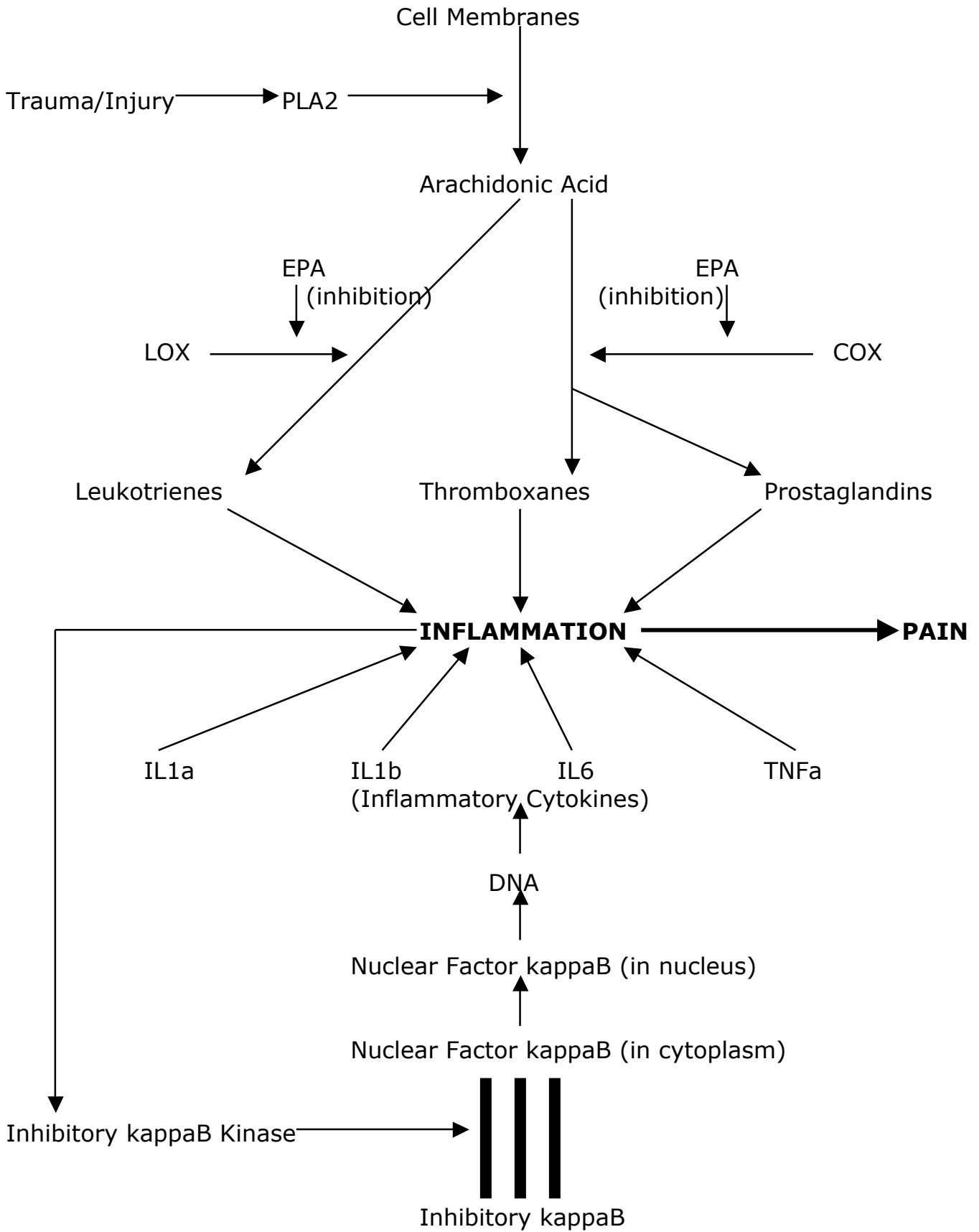
## CONCLUSIONS

Anti-inflammatory agents such as NSAIDs "can have undesirable side effects such as gastric ulceration and, infrequently, myocardial infarction and stroke."

"For centuries, natural anti-inflammatory compounds have been used to mediate the inflammatory process and often with fewer side effects [than NSAIDs]."

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- PLA2 = Phospholipase A2 (the enzyme that cleaves AA from the cell membrane following trauma / injury)
- AA = Arachidonic Acid (an omega-6 fatty acid commonly found in cell membranes)
- LOX = Lipoxygenase (the enzymes that converts AA into pro-inflammatory LT hormones)
- COX = Cyclooxygenase (the pro-inflammatory enzymes that convert AA into the pro-inflammatory PG and TXA hormones)
- LT = Leukotrienes
- TXA = Thromboxanes
- PG = Prostaglandins
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- Interleukin-1a = IL1a (a pro-inflammatory cytokine protein)
- Interleukin-1b = IL1b (a pro-inflammatory cytokine protein)
- Interleukin-6 = IL6 (a pro-inflammatory cytokine protein)
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- Tumor Necrosis Factor alpha = TNFa (a pro-inflammatory cytokine protein)
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- NF-kB= Nuclear Factor kappaB (pro-inflammatory protein that lives in the cell cytoplasm)
- IkB = Inhibitory kappaB ( a protein that when attached to NFkB inhibits its pro-inflammatory influence; consequently it's an anti-inflammatory protein)
- IkBK = Inhibitory kappaB Kinase (an enzyme that cleaves NFkB away from its inhibitory Ikb protein, allowing NFkB to cross into the nucleus and activate the genes that produce pro-inflammatory cytokines)
- CK = Cytokines (pro-inflammatory proteins made by immune system cells)
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- EPA = Eicosapentaenoic Acid (anti-inflammatory omega-3 fatty acid)





These authors indicate that the inflammatory mediators above can be triggered as a consequence of:

**Stress**  
**Infection**  
**Radiation**  
**Trauma/Injury**  
**Arachidonic Acid**  
**Inflammatory Diet**  
**Allergic Immune Response**

This inflammation is a factor in:

**Pain**  
**Cancer**  
**Thrombosis**  
**Atherosclerosis**  
**Insulin Resistance**  
**Neurodegeneration**

