DIETARY SUPPLEMENTS FOR ARTHRITIS AND OTHER INFLAMMATORY CONDITIONS: KEY ROLE OF MAST CELLS AND BENEFIT OF COMBINING ANTI-INFLAMMATORY AND PROTEOGLYCAN PRODUCTS*

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Arthritis is estimated to affect over 30% of all adults and all the available drugs add considerable morbidity and mortality of their own. A recent therapeutic approach targets the mast cells that are currently considered critical in a variety of inflammatory diseases, especially arthritis. Mast cells could be activated by many immune and neural triggers, as well as by many food substances and drugs leading to secretion of numerous vasoactive and inflammatory molecules. Recent studies have shown that mast cells can be inhibited by certain naturally occurring flavonoids, such as *quercetin*, and the sulfated proteoglycan *chondroitin sulfate*. Glucosamine and chondroitin are present in many dietary supplements, but neither the source nor the purity of the active substances is listed; moreover, these formulations do not permit sufficient absorption, due to the high molecular weight and negative charge. Moreover, a common source of chondroitin sulfate is cow trachea with the risk of spongioform encephalopathy (mad cow disease). A new series of dietary supplements (Algonot-Plus®) are based on published scientific evidence and combine quercetin, glucosamine sulfate and chondroitin sulfate of high purity in formulations that include kernel olive oil to increase absorption of the inhibitory substances.

Recent news reports have highlighted the widespread problem of arthritis (The coming epidemic of arthritis. *Time*, Dec. 9, 2002) and the increasing use of alternative therapy (The Science of alternative medicine. *Newsweek*, Dec. 2, 2002). A publication from the US Center for Disease Control (CDC) indicated that 1/3 of all adults in the USA (almost 70 million) suffer from arthritis or chronic joint pain, up from 1/5 in 1993; the associated annual cost was estimated at $82 billion (Dembner, A. One-third of adults in US have arthritis, according to survey. *The Boston Globe*, Oct. 25: A3, 2002) This number includes both osteoarthritis and rheumatoid arthritis (RA), the latter of which is characterized by active joint inflammation. Due to the chronic nature of these conditions, as well as the serious adverse effects of many of the prescription drugs used, increasingly more individuals turns to dietary supplements for these conditions (1-2).

Many of the available dietary supplements contain a multitude of ingredients, some of which may have biologic effects of their own or may interact with other supplements or drugs. A number of these have recently been found inactive in spite of anecdotal reports to the contrary; for example, Ginkgo has been promoted as a CNS stimulant, but was recently shown to be ineffective in this regard (3). Worse yet, a number of OTC drugs, as well as prescription drugs, such as morphine, can stimulate mast cell secretion of detrimental molecules, especially histamine (4-6). Histamine toxicity can also occur through bacterial histidine decarboxylase in uncooked tuna burgers (7) or cis-Urocanic acid-induced gastrointestinal mast cell release of histamine and other mediators. A prime example of dietary supplements that could activate mast cells is those containing Ma Huang extract that is rich in ephedra alkaloids. Ephedrine has been associated with sudden cardiac death (8)

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and other vasoactive effects (9) that may derive from mast cell activation.

Mast cells and arthritis

However, even reviews for clinicians have consistently failed to address mast cells, which have recently emerged as key players in arthritis (10). The evidence of mast cell involvement in arthritis recently became indisputable since inflammatory arthritis could not develop in mast cell deficient mice (11-12). Increasing evidence indicates that mast cells are involved in the pathophysiology of arthritis (13-23). In fact, stress has been shown to activate mast cells (6) and worsen arthritis (24-26). Moreover, corticotropin-releasing hormone (CRH) secreted immediately after stress and its structural analogue urocortin, have been shown to be increased in the joints of rheumatoid arthritis patients (27-32). In this context, it is important to note that CRH receptors were identified on mast cells from rheumatoid arthritis joints (28) and CRH (33), as well as urocortin (34), have been shown to activate mast cells.

Mast cells are found in most parts of the body and are well known for their involvement in allergic and anaphylactic reactions (35-36) through degranulation. However, in addition to immogobulin E and specific antigen, numerous other non-immune triggers or conditions can activate mast cells; these include anaphylatoxins, neuropeptides, bee, ant and jelly fish venum, as well as physical and emotional stress. Upon stimulation, over 30 molecules (mediators) are secreted either preformed from almost 500 secretory granules, or made *de novo* during stimulation. These molecules include arachidonic acid products, biogenic amines, chemoattractants, cytokines, growth factors, neuropeptides, proteoglycans and proteolytic enzymes (37-38). However, the involvement of mast cells in the pathophysiology of arthritis was missed because they did not appear degranulated. Increasing evidence, however, indicates that biogenic amines (39-40), arachidonic acid products (41), and cytokines (42) are released from mast cells without degranulation, a process termed "differential release". The morphological appearance of this process is characterized by a more subtle process of changes within the electron dense content of the secretory granules and has been called "piece-meal degranulation" or "intergranular activation" (43). Mast cells are, therefore, now recognized as key cells in the development of a number of inflammatory diseases (44), including the joints (13, 15).

Mast cell inhibitors

There are no effective clinically available mast cell inhibitors, even through disodium cromoglycate, doxandrozole, ketotifen and some histamine-1 receptor antagonists have variable inhibitory effects (45). Aloe vera has been reported to reduce mast cell secretion (46) and mast cell infiltration in an inflamed synovial pouch model. Chondroitin sulfate was recently shown to inhibit activation of connective tissue mast cells (47). Even though many publications reported an inhibitory action of plant flavonoids on mast cells (48), this inhibition is not shared by all of the 3,000 or so flavonoids known. It was recently shown that the inhibition by the flavones kaempferol, quercetin and myricetin depends on the hydroxylation pattern of their B ring (48). In fact, some flavonoids like morin do not have any inhibitory activity, while others may actually increase mast cell secretion (49).

Dietary supplements for arthritis

Over the last few years, use of dietary supplements containing D-glucosamine have become quite popular for arthritis; most recently, the proteoglycan chondroitin has also been added (50). However, there are a number of problems with the available preparations. Firstly, D-glucosamine and similar sugars normally found in glycosaminoglycans (GAGs) in joints and elsewhere could actually promote bacterial adhesion, aggregation and inflammation (51). Glucosamine is made from shellfish chitin and, if it not of high purity, should be avoided by those allergic to shellfish. Moreover, a common source of chondroitin sulfate is from cow trachea with the risk, remote as it may be, of spongi form encephalopathy ("mad cow disease"). Most importantly, very little oral chondroitin is absorbed in powder form due to its high molecular weight (150,000 – 1,000,000 daltons) and the extensive negative-charge due to sulfation; in fact, the more sulfated the molecule, the better its beneficial effect, but the worse the absorption. Unfortunately, popular magazines and newsletters

Tab. I. *Example sof Cartilage rebuilding products.*

Nutramax Laboratories, Inc
(Edgewood, MD 21040, USA;
Phone: 800-925 5187)

Cosamin DS™ (pills)

Glucosamine HCl (99%)	500 mg
Sodium chondroitin sulfate (95%)	400 mg
Ascorbate (Manganese Ascorbate)	66 mg
Manganese (Ascorbate)	5 mg

⇒ Source unknown

Life Extension
(Ft. Landerdale, FL 33309, USA;
Phone 800-208 3444)

ArthriProsystem™
2 enterically coated fish and ginger oil softgels

EPA	720 mg
DHA	360 mg
Ginger oil (rhizome)	120 mg

2 dry powder capsules

Nettle leaf extract	750 mg
Glucosamine	500 mg
Chondroitin sulfate	400 mg
Salicin combination	120 mg

⇒ Sources unknown
⇒ Purity unknown

Tab. II. *Examples of single anti-inflammatory products.*

Desert Harvest (Colorado Springs, CO 80907, USA; Phone: 800-222-3901)
- **Aloe Vera dry powder** (capsules)
600 mg of freeze- dried aloe vera from whole leaf

NutriCology, Inc. (Hayward, CA 94544, USA; Phone: 510-487-8526)
Quercetin (pills)

Quercetin 300 mg	
Vitamin C (as calcium ascorbate)	75 mg
Vitamin E (as DL-alpha-tocopheryl acetate)	70 IU

⇒ Source unknown
⇒ Purity unknown

Tab. III. *Combination "cartilage rebuilding" and anti-inflammatory products.*

Algonot, LLC Sarasota, FL 34242, USA; Phone: 800-Algonot or 941-346- 5304; www.algonot.com)

Let Nature Ease Your Pain
ArthroSoft® (soft gel capsules for arthritis)

	Purity	Source	Amount/Capsule
• Kernel olive oil*	100%	Olive trees	550 mg
• Glucosamine sulfate	99%	Shark cartilage	150 mg
• Chondroitin sulfate	99%	Shell fish chitin	150 mg
• Quercetin dihydrate	99%	Saphora plant	150 mg

ArthroSoft® cream for arthritis
- Aloe vera
- Kernel olive oil
- Quercetin
- Chondroitin sulfate
- Bitter willow bark extract
- Vitamins A, C and E

⇒ Purity and source same as above

**Acidity <0.5%; H_2O<5%; filtered through 0.5 micron filter.*
These products are hypoallergenic, free from artificial colors or flavors, corn, milk products, preservatives, salt, starch, sugar, wheat or yeast. There are 4 USA and 4 International patents pending.

Tab. IV. *Other Algonot-Plus® products for inflammatory conditions.*

Algonot, LLC (Sarasota, FL 34242, USA; Phone: 800-Algonot or 941-346-5304; www.algonot.com)
Let Nature Ease Your Pain®

CystoProtek®
(softgel capsules for interstitial cystitis)
- Glucosamine sulfate
- Chondroitin sulfate
- Sodium hyaluronate
- Quercetin
- Kernel olive oil

ProstaProtek®
(softgel capsules for chronic prostatitis)
- Glucosamine sulfate
- Chondroitin sulfate
- Sodium hyaluronate
- Quercetin
- Rutin
- Kernel olive oil

Tab. V. *Beneficial Effects of Algonot-Plus® Products.*

- ***Quercetin***
  - ⇒ From Saphora plant to avoid common fava bean source that may cause hemolytic anemia in G_6PD deficient individuals of Mediterranean origin
  - ⇒ Potent anti-inflammatory effects
  - ⇒ Inhibits mast cell and macrophage activation
  - ⇒ Inhibits histamine and tryptase release
  - ⇒ Inhibits IL-6, IL-8 and TNF-α release
- ***Rutin***
  - ⇒ Quercetin glycoside
  - ⇒ Natural source of quercetin
  - ⇒ Known anti-inflammatory properties
- ***Chondroitin sulfate***
  - ⇒ From shark cartilage to avoid the most common source of cow trachea that may be associated with spongioform encephalopathy ("Mad Cow Disease")
  - ⇒ Inhibits histamine and tryptase release
  - ⇒ Helps rebuild damaged cartilage
  - ⇒ Acts as decoy for microbial adherence
- ***Glucosamine sulfate***
  - ⇒ Building block for cartilage synthesis
  - ⇒ Acts as decoy for microbial adherence
- ***Kernel Olive Oil***
  - ⇒ Low acidity and special filtration from the island of Crete
  - ⇒ Unsaturated fatty acids provide fluidity of biological membranes
  - ⇒ Antioxidants protect against peroxidation
  - ⇒ Polyphenols have anti-inflammatory actions
  - ⇒ Helps heal damaged gastric mucosa, especially due to NSAIDs
  - ⇒ Provides greater solubility and absorption of chondroitin sulfate and quercetin

* *Shark is caught for food and cartilage is used for chondroitin isolation*
NSAIDs = non-steroial anti-inflammatory drugs

from reputable institutions neglect to mention these problems in articles addressed to the consumer.

In particular, less than 5% of chondroitin sulfate is absorbed intact when administered orally (52, 53). For instance, after oral administration of ^{3}H- chondroitin sulfate to the rat and dog, 70% of the radioactivity was absorbed, but the high molecular weight fraction, which is the one most useful, was less than 10%. Additionally, if the degree of sulfation was high, the absorption was almost negligible. In another study, oral administration of a small molecular weight chondroitin sulfate (16,000 daltons) led to only 13% bioavailability, but when chondroitin sulfate of about double the size (26,000 daltons) was used, less than 4% the oral dose administered in rats reached the blood as intact chondroitin sulfate (54). Other papers found no oral absorption of chondroitin sulfate and concluded that any protective effect in the joints after oral administration unfounded (55).

Unfortunately, most of the companies that market products containing glucosamine and/or chondroitin do not list the exact amounts, the source, degree of sulfation or the purity of the active ingredients (eg. Tab. I). The US Federal Trade Commission (FTC) only ensures that the label conforms to certain requirements, such as that direct therapeutic claims are not made. Nevertheless, many companies still make unfounded claims and simply change their labels, if pressed to do so. It is, therefore, very important that health professionals familiarize themselves with which products are safe, scientifically based and likely to be of benefit. Some products and their advantages or disadvantages are discussed briefly (Tab. I-III).

Mechanism of action: cartilage "rebuilding vs. inflammatory action

Glucosamine sulfate supposedly acts as a building block for new cartilage, while chondroitin sulfate presumably acts as "ready made" cartilage. However, chondroitin sulfate has also anti-allergic and anti-inflammatory properties, primarily through mast cell inhibition (47). It is particularly critical that both the glucosamine and chondroitin must be *highly sulfated* because the sulfated molecules have many negative charges that better inhibit the function of inflammatory cells (47). Moreover, the sulfated molecules act as decoys attracting

bacteria and preventing them from adhering to the cell surface and causing infection (51). A natural molecule that has been recently used is the flavonoid *quercetin*, which has potent antioxidant and anti-inflammatory properties (48). Quercetin is commonly obtained from fava beans that may lead to hemolytic anemia in G_6PD deficient persons.

Algonot – Plus® combines "cartilage rebuilding" and anti-inflammatory products

While glucosamine sulfate may be incorporated into new cartilage, chondroitin sulfate appears to block mast cell activation and the bioflavonoid, quercetin, blocks mast cell secretion; the two together lead to better inhibitory results, as published recently (47, 48). The dietary supplements product line, Algonot-Plus® operates under the slogan "Let Nature Ease Your Pain®". It includes ArthrotSoft® softgel capsules and a cream. ArthroSoft® contains *glucosamine sulfate* from shellfish chitin, together with *chondroitin polysulfate* obtained from shark cartilage, instead of the most common source of cow trachea extract, and quercetin from the saphora plant to avoid fava beans. ArthroSoft® achieves increased absorption of all three ingredients, due to the fact that the active substances are mixed with unprocessed Kernel olive oil. No side effects have been reported.

The ArthroSoft® cream was developed to be used together with ArthroSoft® capsules and would also be useful for anyone with skin inflammation, especially psoriasis, which worsens by stress (56). The ArthroSoft® cream not only contains substantial amounts of all the key ingredients found in ArthroSoft® capsules, but delivers more of the same locally due to the presence of kernel olive oil that increases skin absorption. *ArthroSoft®* can be taken along with any treatments for several months to reap the benefits.

Two new products from the Algonot-Plus® were just made available, CystoProtek® and ProstaProtek® (Tab. IV) for interstitial cystitis and chronic prostatitis, inflammatory conditions of the urinary bladder and prostate, respectively. ProstaProtek® also contains rutin, the glycoside form of quercetin that also has anti-arthritis properties (57).

Unique benefits of Kernel olive oil

Kernel olive oil from the island of Crete is of low acidity and water content and undergoes special filtration to remove any particular matter. It is considerably richer than olive oil in all the well-known antioxidant and other cytoprotective components (58), such as polyphenols, that endow olive oil with anti-inflammatory and anti-arthritic actions (59-62) (Tab. V). In fact, olive oil has been reported to have beneficial in rheumatoid arthritis 63)" (58, 63), as well as permit concurrent administration of non-steroidal anti-inflammatory drugs because of its gastric mucosa healing properties (58). A study just released also indicated that adherence to a Mediterranean diet rich in olive oil reduced inflammatory activity in rheumatoid arthritis patients (64). Moreover, supplementation of olive oil with polyphenolic compounds, such as those found in kernel olive oil, protected against experimental inflammation (59).

CONCLUSION

Arthritis now appears to affect about 70 million Americans with a staggering financial burden; similar projections are made for other industrialized countries. The use of alternative therapies for arthritis has increased dramatically in the last few years with glucosamine and chondroitin being the most commonly used substances. Even though preliminary reports indicate a potential benefit in osteoarthritis, potential adverse effects and lack of sufficient absorption are not mentioned. Moreover, the problem of ongoing joint inflammation especially prevalent in rheumatoid arthritis is not addressed at all. The new series of Algonot-Plus®, ArthroSoft®, CystoProtek® and ProstaProtek® under the logo "Let Nature Ease your Pain®", combine glucosamine sulfate, with chondroitin sulfate and quercetin of high purity and from safe sources in a formulation with kernel olive oil that increases absorption. A companion skin cream also delivers more of the active ingredients locally.

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