HistaEze™

*Supports Normal Histamine Levels**

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HistaEze™ is a synergistic blend of nutrients that provides support to help balance the body's immune response.* HistaEze™ features ingredients that have been shown to support a normal histamine response, stabilize mast cells, and manage healthy inflammatory responses, including quercetin, nettle leaf, bromelain, luteolin, and vitamin C.* HistaEze™ supports vitamin C status with ascorbic acid and nettle leaf extract, which further promotes overall immune function, and antioxidant status.* Additionally, bicarbonate salts are included for their role in maintaining normal histamine metabolism and immune function.* HistaEze™ is ideal for individuals suffering from common immune disruptors during allergy season, such as being exposed to environmental triggers.*

Formula Highlights

- Clinically relevant amounts of quercetin, nettle extract, bromelain, luteolin, and vitamin C to support a normal histamine and immune response.*
- Bicarbonate salts to support histamine metabolism.*

Benefits*

- Supports normal histamine metabolism, particularly to common environmental triggers.[6,7,12,24,25,27,31]
- Supports a normal immune response.[10,18-20,24,27,29,32]
- Supports mast cell stabilization.[6,12,13,14,17,19,23,30]

Supplement Facts

Serving Size 4 capsules
Servings Per Container 30

Amount Per Serving		% Daily Value
Vitamin C (as Ascorbic Acid)	500 mg	556%
Sodium (from Sodium Bicarbonate)	80 mg	3%
Potassium (from Potassium Bicarbonate)	120 mg	3%
Nettle Extract (*Urtica dioica*)(leaf)	600 mg	*
Quercetin	600 mg	*
Bicarbonate Salts (as Potassium Bicarbonate 300 mg and Sodium Bicarbonate 300 mg)	600 mg	*
Bromelain (*Ananas comosus*)(stem)	200 mg	*
Luteolin (*Sophora japonica*)(flower)	100 mg	*

*Daily Value not established.

Other Ingredients: Cellulose (capsule), microcrystalline cellulose, dicalcium phosphate, stearates (vegetable source).

Approximately one-third of adults aged 18 and over were diagnosed with seasonal allergies, eczema, or food allergy in 2021 and this estimate appears to be increasing.[1,2] Mast cells are multifunctional immune cells involved in Type I hypersensitivity reactions which involves immunoglobulin E (IgE)-mediated release of several inflammatory compounds including cytokines, histamine, and antibodies.[3] When the body recognizes a potential environmental threat, such as antigens from environmental allergens, the antigen attaches to its respective receptors found on mast cells (e.g., FceR1, FcgR1, C3aR, and C5aR, among others)[4], and through a complex orchestrastration of cellular reactions, the mast cell degranulates, releasing histamine into the extracellular space — producing a robust immune response. This exaggerated immune response can result in fever; sneezing; itching of the nose, eyes, or mouth; runny or stuffy nose, and redness and swelling in the eyes. By supporting a normal immune response through mast cell stabilization and histamine metabolism, the immune response to common environmental triggers can be mitigated and symptom severity may be better managed.

Quercetin, also known as the "king of the flavonoids," is considered among the top plant-based polyphenolic compounds due to its demonstrated powerful antioxidant properties and ability to support a healthy inflammatory response in the body.[5,6] Quercetin is a potent flavonol found in many foods that are recognized for their health benefits, such as red onions, yellow onions, apples, olive oil, dark berries and grapes, capers, broccoli, salad greens, and culinary herbs such as dill, cilantro, watercress, and radicchio.[5]

To appreciate quercetin's role in managing allergic reactions, an understanding of the process that initiates mast cell destabilization and degranulation is needed. Upon interaction with an antigen-linked IgE molecule, a molecular signaling cascade is initiated inside the mast cell. Through a series of phosphorylation reactions including the stimulation of phospholipase C (PLC), inositol triphosphate (IP3) and protein kinase C (PKC) are formed and are responsible for the release of calcium (Ca^{2+}) ions into the intracellular space.[7] This increased concentration of Ca^{2+} causes histamine-containing granules to fuse with, and be released by, the plasma membrane of the mast cell.[7] Additionally, other calcium-dependent proteins, such as calmodulin and calcineurin, are involved in several of the steps outlined above and are a key target through which quercetin exerts its anti-allergy effects.[8,9] In a recent study, quercetin was capable of decreasing the release of histamine-induced Ca^{2+} elevation in human keratinocytes in a dose-dependent manner by modulation of the histamine 4 (H4) receptor.[8] These findings suggest that quercetin's inhibitory effect on Ca^{2+} influx is influenced by the interaction between the H4 receptor, PLC, and PKC.

Important for any immune reaction, quercetin has been shown in vitro to help lower pro-inflammatory responses, such as decreasing phospholipase A2, lipoxygenase, and interleukin(IL)-1ß.[10] Additionally, studies have demonstrated its potential to inhibit histamine release from mast cells, which may help support a normal immune response to environmental challenges.[5,6,11] It has also been shown in vitro to attenuate the effects of oxidative stress by promoting antioxidant enzyme activity, such as superoxide dismutase, catalase, and glutathione peroxidase.[12]

Nettles, also known as "stinging nettle" (*Urtica dioica* L.), have traditionally been used worldwide as a folk medicine remedy for supporting respiratory and joint health and various other applications, such as hypertension.[13] Documentation points to its use in ancient Egypt and ancient Greece and among the indigenous peoples of North America. It can be consumed directly or made into soups and tea and even brewed into beer. Nettle has a very high vitamin C and iron content, which underlies its role in promoting healthy immune responses by promoting antioxidant status, healthy inflammatory responses, and modulating histamine release.[14] Research has shown that nettles are able to promote a healthy inflammatory response and antioxidant status due to its ability to interrupt the production and actions of pro-inflammatory mediators such as cytokines, leukotrienes, prostaglandins, and interleukins.[5,6,15-17]

Luteolin (*Perilla frutescens*) is a flavonoid found in various fruits, vegetables, herbs, and teas with well-researched anti-inflammatory and antioxidant properties that may contribute toward a normal immune response.* Luteolin was recently shown in vitro to inhibit histamine release in LADR, a human mast cell line, significantly more than applied cromolyn at both the 60 and 120 minute mark ($P < 0.001$ vs. $P < 0.01$).[18] Cromolyn is the only "mast cell blocker" drug available. Additionally, after treatment with either luteolin or cromolyn, the fluid left over from the stimulated LADR cells was collected and assayed by enzyme-linked immunosorbent assay (ELISA) for the histamine, tryptase, and MMP-9 concentrations. Compared to cromolyn, luteolin significantly inhibited histamine release (58% and 76%, respectively), tryptase release (40% and 76%, respectively), and MMP-9 release (20% and 80%, respectively).[18] Importantly, preincubation with luteolin was shown to significantly inhibit the release of inflammatory mediators including tumor necrosis factor (TNF), IL-1b, IL-6, and CXCL8.[18] These findings are corroborated by earlier work.[19-22]

Luteolin may be clinically beneficial for adults and children with allergies with the adjunctive use of quercetin and vitamin D_3.[23,24,25] In a small (n = 23) clinical study, adults with a history of allergic rhinitis and who displayed a positive skin prick test to pollen were given a combination of perilla extract, quercetin, and vitamin D_3 at concentrations of 80 mg, 150 mg, and 5 mg, respectively, for 30 days. Primary outcomes included nasal and eye symptoms, anti-allergic drug use, and side effects via the Total Symptoms Score evaluation scale. From baseline to follow-up, symptom scores and use of anti-allergic drugs reduced approximately 70% and 73%, respectively.[25] Other promising findings were the reduction in common allergic symptoms including sneezing, rhinorrhea, nasal obstruction, ocular itching, lacrimation, and conjunctiva congestion (all $P < 0.00001$).[25]

Bromelain is a family of sulfhydryl-containing proteolytic enzymes obtained from the stem of *Ananas comosus*, the pineapple plant. It has been used as a digestive enzyme after pancreatectomy and for cases of exocrine pancreatic insufficiency.[26] In addition to its protein-digesting action in the gastrointestinal (GI) tract, bromelain has been shown to possess anti-inflammatory properties by indirectly reducing the biosynthesis of pro-inflammatory prostaglandin E2 and cyclooxygenase-2 (COX-2) without influencing anti-inflammatory prostaglandin activity.[27] Evidence also shows that bromelain stimulates antioxidant enzyme secretion of superoxide dismutase, catalase, and reduced glutathione by upregulating the nuclear factor-2 erythroid-related factor (Nrf)-1 and Nrf2 pathways.[27] Bromelain also has anti-thrombotic, fibrinolytic, and immunomodulatory biological properties.[27,28] Due to its ability to decrease pro-inflammatory prostaglandin production and to reduce mucus production and nasal swelling, bromelain may be a potential adjunct mucolytic agent in paranasal sinus conditions, such as allergic rhinitis and rhinosinusitis.[27,29]

Vitamin C supports immune function and antioxidant status and promotes a healthy inflammatory response.* It may also reduce histamine levels, especially in response to an allergic response.[30] Ascorbic acid breaks up the imidazole ring structure of histamine.[30] It may also support a nonenzymatic degradation of histamine and inhibit the enzyme histidine decarboxylase, which is involved in the formation of histamine.[30] Interestingly, serum histamine levels have been found to be inversely associated with vitamin C status, promulgating its potential in the management of allergies.[31]

Sodium and Potassium Bicarbonate support a normal histamine metabolism.* The ion channels, including sodium and potassium, also play a role in immune function including potentially supporting a normal immune response.[32]

Recommended Use: Take 4 capsules per day or as directed by your health-care practitioner. (Divided dosing recommended.)

For a list of references cited in this document, please visit:
https://www.designsforhealth.com/api/library-assets/literature-reference---histaeze-tech-sheet-references

Dosing recommendations are given for typical use based on an average 150 pound healthy adult. Health-care practitioners are encouraged to use clinical judgement with case-specific dosing based on intended goals, subject body weight, medical history, and concomitant medication and supplement usage.

To contact Designs for Health, please call us at (860) 623-6314 or visit us on the web at www.designsforhealth.com.