

Flavocoxid: A Medicinal Extract of *Scutellaria bicalensis* and *Acacia catechu* Acts as a Dual Inhibitor of Cyclooxygenase and 5-Lipoxygenase to Reduce Inflammation

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There is great concern in the medical community over the excessive use of non-steroidal (NSAID), including COX-2 inhibitors, and steroidal anti-inflammatory medications, as well as narcotic pain relievers, due to potentially serious side-effects and dependency. In fact, patients generally use significant doses of these as prescription drugs on a chronic or ongoing episodic basis thereby resulting in long-term side effect risks particularly among the elderly. There are emerging highly standardized and evidence-based natural agents that effectively modulate the same enzyme pathways as anti-inflammatory medications with much lower side-effect profiles. One such extract with strong supporting human outcome studies, flavocoxid, will be discussed in this article with emphasis on its safety profile and balanced action across a multitude of inflammatory pathways.

DISCUSSION:

Integrative medicine clinicians from various professional backgrounds and fields are encountering an ever-growing population of patients/clients suffering from acute and chronic pain conditions, many of these being inflammatory in nature including; sports injuries, degenerative and inflammatory arthritis, autoimmune-related disorders, and many more. Many of these patients experience significant gastrointestinal, renal, and coagulation side-effects, and more, and may not even be aware of them until they cause a serious medical disorder¹⁻². Many of these same individuals would be interested in evidence-based, effective natural agents that reduce, and in many cases eliminate the drug-associated side-effects. Integrative providers need to understand the benefits and risks of standard interventions, as well as those of the available evidence-based complementary approaches.

Some important facts about commonly used natural anti-inflammatory compounds³⁻⁸⁴:

1. Natural anti-inflammatory compounds do not act as selective cyclooxygenase (COX) inhibitors. They constitute an array of compounds that have various combination effects of inhibiting both COX-2 and COX-1, in addition to the lipoxygenase (LOX) and phospholipase A2 enzymes. It is important that they also inhibit COX1 to some degree because this provides a mild blood thinning effect, counteracting the blood clotting effect of COX-2 inhibition. In this sense, they act somewhat similar to non-selective NSAID's (such as naproxen, diclofenac, and ibuprofen), although these medications do exert some dominance on the COX-1 isoenzyme, but they also have many additional benefits, such as antioxidant activity, and do not promote G.I. bleeding.
2. Natural anti-inflammatory agents may be a better choice for blood thinning than aspirin, which acts

predominantly as a selective COX-1 inhibitor. Aspirin binds to the platelets in an irreversible manner, with serious risk of bleeding in cases of overdose, and so come with strong GI side-effects. This is not the case with natural anti-inflammatory agents.

3. Natural anti-inflammatory compounds prevent the expression of "inducible" COX-2 which results from oxidative stress, due to the potent antioxidant effect of many of these compounds.
4. Proteolytic enzymes help reduce acute and chronic inflammation in ways unrelated to COX and LOX inhibition, such as the molecular debriement of the chemotaxis-promoting protein fragments and inflammatory mediators liberated from injured cells. These enzymes also have additional anti-thrombotic and anti-inflammatory effects.

**Please see the table on the next page for a more complete understanding of the differences between the compounds referenced above³.*

FLAVOCOXID:

Flavocoxid is a specially manufactured and extensively studied natural food-based product composed of enriched plant extracts from two botanicals, *Scutellaria baicalensis* and *Acacia catechu*. Flavocoxid contains the same "active" constituents and micronutrients that can be found in many fruits, nuts, vegetables, and teas⁸⁵. Flavonoids, low molecular weight compounds and part of the larger class of compounds known as polyphenols, are ubiquitous in plants⁸⁶. More than 9,000 different flavonoids have been characterized, many of which are consumed regularly in the human diet. Their basic structure consists of a three-ring nucleus with a huge number of side chain possibilities⁸⁶. Flavocoxid has two primary active ingredients, baicalin and catechin. Baicalin is part of a larger class of flavonoids known as free-B-ring flavonoids, whereas

Anti-inflammatory classes	COX1 inhibition	COX2 inhibition	Reduce inducible COX2 expression	LOX inhibition	Anti-oxidant effect	Other anti-inflammatory effects	GI side effects, bleeding	Increases clotting and blood pressure
Natural anti-inflammatory compounds	yes	yes	yes	yes	yes	proteolytic enzyme actions	low	no
NSAID's (Naproxen, Motrin®)	yes	yes	no	no	no	no	yes	no
Selective COX-2 inhibitors (Vioxx®, Celebrex®, Bextra®)	no	yes	no	no	no	no	low	yes
Aspirin	yes	very mild	no	no	no	no	strong	no

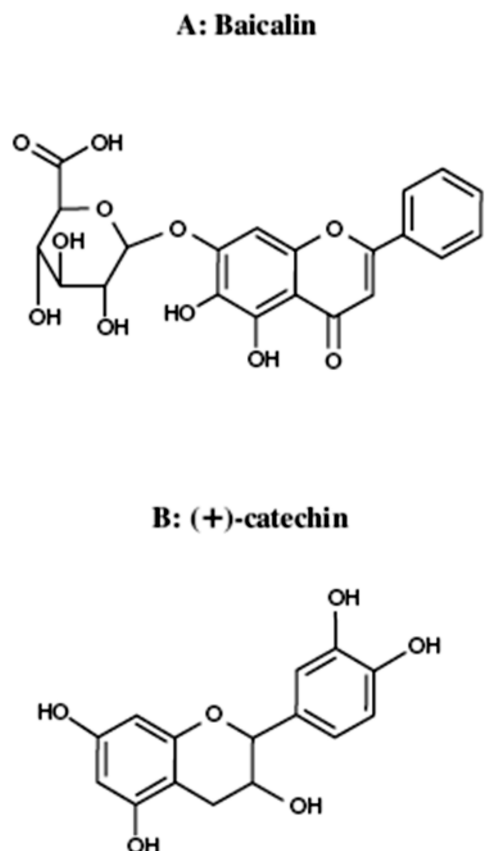
catechin is part of a class known as flavans (Figure 1). The plant sources for the free-B-ring, baicalin, and the flavan, catechin, have nutritional value and have been used in medicinal preparations and in foods for many years especially in Asian countries.

The development path for flavocoxid began in January of 1996 when a scientifically based Korean ingredients supplier using pharmaceutical-like screening and development practices began to isolate multiple anti-inflammatory compounds from Aloe vera and Picrorhiza kurroa. This work was then followed by the development of high throughput (HTP) extraction and fractionation methods of plant extracts in 1998. At the same time, screening of over 1200 plant extracts and tens of thousands of HTP fractions using the COX-1, COX-2, and 5-LOX enzymes began in earnest⁸⁷. Twenty-two initial plant extracts were identified having COX-1, COX-2, and 5-LOX activity. In secondary screening in cells, the company found that 14 of the initial 22 were cytotoxic in monocytes. Further animal toxicity analysis showed that only 2 did not produce any significant changes in the physiology of animals in both acute and sub-

chronic toxicity. These plant extracts from Scutellaria baicalensis and Acacia catechu were further characterized by HTP fractionation. They further discovered that baicalin from Scutellaria baicalensis, and catechin from Acacia catechu, were the primary active ingredients in both plant fractionations having COX-1, COX-2, and 5-LOX activity⁸⁷.

Extensive laboratory and animal toxicology testing followed in 2002-2003 characterizing the safety of the combination of naturally derived compounds⁸⁸. This science showed that the molecules composing flavocoxid at certain ratios inhibited COX-1 and COX-2 enzymes to an equal level while also inhibiting the 5-LOX enzyme (Figure 2). These experiments in enzyme assays were also correlated with similar observations in cells. Animal models of inflammation also showed that flavocoxid could manage arachidonic acid-induced arthritis, part of the basis for osteoarthritis. In addition, later proteomic and genomic studies demonstrated that flavocoxid down-regulated specific cytokines involved in the initial inflammatory cascade after cell damage due to trauma, as well as COX-2 and 5-

Figure 1: Chemical structures of baicalin and catechin⁸⁸

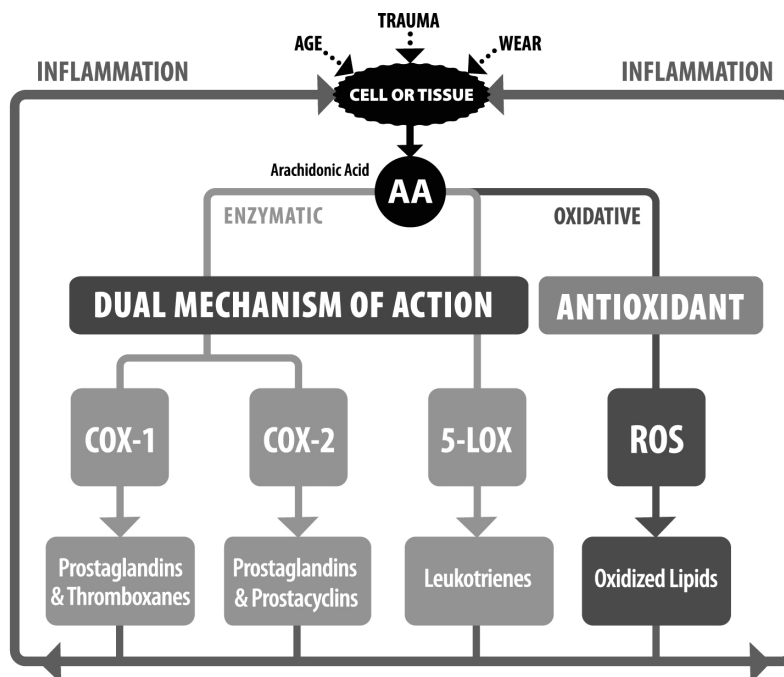


LOX production. These results suggest that flavocoxid has both protein and genomic inhibition effects for the management of inflammation. Drug interaction studies as well as mutagenesis studies have also been performed to assure safety of the extract⁸⁹.

In 2002 through early 2003, human safety and efficacy testing ensued at Georgetown University against placebo (n=39) for flavocoxid (n=29) at 250 mg per day⁸⁸. No changes in blood electrolyte, serology, liver enzymes, renal markers, or general health were observed in this study. Observed adverse events were found to be comparable to placebo. Concurrently, initial efficacy testing was done at McGill University in Canada against placebo (n=15), flavocoxid (n=15) at 125mg bid, flavocoxid (n=15) at 250mg bid, and celecoxib (n=15) at 100mg bid. Significant reductions in pain and stiffness, as well as improvements in mobility were observed for flavocoxid at both doses versus celecoxib⁹⁰. These initial safety and efficacy studies were performed and results obtained almost a year before marketing of flavocoxid as a medical food began in Puerto Rico in March of 2004.

In the GOAL study, a total of 1067 individuals at 41

Figure 2: Balanced arachidonic acid metabolism modulation via the COX/LOX/ROS pathways with flavocoxid⁸⁹



rheumatology practices were enrolled and prescribed flavocoxid, 500 mg bid, for 60 days. The Physician Global Assessment of Disease (PGAD) visual analog scale (VAS) was used as a global measure to assess signs and symptoms of osteoarthritis (OA), including joint discomfort, functional stiffness, functional mobility and quality of life. In addition, GI tolerability were assessed by individual questions scored on a 5-part Likert scale. Of the 1005 patients who completed all follow-up visits, physicians recorded an average improvement in VAS scores from 60.1 + 18.8 at baseline to 42.5 + 21.9 at 8 weeks (p<0.001) in 65.8% of patients, with the highest degree of improvement seen in those subjects with moderate to severe OA at baseline. An additional important finding was that of those patients who had previously paused or interrupted their use of NSAID due to upper GI-related issues, ~90% tolerated flavocoxid and completed the study. The use of flavocoxid also resulted in a >30% reduction or cessation of the use of gastroprotective medications such as proton pump inhibitors (PPI) or histamine-2 receptor (H2s) in subjects⁹¹.

POST-MARKETING REPORTED ADVERSE EVENTS:

Since the release of flavocoxid in 2004 there have been 4 reported cases of acute liver toxicity and elevated liver enzymes which are suspected to have been attributed to individual reactions to flavocoxid. All subjects were

women ranging in age from 57 to 68 years. All developed symptoms and signs of liver injury within 1 to 3 months of starting flavocoxid and demonstrated elevated liver function tests (LFT's) and serum bilirubin. All serum markers returned to normal within 3 to 12 weeks after flavocoxid was discontinued, and all patients recovered without experiencing acute liver failure of chronic liver injury. Causality was adjudicated as highly likely in 3 patients and as possible in 1 patient⁹².

There have also been 7 confirmed reports of hypersensitivity pneumonitis⁹³. These occurred sporadically, unpredictably and without warning or apparent predisposing factors. All required cessation of flavocoxid and treatment with supplemental oxygen and parenteral corticosteroids. This is in contrast to the reduction in respiratory adverse events of an infectious nature seen in clinical trials of flavocoxid against placebo⁹⁴ and naproxen⁹⁵. These types of lung events are extremely rare but you should be aware of them in the unlikely event that you encounter one.

All therapeutic products that have significant physiological effects may have some level of potential toxicity and adverse effects, even a medical food with GRAS status like flavocoxid. Considering the hundreds of thousands of prescriptions filled for flavocoxid vs. the number of reported significant side-effects it maintains an impressive safety record when compared to other anti-inflammatory agents. However, it is recommended that, just as you would do with other anti-inflammatory agents, or medications, you monitor liver function tests on your flavocoxid patients on the schedule you usually use for your practice. Post-marketing surveillance on flavocoxid is collected on an ongoing basis to survey adverse events of patients while on flavocoxid. Currently, over 100,000 patients have been monitored by self-reporting or by physician reported incidences with an adverse event rate of ~0.1%. An additional clinical trial sponsored by an NIH grant (Phase I SBIR Grant #: 1 R41 AR051232-01) with over 70 patients for safety at the University of Alabama-Birmingham using 250 mg bid flavocoxid versus bid placebo was published in 2009⁹⁴.

GENOMIC/PROTEIN MECHANISM OF ACTION (MOA) DATA:

Flavocoxid reduced the protein expression of COX-2 and 5-LOX, but not COX-1 presumably through an antioxidant mechanism of action (MOA) in a macrophage cell model⁹⁶. This MOA was correlated to decreased NF κ B activation and increased I κ B α expression, the cytoplasmic control factor of NF κ B. NF κ B expression is controlled in part by oxidative activation. Tumor necrosis factor- α (TNF α) gene and protein expression as well as iNOS protein expression was also decreased through the same

mechanism. Consequently, levels of PGE2, LTB4 and nitric oxide (NO) metabolites were decreased due to the corresponding protein down-regulation. Flavocoxid acted as an antioxidant, decreasing malondialdehyde (a direct oxidative product of arachidonic acid) concentrations in cell culture. This MOA data was confirmed in a Duchene muscular dystrophy (DMD) animal model by Messina et al⁹⁷.

The importance of this antioxidant mechanism cannot be underestimated, especially for the management of chronic discomfort which occurs in osteoarthritis. All the molecules produced from the COX-2, 5-LOX and iNOS pathways (e.g., prostaglandins, leukotrienes, and nitric oxide) bind to and activate the pain receptors to cause nociceptive pain signals to be transmitted back to the brain. In addition, cytokines also bind these receptors as do a myriad of reactive oxygen species (ROS). Flavocoxid, indicated for the clinical dietary management of osteoarthritis under physician supervision, works in all these pathways and as a direct antioxidant on most of the ROS.

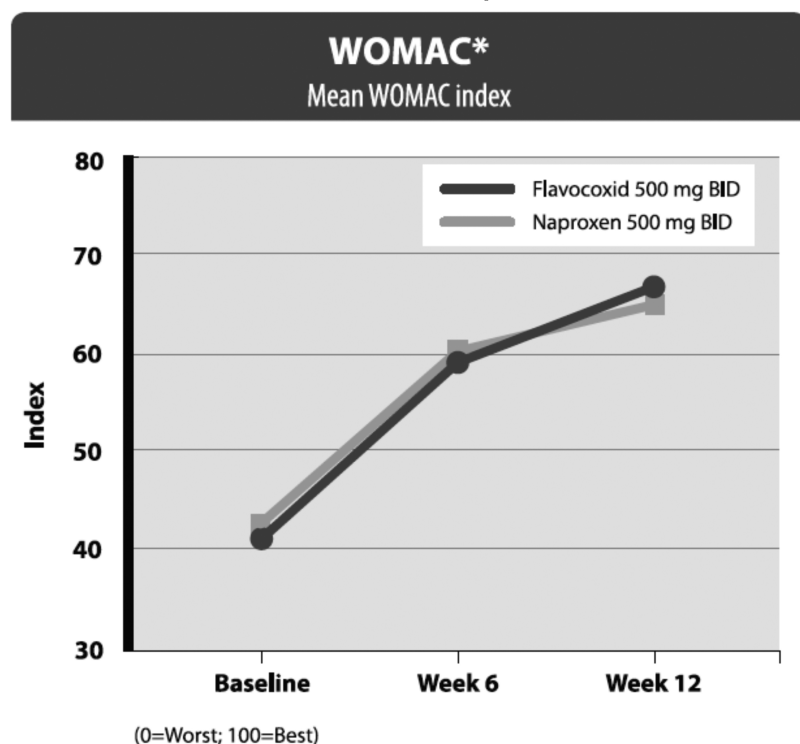
HEAD-TO-HEAD COMPARATIVE CLINICAL TRIALS VS. NAPROXEN:

Clinical trials of flavocoxid have continued with a well-controlled, head-to-head comparative study (n=103) of flavocoxid 500 mg bid vs. naproxen 500 mg bid for 4 weeks which was presented at the World Congress of the International Cartilage Repair Society (ICRS) in 2007 as a conference paper and the complete paper has been published in the Nutrition Research journal (98). In addition, further substantiation that flavocoxid does not interact with aspirin, or affect bleeding times or platelet aggregation was conducted and published by Pillai et al⁹⁹. A larger, well-controlled, head-to-head comparative study (n=220) of flavocoxid 500 mg bid vs. naproxen 500 mg bid for 12 weeks was then published by Levy et al showing comparative improvements in Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] scores (Figure 3)⁹⁴. Newer work on flavocoxid has included the study of its effect on collagen-induced arthritis in animal models¹⁰⁰, and its effect in an animal model of induced pancreatitis¹⁰¹.

COMMERCIAL AVAILABILITY:

Flavocoxid is currently available in two commercially marketed medical food products under the supervision of a qualified licensed health care provider; *Limbrex*[®], a medical food available in 250mg and 500mg versions through conventional prescription pharmacy fulfillment (*Primus Pharmaceuticals, Inc.*-Scottsdale, AZ, USA), and *Arthroben*, a professionally dispensed (via licensed health care provider practice dispensary or authorized

Figure 3: Improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAN) with Flavocoxid v. Naproxen⁹⁵



patient-direct order from the manufacturer) medical food product also containing novel functional collagen peptides for joint health (*SitoMedica*, the Medical Foods Division of *Designs for Health, Inc.*, Suffield, CT, USA).

The concept of a “medical food” is a relatively recent one and this product category is growing rapidly. Products now regarded as medical foods were first regulated as drugs by FDA until 1972, when the agency issued an advance notice of proposed rulemaking (ANPR), which it has since withdrawn. In 1988, Congress established the legal category of medical foods in the Orphan Drug Amendment, which states medical foods are those designed to be orally consumed, administered under the supervision of a physician, specially formulated and processed (i.e., cannot be derived at the given concentration or formulation through a change in diet alone), and intended for the specific dietary management of a disease or condition that has distinctive nutritional requirements. That definition was subsequently incorporated into the Nutrition Labeling and Education Act of 1990 (NLEA), where Congress exempted medical foods from the nutrition labeling, health claim and nutrient disclosure requirements applied to most other foods. This has created a territory somewhere between supplement and drug where products, if they contain only ingredients with GRAS (Generally

Recognized as Safe) status by FDA as supported by robust dossiers of consensus scientific support, including published direct human outcome data as well as toxicology data, and are labeled for the dietary management of a specific disease or condition that has distinctive nutritional requirements, then they can be marketed with the supported medical claims. These products are expressly required to follow “good scientific principles” which broadly includes being supported by well controlled clinical and scientific studies (using the formulation in the finished product) recognized by experts in the field such as peer review in recognized medical and scientific journals. This lifts the bar for natural products well beyond what is currently required to produce and market a product in the nutritional supplement regulatory category, where the manufacturer is extremely restricted on making any disease or health-related claims for the product, even when support for the individual ingredients may exist in the literature.

CONCLUSION:

While there are many traditionally used natural agents with anti-inflammatory properties, there are not many with rigorous scientific studies proving safety and efficacy which meet the standards of classification as a medical food. Flavocoxid is such a natural material and provides the integrative clinician with a reliable, proven, low-side effect profile, natural option for the dietary management of metabolic inflammatory processes in conditions such as osteoarthritis.

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Case History by Rebecca A. Boros, DC, DACBN, continued from page 27

The patient was placed on a reduced caloric diet (800-900 a day) emphasizing fish, meat, vegetables and fruit. He would have 200 calories for his breakfast either oatmeal or eggs with his coffee. He was encouraged to have a snack which would be an apple or a fruit in between meals. His lunch would be 250 calories which would come from meat and salad/vegetables. Dinner would be again 250 calories coming from fish or meat with green vegetables. He was not allowed to eat pasta, rice or cereals. He could have one piece of Melba toast a day but most days he didn't have it. He had to drink half of his body weight in water everyday to flush the toxins out of his system and to maintain good hydration.

He began the diet with his wife so the buddy system worked really well for the two of them. He does all of the cooking and shopping as his wife works late. His goal is to get under 200 lbs which he is close to being now. He never plans to return to his old ways of eating and has learned a lot about food preparation.

Another outcome of his new diet is that he has reduced his lipid values considerably to a more healthy level. He was also concerned about Diabetes later in life as it runs in his family. Now that he has better glucose values and he knows how to make better choices regarding his "sweet tooth" he is convinced Diabetes will never be a future issue for him.

The patient will stay on Vitamin D3 as it has helped him to reach optimum levels with supplementing it orally. I have encouraged him to stay on the current supplement protocol indefinitely to maintain optimum health.

The DHEA has increased his energy and vitality sexually. We will continue to monitor his hormones as he is in Early Andropause. Testosterone did go up almost 80 points which is substantial. Him and his wife started a family late in life and they have two young children now. As of this writing, I am happy to say that they are expecting their third child. Needless to say, the patient loves DHEA!