Understanding the Role of Mast Cell Activation in Chronic Disease

DEBBY HAMILTON, MD, MPH
RESEARCHED NUTRITIONALS
Objectives

- Understand the symptoms associated with activated mast cells and how to diagnose mast cell issues
- Discuss mast cells location and function in the immune system
- Learn about abnormal mast cell activation from infections, inflammation, and toxins
- Describe the role that mast cells play in the underlying pathology of chronic disease including digestive issues, infections, and degenerative diseases such as autism
- Learn about natural herbal treatments for inhibiting mast cell activation and blocking the histamine receptor
- Discuss a comprehensive treatment approach to chronic disease that targets mast cell activation, inflammation, oxidative stress, mitochondrial dysfunction, and glutathione depletion
Symptoms Associated with Elevated Histamine from Activated Mast Cells

- Allergies
- Asthma
- Eczema
- Hives
- Anaphylaxis
- Histamine Intolerance
- Mast Cell Activation Syndrome (MCAS)
- Mastocytosis
**Histamine Release from Mast Cells**

- **Causes:**
  - Blood vessel dilation
  - Bronchoconstriction
  - Increased heartbeat
  - Release of adrenaline
  - Increased capillary permeability
  - Increased gastric acid secretion
  - Pruritis
Histamine Intolerance

1. Too much histamine absorbed from food
2. Eating too much food containing histamine
3. Too little DAO
4. Ingesting substances that block DAO
Histamine Intolerance Symptoms

- Headaches
- Migraines
- Vertigo or dizziness
- Insomnia
- Anxiety
- Circadian rhythm problems
- Flushes
- Hives, rashes, eczema
- Itchy skin
- Excessive sudden sweating
- Swelling (lids, water retention)
- Difficulty breathing
- Chronic coughing
- Asthma
- Throat clearing
- Post nasal drip
- Sore throat
- Racing heart
- Palpitation
- Arrhythmia
- Low blood pressure
- Blood clots
- Period cramps and dysregulation
- Missed periods
- Endometriosis
- Estrogen dominance
- Muscle and joint pain
- Fibromyalgia
- Muscle twitches
- Nausea/Vomiting
- Diarrhea
- Loose stool
- Stomach pain
- Bloating
- Acid reflux
Mast Cell Disorders

- Mastocytosis: Increase in number of mast cells
- Mast Cell Activation Syndrome: abnormal increase in activation of existing mast cells
<table>
<thead>
<tr>
<th>System</th>
<th>Potential Manifestations of MCAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fatigue, subjective or objective hyperthermia and/or hypothermia, sweats, flushing, plethora or pallor, increased or decreased appetite, weight gain or loss, pruritus, chemical/physical sensitivities (often odd), poor healing</td>
</tr>
<tr>
<td>Dermatologic/integument</td>
<td>Rash/lesions of many sorts (eg, classic urticaria pigmentosa, telangiectasias, xerosis, striae, warts, tags, folliculitis, ulcers, dyshidrotic eczema, migratory but sometimes focally persistent patchy macular erythema), migratory pruritus (sometimes aquagenic), angioedema, dermatographism, alopecia, onychodystrophy</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Irritated eyes, episodic difficulty focusing, lid tremor/tic (blepharospasm)</td>
</tr>
<tr>
<td>Otologic/osmic</td>
<td>Infectious or sterile otitis externa and/or media, hearing loss and/or tinnitus, dysosmia, coryza, congestion, epistaxis.</td>
</tr>
<tr>
<td>Oral/oropharyngeal</td>
<td>Pain or irritation (sometimes “burning”), leukoplasia, ulcers, angioedema, dysgeusia, dental or periodontal inflammation/decay</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>Adenopathy (usually subpathologic and spontaneously waxing/waning in size, sometimes migratory), adenitis, splenitis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Airway inflammation at any or all levels, cough, dyspnea (usually mild, episodic, and accompanied by normal pulmonary function tests), wheezing, obstructive sleep apnea, pulmonary hypertension</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Presyncope or syncope, hypertension and/or hypotension, palpitations, migratory edema, chest pain (usually nonanginal), atherosclerosis, odd heart failure (eg, takotsubo), allergic angina (Kounis syndrome), vascular anomalies</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dyspepsia, reflux, nausea, vomiting (sometimes cyclical), diarrhea and/or constipation (often alternating), angioedema, dysphagia (often proximal), bloating/gas, migratory abdominal pain from luminal or solid organ inflammation, malabsorption, ascites</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Migratory luminal and solid organ inflammation, chronic kidney disease, endometriosis, chronic back/flank/abdominal pain, infertility, decreased libido; miscarriages may signal an MCAS-rooted antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Migratory bone/joint/muscle pain, joint laxity/hypermobility, osteopenia and/or osteosclerosis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, sensory, and/or motor neuropathies, seizure disorders, pseudoseizures, dysautonomia</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Mood disturbances, anxiety/panic, psychoses, cognitive dysfunction (most commonly memory and word-finding difficulties), sleep disruption</td>
</tr>
<tr>
<td>Endocrinologic/metabolic</td>
<td>Abnormal electrolytes and liver function tests, hypothyroidism, hyperthyroidism, dyslipidemia, impaired glucose control, hyperferritinemia, nutritional deficiencies, delayed puberty, dysmenorrhea</td>
</tr>
<tr>
<td>Hematologic/coagulopathic</td>
<td>Polycythemia or anemia (macrocytic, normocytic, or microcytic), leukocytosis or leukopenia, monocytosis/ eosinophilia/basophilia, thrombocytosis or thrombocytopenia, arterial and/or venous thromboembolic disease, otherwise inexplicable “easy” bruising/bleeding; usually no histologic or molecular evidence of MC aberrancy in the marrow in MCAS</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Hypersensitivity reactions, increased risk for malignancy and autoimmunity, impaired healing, increased susceptibility to infection, increased or decreased levels of immunoglobulin of any isotype, monoclonal gammopathy of undetermined significance</td>
</tr>
</tbody>
</table>

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*Most symptoms are chronic and low-grade; some are persistent, but many are either episodic or waxing/waning. More comprehensive lists and discussions are available. MC = mast cell; MCAD = mast cell activation disease; MCAS = mast cell activation syndrome. Data from: Afirn L. Presentation, diagnosis, and management of mast cell activation syndrome. In: Murray D. Mast cells: phenotypic features, biological functions, and role in immunity. 2013. [9]
<table>
<thead>
<tr>
<th>Mediator</th>
<th>Symptoms/signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Headache, hypotension, pruritus, urticaria with or without angioedema, diarrhea, anaphylaxis</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Endothelial activation with consecutive inflammatory reactions, bleeding diathesis</td>
</tr>
<tr>
<td>Prostaglandin D₂</td>
<td>Flushing, mucus secretion, bronchoconstriction, vascular instability, headache, “mixed organic brain syndrome” (poor concentration, memory loss), nausea, abdominal pain</td>
</tr>
<tr>
<td>Platelet-activating factor</td>
<td>Abdominal cramping, pulmonar edema, urticaria, bronchoconstriction, hypotension, arrhythmia, anaphylaxis</td>
</tr>
<tr>
<td>Cytokines (IL-1, IL-6, TNF-) and chemokines</td>
<td>Constitutional symptoms (fatigue), inflammation, osteoporosis</td>
</tr>
<tr>
<td>Leukotriene C₄ and leukotriene D₄</td>
<td>Mucus secretion, bronchoconstriction, edema formation, vascular instability</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Acute inflammation and leukocyte recruitment, leukocyte migration</td>
</tr>
<tr>
<td>Renin</td>
<td>Cardiac arrhythmias, myocardial infarction</td>
</tr>
</tbody>
</table>

Mast Cell Activation Syndromes.
Bonamichi-Santos R. Current Treatment Options in Allergy. 2016. 3(4):384-400.
Diagnosis:
Lab tests sensitive to heat
Often negative
Clinical Diagnosis

- Histamine: plasma
  - Normal range: 28-51 ug/l.
- N-Methylhistamine: 24-hour urine
  - Normal range: less than 200 mcg
- Prostaglandin D2: plasma
  - Off of NSAIDS or aspirin for test
- Prostaglandin D2 (PGD2): 24-hour urine
  - Off of NSAIDS and aspirin for test
- Chromogranin A
  - Off proton pump inhibitors and H2 blockers for test
- Tryptase
Mast Cells role in the Immune System
The Human Mast Cell: Functions in Physiology and Disease.
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>H4</td>
<td>Mast, eosinophil, T, dendritic cells</td>
<td>Immune response regulation</td>
</tr>
<tr>
<td>H3</td>
<td>Central Nervous System</td>
<td>Neurotransmitter control</td>
</tr>
<tr>
<td>H2</td>
<td>Gastric parietal cells</td>
<td>Gl gastric acid secretion</td>
</tr>
<tr>
<td>H1</td>
<td>Smooth muscle, Endothelial cells</td>
<td>Acute allergic response</td>
</tr>
</tbody>
</table>

Histamine Receptors
Diseases associated with Mast Cell Activation

- Irritable bowel syndrome
- CIRS
- Dysbiosis: gastrointestinal
- Candida overgrowth
- Obesity
- Diabetes
- Asthma and allergies
- Autism
- Autoimmune diseases (such as lupus, rheumatoid arthritis, and Hashimoto’s)
- Celiac disease
- Skin conditions such as eczema and psoriasis
- Food intolerances and allergies
- Gastroesophageal reflux (GERD)
- Infertility and endometriosis
- Chemical and medication sensitivities
- Postural orthostatic hypotension (POTS)
- Mold
- Migraines
- Depression
- Fibromyalgia
- Tinnitus
- Multiple Sclerosis
- Cancer
- Tick-born infections: Lyme
- Ehlers-Danlos Syndrome
Interrelationship between Mast Cell Activation and inflammation, oxidative stress, and mitochondrial dysfunction

- Inflammation
- Oxidative Stress (Reactive Oxygen Species)
- Extracellular mitochondrial components from damaged mitochondria
- Glutathione depletion (can’t clear free radicals)

All Trigger Mast cell activation
Mast Cells Involved in Neuroinflammation
Oxidative stress, mitochondrial dysfunction and inflammation are common events in skin of patients with Fibromyalgia. Sanchez-Dominguez B. Mitochondrion. 2015 Mar;21:69-75.

Recent studies have shown some evidence demonstrating that oxidative stress, mitochondrial dysfunction and inflammation may have a role in the pathophysiology of fibromyalgia.

Overlap of symptoms between MCAS and Fibromyalgia

- Fatigue
- Sleep disturbance
- Cognitive problems
- Memory problems
- Headaches
- Dizziness
- Pain in muscles
- Paired tender points
- Problems with vision
- Jaw pain
- Nausea
- Skin problems
- Urinary problems
  - Dysmenorrhea (in women)
- Joints pain and morning stiffness
- Restless leg syndrome
Mast Cell Disorders in Ehlers–Danlos Syndrome

SURANITH L. SENEVIRATNE, ANNE MAITLAND, and LAWRENCE AFIRN

Well known for their role in allergic disorders, mast cells (MCs) play a key role in homoeostatic mechanisms and surveillance, recognizing and responding to different pathogens, and tissue injury, with an array of chemical mediators. After being recruited to connective tissues, resident MCs acquire the ability to secrete potential mediators. MCs can modulate the function of local and distant structures (e.g., other immune cell populations, fibroblasts, angiogenesis), and MC degranulation has been implicated in immediate and delayed hypersensitivity syndromes, neuropathies, and connective tissue disorders (CTDs). This report reviews basic biology of mast cells and their role in recent research efforts, which implicate a role of MC dysfunction in several diseases and in a cluster of Ehlers-Danlos Syndromes, non-CTD-mediated hypersensitivity disorders, and dysautonomia.


INTRODUCTION: MAST CELLS AND THEIR PROPERTIES

In the late 19th century, Paul Ehrlich named a granule-laden cell “mastzellen,” situated near blood vessels in the mucous and connective tissue. He described these cells were providing nourishment to the local tissue environment. Using commercial dyes such as safranin, toluidine blue, methylene blue, and neutral red, he noted morphologically distinct mature mast cells (MCs) in the connective tissue of several organs.

MCs develop from multipotent hematopoietic progenitors in the bone marrow [Hollenberg et al., 2011]. Stem cell factor (SCF) ligand binds to homodimeric KIT (a transmembrane tyrosine kinase receptor) and influences MC differentiation, growth, survival, migration, and effector functions. MCs acquire a tissue-specific phenotype depending on signals they receive from the local tissue environment. Several factors such as interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-9 (IL-9), and transforming growth factor β1 (TGFβ1) have been shown to influence the number and maturation of MCs [Gabi et al., 2011].

Under normal pathological states, mature differentiated MCs are found exclusively within tissues, compared to other innate immune cells, such as basophils, neutrophils, and eosinophils. Within tissues, MCs aggregate around nerves, blood vessels, and lymphatic vessels. Based on their location (connective tissue or mucosal) and content of their granules, two types of MCs have been described: MCs residing in connective tissue, skin, and the submucosal mast cells in the mucosal layer between muscularis mucosae and muscularis propria. MCs synthesize and release a variety of chemical mediators upon stimulation, such as histamine, heparin, platelet-activating factor, and many others.

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Correlation between mast cells and gastrointestinal disorders: Role in IBS

Review Article
The Role of Mast Cells in Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders, but its treatment is unsatisfactory as its pathophysiology is multifactorial. The putative factors of IBS pathophysiology are visceral hypersensitivity and intestinal dysmotility, also including psychological factors, dysregulated gut-brain axis, intestinal microbiota alterations, impaired intestinal permeability, and mucosal immune alterations. Recently, mucosal immune alterations have received much attention with the role of mast cells in IBS. Mast cells are abundant in the intestines and function as intestinal autoregulators at the interface between the luminal environment in the intestine and the internal milieu under the intestinal epithelium. As a gatekeeper at the interface, mast cells communicate with the adjacent cells such as epithelial, neuronal, and other immune cells throughout the gut and release cytokines when they themselves are activated. Many studies have suggested that mast cells play a role in the pathophysiology of IBS. This review will focus on studies of the role of mast cells in IBS and the limitations of studies and will also consider future directions.

1. Introduction
Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal (GI) disorders with a worldwide prevalence of 5–20% [1, 2]. IBS diagnosis is based on symptoms such as recurrent abdominal pain related to defecation and accompanied by a change in the frequency or form of stool [3]. However, neither diagnostic nor therapeutic approaches are satisfactory because IBS is a multifactorial disorder and its manifestation differs from patient to patient. It has traditionally been thought to result from two abnormalities: visceral hypersensitivity and intestinal dysmotility. However, recent intensive studies have revealed that low-grade inflammation of the intestine [4], as well as alterations of gut barrier function, epithelial permeability, mucosal immunity, and gut-brain axis [5–8], is also involved.

It has been suggested that intestinal mast cells are intimately involved in these pathophysiologic changes [9, 10]. Mast cells can activate adjacent cells by releasing mediators and can also be activated themselves via IgE-mediated or non-IgE-mediated pathways. They are thus closely associated both anatomically and functionally with intestinal components such as intrinsic and extrinsic nerves of the GI tract, intestinal smooth muscles, and accessory glands [10–13]. Furthermore, symptoms of IBS are often provoked by the ingestion of food or psychological stress, which is one of the factors to activate intestinal mast cells [12].

This connection between mast cells and IBS pathophysiology and symptomatology has been supported by numerous studies. In this review, we describe the results of those studies and their limitations and consider potential future developments.

2. Mast Cells in the Regulation of GI Physiology and Pathophysiology
The many roles of mast cells depend on their ability to secrete mediators after being activated by a variety of stimuli [13]. Mast cells can be activated via either IgE-dependent or IgE-independent pathways [16, 17]. First, IgE-dependent pathways are activated, as in allergic reactions, by binding of allergens to IgE bound to high affinity Fc epsilon receptor (FcεR) and their subsequent cross linking [18]. Second, IgE-independent pathways are activated by various receptors on mast cells to other agents, including cytokines, neurotransmitters, anaphylatoxins such as venom, and physical...
Asthma: oxidative stress, mast cell activation, inflammation: leads to “leaky lungs” increased epithelial permeability
Histamine Intolerance Treatment

Breakdown on Histamine dependent on genetic SNP’s of HNMT and DAO
DAO: Diamine Oxidase Enzyme

DAO Inhibitors

- Alcohol
- NSAID’s
- Immune modulators: Enbrel, Plaquenil
- Anti-histamines: Benadryl, Zyrtec, Zantac

Decrease DAO

- SIBO, leaky gut, dysbiosis from histamine producing probiotics
- Deficiencies in cofactors: Copper, vitamin C, B6
- Genetic polymorphisms: DAO enzyme
Foods to Avoid if You Are Histamine Intolerant

**Histamine-Rich Foods**
- Fermented Alcoholic Beverages,
- Fermented Foods: Sauerkraut, Vinegar, Soy Sauce, Kefir, Yogurt, Kombucha, etc.
- Vinegar-containing Foods: Pickles, Mayonnaise, Olives
- Cured Meats: Bacon, Salami, Pepperoni, Luncheon Meats and Hot Dogs
- Soured Foods: Sour Cream, Sour Milk, Buttermilk, Soured Bread, etc.
- Dried Fruit: Apricots, Prunes, Dates, Figs, Raisins
- Most Citrus Fruits
- Aged Cheese Including Goat Cheese
- Nuts: Walnuts, Cashews, and Peanuts
- Vegetables: Avocados, Eggplant, Spinach, and Tomatoes
- Smoked Fish and Certain Species of Fish: Mackerel, Mahi-Mahi, Tuna, Anchovies, Sardines

**Histamine-Releasing Foods**
- Alcohol
- Avocados
- Bananas
- Chocolate
- Cow’s Milk
- Nuts
- Papaya
- Pineapple
- Shellfish
- Strawberries
- Tomatoes
- Wheat Germ
- Many Artificial Preservatives and Dyes
DAO enzyme Supplements

- Break down histamine in the digestive tract
- Good for histamine intolerance but not mast cell activation issues
- Will not change the amount of histamine released
- Break down histamine from foods contributing to overall histamine level

- DO NOT inhibit release of histamine from mast cells
- DO NOT block IgE binding on mast cell receptor
Histamine Degrading Probiotics

- Bacteroides fragilis
- Bifidobacterium lactis
- Bifidobacterium infantis
- Bifidobacterium longum
- Lactobacillus casei
- Lactobacillus gasseri
- Lactobacillus rhamnosus
- Lactobacillus plantarum
- Lactobacillus salivarius
Mast Cell Disorders Treatment
Anti-Histamines

- H1 receptor: Blocked
  - Benadryl, Claritin
  - Natural H1: Stinging nettle,

- H2 receptor: blocked
  - Zantac, Pepcid
  - Natural H2: Peppermint, Ginger

- Compete for and block receptor sites
- Results in less severe allergic reactions
Mast Cell Release Inhibitors
Flavonoids

- Group of polyphenolic compounds found in fruits, flowers, seeds, and vegetables
- Flavonoids are naturally occurring molecules with
  - antioxidant
  - cytoprotective
  - anti-inflammatory actions
- Inhibit IgE mediated histamine release
- Decrease production of proinflammatory cytokines
- Down-regulate mast cell activation

WHAT ARE THE BENEFITS OF Fisetin?

Conclusions and implications:

- Fisetin suppressed activation of HMC-1 cells by activated T cell membranes by interfering with cell-to-cell interaction and inhibiting the activity of NF-κB and MAPKs and thereby suppressing gene expression. **Fisetin may protect against the progression of inflammatory diseases by limiting interactions between mast cells and activated T cells.**
Asthma and Fisetin research

Bronchodilation of lungs comparable to medicine
Quercetin: Flavonoid

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Quercetin Content (mg/100gm edible portion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderberries</td>
<td>42</td>
</tr>
<tr>
<td>Red Onions</td>
<td>33</td>
</tr>
<tr>
<td>White Onions</td>
<td>21</td>
</tr>
<tr>
<td>Cranberries</td>
<td>15</td>
</tr>
<tr>
<td>Green Hot Peppers</td>
<td>15</td>
</tr>
<tr>
<td>Kale</td>
<td>7.7</td>
</tr>
<tr>
<td>Blueberries</td>
<td>5.1</td>
</tr>
<tr>
<td>Red Apples</td>
<td>4.7</td>
</tr>
<tr>
<td>Romaine Lettuce</td>
<td>4.5</td>
</tr>
<tr>
<td>Pears</td>
<td>4.5</td>
</tr>
<tr>
<td>Spinach</td>
<td>4.1</td>
</tr>
</tbody>
</table>
Quercetin Health Benefits

- Anti-Inflammatory
- Balanced Blood Pressure
- Pain Fighter
- Anti-Cancer Agent
- Protects Against Stress
- Natural Antihistamine
- Cardiovascular Health
- Helps with Asthma
- Promotes Healthy Skin
Quercetin

- Concern with absorption

“If a supplement provides 40 mg of quercetin as isoquercitrin per day, an individual would need to consume the equivalent amount of quercetin from food, by eating approximately 8 1/2 cups of fruits or vegetables that have a quercetin content of 2 mg per 100 grams per day.”

— Lauren Martin, MS, CNS
Improved Oral Absorption of Quercetin from Quercetin Phytosome®,
a New Delivery System Based on Food Grade Lecithin

Antonella Riva1, Massimo Ronchi1, Giovanna Pietrangeli1, Stefania Boscio1, Pietro Allegri1

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Abstract
Background and Objectives. The importance of quercetin and flavonoids in the diet and as food supplements is well known, and literature studies support their potential use to treat several human diseases. Many beneficial properties have been described for quercetin, so much effort has been directed into overcoming the major drawbacks of this natural compound—its poor solubility and low oral absorption. The aim of this study was to compare a new food-grade lecithin-based formulation of quercetin, Quercetin Phytosome®, to unformulated quercetin in terms of solubility in simulated gastrointestinal fluids and oral absorption in a randomized crossover pharmacokinetic study of healthy volunteers.

Methods. The solubility of the new formulation was determined by in vitro incubation in simulated gastrointestinal fluids, and quercetin was detected by ultraperformance liquid chromatography. A single-dose, randomized, six-sequence/three-period crossover clinical trial (3×3×3 crossover design) with a balanced carryover effect was conducted in healthy volunteers under fasting conditions. Twelve healthy volunteers of both sexes with an age range of 18–50 years were recruited, one dose of quercetin and two different doses of Quercetin Phytosome were administered orally as film-coated tablets. Pharmacokinetic samples were collected at twelve time points (from 0 to 24 h) after administration, and quercetin levels were measured by HPLC/MS/MS. Data were analyzed using the Phoenix WinNonlin (v6.6) software package, and the most significant pharmacokinetic parameters were calculated. Statistical analyses involved performing a two-way ANOVA with repeated measures followed by post hoc analysis (Tukey’s test).

Results. Significant improvements in both in vitro solubility and oral absorption (in terms of both exposure and maximum concentration achieved) by healthy volunteers in a human clinical study were obtained with the Quercetin Phytosome formulation as compared to unformulated quercetin.

Conclusions. A more soluble formulation of quercetin based on lecithin, Quercetin Phytosome, has recently been developed, and was found to facilitate the attainment of very high plasma levels of quercetin—up to 20 times more than usually obtained following a dose of quercetin—when the novel formulation was administered orally in human volunteers, and it did not have any notable side effects. These results suggest that Quercetin Phytosome allows the oral administration of quercetin in a safe and bioavailable manner, thus facilitating the effective utilization of this natural compound to treat various human diseases.

Key Points
It is well known from the literature that flavonoids, especially quercetin, are very important biological molecules, strongly suggesting their potential use to treat several human diseases.

A new food-grade lecithin-based formulation of quercetin, Quercetin Phytosome, was developed and validated in healthy volunteers.

Quercetin Phytosome overcomes the low bioavailability hurdle of quercetin and should help to fulfill the great health benefit potential of this flavonoid in the diet and as food supplements.

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Impact of polyphenols on mast cells with special emphasis on the effect of quercetin and luteolin

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Abstract
Polyphenols are ubiquitous in food and have long been recognized as possessing antioxidant, anti-inflammatory and anticancer activities. Mast cells (MCs) are implicated in the pathogenesis of inflammatory diseases, allergy, autoimmunity and cancer. MCs derive from hematopoietic progenitor cells, reside virtually in all vascularized tissue and are activated by cross-linking of FcεRI-bound IgE (at very high affinity: $K_d = 10^{-5}$ M) with multivalent antigen. MCs in cytoplasmic granules release preformed chemical mediators, and also they can release lipid mediators and cytokines/hormones without degranulation. Luteolin, 5, 6, 7, 4’-tetrahydroxyflavone, is a flavonoid contained in many kinds of plants including vegetables and fruits. This anti-oxidant product inhibit interleukin (IL)-6, IL-8 and vascular endothelial growth factor (VEGF) production from tumor necrosis factor (TNF)-stimulated keratinocytes, and it is a candidate for use in alternative therapies in the treatment of inflammatory skin disorders. Quercetin (3, 3’, 4’, 5, 7-pentahydroxyflavone) is a ubiquitous flavonoid which exhibit anti-cancer, anti-oxidative and anti-inflammatory properties and cause a reduction in the availability of nitric oxide synthase. Quercetin exerts physiological functions though the interaction with protein tyrosine phosphatase 1B (PTP1B), mitogen-activated protein kinase (MAPK), extracellular signal regulated kinase (ERK), kinase (MEK) 1, and others, and has a negative effect on FcεRI cross-linking and other activating receptors on mast cells. In this article we report for the first time the interrelationship between mast cells and quercetin.

Key words: polyphenols, mast cells, immunity, inflammation.

(Cent Eur J Immunol 2015; 43 (4): 1-6)

At the beginning of the last century, Raczynak and Szent-Györgyi reported that citrus fruits contain diverse substances other than vitamin C, which can prevent capillary fragility. These substances were the polyphenols (flavonoids, phenolic acids, lignans, coumarins) or flavonoids contained in large quantities in fruit, vegetables, cereals, and beverages, and which may have a positive effect under conditions of stress and other neurological dysfunctions [1]. Constituents of grapes, such as resveratrol, kaempferol, catechin, epicatechin and anthocyanins, constitute more than 70% of the grape polyphenols. Natural compounds have long been recognized to possess anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antiinflammatory, antiviral and anticancer activities.

Flavonoids, previously called vitamin P or vitamin C2, are numerous; in fact, about 800 different flavonoids have been isolated. Flavonoids are polyphenolic secondary metabolites classified into anthocyanins, flavonols, flavones, flavan-3-ols, flavones, isoflavones, and chalcones; they are ubiquitous in food and potentiate the anti-inflammatory activity shown in a number of animal studies. Flavonoids cannot be considered vitamins, since they produce pharmacologic effects rather than nutritional ones. It is well known that polyphenols such as curcumin, curcumin, catechins, resveratrol, anthocyanins, tannins, stilbenes, quercetin, etc. exert antioxidant properties, and these are found in red wine, chocolate, tea, pomegranate and fruit juices, where they are the greatest contributors of flavonoids in the human diet along with vegetables [2].

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Luteolin


1. Perilla frutescens is a dietary leafy herb consumed as a traditional Japanese condiment

2. Suppresses IgE-mediated type I hypersensitivity reactions.

3. Significantly inhibits IgE-mediated histamine release

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.
Research Article

Ethanol Extract of Perilla frutescens Suppresses Allergen-Specific Th2 Responses and Alleviates Airway Inflammation and Hyperreactivity in Ovalbumin-Sensitized Murine Model of Asthma

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This study was to investigate the effects of different fractions of Perilla frutescens (PE) leaves extracted by water or ethanol on asthmatic BALB/c mice sensitized intraperitoneally and challenged with ovalbumin (OVA) divided into six groups. Each group of mice was tube-feeding with control, 80 μg (FW/WL), or 240 μg (FW/WL) water extracts or 80 μg (PEL) or 240 μg (PEHL) ethanol extracts of perilla leaves daily for 3 weeks. A negative control group (PRI) was neither sensitized nor treated with OVA. The perilla leaf extracts on allergic immune response were evaluated. The results showed that OVA-specific IL-5 and IL-13 secretions from OVA-stimulated splenocytes were significantly suppressed in the ethanol extract groups PEL and PEHL. Serum level of anti-OVA IgE tended to be lower in the PEHL group. The inflammatory mediators, such as eotaxin and histamine, and total cells, particularly eosinophils in bronchoalveolar lavage fluid (BALF), were also decreased in the PEL and the PEHL groups. Therefore, the PEL and the PEHL groups had significantly lower methacholine-induced hyperresponsiveness (AHR) in conclusion, ethanol extract, rather than water extract, of perilla leaves could significantly suppress Th2 responses and airway inflammation in allergic murine model of asthma.

1. Introduction

Allergic asthma is a chronic disease that clinically augments bronchial hyperresponsiveness and inflammation. The asthmatic inflammation is clearly associated with the high level of type 2 T cell (Th2) cytokines that induced immunoglobulin (Ig) E production and eosinophilic infiltration [1]. The Th2 cytokines IL-4, IL-5, and IL-13 are the major cytokines for development of atopic diseases, such as asthma, rhinitis, and dermatitis [2]. IL-4 promotes the immunoglobulin class switch from IgM to IgE [3]. IL-5 induces eosinophils activity and infiltration, which is the critical response in the allergic asthma [4]. IL-13 acts to induce airway hyperresponsiveness (AHR) that contributes to atopic disease [5]. The suppression of Th2 responses is a feasible attempt to attenuate the symptoms of allergic asthma. Therefore, biologic targeted therapies have been developed to target the specific molecular pathways to treat asthma, especially those targets at IL-4, IL-5, IL-13, and IgE [6]. However, due to complex clinical symptoms and multiple mechanisms involved, the outcome of these trials has not been satisfied. Epidemiological studies indicate that patients often turn to complementary and alternative therapies, including dietary supplements [7]. Studies also showed that dietary oil, fiber, and medicinal herbs, such as Gastroderma and Andrographis, decreased Th2 cytokines productions and thus alleviated allergic responses in a murine model of asthma [8–12], suggesting the potential application of traditional herbal medicine for immunomodulation.
The Health Benefits of Butterbur (Petasites)

Treatment For Migraine
Relieves migraines by reducing the spasm of the muscle linings of blood vessels in the brain

Treatment For Allergies
Butterbur can reduce histamine activity, so it is also effective for allergic conditions like asthma and rhinitis

Treatment For Inflammation
Inhibits the lipooxygenase pathway and production of leukotrienes so it can also be effective for inflammation
Anti type I allergic property of Japanese butterbur extract and its mast cell degranulation inhibitory ingredients.


- Inhibitory activity on mast cell degranulation
- Fukinolic acid, a principal polyphenol constituent, showed potent inhibitory activity.
- Suppress the type I allergic reaction.

- A nettle (Urtica dioica) extract shows in vitro inhibition of several key inflammatory events that cause the symptoms of seasonal allergies.
- Antagonist against the Histamine-1 (H(1)) receptor
- Inhibition of mast cell tryptase
- Inhibits prostaglandin formation
HistaQuel™

Two-Fold Mechanism of Action

- Block histamine and other mediator release from Mast cells
- Block histamine receptors
- Quercefit: 10x absorption of regular quercetin
## HistaQuel™ Ingredient Blends

<table>
<thead>
<tr>
<th>Ingredient Blend</th>
<th>Constituents</th>
<th>Mechanisms of Action*</th>
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| Mast Cell Secure™ (Flavonoids) | • Fisetin  
• Luteolin  
• Perilla Frutescens  
• Quercefit™ (10x the absorption of regular quercetin) | • Targeted flavonoid blend supports a decrease in mast cell release of histamine  
• Moderates interactions between mast cells and activated T cells.  
• Decreases Th2 release of allergy promoting cytokines IL-4 and IL-5 |
| HistaCheck™            | • Stinging Nettle leaf  
• Butterbur extract | • Decreases ability of histamine to bind to its receptors by competitive inhibition  
• Supports management of a healthy immune response to allergens |

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HistaQuel™
Mast Cell Secure™ Blend Ingredient Research-Summary

- **Flavonoids (general)**
  - Inhibit IgE mediated histamine release\(^1\)
  - Decrease production of proinflammatory cytokines\(^1\)
  - Down-regulate mast cell activation\(^1\)

- **Fisetin**
  - Significantly inhibited infiltration of inflammatory cells including eosinophils, mast cells and CD4(+) T and CD8(+) T cells\(^2\)
  - Total serum immunoglobulin E (IgE) levels were markedly reduced by Fisetin\(^2\)
  - Reduced the production of interferon-gamma and interleukin-4 by activated CD4(+) T cells in a dose-dependent manner\(^2\)
  - Limits interactions between mast cells and activated T cells\(^3\)

- **Quercefit™**
  - 20x the absorption of regular Quercetine\(^4\)

- **Perilla Frutescens**
  - Suppresses IgE-mediated type I hypersensitivity reactions\(^7\)
  - Significantly inhibits IgE-mediated histamine release\(^7\)

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nettle extract
- Shows in vitro inhibition of several key inflammatory events that cause the symptoms of seasonal allergies\(^5\)
- Antagonist against the Histamine-1 (H(1)) receptor\(^5\)
- Inhibition of mast cell tryptase\(^5\)
- Inhibits prostaglandin formation\(^5\)

butterbur extract
- Showed inhibitory activity on mast cell degranulation\(^6\)
- Suppresses the type I allergic reaction\(^6\)

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Treating Chronic Disease through Treating Chronic Pathology

- Repair and support mitochondria
  - Membrane repair
  - Support nutrients in ATP production from breakdown of macronutrients to Krebs cycle to oxidative phosphorylation
- Decrease causes of oxidative stress and inflammation
- Increase anti-oxidants to counteract oxidative stress including activating Nrf2
- Decrease inflammation through down regulating inflammatory mediators and improving microbiome
- Decrease mast cell activation by inhibiting release and blocking histamine receptors
Support for Inflammation and Abnormal Cytokines

- Glutathione
- Molecular Hydrogen \((\text{H}_2: \text{Hydrogen gas})\)
- Vitamin E: mixed tocopherols and tocotrienols
- Curcumin
- Tea: EGCG
- Resveratrol
- N-acetyl-cysteine
- Probiotics
CytoQuel®
Key Ingredients

- Black Tea extract (EGCG)
  - High EGCG content
  - Promotes healthy levels of IL-23, which controls IL-17 levels
  - Supports healthy levels of NF-k Beta, TNF-a, IL-1 beta, IL-6, IL-8 (Herxheimer reactions increase TNF-a, IL-6 & IL-8)

- N-Acetyl Cysteine
  - Promotes healthy NF-k Beta, IL-6, IL-8 levels

- CurcuWIN™ brand Curcumin
  - Promotes healthy inflammation response
  - 46x more absorbable vs standard curcumin

- Tocotrienols (Vitamin E) from Annatto (not rice or palm derived)
  - Pure delta and gamma tocotrienols --- no tocopherol
  - Promotes healthy inhibition levels of NF-k Beta & nitric oxide
  - Protects against oxidative stress
  - Promotes healthy cardiovascular function
  - Protects from neurodegeneration

- Resveratrol
  - Promotes healthy inhibition levels of TNF-a, IL-1 beta & NF-k Beta
  - Activates Sirt-1 & Nrf2
Participants with chronic pain for at least 6 months were given CytoQuel® for 8 weeks.

Pain scoring and activities of daily living questioners were given throughout the study.

Study results...

- 65% decrease in primary pain within the last 24 hours*
- 44% improvement in quality of sleep*
- Normalization of the ankle brachial index*

**Conclusion:** Consuming CytoQuel® helped manage pain, increased comfort during daily activities, and improved vascular function... *
Support for Oxidative Stress

Anti-oxidants to combat oxidative stress
- Glutathione
- Vitamin C
- Alpha-lipoic Acid
- Molecular Hydrogen (H₂: Hydrogen gas)
- Vitamin E: mixed tocopherols and tocotrienols
- Curcumin
- Tea: EGCG
- Resveratrol
- N-acetyl-cysteine
Research Summary

In just 2 weeks...

- **28%** increase in red blood cell glutathione levels
- **400%** increase in natural killer cell activity
- **25%** reduction in lipid peroxidation (oxidative stress marker)

Research conducted at Penn State University

Published in European Journal of Clinical Nutrition, 2017
C-RLA™
Liposomal High Dose Vitamin C and R-Lipoic Acid

Suggested Use: Take 2 teaspoons daily. May be taken straight or mixed in water.

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ATP 360™
Mitochondrial Dysfunction Support

- **Phospholipid blend**
  - Repairs damaged mitochondrial membranes
- **PQQ**
  - Increases mitochondrial mass
- **Pure Tocotrienols and R-Lipoic Acid**
  - Reduces oxidative stress which damage membranes
- **NADH & CoQ10**
  - Supports Kreb’s cycle

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8-week study with 24 patients complaining of long-term fatigue demonstrated...

- **52%** Reduction in Fatigue
- **68%** Improved Sleep
- **12%** Reduction in Diastolic Blood Pressure

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Summary of Mast Cell Activation Syndrome

- Symptoms involve all body systems
- Component of most chronic diseases
- Clinical diagnosis- positive lab tests helpful but not necessary

Treatment
- Diet: Low histamine diet and DAO enzymes can be helpful for food histamine levels and break down of food histamines
- Inhibit mast cell activation
- Block histamine receptors
- Anti-inflammatory
- Anti-oxidants
- Mitochondrial support
Treating Chronic Disease through Treating Chronic Pathology

- **Mast Cell Activation:**
  - *HistaQuel™* decrease mast cell activation by inhibiting release and blocking histamine receptors

- **Inflammation:**
  - *CytoQuel®* - support healthy cytokine activity and manage oxidative stress and inflammation
  - *CoreBiotic™*: dysbiosis triggering inflammation and mast cell activation

- **Mitochondrial Dysfunction:**
  - *ATP360™* - repair mitochondrial membranes and support mitochondrial function

- **Oxidative Stress:** neutralize free radicals
  - *Tri-Fortify® Liposomal Glutathione*
  - *C-RLA™*