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The Role of Flavonoids in Osteoarthritis

Introduction

Humans have used botanical products for medicinal purposes for thousands of years with many of the pharmaceuticals used today derived, in part, from natural substances. Ethnopharmacology has become a major thrust in research and development of new pharmaceutical compounds. Many natural compounds have biologic activity in multiple diseases and physiologic processes from maintaining cardiovascular, renal and gastrointestinal function to safely helping to manage cancer, ulcers, arthritis, and liver disease. Among these safe and effective botanical compounds are flavonoids with more than 9,000 distinct molecular species.

In general, flavonoids are the natural ingredients with health benefits found in colored fruits, vegetables and spices as well as cocoa, teas and even red wine. When your parents said "eat your vegetables," they really meant "eat your flavonoids because it has health benefits." With today's mass food production, food companies have sometimes processed the nutrition, including flavonoids, out of food in favor of food dyes, texturizers, preservatives, salt and fat.

Though flavonoid molecules have been known for decades to possess anti-inflammatory activity, only relatively recently have any of these molecules entered osteoarthritis (OA) clinical trials and found their way to market. One example is the combination of the flavonoids, baicalin and catechin (composition is named flavocoxid), found in the prescription medical food product Limbrel®. Curcumin, found in the spice turmeric, is fairly prevalent in many dietary supplements to maintain joint health, and it is supported by a few well-controlled clinical trials for OA. Some curcumin products have been marketed with great success as prescription anti-inflammatories in India. Flavonoid extracts from *Garcinia kola* were equivalent to naproxen (active ingredient in prescription drug Naprosyn® and OTC drug Aleve®) and celecoxib (active ingredient in the prescription drug Celebrex®) and better than placebo in managing the pain, stiffness and mobility of people suffering from OA. In other randomized, double-blind pilot studies, French pine bark extracts (Pycnogenol®) improved Western Ontario and McMaster University Osteoarthritis Index (WOMAC) composite scores for pain, stiffness and mobility compared to placebo. There are many other flavonoid compositions which have been scientifically and clinically tested throughout the world for a variety of disease states and conditions.

Osteoarthritis – Not Just a Wear-and-Tear Disease Anymore

There are multiple underlying causes and contributing factors to OA including trauma, repetitive motion, inflammation, obesity, genetic predisposition and diet. It is only relatively recently that, with a substantial increase in our understanding of the biochemical processes involved in the degradation and repair of articular cartilage and subchondral bone in the joint, the role of nutrition and lifestyle have become more appreciated. Much of the tissue injury and symptoms of pain and stiffness is due to chemicals produced naturally in our bodies and generated by metabolism of the omega-6 fatty acid, arachidonic acid (AA), which is derived from too much dietary intake of processed foods containing soy and corn fillers. Tissue injury in the joint is also due to the lack of intake of anti-inflammatory omega-3 oils and micronutrients such

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as flavonoids which act naturally to manage inflammation and help to protect against oxidative and other damaging effects to cartilage in joints.

The process of joint damage usually starts with an injury and then repetitive motion which causes wear and tear as the body produces elevated levels of inflammatory proteins and AA from damaged cell membranes. This AA, as well as a large amount of AA from processed foods in our diet, is also converted into other inflammatory chemicals which are produced naturally in the body through metabolic and enzymatic processes. These inflammatory chemicals, known as fatty acid metabolites of AA generated through the cyclo-oxygenase (COX) and 5-lipoxygenase (5-LOX) enzymes, can breakdown cartilage. Normally, these fatty acid metabolites occur as a natural part of the body's function, but in the case of breakdown of joint tissue and poor diet, they are produced at higher levels causing too much inflammation. Poor diet also contributes to oxidation which directly destroys cartilage. You may have heard of how traditional NSAIDs (non-steroidal anti-inflammatory drugs) like aspirin, naproxen and ibuprofen can cause side effects on the stomach and kidneys and selective COX-2 NSAIDs, like Celebrex, can cause side effects like high blood pressure and potentially heart attacks and strokes. The truth is that all NSAIDs, whether COX-2 selective or not, have the potential for such side effects. These drugs really should be used for the shortest time possible to help relieve pain, rather than manage inflammation or OA long term. Nutrition is one way to manage OA long term. In any case, people should be under the care of a physician for OA.

One of the key problems for OA and other inflammation-related diseases is the lack of anti-inflammatory micronutrients like flavonoids in the modern diet which help the body naturally manage inflammation and oxidation. By eating large amounts of processed and junk food, too much red meat and few colored fruits and vegetables, we just don't get a high enough intake of these nutrients to nutritionally manage the chronic disease progression of OA over time. In some cases, if the disease is far enough along, we may not be able to obtain enough of these nutrients through the ordinary diet(s). How many servings of flavonoid-rich foods do we consume on a daily basis, really? Again, certain flavonoids can help to manage down the production of the harmful chemicals produced in our bodies that cause OA. Also, diets rich in flavonoids correspond to less obesity compared to people with poor or deficient diets. This also places less stress (weight) and thus wear and tear on the joints to slow the progression of OA.

Role of Nutrition in OA

Epidemiological studies demonstrate that Asian and Mediterranean populations have a substantially lower incidence of knee OA. One of the important suggested factors contributing to OA in Western societies is poor nutrition. Excess consumption of omega-6 fatty acids from processed foods may account, in part, for this difference. Fatty acid imbalances are commonly seen in people with chronic inflammatory conditions such as arthritis. Osteoarthritic joints typically show increased levels of lipids and AA accumulation which correlate with the severity structural changes in the cartilage. Arachidonic acid levels in subchondral bone have been shown to be 50%–90% higher in people with OA. Dietary lipids have also been shown to modify the fatty acid composition of cartilage. Clinical studies have shown a strong linkage between metabolic defects in essential fatty acid metabolism or an overabundance of the wrong fatty acids that lead to OA. Consumption of certain fatty acids, such as the omega-3 fatty acid, DHA, can help to balance the excess consumption of AA. Further, administration of clinical levels of

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certain flavonoids, such as curcumin, baicalin and catechin, can help to balance the production of AA by the body into other substances that can be harmful to cartilage, particularly over time.

All metabolic activity in the body consists of chemical reactions, many of which lead to the generation of reactive oxygen species (ROS) which can directly damage tissue, a process called oxidation. These small molecules readily react with proteins, nucleic acids (DNA), lipids and other large molecules causing structural and functional damage to cells. Our bodies contain a number of natural "antioxidant" molecules that "soak up" ROS, however, these may be insufficient in locations of inflammation where greatly increased generation of ROS occurs. Dietary antioxidants can augment the body's ability to control and manage the damage done by ROS.

Flavonoids and other strong dietary antioxidants have been shown to slow the progression of OA, possibly by managing the structural changes ROS cause. For example, AA can be structurally changed by ROS to yield other fatty acids or fragments of the original molecule which are markers for specific diseases (i.e., isoprostanes for cardiovascular disease and malondialdehyde for arthritis). Reactive oxygen species can also induce more inflammation on the genetic level contributing to joint damage. Flavonoids have the ability to act at many points in these damaging processes, modulating the COX and 5-LOX enzymes differently from NSAIDS in the face of elevated dietary intake of omega-6 and AA, soaking up ROS and managing the genetic induction of further inflammation. Therefore, flavonoids like catechins from green tea, quercetin from apples and curcumin from turmeric are ideally suited to provide the clinical dietary management of chronic diseases involving certain common inflammatory and oxidative processes like OA if given in pure form at much larger doses than is attainable by dietary change. Nature provides a way.

Among some of the best studied flavonoids are catechin molecules, quercetin, anthocyanidins, procyanidins, baicalin and isoflavones. There are literally thousands of papers in the scientific literature related to one compound or another. A couple of specific examples of flavonoids with clinical and scientific studies in OA and its related processes are summarized below.

Limbrel (flavocoxid)

Flavocoxid is a proprietary blend of concentrated and standardized free-B-ring flavonoid, baicalin (derived from the plant *Scutellaria baicalensis*) and the flavan, (+)-catechin (derived from the plant *Acacia catechu*). The active molecules in the specific mixture of these flavonoid compounds have been shown to modulate the COX-1 and COX-2 at a site different in the enzymes from NSAIDS providing for fewer side effects. In addition, flavocoxid modulates the 5-LOX enzyme which is responsible for the generation of highly inflammatory leukotrienes that cause white blood cells to accumulate at the site of damage and blood vessels to narrow. By working in a balanced manner and differently from NSAIDs on all of these pathways, flavocoxid has a favorable safety profile. Flavocoxid is also a more potent antioxidant than Vitamins C and E and scavenges a greater variety of reactive oxygen species which damage tissues. Flavocoxid also helps to manage the ROS-driven genetic induction of further inflammation. The net result is a botanically based product that mediates its activity through multiple pathways and manages inflammation and oxidation for people who have OA with a favorable side effect profile.

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In several published clinical studies, flavocoxid has been shown to be very safe while equal in OA efficacy to the prescription dosing of naproxen over one, two and three months. In a three month safety and efficacy study, flavocoxid showed superiority to naproxen on some efficacy measures with longer time on therapy for study participants with moderate OA and a better upper gastrointestinal and renal safety profile. Yet, in a large-open label study in 41 rheumatological offices across the U.S., flavocoxid was shown to have better management of discomfort in people with the most severe disease and was better tolerated in patients who had to stop NSAID usage due to stomach problems while on the drugs. Hematological (blood) studies showed no effect on measures of coagulation in cardiovascular patients taking Coumadin® nor on bleeding time or platelet aggregation in normal volunteers. Flavocoxid is now used under the supervision of physicians for the dietary management of the metabolic processes of OA as a medical food. It is available only by prescription.

Curcumin

Curcumin, the active component of turmeric (the major component of the spice, curry) has been used for a wide variety of indications in Ayervedic medicine for more than 1500 years. It is one of the best studied of all botanical molecules with thousands of papers appearing in the literature. Curcumin is known to interact with a huge variety of molecular structures, but in positive ways leading to a range of health benefits. Interest in curcumin continues to grow and clinical trials are now in progress to study its effects in inflammatory conditions, infectious diseases, metabolic conditions and a wide variety of cancers.

Curcumin is known to affect the cellular immune and micro-molecular milieu in many ways. In fact, curcumin has been shown to target genetically inducible genes (with their downstream effects) including many related to inflammation in OA. In experimental joint inflammation, curcumin also inhibits inflammatory cell infiltration and attenuates the rise in certain inflammatory metabolites including AA and ROS. When cultured cartilage cells are exposed to curcumin, there is a reduction in levels of inflammatory molecules, cartilage destroying enzymes (proteinases), adhesion molecules which literally grab onto lipids to coat arteries, COX-2, inducible ROS enzymes and vascular endothelial growth factor (VEGF), a protein that causes blood vessels to form that feed tumors or cause disease in the eye.

Modestly sized clinical trials using standard measurement endpoints have demonstrated that curcumin is effective in reducing the signs and symptoms of OA with minimal side effects. The efficacy and safety of a curcumin-phosphatidylcholine complex was also demonstrated during extended administration in people with OA, and then published in a respected medical journal. In a study of rheumatoid arthritis, 1200 mg curcumin taken daily for 5-6 weeks was found to significantly reduce morning stiffness and improve endurance in a manner comparable to phenylbutazone. This ingredient is now used widely in India as a prescription drug ingredient for OA and in many other countries as a dietary supplement to promote joint health.

Conclusion

The goal of a nutritional, metabolic therapy for OA is to manage oxidative stress and restore a more normal balance of fatty acid metabolism in the presence of excess omega-6 and

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AA dietary intake (and thus restore the metabolic processes of inflammation and oxidization to more normal levels). Botanical flavonoid molecules, such as those contained in flavocoxid and curcumin, have been shown to manage OA as suggested by modulating the production of inflammatory oxidized lipids, enzymatically formed chemicals produced in the body as a part of AA metabolism and reducing and controlling induced inflammatory molecules by decreasing the generation of cell damaging ROS. Further scientific and clinical testing would be useful to determine if flavonoids can be proven as cartilage restorative. Many of the physiological mechanisms and systems with which the flavonoids interact are highly conserved over evolutionary time. Intuitively, it makes considerable sense that humans would have evolved such systems in ways that allowed them to "take advantage of" the anti-inflammatory properties of the molecular species available in their environment with a minimum of toxicity if the species was to survive. So, make sure to eat plenty of colored fruits and vegetables and consume medical products which contain concentrated and purified flavonoids to either maintain joint health or to help to nutritionally manage the metabolic processes of OA. Natural sources under the care of your physician can be very effective in helping osteoarthritis.

Story Source: *The above story is reprinted from materials provided by J.D. Weir, President and CEO of Primus Pharmaceuticals and Secretary of the NPF Board of Directors.*