Flavocoxid: A Medicinal Extract of Scutellaria Bicalensis and Acacia Catechu Acts As a Dual Inhibitor of Cyclooxegenase and 5-Lipoxegenase to Reduce Inflammation

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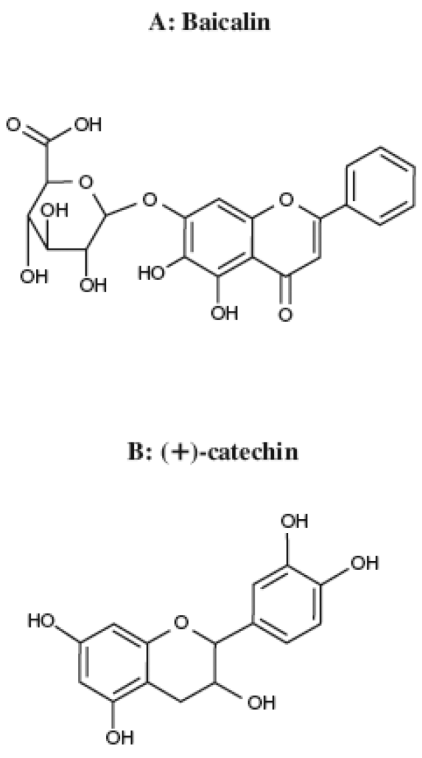
Introduction

There is great concern in the medical community over the excessive use of nonsteroidal anti-inflammatory drugs (NSAIDs), 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.

Figure 1: Chemical structures of baicalin and catechin.[88]



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, and autoimmune-related disorders. Many such 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 disorder.[1,2] 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 compounds[3–84]:

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 COX-1 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 nonselective NSAIDs (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 GI 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

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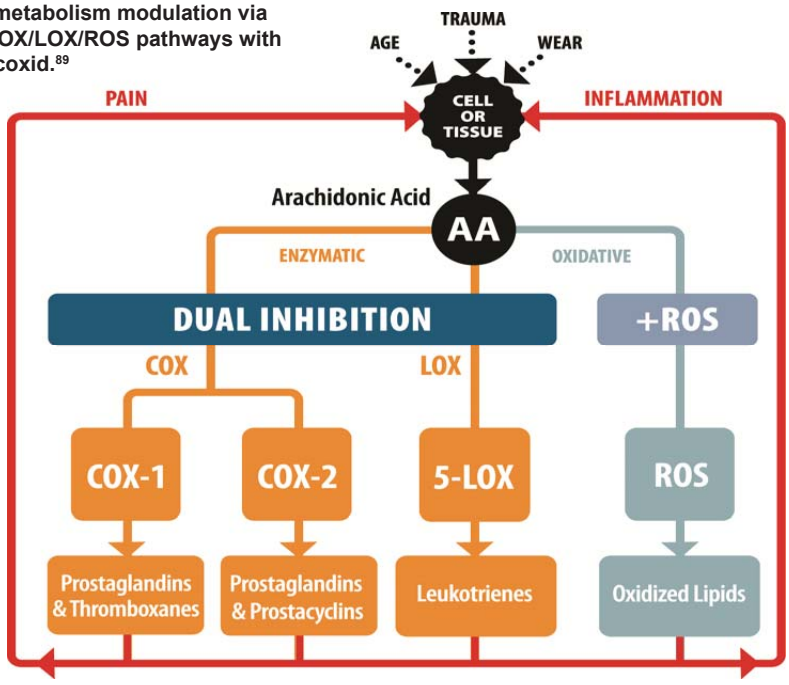
Figure 2: Balanced arachidonic acid metabolism modulation via the COX/LOX/ROS pathways with flavocoxid.[89]



platelets in an irreversible manner, with serious risk of bleeding in cases of overdose, and so comes 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 debridement of the chemotaxis-promoting protein fragments and inflammatory mediators liberated from injured cells. These enzymes also have additional antithrombotic and anti-inflammatory effects.

Figure 3: Comparative anti-inflammatory and antioxidant activity of flavocoxid and various drug agents.
(Compiled by Cristiana Paul, MS, and used with permission.)

Products	Ratio of COX-1/COX-2 inhibition	Inhibits 5-LOX	Antioxidant	Side Effects
Aspirin	15:1	NO	NO	causes blood thinning, reduces GI repair
Ibuprofen	8:1	NO	NO	increases blood pressure, dyspepsia, GI bleeding, inhibit mitochondrial function
Flavocoxid	**1:1**	**YES**	**YES ORAC=5,517**	**virtually no side effects observed in clinical trials**
Rofecoxib	1:250	NO	NO	increases blood clotting, risk of heart attack
Celecoxib	1:432	NO	NO	
Acetaminophen	No COX1/COX2 inhibition	NO	NO (depletes glutathione)	liver toxicity

Please see Table 1 (p. 79) for a more complete understanding of the differences between the compounds referenced above.[3]

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 teas.[85] Flavonoids, low molecular weight compounds and part of the larger class of compounds known as polyphenols, are ubiquitous in plants.[86] More than 9000 different flavonoids have been characterized, many of which are consumed regularly in the human diet. Their basic structure consists of a three-

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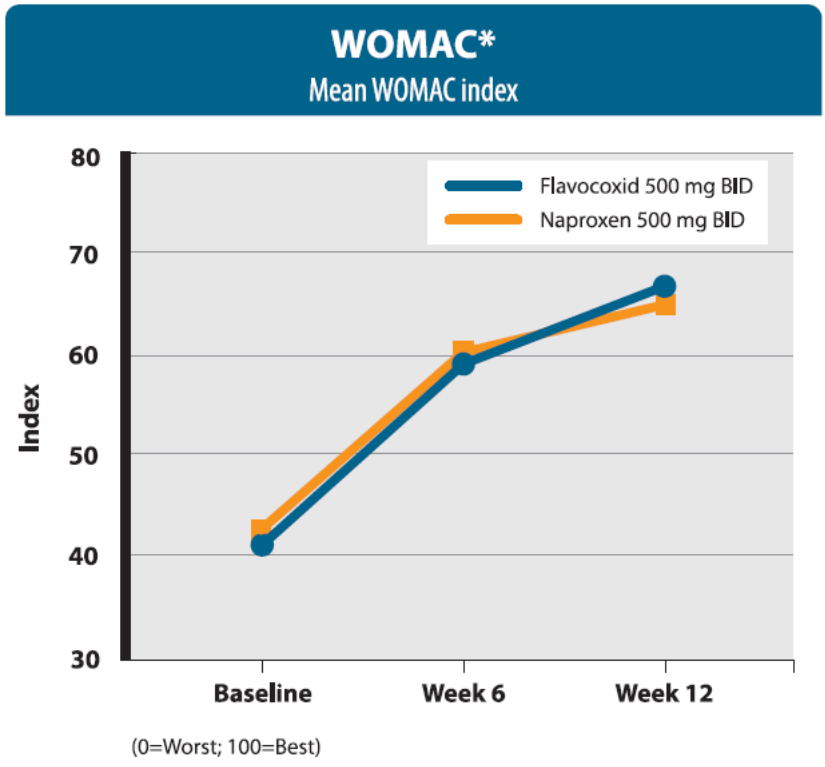
Figure 4: Improvement in Western Ontario and McMasters Universities Arthritis Index (WOMAC) with flavocoxid vs. naproxen.[94]



ring nucleus with a huge number of side chain possibilities.[86] 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 catechin is part of a class known as flavans (Figure 1, p. 74). 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 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 earnest.[87] 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 subchronic 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 activity.[87]

Extensive laboratory and animal toxicology testing followed in 2002-2003 characterizing the safety of the combination of naturally derived compounds.[88] This science showed that the molecules composing flavocoxid at certain ratios, unlike the commonly used anti-inflammatory medications, inhibited COX-1 and COX-2 enzymes to an equal level while also inhibiting the 5-LOX enzyme (Figures 2 and 3, p. 76). 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-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 extract.[89]

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 day.[88] 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 125 mg b.i.d., flavocoxid (n = 15) at 250 mg b.i.d., and celecoxib (n = 15) at 100 mg b.i.d. Significant reductions in pain and stiffness as well as improvements in mobility were observed for flavocoxid at both doses versus celecoxib.[90] 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 2004.

In the GOAL study, a total of 1067 individuals at 41 rheumatology practices were enrolled and prescribed flavocoxid, 500 mg b.i.d., 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 was 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

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Table 1

Anti-inflammatory classes	COX-1 inhibition	COX-2 inhibition	Reduce inducible COX-2 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
NSAIDs (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

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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 NSAIDs due to upper GI-related issues, approximately 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 subjects.[91]

Postmarketing 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 (LFTs) 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 or chronic liver injury. Causality was adjudicated as highly likely in 3 patients and as possible in 1 patient.[92]

There have also been 7 confirmed reports of hypersensitivity pneumonitis.[93] 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 placebo and naproxen.[94,95] 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 such as 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 with 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 that you usually use for your practice. Postmarketing 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 b.i.d. flavocoxid versus b.i.d. placebo was published in 2009.[94]

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 model.[96] This MOA was correlated to decreased NFκB activation and increased IκBα expression, the cytoplasmic control factor of NFκB. NFκB expression is controlled in part by oxidative activation. Tumor necrosis factor-α (TNFα) gene and protein expression as well as iNOS protein expression were also decreased through the same mechanism. Consequently, levels of PGE2, LTB4, and nitric oxide (NO) metabolites were decreased due to the corresponding protein downregulation. Flavocoxid acted as an antioxidant, decreasing malondialdehyde (a direct oxidative product of arachidonic acid) concentrations in cell culture. These MOA data were confirmed in a Duchene muscular dystrophy (DMD) animal model by Messina et al.[97]

The importance of this antioxidant mechanism cannot be underestimated, especially for the management of chronic discomfort that 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 b.i.d. vs. naproxen 500 mg b.i.d. 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 journal *Nutrition Research*.[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 al.[99] A larger, well-controlled, head-to-head comparative study (n = 220) of flavocoxid 500 mg b.i.d. vs.

naproxen 500 mg b.i.d. for 12 weeks was then published by Levy et al., showing comparative improvements in Western Ontario and McMasters Universities Arthritis Index [WOMAC] scores (Figure 4).[94] Newer work on flavocoxid has included the study of its effect on collagen-induced arthritis in animal models, and its effect in an animal model of induced pancreatitis.[100,101]

Commercial Availability

Flavocoxid is currently available in two commercially marketed medical food products under the supervision of a qualified licensed health-care provider: Limbrel, a medical food available in 250 mg and 500 mg versions through conventional prescription pharmacy fulfillment (Primus Pharmaceuticals Inc.; Scottsdale, Arizona, US), and Arthroben, a professionally dispensed (via licensed health-care provider practice dispensary or authorized 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, Connecticut, 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 that 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), wherein 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, can then be marketed with the supported medical claims. These products are expressly required to follow "good scientific principles," which broadly include 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 in 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 that 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.

Disclosures

Dr. David M. Brady is the chief medical officer of Designs for Health Inc. and its subsidiary division SitoMedica, and is also a clinical consultant to Genova Diagnostics.

Notes

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