

Herbal COX-2 Inhibitors: A Natural Alternative

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On Sept. 30, 2004, the pharmaceutical giant Merck & Co. Inc. announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain COX-2 inhibiting medication. The company's decision was based on data from a new, three-year prospective, randomized, placebo-controlled clinical trial, which showed that after 18 months of use, VIOXX increased relative risk for confirmed cardiovascular events, such as heart attack and stroke. Almost immediately commentary began about the potential for natural COX-2 inhibitors to fill the VIOXX void.

Undoubtedly, you've had customers asking about this issue. But do natural COX-2 inhibitors really offer a viable alternative to VIOXX? It is our position that they do. To understand why this might be so, it's important to understand the role of the COX-2 enzyme.

There are two cyclo-oxygenase (COX) enzymes that work in the body, COX-1 and COX-2. The COX-1 enzyme is expressed in most tissues, and is necessary for a variety of important internal housekeeping functions, such as protecting the stomach lining, maintaining renovascular function and platelet aggregation. The COX-2 enzyme is necessary for inflammation, a normal, healthy attempt by the body to heal itself. However, when inflammation gets out of control (such as in the case of arthritis, or other chronic inflammatory disorders) ongoing pain and discomfort is the result. That's where botanical COX-2 inhibitors can help. Botanical COX-2 inhibitors block the action of the COX-2 enzyme, which helps reduce inflammation and pain.

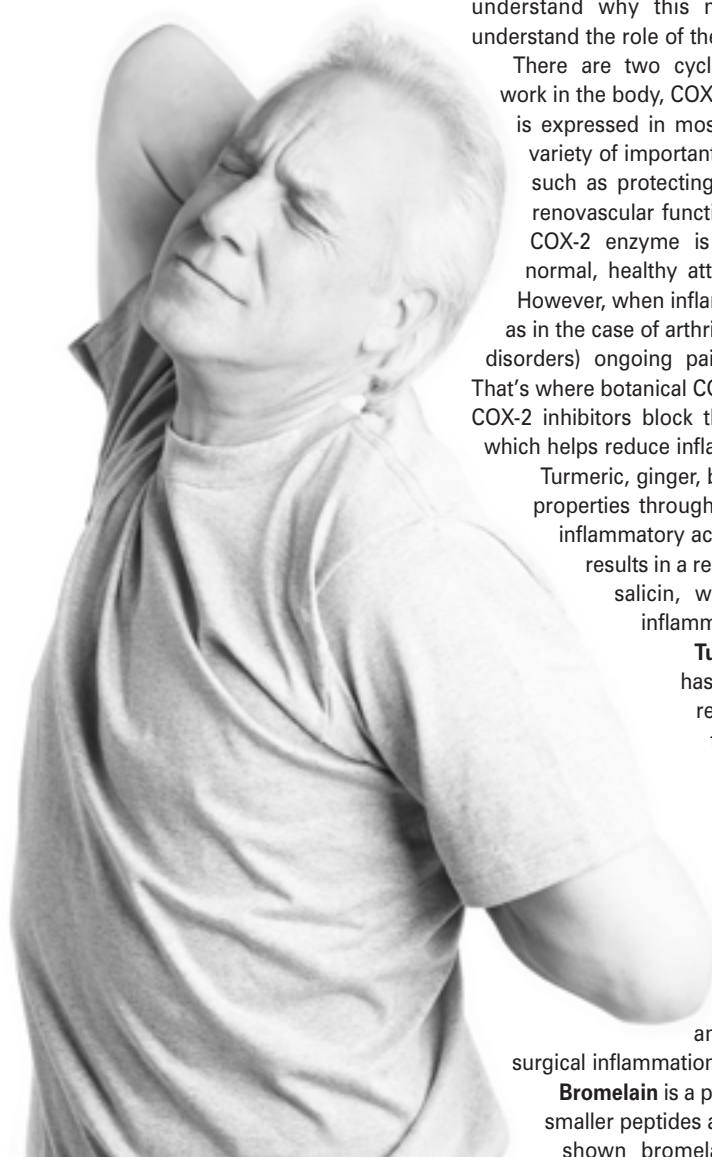
Turmeric, ginger, boswellia, hops and salicin all have demonstrated anti-inflammatory properties through their role as botanical COX-2 inhibitors. Bromelain also has anti-inflammatory activity, but not as a COX-2 inhibitor. A reduction of inflammation also results in a reduction of pain. White willow bark and meadowsweet are sources of salicin, which has analgesic (pain-relieving) properties as well as anti-inflammatory properties.

Turmeric is a bright yellow, ancient spice and a traditional remedy that has been used as a medicine, condiment and flavoring based on records dating back to 600 B.C. Its medicinal value is essentially due to its curcuminoid content. The curcuminoids inhibit 5-lipo-oxygenase (LOX) and COX, resulting in a well-established anti-inflammatory action.^{1,2} Treatment with curcuminoids was found to be as effective as cortisone or phenylbutazone in instances of acute inflammation, and about half as effective as these drugs for chronic inflammation.³

In research on people with rheumatoid arthritis, curcuminoids were found to be useful for reducing inflammation, pain and stiffness.⁴ In a double blind study, curcuminoids were found to be superior to a placebo or the non-steroidal anti-inflammatory drug phenylbutazone for alleviating post-surgical inflammation.⁵

Bromelain is a proteolytic enzyme found in pineapples that breaks down protein into smaller peptides and amino acids. Beyond its protein digesting capacity, research has shown bromelain has anti-inflammatory activity. At least four studies using

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bromelain have demonstrated its effectiveness in the treatment of minor injuries (bruises, sprains, strains, hematomas, lacerations, abrasions) as well as severe injuries (low back pain, fractures, minor surgery).⁶ Research has also shown this enzyme was effective at decreasing the inflammation and edema resulting from surgery and injury.⁷ Furthermore, there have been positive reports in clinical trials showing decreased thrombophlebitis (inflammation of veins) and pain from angina and thrombophlebitis.^{8,9} Research has also shown that bromelain helped patients with rheumatoid arthritis; 73 percent of whom had good to excellent results.¹⁰

One unexpected application for bromelain's anti-inflammatory benefits has been to relieve symptoms of acute sinusitis. In a double blind study comparing the use of bromelain with placebo, 87 percent of patients who took bromelain reported good to excellent results.¹¹ Other double blind research has shown that bromelain reduces symptoms of sinusitis.^{12,13}

Bromelain's does not appear to be a COX-2 inhibitor, and all of its mechanisms of action are still not completely resolved. For example, it may selectively decrease thromboxane generation and change the ratio of thromboxane/prostacyclin (PGI₂) in favor of prostacyclin. Nonetheless, it has been demonstrated to be a safe and effective supplement.¹⁴ The potency of Bromelain is measured in GDUs (gelatin digesting units), and it appears more is better.

Although it's probably more known for its anti-nausea properties (i.e., treatment of motion sickness and morning sickness), **ginger** is also an effective anti-inflammatory herb that has historically been used for arthritis and rheumatism. In a study of patients with rheumatoid arthritis, osteoarthritis and muscular discomfort, the majority experienced, to varying degrees, relief of pain and swelling.¹⁵ None of the patients reported adverse effects during the period of ginger consumption, which ranged from three months to 2.5 years. Another double blind trial found ginger extract to be more effective than placebo at relieving pain in people with OA of the hip or knee.¹⁶ Likewise, in another double blind study, ginger was significantly more effective than a placebo in pain relief and overall improvement.¹⁷ Ginger is considered to exert its anti-inflammatory activity by inhibiting COX-2 and LOX pathways.¹⁸ Commercial ginger products are generally standardized to levels of gingerol, which are oleo-resins considered to be main active principles.

The resin of **Boswellia serrata** is used traditionally for a variety of inflammatory diseases, such as rheumatoid arthritis, osteoarthritis and cervical spondylitis (inflammation of the vertebrae). The main constituents of the resin are boswellic acids, to which most preparations are standardized, which have been found to inhibit the synthesis of leukotrienes (inflammatory compounds produced when oxygen interacts with polyunsaturated fatty acids). A number of chronic inflammatory conditions are associated with leukotriene formation. Unlike pharmaceutical corticosteroids that inhibit leukotriene synthesis, boswellic acids exhibit no significant side effects or toxicity.^{19,20} Boswellic acids have been found specifically to inhibit 5-lipoxygenase, the key enzyme of leukotriene biosynthesis.²¹

In a clinical investigation, boswellic acids were given to more than 260 patients with rheumatoid arthritis.²² Definite effects were found in the reduction of swelling and pain as compared to placebo; morning stiffness was reduced; patients reported cutting back on their intake of NSAIDs during the treatment period; and patients' general health and well-being showed improvement. The boswellic acids were found to be effective in reducing the symptoms of rheumatoid arthritis in 50 percent to 60 percent of the patients involved in the investigation.

There are 300 species of *Salix* we call willow, native to England, Europe, Asia and North America. According to Dioscorides in his *De Materia Medica* (first century A.D.), willow was used therapeutically for gout and rheumatic joint diseases. Ancient Egyptians used the bark, as we do today, for pain and inflammation; and Native Americans relied on willow for its analgesic properties.²³ In 1829, willow's active chemical, **salicin**, was discovered. In 1838, pure salicylic acid was synthesized by an Italian chemist, not from willow but from wintergreen and other plants. Salicin and salicylic acid were widely used through the 19th century for fever, gout, pain and inflammation. However, as usual, when you isolate chemicals from plants or synthesize them, you almost always increase their toxicity. The high doses of salicylic acid used routinely led to gastric irritation and vomiting. In 1893, Felix Hoffman at the Bayer Company in Germany was able to synthesize acetylsalicylic acid (which had less gastric side effects than salicylic acid), and aspirin was born.

It is important to realize that salicin from willow, meadowsweet or other plants can be split-off by the body to create salicylic acid, providing anti-inflammatory and pain-relieving actions with the same COX-2

inhibition properties as aspirin,²⁴ although salicin will not function as an anticoagulant (blood thinner) like aspirin.²⁵ In one study, 240 mg of salicin (from white willow bark extract) showed modest effectiveness in treating pain associated with knee and/or hip osteoarthritis over a period of weeks.²⁶ In another study, 120 to 240 mg of salicin (again from white willow bark extract) showed promise in reducing low back pain.²⁷ The higher concentration of 240 mg salicin was more effective, although it took up to one week for significant relief.

Hops is perhaps best known as a flavoring agent in beer, although it has also been used to reduce anxiety²⁸ and insomnia.²⁹ More recent research has shown a hops extract high in alpha acids exhibited COX-2 inhibition over nine hours, equivalent to ibuprofen 400 mg.³⁰ What was especially nice was that this extract had very mild COX-1 inhibition, which means it is less likely than its pharmaceutical counterparts to induce gastric problems. In another open-label, eight-week trial, the effectiveness of a combination of alpha acids from hops, rosemary extract and oleanolic acid were tested in subjects with osteoarthritis, rheumatoid arthritis and fibromyalgia.³¹ The results were that osteoarthritis subjects showed a 50 percent decrease in pain, whereas there were no statistically significant differences in the rheumatoid arthritis and fibromyalgia subjects.

The aforementioned natural ingredients have demonstrated COX-2 inhibiting properties (with the exception of bromelain, where the anti-inflammatory activity works by a different mechanism). Hence, singly or in combination, and if properly concentrated and dosed, they may offer a viable alternative to the now defunct VIOXX. Nevertheless, it is prudent to recommend that customers work with their physicians if they wish to substitute these or any other natural substances for pharmaceutical medications.

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