Mast cells and mast cell mediators as targets of dietary supplements

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Objective: To review the increasing amount of data that support or dispel the use of dietary supplements in the treatment of inflammatory conditions that involve mast cells, such as allergies, arthritis, and chronic pelvic pain syndrome.

Data Sources: A search was conducted in MEDLINE for natural substances, dietary supplements, flavonoids, and proteoglycans for their in vitro or in vivo effects on allergic and inflammatory conditions.

Study Selection: Studies were selected for inclusion because of the impact factor of the journal, the definitive nature of the findings, the soundness of the study design, and the expert opinion of the authors.

Results: Dietary supplements include a large group of products, such as vitamins, minerals, plant, or animal extracts, as well as herbal preparations that are often called *medicinal herbs*. Many of the available dietary supplements contain a multitude of ingredients, the source and/or purity of which is seldom disclosed; some of these may have biologic effects of their own or may interact with other supplements or drugs, often leading to adverse effects. The most well-documented evidence published to date is on the inhibitory action of natural compounds, especially flavonoids, on mast cells and allergic symptoms. Some flavonoids have weak inhibitory activity, whereas others may have no benefit or may be detrimental. Sulfated proteoglycans could provide synergistic action but require formulations with increased absorption.

Conclusions: Combining the most active flavonoids with proteoglycans could be helpful in atopic and inflammatory conditions. However, a complete list of active ingredients and their source, purity, and exact concentration should be a requirement for nutraceuticals to standardize, compare, and promote their safe use.

Ann Allergy Asthma Immunol. 2004;93(Suppl 1):S24–S34.

INTRODUCTION

Complementary and alternative medicine (CAM) therapies have become a major component of health care in the United States such that some have questioned the term *complementary* as a valid description of these treatment modalities, especially since dietary supplements appear to be a common component of health care in our society.[1] The second most common group of chronic conditions for which individuals seek CAM therapies is atopic disorders.[2] With more than 20% of the US population having an atopic disorder and more than 42% of these individuals using CAM for their condition,[3] it is apparent that the health care providers who manage patients with atopic disorders should be aware of the widespread use of CAM in this patient population.[4] In addition, mast cells appear to play a role in other chronic inflammatory diseases, such as multiple sclerosis, arthritis, and genitourinary conditions,[5] in which CAM use has also been noted.[6] The need for scientific evidence to help navigate among the numerous CAMs is, therefore, of great importance.[7] This article reviews the increasing amount of data that support or dispel the use of dietary supplements in the treatment of inflammatory conditions that involve mast cells. An extensive search was conducted in MEDLINE using a number of relevant keywords that included *natural substances*, *flavonoids*, *proteoglycans*, *dietary supplements*, and *alternative therapy for atopic and inflammatory conditions*. Papers were selected for inclusion based on the impact factor of the journal, the soundness of the findings, the study design, and the expert opinion of the authors. Unpublished results from the authors' own work have also been included.

MAST CELLS AND CHRONIC INFLAMMATORY DISORDERS

Mast cells are found in most parts of the body and are well known for their involvement in allergic and anaphylactic reactions through degranulation.[8,9] Many molecules secreted are preformed and stored in almost 500 secretory granules, whereas others are synthesized de novo during stimulation.[10,11] Mast cell mediators include arachidonic acid products, biogenic amines, chemoattractants, cytokines, growth factors, neuropeptides, proteoglycans, and proteolytic enzymes.[10–12] Mast cells are increasingly recognized as key cells in the development of a number of inflammatory diseases,[13–15] including the skin,[16] joints,[17,18] and urinary bladder,[15,19] that worsen by stress. The possible involvement of mast cells is seldom discussed in the context of inflammatory diseases because of lack of evidence of overt degranulation.

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This article was based on an invited lecture at the First International Conference on Alternative and Complementary Medicine organized by the American College of Allergy, Asthma and Immunology, San Antonio, TX, November 14, 2002.

Received for publication April 16, 2003.

Accepted for publication in revised form December 30, 2003.

Their participation in these conditions, however, may depend on their ability to secrete biogenic amines,[20,21] arachidonic acid products,[22] and cytokines[23,24] without degranulation, a process termed *differential release*.[20] The morphologic appearance of this process is characterized by more subtle changes within the electron dense content of the secretory granules[25] and has been called "piece-meal degranulation"[26] or "intergranular activation"[27]; these changes are not recognizable by light microscopy. Furthermore, it was recently shown that selective mast cell secretion of interleukin 6 (IL-6) without degranulation and histamine or tryptase secretion could be induced by IL-1 through a unique vesicular shuttle.[24]

In addition, many mast cell–related conditions, such as asthma, atopic dermatitis, and psoriasis, are reportedly triggered or exacerbated by stress.[15,28] All of these conditions involve chronic inflammation that may develop in response to external or internal triggers for which the mast cells could act as a universal sensor.[16] For instance, it was recently suggested that skin may have its own equivalent of a hypothalamic-pituitary-adrenal (HPA) axis,[29] the main regulator of which corticotropin-releasing hormone (CRH) and its receptors were shown to be present in the skin.[30] Furthermore, CRH-2 receptors were shown to be up-regulated in stress-induced alopecia.[31] We showed that short-term stress can induce local CRH release in skin,[32] as well as lead to mast cell secretion and vascular permeability[33]; these effects were mimicked by intradermal administration of CRH[34] or its structurally related peptide urocortin[35] and were absent in W/W^v mast cell–deficient mice. CRH was also shown to stimulate human skin vasodilation in a mast cell–deficient fashion. These findings support the premise of a local neuroimmunoendocrine axis through activation of mast cells.[28]

In addition to IgE and antigen, many other molecules could trigger mast cell activation,[15] such as the anaphylatoxins C3a and C5a, as well as many neuropeptides and bacterial products through Toll-like receptors.[36] Furthermore, a number of over-the-counter and prescription drugs containing opioid analgesics[37] and high doses of acetylsalicylic acid[38] could stimulate mast cell secretion[39]; the latter finding is particularly important given that salicylic acid is found in many foods popular in alternative medicine practices.[40,41] Another example is the ma huang extract, which is rich in ephedra alkaloids and is used to reduce allergic symptoms and boost energy; it has been associated with sudden cardiac death[42] and other vasoconstrictive effects[43] that may derive from mast cell activation.[44] Histamine toxicity can also occur through bacterial histidine decarboxylase in uncooked tuna burgers[45] or through cis-urocanic acid–induced gastrointestinal mast cell release of histamine and other mediators.[46]

CAM USE, DIETARY SUPPLEMENTATION, AND HERBAL INTERVENTIONS

Dietary supplements include a large group of products, such as vitamins, minerals, plant, or animal extracts, as well as herbal preparations that are often called *medicinal herbs*.[47,48] Unfortunately, more often than not, such products make blatant claims that they can prevent or treat diseases[49]; as a result, there are increasing demands that dietary supplements should be regulated.[50,51] The lack of sufficient knowledge about the herbal products among health professionals[52] compounds the problem, because it leads many patients to rely on word of mouth.[53] Furthermore, the use of herbal products and other dietary supplements goes largely unreported even during routine medical visits.[54] The practice of underreporting of dietary supplements has the potential of great harm,[55] because it could result in numerous adverse affects.[56]

Many of the available dietary supplements contain a multitude of ingredients, the source and/or purity of which is seldom disclosed; some of these may have biologic effects of their own or may interact with other supplements or drugs, often leading to adverse effects.[56,57] This danger is particularly true during the preoperative period, because supplements such as St. John's wort could increase the metabolism of various drugs.[58] For instance, St. John's wort can significantly induce cytochrome P450 3A4, leading to increased metabolism and reduced serum levels of alprazolam.[59] Furthermore, St. John's wort was shown to be ineffective in the treatment of major depression.[60] Conversely, grapefruit juice, often used as a source of antioxidants, inhibits this enzyme, leading to elevated serum levels of many drugs and associated adverse effects.[61] Other supplements, such as ginkgo biloba, which is considered a central nervous system stimulant, have also recently been found to be inactive despite anecdotal reports to the contrary.[62] Similarly, although green tea has been publicized as preventing intestinal cancer, it was recently shown to have no such benefit.[63] Worse yet, other dietary supplements could be detrimental. For instance, the Chinese herb *Aristolochia fangchi* could cause urothelial carcinoma.[64] Likewise, despite anecdotal reports that intake of fruits and vegetables may reduce the risk of breast cancer,[65] this was not shown to be the case[66]; the effect of phytoestrogens is still being debated.[67] Furthermore, consumption of wild mushrooms, often encouraged by alternative medicine enthusiasts, has been associated with rhabdomyolysis.[68]

The most well-documented evidence published to date on a beneficial effect involving the inhibitory action of natural compounds on mast cells has focused on the naturally occurring flavonoids.[69] They inhibit not only the prestored mediators histamine and tryptase from normal human mast cells but also the synthesis of the cytokines IL-6, IL-8, and tumor necrosis factor α (Fig 1; Kempuraj et al, unpublished data). Some flavonoids such as morin have weak inhibitory activity, whereas others may increase mast cell secretion.[70] Consequently, the use of formulations that contain bioflavonoids, citrus flavonoids, or soy flavonoids obviously contain many different flavonoids that could have no benefit or may be detrimental. The flavones and flavonols kaempferol, quercetin, and myristein have the highest mast cell inhibitory action that depends on the hydroxylation pattern of their B ring.[69] Most recently, the proteoglycan chondroitin sulfate was

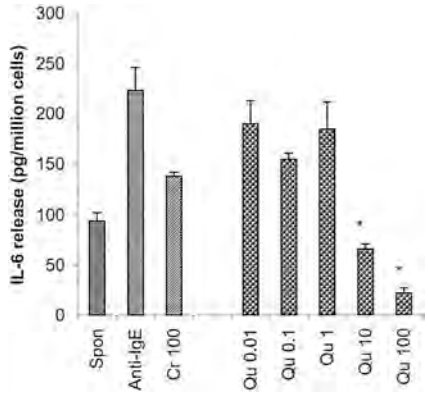

Figure 1. Inhibitory effect of quercetin on human mast cell interleukin 6 (IL-6) secretion. Spon indicates spontaneous; Cr 100, cromolyn, 100 μM; Qu 0.01, quercetin, 0.01 μM; Qu 0.1, quercetin, 0.1 μM; Qu 1, quercetin, 1 μM; Qu 10, quercetin, 10 μM; and Qu 100, quercetin, 100 μM. *$P < .05$.

shown to inhibit activation of connective tissue mast cells (Fig 2).[71] Removal of sulfate reduced the inhibitory action that was still more potent than using glucosamine sulfate (Fig 2). Aloe vera has also been reported to reduce mast cell secretion[72] and mast cell infiltration in an inflamed synovial pouch model.[73]

ARTHRITIS

Reports from the Centers for Disease Control and Prevention indicate that 1 in 3 of all adults in the United States (almost 70 million) have arthritis or chronic joint pain, up from 1 in 5 in 1993, with an estimated annual cost of $82 billion.[74] The impact of arthritis is comparable in Australia, Canada, Europe, and the United Kingdom, with an estimated total of another 60 million affected individuals.[75] Due to the chronic and debilitative nature of these conditions, as well as the serious adverse effects of many of the prescription drugs used, more individuals are increasingly turning to dietary supplements and alternative therapies to address these conditions.

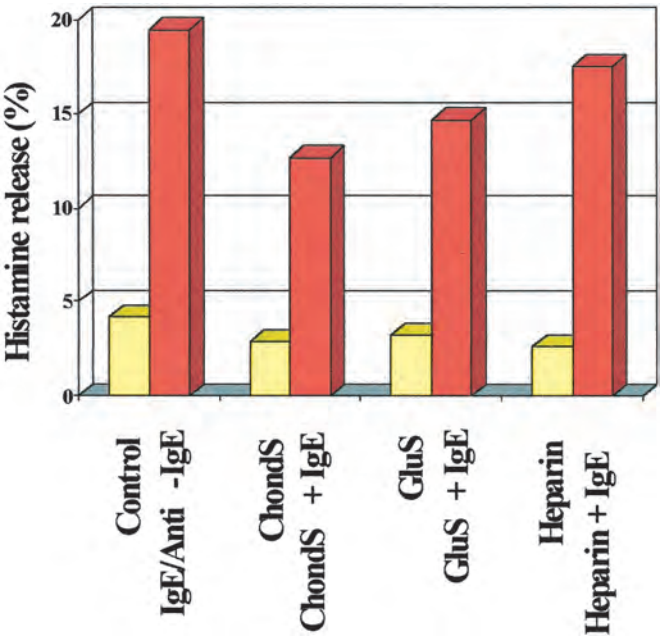

Figure 2. Inhibitory effect of chondroitin sulfate (ChondS), glucosamine sulfate (GluS), and heparin, 0.1 mM, on anti-IgE–induced histamine release from purified rat peritoneal mast cells.

Articular damage in arthritis involves cartilage erosion, inflammatory cell accumulation, and finally bone destruction and reactive bone spur formation; typical therapy for osteoarthritis involves weight loss, exercise, and use of nonsteroidal anti-inflammatory drugs.[76–78] In rheumatoid arthritis, active articular inflammation requires immunosuppressant and immune-modifying drugs.

Increasing evidence indicates that mast cells are involved in the pathophysiology of arthritis.[17,18,79–90] Mast cells are known to secrete IL-6,[91] and recent studies have shown that mast cell–deficient mice could not increase their serum IL-6 in response to short-term stress.[92] This is interesting since IL-6 levels are elevated in rheumatoid arthritis.[93,94] IL-6 is also important in collagen-induced[95] and antigen-induced[96] arthritis, whereas IL-6 knockout mice are resistant to antigen-induced arthritis.[97] Mast cells were also independently shown to be necessary for autoimmune arthritis[98] and experimental inflammatory arthritis,[99] since neither could develop in W/W^v knockout mice. In fact, stress has been shown to worsen arthritis[100–102] and activate mast cells.[15,19]

In particular, inflammatory arthritis induced by the injection of carrageenan in the right hind knee joint increased the joint size by 1.94 $\pm$ 0.41 mm in C57 black mice (Fig 3) (Papadopoulou et al, unpublished data) at 4 days by which time the mice were obviously limping. These effects also occurred in tumor necrosis factor knockout mice but were inhibited in W/W^v mast cell–deficient and CRH knockout mice, which were clinically indistinguishable from mice injected with isotonic sodium chloride solution. These results are of interest because CRH increased in the joints of rheumatoid arthritis patients and CRH receptors were present on articular mast cells,[103] implying that CRH could trigger mast cell activation. In fact, we showed that CRH could trigger mast cells in the skin[34] and increase vascular permeability[35] in rodents. CRH was recently shown to also induce mast cell–dependent vascular permeability in humans.[104] The pathophysiological implications of such a finding are that CRH could be released locally under stress[32] and exacerbate atopic dermatitis,[28,105] as well as many other allergic and inflammatory diseases.[15]

D-Glucosamine and chondroitin are commonly used for arthritis.[106–109] A meta-analysis of clinical trials using glucosamine and/or chondroitin originally indicated potential usefulness in osteoarthritis.[107] The validation of a self-administered health status instrument for osteoarthritis has helped with the design of double-blind studies.[110] Another instrument, the Cedars-Sinai Health Related Quality of Life Instrument, can be used for

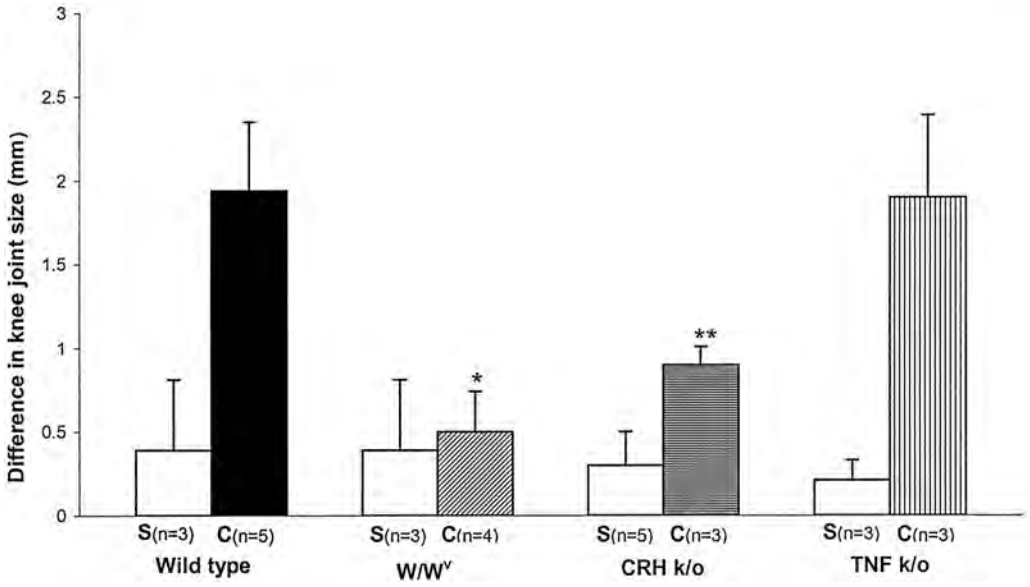

Figure 3. Role of mast cells in experimental inflammatory arthritis. Mice were injected in one of their knee joints, and the swelling was determined with digital calipers 4 days later. S indicates isotonic sodium chloride solution; C, carrageenan; W/W^v, mast cell–deficient mice; CRH, corticotropin-releasing hormone; k/o, knockout mice; and TNF, tumor necrosis factor. *$P < .001$ compared with wild-type C. **$P < .01$ compared with wild-type C.

rheumatoid arthritis research.[111] At least 2 studies have shown that 1,500 mg/d of glucosamine *for 3 years* can delay progression of osteoarthritis and knee space reduction.[108,112] One of the first double-blind studies compared 500 mg of glucosamine sulfate 3 times daily to 400 mg of ibuprofen 3 times daily for 4 weeks. From the second week on, the clinical improvement was the same (approximately 50%) in both groups, but 35% of those taking ibuprofen reported adverse effects compared with 6% taking glucosamine.[113] In another randomized, double-blind, placebo-controlled trial, 212 patients with osteoarthritis of the knee were assigned either 1,500 mg of oral glucosamine sulfate or a placebo for 3 years. Patients undergoing active treatment had clinical improvement of symptoms and no significant joint space loss compared with progressive narrowing of those taking placebo.[108] In a subsequent study, 202 patients with osteoarthritis of the knee were randomized to either 1,500 mg of glucosamine sulfate or placebo for 3 years. Symptoms in the active group improved by approximately 25% and joint space narrowing (>0.5 mm) occurred in 5% of those in the active arm compared with 15% taking the placebo.[112] However, more recent studies with glucosamine have failed to show consistent benefit.[114] Moreover, glucosamine has been shown to reduce insulin sensitivity, and large amounts should be avoided in obese and diabetic individuals.[115]

PROTEOGLYCAN REBUILDING AND ANTI-INFLAMMATORY PROPERTIES

Few clinically available drugs can effectively inhibit human mast cell activation. For instance, even though disodium cromoglycate (cromolyn) had been known to inhibit activation of rodent mast cells,[116] it was unable to inhibit human mast cell activation (Fig 1).[117]

A number of articles have reviewed the long-term use of glucosamine and chondroitin in osteoarthritis.[114,118,119] However, no article has focused on *how* these molecules may be acting, especially during short duration of use. All published studies have used *sulfated* glucosamine, whereas many glucosamine-containing (and chondroitin-containing) dietary supplements use plain glucosamine or chondroitin. However, there is increasing evidence that the higher the degree of sulfation, the greater the benefit, but also the less the oral absorption. There is also some evidence that bacterial adhesion and invasion depend on sulfated surface polysaccharides[120,121]; use of chondroitin sulfate as decoy may prevent bacteria from adhering to the cell surface and causing infection.[120]

Glucosamine sulfate presumably acts as a building block for new cartilage or GAGs, whereas chondroitin sulfate acts as a ready-made component of these protective substances.[122] However, both chondroitin sulfate[71] and the flavonoid quercetin[69] have antiallergic and anti-inflammatory properties, primarily through mast cell inhibition. Rutin, the glycoside form of quercetin, also has antiarthritis properties.[123] Chondroitin sulfate appears to block mast cell activation and histamine release; quercetin blocks mast cell secretion and particularly cytokine secretion. The 2 molecules together could have synergistic actions[69,71] (Fig 4). In view of these findings, it is obviously desirable to use combinations of these molecules, but their oral administration does not allow sufficient absorption because of the large proteoglycan molecular weight and the extreme lipophilicity of quercetin. The

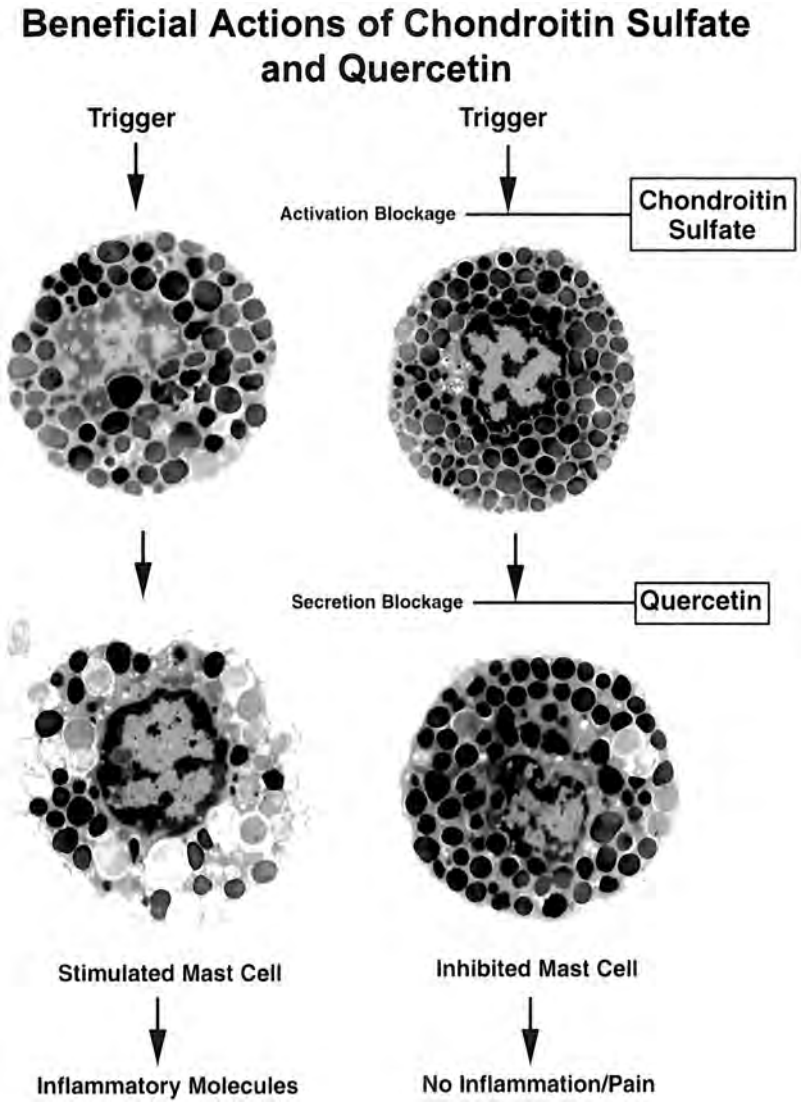

Figure 4. Proposed synergistic inhibitory effect of chondroitin sulfate and quercetin on mast cell activation. Photomicrographs of electron microscope images of purified rat peritoneal mast cells are shown at a magnification of 7,000 diameters; the mast cells (see lower left side panel) were stimulated by 0.1 mM of the neuropeptide substance P for 5 minutes at 37° C, with or without (left side panels) chondroitin sulfate and quercetin (each at 0.1 mM for 10 minutes at 37° C).

dietary supplements most likely to have benefit would be those formulated in kernel olive extract base soft gel capsules.

Patients often wonder whether they may have an allergic reaction to glucosamine sulfate and chondroitin sulfate if they are allergic to sulfonamide antibiotics. This possibility is rather unlikely; a recent study showed absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics.[124]

BLADDER AND PROSTATE INFLAMMATION

Chronic pelvic pain syndrome includes interstitial cystitis (IC) and chronic prostatitis. IC, for which CAM use appears to be increasing,[125] is a syndrome that occurs primarily in women with symptoms of urinary frequency, urgency, nocturia, and suprapubic or pelvic pain.[126–128] IC patients, as well as chronic prostatitis patients,[129] are characterized by mast cell accumulation and activation in the bladder and prostate.[5,130] In fact, bladder mastocytosis was the only pathologic biopsy feature that correlated with the primary symptom of nocturia.[131] A population-based estimate in the United States using the Nurses' Health Study I and II, which started in 1976 and 1989, respectively, provided a prevalence of approximately 60 cases per 100,000 women.[132] Many women with IC have endometriosis and chronic pelvic pain or dyspareunia; furthermore, more than 50% of IC patients have various atopic conditions, approximately 40% have irritable bowel syndrome, and another 30% have fibromyalgia or rheumatoid arthritis.[133–135] In view of these findings, IC has been considered a neuroinflammatory condition,[130] and treatment is currently elusive.[6,136,137]

Both IC and chronic prostatitis, which are considered similar, are triggered by stress[123,134]; short-term stress also results in bladder[138] and intestinal[139,140] mast cell activation. The possible pathologic role of mast cells in IC is supported by the fact that the only oral prescription medication approved by the Food and Drug Administration for IC, pentosan polysulfate (PPS, Elmiron), also blocks mast cell activation.[141] A recent study, however, showed that PPS alone was ineffective, while the combination of pentosan polysulfate with hydroxyzine, which can reduce mast cell activation[142] and neurogenic bladder inflammation,[143] helped most IC patients, even though the results did not reach statistical significance because the study was underpowered and not all patients reached the desired 50 mg/d hydroxyzine.[144] Preliminary studies also suggested that the flavonoid quercetin may be of help in IC[145] and chronic prostatitis[146]; a formula containing quercetin, chondroitin sulfate, and sodium hyaluronate was particularly useful in IC.[146,147]

OTHER HERBALS COMPONENTS: EFFECTS OF MAST CELLS AND THEIR MEDIATORS

Western herbal preparations are extensively used despite the lack of robust scientific evidence and limited support from clinical studies. Many traditional Chinese medicine agents have antihistaminic components demonstrated in various clinical studies.[148] Various herbal preparations differ from the different parts of the world. Some of these are summarized in Table 1.

Urtica dioica (stinging nettle) is a plant that contains various mediators, such as histamine, serotonin, and acetylcholine, in the fresh stinging hairs on its leaves and is commonly used as a homeopathic treatment for allergic rhinitis. In a randomized, double-blinded study of *U dioica* in the treatment of allergic rhinitis, *U dioica* was rated slightly higher (not statistically significant) than placebo for allergic rhinitis.[149]

Butterbur (*Petasites hybridus*) is an Asteraceae herbaceous plant native to Europe, northern Africa, and southwestern Asia. Extracts of butterbur have been used in the treatment of asthma and allergic rhinitis. In vitro studies suggested that an extract of *P hybridus* blocks leukotriene synthesis in monocytes, granulocytes, and eosinophils.[150,151] Levels of inflammatory mediators in nasal fluids and serum revealed a significant reduction of histamine and leukotriene levels, including cysteinyl-leukotriene.[152] Inhibition of cellular calcium levels may explain its spasmolytic actions.[152] One of the active components, petasin, was shown to be equally effective to an established antihistamine in treating allergic rhinitis.[153] The Petasites Study Group performed one of the few randomized controlled trial in seasonal allergic rhinitis patients, comparing butterbur to cetirizine, using subjective measures including quality-of-life assessments (36-Item Short-Form

Table 1. Mast Cell–Related Activity, Clinical Effect, and Adverse Effects of Some Herbal Products

Formulation	Origin	Physiologic activity	Clinical effect	Adverse effects
Aloe vera*	Middle East, China	Inhibits histamine release	Decreases allergies	None reported
Bu-zhong-yi-qi-tang		Decreases capillary permeability, eosinophils	Decreases inflammation	None reported
Butterbur*	Asia	Inhibits histamine and leukotriene release	Decreases symptoms of allergic rhinitis, spasmolytic	Rare cholestatic hepatitis
Chondroitin sulfate*	China, Europe	Inhibits mast cell activation Cartilage, bladder mucosal component	Decreases inflammation, rebuilds cartilage and GAG layer	None reported
Echinacea	Europe	Unknown	Decreases symptoms of common cold	None reported
Eucalyptus	Indonesia	Inhibits histamine release	Nasal allergies	None reported
Hi-Chum	Korea	Inhibits histamine release	Antianaphylactic activity	None reported
Jisil	Korea	Decreases IgE production	Antianaphylactic activity	None reported
Ma huang (wu-hu-tang)	China	Sympathetic activity, stimulates mast cell activation	Dries secretions, bronchodilator	Cardiac arrhythmias, nephrolithiasis, strokes, sudden death, acute hepatitis
Peppermint (*Mentha piperita*)	Japan, Kampo	Stabilizes mast cell membranes	Decreases inflammation	None reported
Quercetin* (*Saphora plant*)	Latin America	Inhibits mast cell activation, histamine, tryptase and cytokine release	Decreases allergies and inflammation	None reported
Salviae	Korea	Increases cyclic adenosine monophosphate	Antianaphylactic activity	None reported
Sho-seiry-to	Japan, Kampo	Anticholinergic effects	Dries secretions, decreases inflammation	None reported

* Peer-reviewed publications.

Health Survey) with similar improvements between the 2 groups. Sedative effects were reported in 12% of patients receiving cetirizine; however, no adverse effects were reported in the group receiving butterbur.[154] However, long-term use has been associated with cholestatic hepatitis.

Echinacea (*Echinacea angustifolia* and *Echinacea purpurea*) is the cousin of the ragweed that has gained much popularity in Western societies as an herbal remedy for upper respiratory tract disorders, including allergies.[155] Melchart et al[156] reviewed a number of clinical trials and reported that Echinacea appeared to have positive effects in preventing symptoms related to colds. The basic science evaluations have focused on the relative phagocytic activity of polymorphonuclear neutrophil granulocytes, but this has limited potential for any effect in allergies.[157] Consequently, no particular preparation was recommended.

Eucalyptus and cinnamon (*Eucalyptus globulus* leaves and fruit and *Cinnamomum massoiae* cortex) appeared to have some effect on mast cells as reflected by the inhibition of IgE-dependent histamine release from rat basophilic leukemia cells (RBL-2H3), a tumor analog of mast cells.[158]

CONCLUSION

Mast cells, well known for their involvement in allergy and asthma, are now implicated in many inflammatory conditions, especially arthritis and pelvic pain syndrome. The need for substantiating the clinical and scientific validity of CAM therapies for mast cell–mediated atopic disorders and perhaps other mast cell–associated inflammatory diseases has been clearly emphasized by many who practice both CAM and conventional medicine.[7] The financial burden of such chronic inflammatory disorders and the use of dietary supplements and herbal interventions is of major concern to the economy. However, there is a lack of scientific information on the mechanism of action and a paucity of randomized, placebo-controlled studies. To make matters worse, issues of pharmacological delivery (ie, absorbance and potential adverse effects) are not generally known, disclosed, or discussed. Furthermore, the impact on the ongoing inflammation, which is much more prevalent in conditions such as asthma, atopic dermatitis, or rheumatoid arthritis, is not addressed with the inclusion of anti-inflammatory molecules. Combining select proteoglycans with flavonoids formulated in a kernel olive extract base provides increased absorption and synergistic beneficial effects by inhibiting mast cell activation. A complete list of active ingredients and their source, purity, and exact concentration should be a requirement for nutraceuticals to standardize, compare, and promote their safe use.

ACKNOWLEDGMENTS

Thanks are due to Jessica Christian for her patience and word processing skills. Use of proteoglycans and flavonoids, with or without kernel olive extract, for atopic and inflammatory conditions is covered by US patents 6,635,625; 6,641,806; 6,645,482; and 6,689,748 awarded to Dr. Theoharides and assigned to Theta Inc (Brookline, MA). Aspects of this work were supported in part by grants from the National Institutes of Health (R13 AT01224–01), National Center of Complementary and Alternative Medicine; Scientific Advances in Complementary and Alternative Medicine: Advances in Allergy, Asthma and Immunology to Dr. Bielory, and DK42409, DK44815, NS38326, and AR47662, as well as Theta Biomedical Consulting and Development Co. (Brookline, MA) to Dr. Theoharides.

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