

Article

Microcrystalline Quercetin and Seasonal Histamine-Response Biology: Mast-Cell Findings Integrated with Human Pollinosis Evidence

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Abstract: The NVTIA® microcrystalline quercetin ingredient was examined at two levels: physicochemical quality and mast-cell mediator response. The optimized batch contained 91.6% quercetin, 1.9% residual quercetin glycosides and 94.8% total flavonols, with residual ethanol of 218 ppm, D50 of 9.6 µm and D90 of 28.4 µm. In RBL-2H3 cells stimulated with calcium ionophore A23187, the model-group histamine-release level was set to 100%. Ordinary coarse quercetin at 20 µg/mL yielded 82.7%, whereas the optimized material produced 81.4%, 67.5% and 55.8% at 10, 20 and 40 µg/mL; cell viability at these concentrations was 97.2%, 96.1% and 93.5%. Two additional microcrystalline batches gave 71.8% and 65.9% histamine release at 20 µg/mL. Human pollinosis trials have reported changes in selected nasal or ocular symptoms after quercetin-related flavonol interventions, while a 2025 meta-analysis of polyphenolic interventions found improvement in several seasonal allergic-rhinitis symptom domains. The experimental data therefore identify a concentration-dependent mast-cell response for a defined, highly dispersible quercetin material. A formulation-specific human study can extend this work by measuring quercetin exposure, histamine-related mediators and validated seasonal symptom outcomes in the same protocol.

Keywords: *quercetin; histamine release; mast cells; pollinosis; seasonal comfort; microcrystalline dispersion; flavonols.*

1. Introduction

Mast-cell activation and mediator release are central to pollen-related nasal and ocular symptoms. Quercetin has been studied in this setting because flavonols can influence histamine release, inflammatory signaling and oxidative responses. Reviews of quercetin and dietary polyphenols describe effects on mast cells, cytokine networks and allergic immune pathways rather than a single isolated mechanism [1]-[4].

Oral exposure is a separate issue. Quercetin aglycone has limited aqueous dispersibility, and human pharmacokinetic studies show that absorption changes with molecular form, food matrix and delivery technology [5]-[8]. The NVTIA® ingredient was therefore engineered as an aglycone-rich microcrystalline powder rather than treated as an interchangeable quercetin source. Its production sequence uses low-alcohol extraction of onion skins, staged resin enrichment, multienzyme deglycosylation, controlled crystallization and wet micronization.

We examined whether the material altered stimulated histamine release over 10-40 µg/mL while cell viability remained high. The physicochemical data were then read alongside controlled human studies of pollinosis and seasonal allergic rhinitis. The mechanistic cell endpoint and the clinical symptom endpoints were kept separate so that the evidence chain could be interpreted without converting an in-vitro response into a human efficacy claim.

2. Materials and Methods

2.1 Ingredient preparation and physicochemical characterization

Onion skins were dried, milled and pre-wetted with citrate buffer containing ascorbic acid. Quercetin-containing material was extracted with 35-45% aqueous ethanol under ultrasonic countercurrent conditions. Ethanol was recovered, the extract was adjusted and subjected to staged adsorption-resin enrichment, and a β-glucosidase/pectinase/cellulase system was applied under mildly acidic conditions. Seed-induced crystallization, wet-crystal washing, wet micronization and low-temperature vacuum drying produced the final microcrystalline powder. HPLC was used for quercetin and residual glycosides, gas chromatography for residual ethanol and laser diffraction for particle size.

2.2 Mast-cell histamine-release model

RBL-2H3 cells were pretreated with each test sample for 2 h and then stimulated with calcium ionophore A23187. Histamine in the supernatant was measured by ELISA and cell viability by CCK-8. The stimulated model group was defined as 100% relative histamine release. The optimized material was tested at 10, 20 and 40 µg/mL; ordinary coarse quercetin and two additional microcrystalline production batches were tested at 20 µg/mL. Final dimethyl sulfoxide concentration did not exceed 0.1%. The available data are group-level endpoint values, so no additional inferential statistics were generated.

2.3 Focused human-evidence synthesis

PubMed and ClinicalTrials.gov were searched for randomized or controlled human studies of quercetin, quercetin delivery systems and related quercetin glycosides in pollinosis or allergic-rhinitis settings. The human evidence included the Yamada, Kawai and Hirano trials and the 2025 meta-analysis by Lai et al. [9]-[12]. Mechanistic mast-cell studies were used later as biological context [13]-[15]. Findings from those sources were not treated as results of the present microcrystalline formulation.

3. Results

The optimized batch contained 91.6% quercetin, 1.9% residual quercetin glycosides and 94.8% total flavonols. Residual ethanol was 218 ppm. D50 and D90 were 9.6 µm and 28.4 µm, respectively, and 30-s dispersion uniformity reached 91.2%.

3.1 Histamine-release response

Group	Concentration (µg/mL)	Relative histamine release (%)	Cell viability (%)
Blank	–	22.6	100.0
Stimulated model	–	100.0	96.8
Ordinary coarse quercetin	20	82.7	94.6

NVTIA batch	optimized	10	81.4	97.2
NVTIA batch	optimized	20	67.5	96.1
NVTIA batch	optimized	40	55.8	93.5
NVTIA batch 2		20	71.8	95.7
NVTIA batch 3		20	65.9	96.4

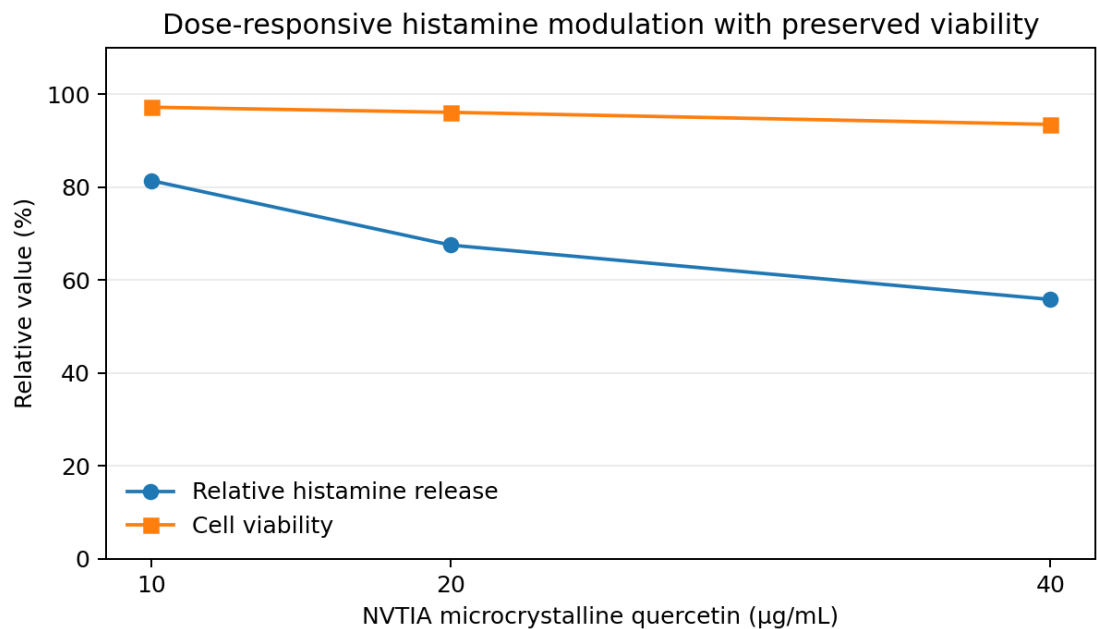


Figure 1. Concentration-dependent histamine-release response and cell viability for the optimized microcrystalline quercetin material.

At 20 µg/mL, relative histamine release was 67.5% with the optimized microcrystalline material and 82.7% with ordinary coarse quercetin. Across the optimized 10, 20 and 40 µg/mL series, histamine release declined from 81.4% to 67.5% and 55.8%, while viability was 97.2%, 96.1% and 93.5%. The two additional microcrystalline batches produced 71.8% and 65.9% at 20 µg/mL, with viability of 95.7% and 96.4%.

3.2 Human seasonal evidence

Study	Population	Intervention	Main relevance
Yamada et al., 2022	66 adults with pollinosis	Quercetin formulation, 4 weeks	Improvement in selected eye/nasal symptoms and QoL domains
Kawai et al., 2009	20 subjects, Japanese cedar pollinosis	EMIQ, 8 weeks	Seasonal symptom improvement in a double-blind placebo-controlled trial
Hirano et al., 2009	24 subjects, Japanese cedar pollinosis	100 mg EMIQ, 8 weeks	Preventive benefit reported for ocular symptom measures
Lai et al., 2025	13 RCTs; 823 participants	Polyphenolic interventions	Meta-analysis: lower total nasal symptoms, sneezing and nasal itching in seasonal AR

4. Discussion

The concentration series is the clearest feature of the mast-cell experiment. Relative histamine release fell from 81.4% at 10 µg/mL to 67.5% at 20 µg/mL and 55.8% at 40 µg/mL. Viability remained above 93% throughout that range. At the matched 20 µg/mL concentration, the optimized material also produced a lower histamine-release value than ordinary coarse quercetin, and the two additional production batches moved in the same direction. Those comparisons make the mediator response easier to interpret than a single isolated concentration.

The material itself is also well defined: 91.6% quercetin, 1.9% residual glycosides, 218 ppm residual ethanol and a D90 of 28.4 µm. Human studies show that quercetin exposure changes substantially with chemical form and delivery system [5]-[8]. The present formulation addresses that issue through particle-size control, dispersion and enrichment of free quercetin rather than through phospholipid complexation or glycoside modification.

Yamada et al. randomized 66 adults with pollinosis-related eye and nasal discomfort to a quercetin-containing supplement or placebo for four weeks and reported improvement in several JRQLQ domains, including eye itching, sneezing, nasal discharge and sleep disturbance [9]. Kawai et al. and Hirano et al. studied enzymatically modified isoquercitrin during Japanese cedar pollen seasons and reported favorable seasonal or ocular symptom findings [10], [11]. These studies used different quercetin-related forms, which is precisely why exposure and formulation should remain explicit in any comparison.

Lai et al. synthesized 13 randomized trials involving 823 participants and reported lower total nasal symptom scores, sneezing and nasal itching with polyphenolic interventions, although the certainty and magnitude were not uniform across outcomes [12]. The pooled literature is useful for choosing human endpoints, not for assigning a fixed effect size to the NVTIA® material.

The cell biology gives a more specific mechanistic bridge. Kimata et al. showed that quercetin can modify IgE-mediated mediator release from human cultured mast cells [13], and Min et al. reported reduced inflammatory-cytokine expression through NF-κB and p38 MAPK pathways in HMC-1 cells [14]. Boots et al. further showed that physiologically attainable quercetin concentrations can produce anti-inflammatory activity in vitro, while the corresponding in-vivo or ex-vivo signal in healthy volunteers was more limited [15]. A human NVTIA® protocol can therefore measure circulating quercetin metabolites together with seasonal symptoms and selected mediator biomarkers rather than relying on the mast-cell assay alone.

5. Research Scope and Future Perspectives

A direct seasonal study could prespecify pollen exposure, baseline symptom burden and the time of supplementation before peak exposure. Plasma quercetin metabolites, validated rhino-conjunctivitis scores and a small mediator panel can be collected prospectively. The current cell experiment then serves as the formulation-specific mechanistic starting point, while the clinical study tests the complete ingredient in its intended exposure context.

6. Conclusion

NVTIA® microcrystalline quercetin combined a fine particle-size distribution and low residual ethanol with a concentration-dependent reduction in stimulated histamine release. At 20 µg/mL, relative release was 67.5% for the optimized material versus 82.7% for ordinary coarse quercetin, with 96.1% cell viability. Controlled pollinosis studies of quercetin-related flavonols provide human seasonal-symptom endpoints that can be carried into a direct formulation-specific trial. Exposure measurement and mediator biomarkers can be added without conflating the in-vitro mast-cell result with the clinical outcome.

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