


Nutraceutical Aid for Allergies – Strategies for Down-Regulating Mast Cell Degranulation

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Abstract: Interactions of antigens with the mast cell FcεRI-IgE receptor complex induce degranulation and boost synthesis of pro-inflammatory lipid mediators and cytokines. Activation of spleen tyrosine kinase (Syk) functions as a central hub in this signaling. The tyrosine phosphatase SHP-1 opposes Syk activity; stimulation of NADPH oxidase by FcεRI activation results in the production of oxidants that reversibly inhibit SHP-1, up-regulating the signal from Syk. Activated AMPK can suppress Syk activation by the FcεRI receptor, possibly reflecting its ability to phosphorylate the FcεRI beta subunit. Cyclic GMP, via protein kinase G II, enhances the activity of SHP-1 by phosphorylating its C-terminal region; this may explain its inhibitory impact on mast cell activation. Hydrogen sulfide (H₂S) likewise opposes mast cell activation; H₂S can boost AMPK activity, up-regulate cGMP production, and trigger Nrf2-mediated induction of Phase 2 enzymes – including heme oxygenase-1, whose generation of bilirubin suppresses NADPH oxidase activity. Phycocyanobilin (PCB), a chemical relative of bilirubin, shares its inhibitory impact on NADPH oxidase, rationalizing reported anti-allergic effects of PCB-rich spirulina ingestion. Phase 2 inducer nutraceuticals can likewise oppose the up-regulatory impact of NADPH oxidase on FcεRI signaling. AMPK can be activated with the nutraceutical berberine. High-dose biotin can boost cGMP levels in mast cells via direct stimulation of soluble guanylate cyclase. Endogenous generation of H₂S in mast cells can be promoted by administering N-acetylcysteine and likely by taurine, which increases the expression of H₂S-producing enzymes in the vascular system. Mast cell stabilization by benifuuki green tea catechins may reflect the decreased surface expression of FcεRI.

Keywords: nutraceuticals, mast cell, degranulation, allergy, FcεRI-IgE receptor, hydrogen sulfide, phycocyanobilin, berberine, biotin, lipoic acid

Introduction

Pharmacological strategies are most commonly employed to control mast cell degranulation and its pathogenic consequences. This essay deals with nutraceutical strategies, which may have analogous therapeutic potential. The functions of mast cells and the molecular biology underlying mast cell degranulation will first be described.

Contemporary Insights into Mast Cell Functions

Mast cell degranulation plays a key role in many human health disorders – not exclusively in allergies. The clinical presentation is wide, involving respiratory, neurologic, digestive, cardiovascular, cutaneous and even musculoskeletal symptoms.¹ Mast cells contribute to the pathogenesis of infection, cancer,

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cardiovascular and many other systemic diseases.² Notably, not only in pathologic conditions, they can play an immunomodulatory role, by secreting anti-inflammatory mediators, and thereby impacting the interaction between the immune cells and the environment.¹⁻³

Mast cells are endowed with a wide range of plasma membrane receptors, enabling them to sense and react to a plethora of stimuli. The chief receptor triggering mast cell degranulation is the high-affinity IgE receptor FcεRI (Figure 1). A more recently described mast cell receptor capable of provoking degranulation is the Mas-related G protein-coupled receptor X2 (MRGPRX2), which responds to a range of basic peptides and small proteins, resulting in allergic or neurologic inflammations, pain and itch; hence, there are more receptors that react to drugs, cytokines, complement anaphylatoxins, physical triggers and physical stimuli.^{1,4} Upon sensing endogenous or exogenous danger signals, the activated mast cell releases mediators by three mechanisms. The immediate and rapid one is exocytosis of secretory granules containing pre-synthesized molecules, including histamine, various proteases, heparin, cysteinyl leukotrienes, prostaglandins, and certain proteoglycans. In the second phase, de novo-synthesized cytokines, chemokines, interferons and several growth factors can be released independently of the degranulation process. Finally, activated mast cells can secrete extracellular vesicles, such as exosomes, thereby exteriorizing cellular proteins, enzymes, RNAs and miRNAs to the extracellular compartment.¹

Mast Cell Degranulation Process

Mast cells can assume a migratory or a secretory behavior, depending on their actin conformation. The secretory actin phenotype supports mobility and exocytosis, in which diaphanous-related formmin, mDia1, plays a major role in intracellular actin rearrangement.¹ Upon reaching its destination and encountering a secretagogue, mast cell degranulation can be executed in three different modes: full, partial, or the kiss-and-run phenomenon. In the full pathway, the granules can fuse completely with the plasma membrane, in the partial one, they form multiple granules fusion and creating a channel, and the third one implies a transiently fuse with the membrane, releasing part of their content. An additional means of degranulation has been discovered by electron microscopy, namely, piecemeal degranulation. Secretory granules can bud, producing vesicles that are transported to and fused with the plasma membrane.⁵ These varying mechanisms whereby mast

cells can release their contents determine the dynamics, intensity and the outcome of degranulation.¹

A schematic presentation of the mast cells activation is presented in Figure 1.

An Outline of FcεRI Receptor Signaling

The FcεRI receptor, whose activation triggers mast cell degranulation and increased production of lipid and cytokine pro-inflammatory mediators, is a heterotetramer that binds tightly to extracellular IgE.^{6,7} The binding of this IgE to specific antigens triggers crosslinking of two FcεRI receptor complexes such that src-family tyrosine kinase Lyn bound to each complex can auto-transphosphorylate. These phosphorylations, in turn, enable Lyn to phosphorylate tyrosine residues on the γ subunit of the FcεRI complex; this enables spleen tyrosine kinase (Syk) to bind to this subunit via its SH2 domain, and this bound Syk is then activated via phosphorylation by Lyn. Activated Syk then phosphorylates multiple tyrosines on a nearby LAT (linker for activated T cells) protein, enabling various other proteins to bind to LAT via their SH2 domains and to promote assembly of a complex signaling platform. Some of these proteins are also phosphorylated by Syk. The resulting signaling platform results in downstream activation of phospholipase C-γ, phosphatidylinositol-3-kinase (PI3K), IκB kinase, the MAP kinases ERK, JNK, and p38, and NADPH oxidase.⁶⁻⁸ These collaborate to promote mast cell degranulation, while boosting synthesis of pro-inflammatory cytokines and lipid mediators. Although the src-family tyrosine kinase Fyn can substitute for Lyn in some of its signaling duties, it is clear that activation of Syk plays a fundamental and essential role in driving mast cell activation.^{9,10}

Tyrosine kinase-mediated signaling is opposed and controlled by tyrosine phosphatase activities. Src homology region 2 domain-containing phosphatase 1 (SHP-1) has been shown in mast cells to oppose antigen-induced FcεRI signaling;¹¹⁻¹⁴ it reverses tyrosine phosphorylations conferred by Syk on LAT and the associated scaffolding protein SLP-76 (Src homology region 2 domain-containing leukocytes protein of 76 kDa).¹¹ Notably, SHP-1 is susceptible to reversible inhibition by physiological concentrations of hydrogen peroxide, via conversion of cysteine sulfhydryl groups to sulfenic acid groups; reversible inactivation of tyrosine phosphatases by hydrogen peroxide is a common mechanism whereby generation of oxidants up-regulates tyrosine kinase signaling.¹⁵⁻²⁰

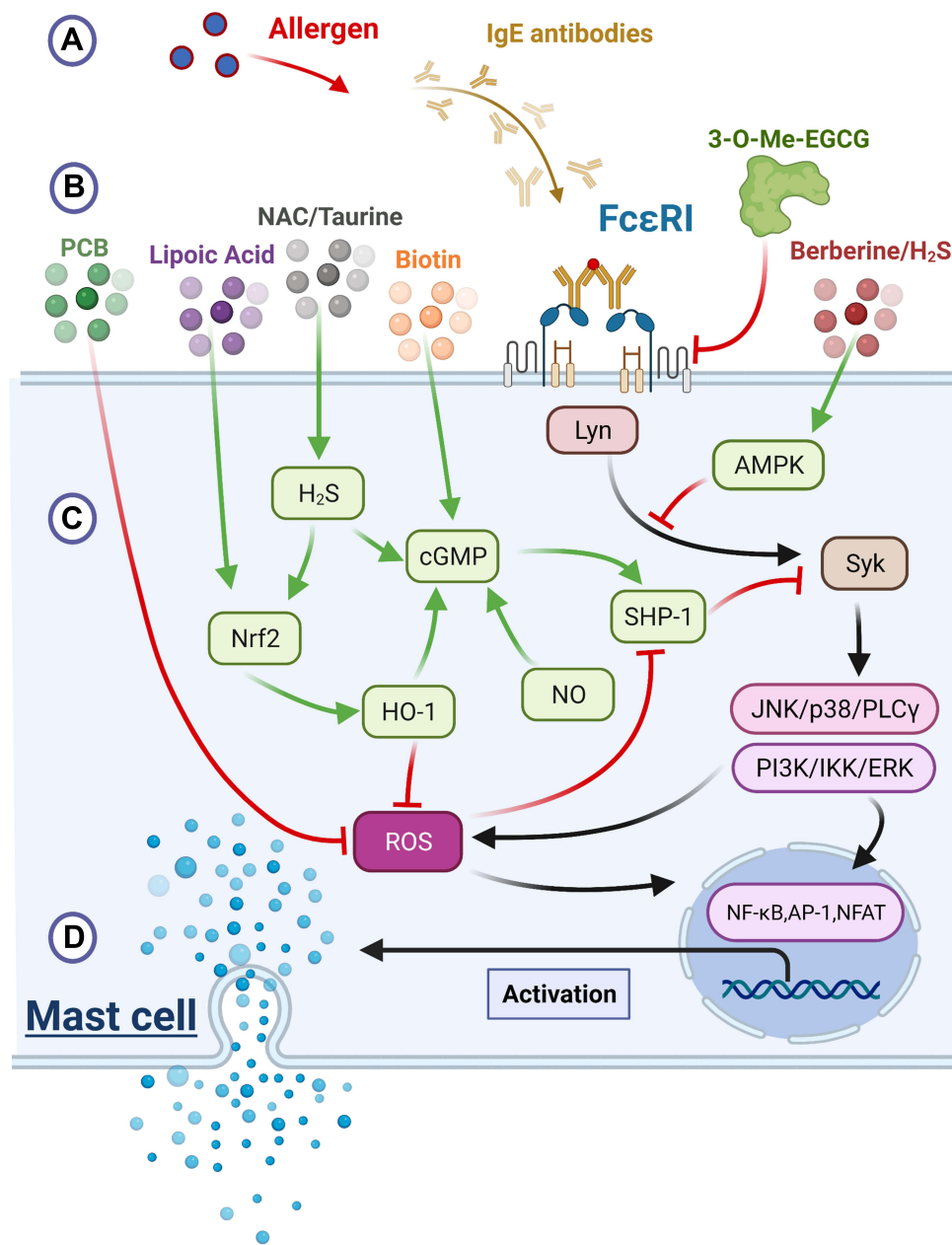


Figure 1 Mast cell activation: environmental stimulants, membrane receptors, intracellular signaling pathways and degranulation.

Notes: (A) Allergens, IgE antibodies and the FcεRI receptor: Interactions of antigenic allergens with IgE antibodies create a complex that activates FcεRI receptor on the mast cell membrane. These initiate intracellular signaling pathways that result in the release of pro-inflammatory mediators and cytokines. (B) Nutraceuticals and their mode of action. The compound 3-O-Me-EGCG down-regulated the cell surface expression of FcεRI, thus inducing mast cell stabilization. Biotin, berberine, H₂S, PCB, lipoic acid and NAC, taurine, are agents that were found to have the clinical potential of allergy control by down-regulating these pathways. (C) Intracellular mediators and pathways. The mechanisms by which these agents may down-regulate pro-inflammatory activity are illustrated. Black arrows represent the up-regulation of pathways that were initiated by FcεRI interaction with antigen-IgE complex. Green arrows up-regulate and red arrows down-regulate, both act as anti-inflammatory by suppressing the black arrows pathways. In the signaling pathway following FcεRI activation, Syk acts as a central hub. Berberine/H₂S can boost AMPK activity leading to Syk suppression, and SHP-1 opposes Syk activity as well. Yet, following Syk activation, ROS reversibly inhibits SHP-1. Biotin can boost cGMP levels, which enhances the activity of SHP-1. NAC/taurine can boost endogenous production of H₂S, which up-regulates cGMP and stimulates Nrf2's transcriptional activity. Nrf2 promotes cGMP production and promotes HO-1 which suppresses ROS and promotes cGMP production. Lipoic acid increases Nrf2 expression, and PCB has an inhibitory impact on ROS. (D) Degranulation. Downstream pathways, which were initiated by FcεRI receptor; include the activation of PLC-γ, p38, JNK, PI3K, IKK, JNK and NADPH oxidase. The combination of these pathways promotes mast cell degranulation, while ramping up gene transcription and boosting synthesis of pro-inflammatory cytokines and lipid mediators. Created with BioRender.com.

Antigen activation of FcεRI in mast cells has been shown to rapidly induce production of superoxide in the extracellular space.⁸ This effect is inhibited by wortmannin, diphenylethylideneiodonium, and apocynin – and hence

points to membrane-bound NADPH oxidase as the superoxide source. Other research has determined that NOX2 is the predominant form of NADPH oxidase in mast cells.^{21,22} Its activation may reflect PLCγ-mediated

production of diacylglycerol (which in turn promotes PKC activity), and PI3K-mediated activation of Rac, likely via Bruton's tyrosine kinase (BTK).^{6,23,24} Importantly, inhibition of this initial burst of superoxide production suppresses antigen-stimulated mast cell degranulation.⁸ A likely explanation is that hydrogen peroxide generated near the plasma membrane inhibits SHP-1 activity, thereby up-regulating Syk-mediated tyrosine phosphorylation of the FcεRI signaling complex. Several studies show that heme oxygenase-1 (HO-1) induction in mast cells opposes mast cell degranulation and activation; this may reflect, in part, the fact that the bilirubin generated by HO-1 functions as an inhibitor of NOX2-dependent NADPH oxidase activity.^{25–32}

AMPK, Cyclic GMP, and Hydrogen Sulfide Down-Regulate Mast Cell Degranulation

Several molecular mechanisms have been shown to inhibit antigen-stimulated mast cell degranulation. These include activation of AMP-activated kinase (AMPK),^{14,33–36} elevation of cyclic GMP (cGMP),^{37–39} and increased generation of hydrogen sulfide (H₂S).^{40–43} With respect to AMPK, this has been shown to suppress the association of Lyn and Syk with the FcεRI receptor complex.⁴⁴ While the basis of this effect has not yet been clarified, activated AMPK has been shown to confer a phosphorylation on the beta chain of this receptor; conceivably, this might suppress Lyn's ability to bind to this chain.⁴⁴

With regard to cGMP, the cGMP-dependent protein kinase G II (PKGII) can confer an activating phosphorylation on the C-terminal region of SHP-1.⁴⁵ Whether the inhibitory impact of cGMP on mast cell degranulation reflects, in whole or in part, increased SHP-1 activity, requires further evaluation. The inhibitory effect of HO-1 activity on mast cell degranulation likely stems in part from the ability of carbon monoxide to promote cGMP production by soluble guanylate cyclase (sGC).^{46,47}

Endogenous generation of H₂S, as well as exposure to H₂S-releasing drugs, have been shown to suppress mast cell degranulation.^{40–43} Several complementary mechanisms may contribute to this effect. In at least certain contexts, H₂S is capable of stimulating AMPK activity, via activation of calcium/calmodulin-dependent kinase kinase-β.^{48–51} H₂S, via S-sulhydrations of Keap1 that blocks its binding to Nrf2 and thereby stimulate Nrf2's transcriptional activity, promotes induction of HO-1.^{52–55} And H₂S can also promote cGMP generation by reversing

oxidative inhibition of sGC, as well as by inhibiting phosphodiesterase 5 (PDE5), which degrades cGMP in mast cells.^{56–58} In regard to the latter mechanism, the drug inhibitor of PDE5, vardenafil, has been reported to oppose mast cell degranulation.³⁹

Discussion on Nutraceutical Strategies for Mast Cell Stabilization

The foregoing considerations offer a basis for proposing nutraceutical measures that could be expected to stabilize mast cells and thereby aid prevention and control of allergic reactions.

Berberine, a compound derived from certain medicinal herbs used in traditional Chinese medicine, is currently widely used in China both for glycemic control in type 2 diabetes, and as a hypolipidemic agent.^{59–61} Its clinical utility in diabetes has been traced to its ability to activate AMPK^{62,63} – in that respect, its mechanism of action appears to be comparable to that of the drug metformin (which itself is a modification of herbal compounds with hypoglycemic activity). Berberine, *in vitro*, has been found to inhibit mast cell degranulation by suppressing Syk phosphorylation – precisely as would be predicted for an AMPK activator.^{64,65} In rodents, it has conferred protection in models of ovalbumin- or house-mite-induced allergic rhinitis, and in passive cutaneous anaphylaxis.^{65–67}

Phase 2 inducing agents, via Nrf2-mediated induction of HO-1, could be expected to inhibit mast cell NADPH oxidase activity, as well as to boost cGMP via carbon monoxide generation. Lipoic acid and sulforaphane evolved from broccoli sprout extract (BSE) are phase 2 inducers with documented clinical utility.^{68–72} Lipoic acid has been found to be protective in rodent models of anaphylaxis, lessening histamine release,^{73–75} In a controlled clinical trial, ingestion of BSE was shown to benefit allergic rhinitis symptoms; another clinical study concluded that BSE ameliorated the nasal allergic response to inhalation of diesel exhaust particles.^{76,77} Melatonin can promote phase 2 induction by increasing Nrf2 expression; also, via induction of Sirt1, it can boost AMPK activity while antagonizing the NF-kappaB-mediated phase of mast cell activation.^{78–80} It has shown efficacy in ovalbumin-induced allergic rhinitis in rats, and has been found to suppress mast cell degranulation provoked by water avoidance stress.^{81,82} It also lessens inflammatory cytokine production by mast cells activated with phorbol ester and calcium ionophore, owing to down-regulation of NF-kappaB signaling.⁸³

While this discussion focuses on strategies for suppressing FcεRI-mediated mast cell activation, it is of interest to note recent evidence that Nrf2 activation can also inhibit the MRFPRX2 signaling that mediates pseudo-allergic mast cell activation.⁸⁴ Another agent with the potential for inhibiting both FcεRI and MRFPRX2 signaling in mast cells is paeoniflorin, a bioactive component in peony flower extracts; the mast cell stabilizing action of this agent has been demonstrated both in mast cell cultures and in rodent allergy models.^{85–88} The direct molecular target of its action in this regard has yet to be defined.

Phycocyanobilin (PCB), a light-absorbing chromophore found in cyanobacteria (such as the food spirulina) and certain blue-green algae, is reduced within cells by biliverdin reductase to phycocaynorubin, a compound almost identical in secondary and tertiary structure to bilirubin.^{89,90} Not surprisingly, PCB has been shown to mimic bilirubin's inhibitory effect on NADPH oxidase complexes – a phenomenon, which may be largely responsible for the profound antioxidant and anti-inflammatory activities of orally administered spirulina (or of its protein phycocyanin, to which PCB is covalently bound) in a wide range of rodent models of health disorders.^{90–93} Indeed, oral administration of spirulina or phycocyanin has been found to alleviate symptoms and reduce histamine release in rat models of anaphylaxis induced by ovalbumin or compound 48/80; spirulina also stabilized mast cells and lessened symptoms in ovalbumin-induced allergic rhinitis.^{94–97} Small clinical trials with modest oral doses of spirulina have found it to confer symptomatic benefits in allergic rhinitis, and oral spirulina has also been shown to decrease interleukin-4 production by peripheral blood mononuclear cells stimulated *ex vivo*.^{98–100} The latter suggests that, independent of its impact on mast cells, spirulina might lessen the propensity to generate IgE.

In supraphysiological concentrations, which are achievable with practical and well-tolerated high-dose supplementation, the B vitamin biotin can directly activate sGC – mimicking the physiological effects of nitric oxide and carbon monoxide in that regard.^{101–103} However, it is incapable of increasing sGC's activity by more than 2–3-fold – explaining why it cannot produce profound hypotension the way that NO overdoses can. The authors are unaware of any past effort to evaluate the impact of supraphysiological biotin concentrations on mast cell activation.

Endogenous production of H₂S can be boosted by supplemental N-acetylcysteine (NAC), as cysteine is the preferred substrate for generation of H₂S by cystathionine

β-synthase (CBS) and cystathionine γ-lyase (CSE).^{104–107} In addition, by promoting increased glutathione synthesis, NAC might help to counter the inhibitory effect of oxidants on SHP-1 activity, as glutathione acts to reverse the oxidative inhibition of this enzyme.^{17,108,109} In vascular tissues, supplemental taurine has recently been found to induce expression of both CBS and CSE.^{105,110,111} It is not clear whether taurine can have this effect in mast cells. However, taurine administration has been found to alleviate ovalbumin-induced allergic rhinitis in mice.^{112,113}

A further resource for mast cell stabilization is offered by benifuuki tea, a cultivar of green tea that is unusually rich in an O-methylated form of the prominent green tea catechin epigallocatechin-gallate (EGCG); the site of methylation is on the 3''-hydroxyl of the gallate group.¹¹⁴ This type of tea has been shown to be clinically effective in seasonal allergies (Japanese cedar pollinosis), and its efficacy is thought to reflect the fact that O-methylated EGCG has far superior pharmacokinetics compared to EGCG *per se*.^{115–118} Both EGCG and O-methylated EGCG can stabilize mast cells *in vitro*, and this effect appears to be mediated through the high-affinity binding of these compounds to the 67 kDa laminin receptor (67LR) on mast cells.^{114,119–126} How this receptor induces mast cell stabilization is at present poorly understood, although the interaction of EGCG with the laminin receptor is associated with down-regulated cell surface expression of FcεRI.¹²⁴ This effect is homologous to the ability of EGCG/67LR interaction to down-regulate the surface expression of epidermal growth factor receptors in cancer cells, an effect reflecting accelerated internalization of these receptors; perhaps EGCG likewise induces endosomal uptake of FcεRI.¹²⁷ Interaction of EGCG with 67LR also inhibits mast cell degranulation induced by calcium ionophores, blocking phosphorylation of myosin II regulatory light chain.¹²⁵ And EGCG-mediated inhibition of NADPH oxidase assembly in stimulated mast cells has been reported.¹²² The clinical practicality of using 3-O-methyl EGCG to manage allergies would evidently be greater if polyphenol extracts of benifuuki tea were commercially available.

Conclusions

In summary, it can be concluded that nutraceutical regimens providing some or all of the following agents – berberine, spirulina (or isolated PCB), lipoic acid (and/or broccoli sprouts), melatonin, NAC, taurine, high-dose biotin, benifuuki catechins – may have clinical potential for

Table 1 Suggested Dose Schedules for Nutraceuticals with Potential for Opposing Mast Cell Degranulation

Nutraceuticals	Dosage
Spirulina	5–15 g daily (or 30–100 mg PCG daily)
Lipoic acid	600 mg, 2–3 times daily
Broccoli Sprout Extract (Avmacol™)	375 mg twice daily
Berberine	500 mg twice daily
Biotin	10–20 mg, twice daily
N-Acetylcysteine	600 mg, 2–3 times daily
Taurine	2–3 g daily
Catechin-enriched Green Tea Extract (Benifuuki)	500 mg, twice daily

mast cell stabilization and allergy control. The mechanisms whereby these agents may down-regulate FcεRI signaling are depicted in Figure 1. It would be of interest to study regimens of this sort in rodent models of allergy. It seems likely that a number of small effects that have a complementary impact could result in a substantial clinical benefit.

Table 1 suggests dose schedules of the various discussed nutraceuticals that might be expected to have some clinical impact. We do not represent these dose schedules as ideal for allergy management – rather, these are dose schedules that have shown clinical impact in other contexts, and hence might have potential to be active in allergy.

Abbreviations

SyK, spleen tyrosine kinase; H₂S, Hydrogen sulfide; PCB, Phycocyanobilin; LAT, linker for activated T cells; PI3K, phosphatidylinositol-3-kinase; SHP-1, Src homology region 2 domain-containing phosphatase 1; BTK, Bruton's tyrosine kinase; HO-1, heme oxygenase-1; AMPK, AMP-activated kinase; cGMP, cyclic GMP; PKGII-cGMP, dependent protein kinase G II; sGC, soluble guanylate cyclase; PDE5, phosphodiesterase 5; BSE, broccoli sprout extract; NAC, N-acetylcysteine; CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; ROS, reactive oxygen species.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and

interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval for the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

Author MFM is co-inventor and co-owner of a patent covering nutraceutical uses of phycocyanobilin oligopeptides derived from spirulina. Author JJD is Director of Scientific Affairs for Advanced Ingredients for Dietary Products. The authors have no other conflicts of interest to disclose.

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