

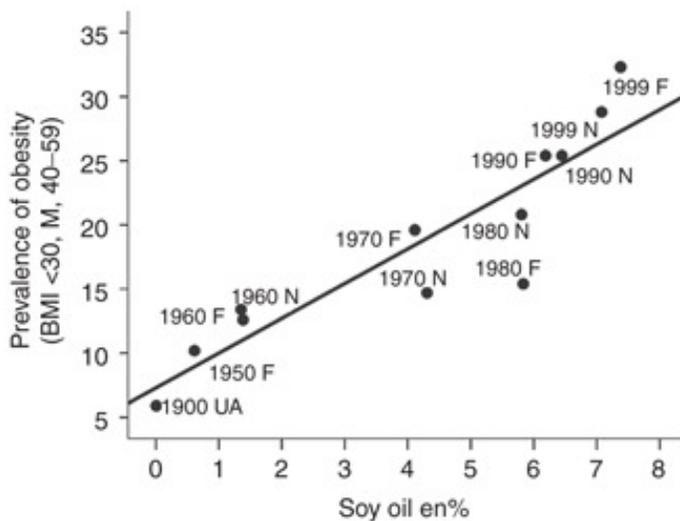
# Dietary Sources of Inflammation

Inflammatory signaling molecules known as leukotrienes trigger inflammation in the human body. Overproduction of these molecules may result in chronic inflammatory conditions. The 5-lipoxygenase (5-LOX) pathway is the major source of proinflammatory leukotrienes. 5-LOX breaks down arachidonic acid to pro-inflammatory compounds like leukotriene, a molecule that attacks joints, arterial walls, and other tissues. 5-LOX itself facilitates undesirable cell division changes. Excessive 5-LOX activity is associated with 7 of the leading 10 causes of death in the US, causing more than 1.5 million deaths annually<sup>1</sup>.

## 5-LOX Pathway



5-LOX activity is stimulated in the presence of high levels of arachidonic acid (AA) which is derived from dietary omega 6 poly unsaturated fatty acids (PUFAs). "In the typical Western diet, 20-25 fold more [omega 6] fats than [omega 3] fats are consumed."<sup>18</sup> The most common dietary source of omega 6 is linoleic acid (LA), found in high concentrations in soy, corn, safflower, and sunflower oils. "In at least the United States and Australia, the widespread dietary use of LA-rich oils such as soybean, corn, sunflower, and safflower oils results in intakes of LA at ~7-8% of dietary energy."<sup>18</sup> Data published by the North American Association for the Study of Obesity has shown that this increase in consumption of oils with high concentrations of LA is correlates with the increasing rate of obesity.



Dietary sources of linoleic acid (LA) and increasing prevalence rates of male obesity in the United States during the 20th century. Prevalence of male obesity (40–59 years, BMI >30) in each year is indicated by source: UA-Union Army Veterans, F-Framingham cohorts, N-NHANES cohorts<sup>19</sup>

A combination of dietary intervention and therapeutic formulations can help to reduce 5-LOX activity and leukotriene formation and may prevent the negative effects associated with high concentrations of LA/AA.

# A Deadly Enzyme

Research has tied numerous medical conditions to a single enzyme - 5-LOX. "5-LOX stimulates the manufacture in the body of pro-inflammatory molecules called leukotrienes."<sup>1</sup>

*"Hundreds of published studies connect leukotrienes to cardiovascular disease, cancer, arthritis, and breathing disorders such as asthma and chronic obstructive pulmonary disease (COPD). They have also been implicated in Alzheimer's, inflammatory bowel diseases, and osteoporosis."*<sup>1</sup>

## **Obesity -**

Chronic inflammation is an underlying factor of obesity and its peripheral diseases including metabolic syndrome and insulin resistance. Leukotriene-producing 5-LOX activity is increased in humans with obesity and insulin resistance. When leukotriene inhibitors were introduced to obese mice, they "were protected from systemic glucose and insulin intolerance and this was associated with a decrease in inflammation in adipose tissue and liver and a decrease in hepatic triglyceride accumulation". This suggests that controlling the 5-LOX enzyme is a valid therapeutic target for controlling obesity and related diseases.

## **Asthma -**

Proinflammatory leukotrienes have been shown to play critical roles in both acute and chronic asthma. "[L]eukotrienes are one of several substances which are released by mast cells during an asthma attack, and it is leukotrienes which are primarily responsible for the bronchoconstriction. In chronic, more severe cases of asthma, general bronchial hyperreactivity (or smooth muscle twitchiness) is largely caused by eosinophils, which are attracted into the bronchioles by leukotrienes..."<sup>16</sup>

Blocking leukotriene activity has therefore become a common target of anti-asthma medication. Reducing leukotriene formation through inhibition of the 5-LOX enzyme has proven to be effective in preventing bronchoconstriction and protecting against asthma attacks. 5-LOX inhibitors "also reduce the influx of eosinophils, thus limiting inflammatory damage in the airway."<sup>16</sup>

## **Arthritis -**

Leukotrienes can provoke most of the signs and symptoms of arthritis as a result of the inflammatory response. "Interplay of synovial cells and the incoming leukocytes leads to production of cytokines and activation of the complement cascade"<sup>17</sup> which leads to perpetual inflammation.

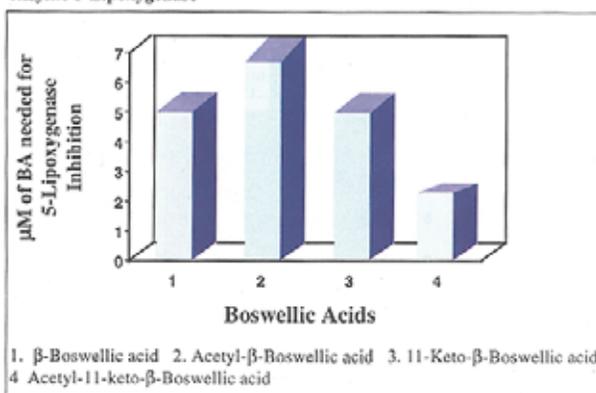
Mouse models of various conditions have given us new insights about human biology and led to the development of effective therapies; arthritis is no exception. "Mice lacking either the enzymes involved in [leukotriene] biosynthesis or the [leukotriene] receptors are completely protected from the development of [arthritis]. . . Prophylactic treatment with a 5-LO[*sic*] antagonist also completely blocked disease from occurring in wild-type mice"<sup>17</sup>

## An Ancient Wisdom

“Novel antiinflammatory<sup>[sic]</sup> therapies can be developed that take advantage of positive interactions between the dietary fats and existing or newly developed pharmaceutical products.”<sup>18</sup>

Frankincense has been used in religious ceremonies for thousands of years. Derived from the *Boswellia Serrata* tree, frankincense has also been utilized in ancient medicine for thousands of years. New research into frankincense and the *Boswellia* resin has revealed the value of this ancient ingredient by finding that boswellic acids are powerful inhibitors of pro-inflammatory molecules and inhibit the enzyme 5-LOX, intervening at the cellular level to block its unwanted effects. Inhibiting this enzyme restricts the synthesis of inflammatory signaling leukotrienes, which is accelerated by dietary LA.

Figure 1 : Biological activity of various  $\beta$ -Boswellic acids in inhibiting the enzyme 5-Lipoxygenase

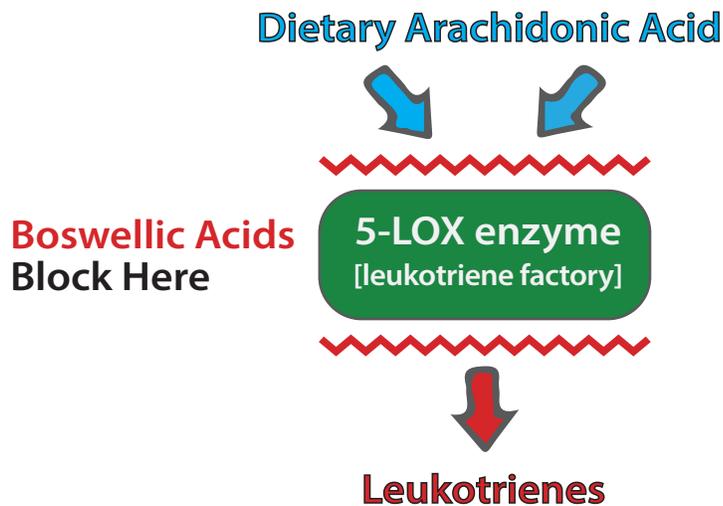


Boswellic acids inhibit the leukotriene biosynthesis by a non-redox, noncompetitive inhibition of 5-lipoxygenase [5-LOX]. The effect is triggered by boswellic acids binding to the enzyme.<sup>7</sup>

A study published in the *Journal of Ethnopharmacology*<sup>9</sup> found that when *Boswellia serrata* was introduced into a 5-LOX test system, where suspensions of rat peritoneal neutrophils were stimulated by calcium and calcium ionophore A23187 to produce leukotrienes, *Boswellia serrata* significantly decreased production of leukotrienes and total 5-LOX products.

The *Boswellia serrata* extract is the first selective, direct, non-competitive and non-redox-type inhibitor of 5-lipoxygenase, the key enzyme for leukotriene biosynthesis. Experimental and clinical usage of *Boswellia* indicates it has none of the side-effects on blood pressure, heart rate, or the gastric irritation and ulcers associated with many anti-inflammatory and anti-arthritis drugs.

## Summary



Chronic inflammation can lead to various debilitating symptoms. The primary treatment for many years has been NSAIDs which have side-effects so severe they rival the symptoms they promise to treat. Those who suffer from chronic inflammation are often so desperate for relief they have had no choice but to accept these side effects.

New research into Boswellia, used for thousands of years in traditional medicine to treat conditions we now recognize as being caused by inflammation, shows that this ancient herb may be not only safer than NSAIDs, but more effective as well. This is largely due to Boswellia's ability to block the enzyme 5-LOX without significant side effects.

## Boswella 5-LOX Inhibitor

Available in capsule and cream forms

**Each capsule contains:** 300mg. of boswellic acids.

**Cream contains:** 10% methyl salicylate and .025% of capsaicin in a base of 10% boswellia serrata and antioxidant vitamins A, C & E with a special liposome delivery system.



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## References

1. Sherman, J. (2011). Neutralize a Lethal Enzyme. *Life Extension*. Retrieved from: <http://www.lifeextension.com/Magazine/2011/SS/Neutralize-a-Lethal-Enzyme/Page-02>
2. (2016). Medical Definition of Prostaglandin E2. *MedicineNet*. Retrieved from: <http://www.medicinenet.com/script/main/art.asp?articlekey=24892>
3. Ogbru, A. (2016). NSAIDs Drug Information. *RxList*. Retrieved from: [http://www.rxlist.com/nsaids\\_nonsteroidal\\_antiinflammatory\\_drugs/drugs-condition.htm](http://www.rxlist.com/nsaids_nonsteroidal_antiinflammatory_drugs/drugs-condition.htm)
4. Gurkirpal, S. (1998). Recent Considerations in Nonsteroidal Anti-Inflammatory Drug Gastropathy. *The American Journal of Medicine*, 105(1B), 31S-38S.
5. (2014). Boswellia: new studies show effective pain relief. *Life Extension*.
6. (2016). *Celecoxib Prescribing Information*. Retrieved from: [http://www.apotex.com/us/en/products/downloads/pil/cele\\_imcp\\_50mg\\_ins.pdf](http://www.apotex.com/us/en/products/downloads/pil/cele_imcp_50mg_ins.pdf)
7. Ammon, H. (2002). Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases. *Wiener Medizinische Wochenschrift* 152(15-16), 373-8
8. Zucker, M. (1995). Boswellia: An Ancient Herb Combats Arthritis. *The Natural Way*, June/July, 60-61.
9. Ammon, H.P.T., Safayhi, H., Mack, T., Sabieraj, J. (1993). Mechanism of antiinflammatory actions of curcumine and boswellic acids. *Journal of Ethnopharmacology*, 38(2-3), 113-9
10. Cameron, M., Chrubasik, S. (2014.) Oral herbal therapies for treating osteoarthritis. *Cochrane Database Syst Rev*, 22(5), CD002947
11. McDonagh, E. W., (1992). Don't Shoot That Horse. *Acres, USA*.
12. Majeed, M., Badmaev, V., Gopinathan, S., Rajendran, R., Norton, T., & Braly, J. (1996). *Boswellin The Anti-Inflammatory Phytonutrient*. New Jersey: Nutriscience Publishers.
13. Sailer, E.R., Schweizer, S., Boden, SE., Ammon, HP., Safayhi, H. Characterization of an acetyl-11-keto-beta-boswellic acid and arachidonate-binding regulatory site of 5-lipoxygenase using photoaffinity labeling. *Eur J Biochem*, 256(2), 364-8.
14. Majeed, M., Nujoma, Y., Badmaev, V., Prakash, L. (1999). *Boswellin: After the Books*. New Jersey: Nutriscience Publishers.
15. A. Kimmatkar, N., Thawani, V., Hingorani, L., Khiyani, R. (2003). Efficacy and tolerability of Boswellia serrata. *Phytomedicine*, 10(1), 3-7.
16. A. Berger. (1999). What are leukotrienes and how do they work in asthma? *BMJ*, 319, 90.
17. Mathis, S., Venkatakrishna, J., and Haribabu, B. (2007). Role of Leukotriene B4 Receptors in Rheumatoid Arthritis. *Autoimmun Rev*. 7(1), 12-17.
18. James, M.J., Gibson, R.A., & Cleveland, L.G. (2000). Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*, 71(1 suppl), 343S-8S
19. Alvheim, A.R., Kjellevoll, M., Osei-Hyiaman, D., et. al. (2012). Dietary Linoleic Acid Elevates Endogenous 2-AG and Anandamide and Induces Obesity. *Obesity*, 20(10), 1984-94.

\*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, mitigate or prevent any disease.