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# Medical Food Arthroben™ for Joint Health

## Managing the metabolic processes of osteoarthritis



### WHITE PAPER ABSTRACT

Medical food for effective, non-NSAID, anti-inflammatory relief of osteoarthritis

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# INTRODUCTION

Osteoarthritis (OA), the most common form of arthritis, affects more than 27-million Americans. It is estimated that this number may double by 2020 because of an aging population and a greater number of overweight adults.

Osteoarthritis is characterized as a chronic condition, whereby cartilage tissue that cushions joints breaks down, causing stiffness, pain and loss of joint movement. It is a gradually occurring condition that is often perceived by patients as a nuisance and a normal symptom of aging, until the stiffness and pain become too painful to ignore.

The OA process actually begins 20 years before a narrowing of the joint space is detectable as a disease, which means early preventive measures are crucial to slowing the disease progression. Studies are ongoing to define biomarkers that reflect changes in composition of joint tissue that correlate with clinical outcomes.[i]

According to a knee health study by the Osteoarthritis Initiative (OAI), the risk of persons age 65 and older becoming immobile due to knee OA is greater than for any other condition. Research shows that certain aspects, such as knee pain, prior knee injury or knee surgery, OA of the hand, and obesity are known factors that may lead to OA.[ii]

Current therapeutics for OA only address symptom relief and are limited to over the counter (OTC) pain relievers, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase 2 inhibitors (COX-2 inhibitors). Though these drugs relieve pain, gastrointestinal complaints are a common side effect, including nausea, heartburn, dyspepsia and abdominal pain.

More serious adverse reports include bleeding ulcers, kidney and/or liver damage, cardiovascular events and congestive heart failure. As many as 107,000 patients are hospitalized annually and 16,500 die from NSAID-related GI complications – not including deaths from OTC NSAIDs.[iii] Another worrisome issue is "a large majority of patients with serious GI complications due to NSAIDs do not even have preceding mild side effects," according to a cohort study of 1921 patients.[iv]

As mentioned earlier, though NSAIDs may relieve pain, they do not address mobility, joint function and the underlying metabolic pathways that lead to OA progression. As patients seek to stay active longer, they are increasingly interested in health options that slow the progression of chronic diseases like OA. One such option is targeted medical foods for the dietary management of OA and musculoskeletal inflammation. The purpose of this white paper is to discuss the role of a specific medical food for managing joint inflammation and improving overall joint health.

# LEUKOTRIENES, PROSTAGLANDINS & OSTEOARTHRITIS

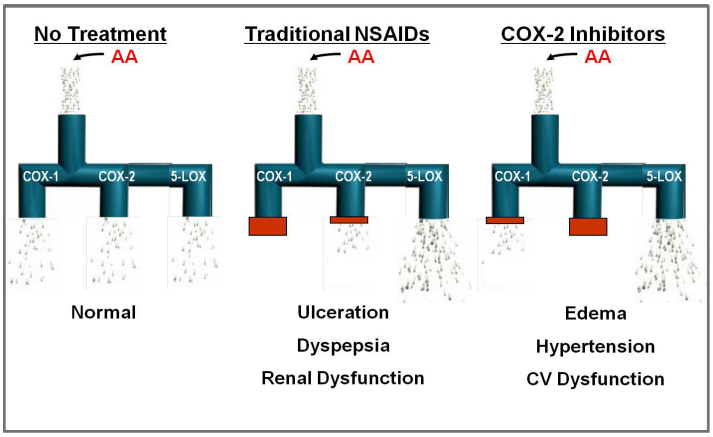
Though the exact cause of OA is not understood, the mediators involved in functional changes and the progression of the disease are understood. The pathophysiology of OA includes cartilage degradation from enzymes, cytokines, leukotrienes (LTs) and prostaglandins (PGs). All of these mechanisms may also contribute to pain and inflammation in OA.

The progressive nature of OA increases production of LTs and PGs from arachidonic acid (AA), which leads to joint damage, pain and inflammation. LTs and PGs are produced by three enzymes: 5-lipoxygenase (5-LOX), cyclooxygenase COX-1 and COX-2, as part of the arachidonic acid (AA) pathway.[v,vi,vii] 5-LOX, along with other enzymes, converts AA to leukotrienes (LTB4, LTC4, LTD4 and LTE4) and COX-1 converts AA to thromboxanes (TXA2) and PGs (PGD2, PGE2, PGF2 and PGI2 ).[viii]

The AA pathway has a cascading affect. Its products and mediating enzymes are crucial to human physiology for vascular homeostasis, renal homeostasis, bone formation, and gastrointestinal protection. Yet, it can also be the cause of unwanted pain and inflammation in OA because disruptions of the AA pathway can lead to pro-inflammatory complications, particularly in the gastric system.

The primary mechanism of pain relief for NSAIDs and selective COX-2 inhibitors is to disrupt the AA pathway. This may well reduce pain, but it may also lead to unwanted side effects. Inhibiting COX-1 and COX-2 enzymes with non-steroidal anti-inflammatory drugs and selective COX-2 inhibitors reduces the levels of PGs, which results in pain reduction. However, the inhibition may also cause an unconventional processing of arachidonic acid via the 5-LOX pathway.[ix] This can lead to inflammatory and toxic LTs, which may lead to gastrointestinal and kidney dysfunction and/or problems with fluid retention, hypertension and cardiovascular issues. See Diagram 1.

## DIAGRAM 1



# FLAVOCOXIDS & ANTI-INFLAMMATION

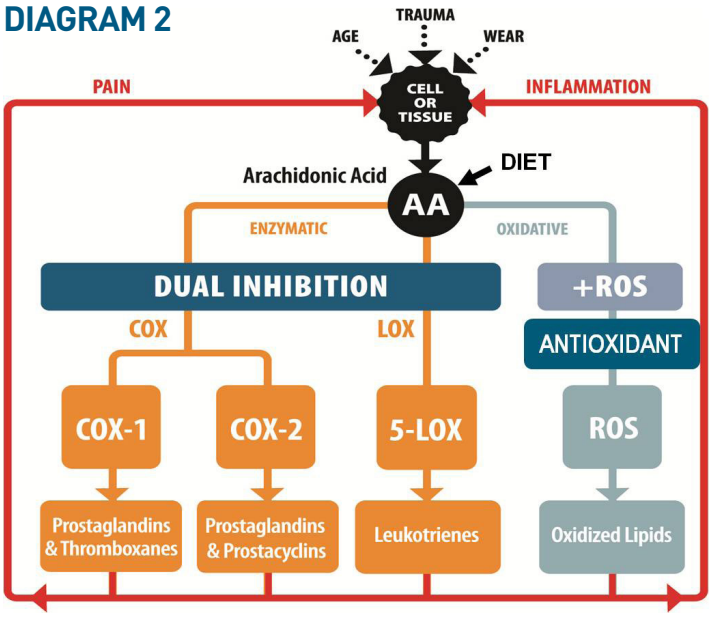
It is increasingly accepted that diet plays a significant role in the genesis and development of OA. Multiple studies show that when OA patients revert to a diet including ample fruits and vegetables and omega-3 fatty acids, the result is an improvement of OA symptoms including improved mobility. Conversely, a lower intake of antioxidants and omega-3 fatty acids is associated with increased incidence of OA. It is believed that when one increases flavonoids and omega-3 polyunsaturated acid intake, it decreases the production of inflammatory mediators and thus, the incidence and progression of OA.

These observations and others substantiate the fact that dietary habits contribute to the metabolic and inflammatory etiology of OA.[x] However, the challenge is how to balance the inhibition of COX-1, COX-2 and 5-LOX metabolic pathways. One answer lies in specific flavonoids from the botanicals, Scutellaria baicalensis and Acacia catechu. Each has been studied for their role in managing the pathways of AA metabolism.

Preclinical and clinical evidence suggests that a specialized compound of Scutellaria baicalensis and Acacia catechu, called flavocoxid, provides effective dietary management of the principal metabolic processes of OA.[xi] Flavocoxid is a medical food available by prescription for the dietary management of OA. It is a proprietary blend of two flavonoids, baicalin and catechins, derived from the botanicals Scutellaria baicalensis and Acacia catechu respectively.

In a specific combination the flavonoids baicalin and catechin, extracted from Scutellaria baicalensis and Acacia catechu, inhibit phospholipase A2 (PLA2), peroxidase activity of COX-1, COX-2, and 5-LOX.[xii, xiii] Inhibiting PLA2 prevents arachidonic acid from being released from injured cell membrane phospholipids and from entering the COX and/or LOX enzymatic pathways that generate the inflammatory process through eicosanoid metabolites. See Diagram 2.

**DIAGRAM 2**

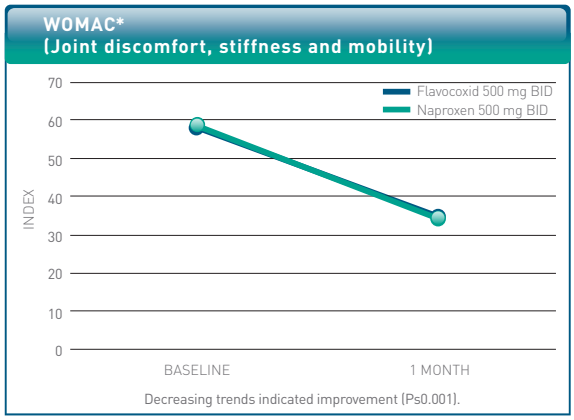


# CLINICAL TRIALS

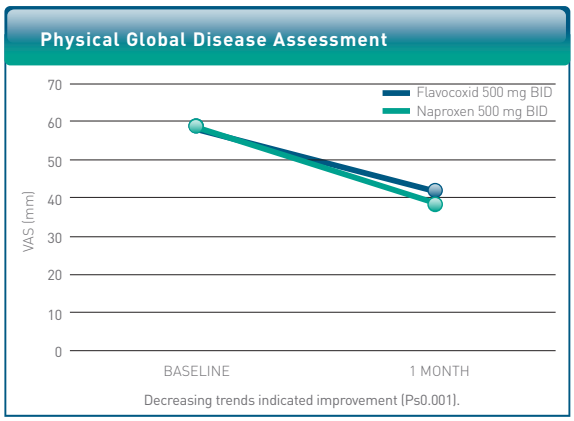
In a randomized, double-blind, active-comparator study of flavocoxid against naproxen, flavocoxid showed a favorable response. When 220 subjects with moderate to severe OA of the knee were given flavocoxid twice-daily, both groups noted a significant reduction in the signs and symptoms of OA. There were no detectable differences in efficacy between the groups. This study was significant as it offered physicians a reliable alternative to NSAIDs for OA.

A post-hoc analysis compared the efficacy of flavocoxid to naproxen in different patient subsets – related to age, gender, and disease severity. Subset analyses revealed statistically significant differences in favor of the flavocoxid group.[xv] As subjects continued therapy, the trends became stronger specifically for older subjects (>60 years), males and those with a milder disease state. The statistics were particularly favorable for those with lower subject global assessment of disease activity and faster walking times at baseline. A post-marketing, open-label study of more than 1000 patients with OA also supported the use of flavocoxid for the dietary management of OA.[xvi] See Diagrams 3, 4, and 5.

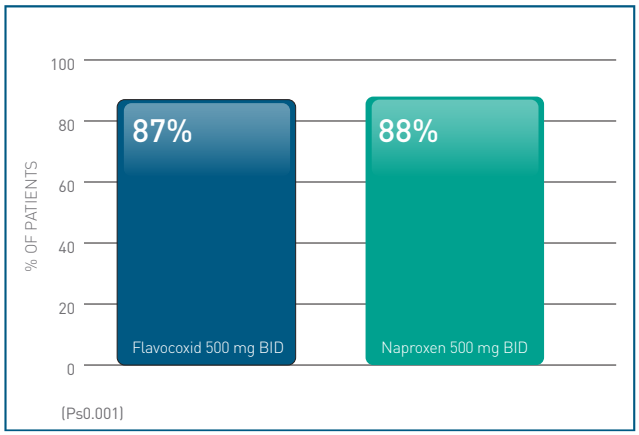
## DIAGRAM 3




## DIAGRAM 4




## DIAGRAM 5



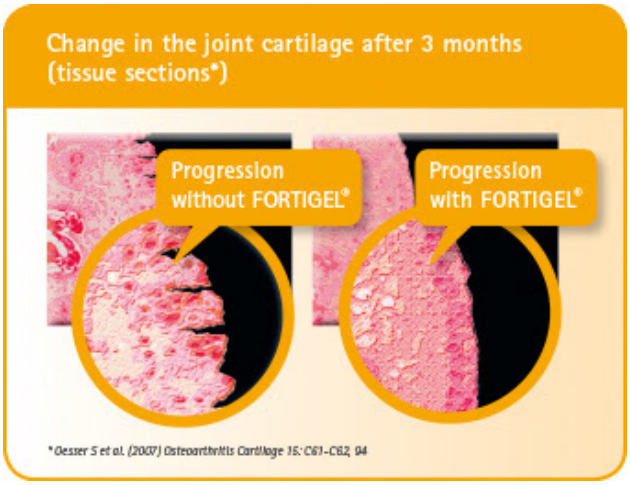
# ARTHROBEN™: FLAVOCOXID AND COLLAGEN PEPTIDES

For improved joint health, Designs for Health has developed Arthroben™, a medical food that combines the benefits of flavocoxid with collagen peptides.

Arthroben™ is designed to reduce inflammation and stiffness via balanced COX and LOX inhibition. It also provides antioxidant protection to reduce joint degeneration, and stimulate connective tissue repair with collagens. Arthroben™ accomplishes this with two Bioactive-Collagen Peptides, FORTIGEL® and VERISOL®, derived from a patented process involving the hydrolysis of type I collagen. These ingredients boost anabolic processes in connective tissues and provide building blocks for all collagen in the body.

In 16 human clinical trials, FORTIGEL® demonstrated positive effects for joint health among 2800 human subjects. Study subjects reported increased joint mobility and improved radiographic markers of cartilage health.[xvii, xviii, xix] Similarly, VERISOL® stimulates anabolic processes in connective tissue. Two recent human clinical studies (pre-publication) showed positive effects on collagen metabolism of the skin, as well as improved skin elasticity and collagen type I content. See Diagram 6.

## DIAGRAM 6



# CONCLUSION

The published data suggests that flavocoxid's balanced inhibition of COX-1, COX-2, and 5-LOX, and its ability to inhibit arachidonic acid metabolism does not pose known risks to cardiovascular, gastrointestinal and renal safety. This is evident even for patients taking concurrent antiplatelet and anticoagulation therapy.[xx,xxi,xxii] Flavocoxids provide effective dietary management of osteoarthritis for patients who want to avoid the side effects of NSAIDs.

A review of research on micronutrients and joint health suggests that given the multiple effects of flavonoids to reduce both inflammation and oxidative stress, they may be beneficial for additional health issues including cardiovascular, immunologic and metabolic disorders.[xxiii]

Increasingly, patients want joint-health options that allow them to maintain an active lifestyle without the negative-side effects associated with NSAIDs and other drugs. When NSAIDs are not an option, medical foods like Arthroben™ allow patients to experience reduced inflammation, and increased mobility.

## BENEFITS OF ARTHROBEN™

- Reduces inflammation
- Balanced inhibition of COX-1, COX-2, 5-LOX
- Potent antioxidant protection to reduce joint damage
- Increases joint mobility and function
- Stimulates joint repair, and provides nutritional support for cartilage, ligaments and skin
- Not associated with the negative side effects commonly seen with NSAIDs and other drugs
- Safe for patients on warfarin, with little or no effect on prothrombin times (PT)

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