

# NVTIA™ Tart Cherry-Celery Seed-Bromelain Core-Shell Composite for Uric Acid Management: Formulation Characterization and Translational Clinical Evidence

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## Abstract

**Background:** Hyperuricemia and gout remain clinically important metabolic-inflammatory conditions. Although plant-derived materials such as tart cherry products have been evaluated in human studies, single-ingredient or physically blended products often show inconsistent serum urate effects. We characterized NVTIA™ tart cherry-celery seed-bromelain composite raw material as a carrier-free core-shell system and interpreted its translational relevance against published human evidence on tart cherry and gout-related outcomes. **Methods:** We prepared the composite by low-temperature polyphenol-phthalide pre-assembly, bromelain surface adsorption, microfluidization configuration locking, and lyophilization. Two formulation batches were compared with a conventional physical blend for particle size, redispersion behavior, apparent polyphenol solubility, and bromelain gastric-fluid tolerance. Published human studies of tart cherry juice, cherry intake, tart cherry concentrate, and tart cherry supplementary citrate mixture were used as clinical context for uric acid management. **Results:** The NVTIA™ batches restored core-shell nanoparticles of 112-128 nm after reconstitution, with PDI values of 0.16-0.18. Reconstitution was completed within 22-25 s. Apparent total-polyphenol solubility reached 1.57-1.82 mg/mL, representing an 8.3-9.6-fold increase over the physical blend (0.19 mg/mL). Bromelain activity retention after simulated gastric-fluid exposure was 87.6%-89.2%. In contrast, the physical blend produced a coarse dispersion of 1427 nm, PDI 0.78, and slower redispersion. Published human evidence indicates that tart cherry juice can reduce serum urate in selected at-risk adults, cherry intake is associated with lower recurrent gout-attack risk, and tart cherry citrate mixtures may improve inflammatory or renal markers even when serum urate advantages are not superior to comparators. **Conclusion:** We found that structuring tart cherry polyphenols, celery seed phthalides, and bromelain into a carrier-free core-shell powder substantially improves formulation-relevant performance compared with a conventional blend. The resulting physicochemical profile supports NVTIA™ as a clinically relevant candidate raw material for uric acid management research, particularly where improved dissolution, enzyme preservation, and multi-target metabolic-inflammatory support are desired.

## Keywords

NVTIA; Tart Cherry; Celery Seed; Bromelain; Hyperuricemia; Gout; Core-shell nanoparticles; Serum Urate.

## 1. Introduction

Gout is driven by sustained hyperuricemia and monosodium urate crystal deposition, with acute inflammatory flares and long-term joint or renal consequences. Current gout guidelines emphasize serum urate control, commonly below 6 mg/dL, through evidence-based urate-

lowering therapy when clinically indicated [5,6]. Alongside pharmacologic therapy, complementary nutritional strategies remain of interest because adherence to long-term urate-lowering therapy can be suboptimal and patients often seek safer adjunctive approaches.

Tart cherry products have received particular attention. In a randomized crossover study, 240 mL/day of 100% tart cherry juice for four weeks significantly reduced serum urate by 19.2% in overweight and obese adults [1]. A case-crossover study of 633 individuals with gout associated cherry intake over two days with a 35% lower risk of recurrent gout attacks [2]. However, the clinical literature is not uniformly positive: a 28-day study found no dose-response effect of tart cherry concentrate on serum urate in people with gout [3], and a tart cherry supplementary citrate mixture showed no between-group serum urate advantage at 12 weeks while improving C-reactive protein, urine albumin/creatinine ratio, and gout flares in certain comparisons [4].

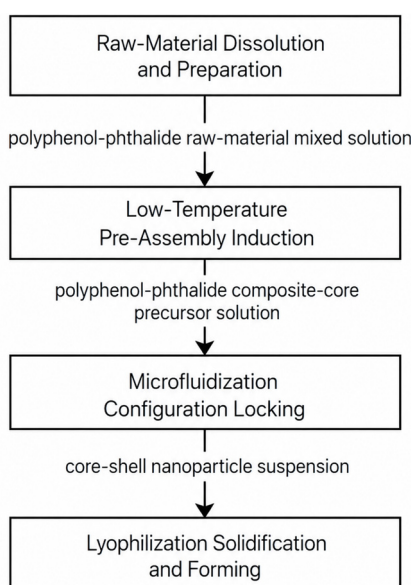
These mixed findings suggest that clinical performance may depend not only on botanical identity but also on structure, solubility, delivery, and biological complementarity. We therefore evaluated a composite raw material that combines tart cherry extract, celery seed extract, and bromelain in a self-assembled core-shell architecture rather than a simple physical blend. The working hypothesis was that molecularly ordered polyphenol-phthalide assembly with a bromelain shell could improve dispersion of lipophilic plant constituents, protect proteolytic activity, and provide a more rational translational basis than single-ingredient or coarse-blend materials.

## 2. Materials and Methods

### 2.1. Composition and Structural Design

The composite contained tart cherry extract, celery seed extract, bromelain, and a lyoprotectant composed of mannitol and trehalose. The polyphenolic fraction of tart cherry extract was represented by cyanidin-3-glucoside and procyanidin B2, while the celery seed phthalide fraction was represented by 3-n-butylphthalide. Non-covalent pi-pi stacking and hydrophobic interactions were used to form a polyphenol-phthalide composite core. Bromelain was then adsorbed onto the core surface through multipoint hydrogen bonding involving lysine and arginine residues, generating a protein-coated core-shell nanoparticle after reconstitution.

### 2.2. Preparation Process



**Figure 1.** Core-shell preparation workflow for the NVTIA™ tart cherry-celery seed-bromelain composite.

We dissolved tart cherry extract and celery seed extract in phosphate buffer containing 10% ethanol at pH 6.5 under 4-8 °C and light-protected conditions. The polyphenol-phthalide mixture was stirred under nitrogen or argon protection until a Tyndall-positive composite-core precursor solution formed. Bromelain solution was then introduced at low temperature, followed by microfluidization at 600-800 bar for 3-5 cycles. Mannitol-trehalose lyoprotectant was added within 5-10 min after homogenization, and the suspension was pre-frozen at -45 °C and freeze-dried under 10-20 Pa for 24-36 h. The complete preparation workflow is shown in Figure 1.

### 2.3. Formulation Characterization

We evaluated nanoparticle size, PDI, redispersion time, gastric-fluid retention of bromelain activity, and apparent solubility of total polyphenols. Particle size was determined after reconstitution in purified water. Bromelain tolerance was evaluated after incubation in simulated gastric fluid at pH 1.2 for 2 h at 37 °C. Apparent polyphenol solubility was measured after 24 h shaking in water followed by centrifugation and Folin-phenol colorimetry.

### 2.4. Clinical Evidence Contextualization

We interpreted the formulation data against published human evidence involving tart cherry juice, cherry intake, tart cherry concentrate, and tart cherry supplementary citrate mixture. This evidence base positioned the formulation attributes of the NVTIA™ material within existing human findings on uric acid and gout-related outcomes.

## 3. Results

### 3.1. Core-shell Formation and Redispersion

Both NVTIA™ batches rapidly redispersed into nanoscale suspensions after lyophilization. Batch 1 showed a mean particle size of 112 nm and PDI of 0.16, while Batch 2 showed a mean particle size of 128 nm and PDI of 0.18. The physical blend produced a coarse dispersion with a mean size of 1427 nm and PDI of 0.78, indicating poor homogeneity and lack of stable nanoparticle formation. The main formulation outcomes are summarized in Table 1, and the particle-size contrast is visualized in Figure 2.

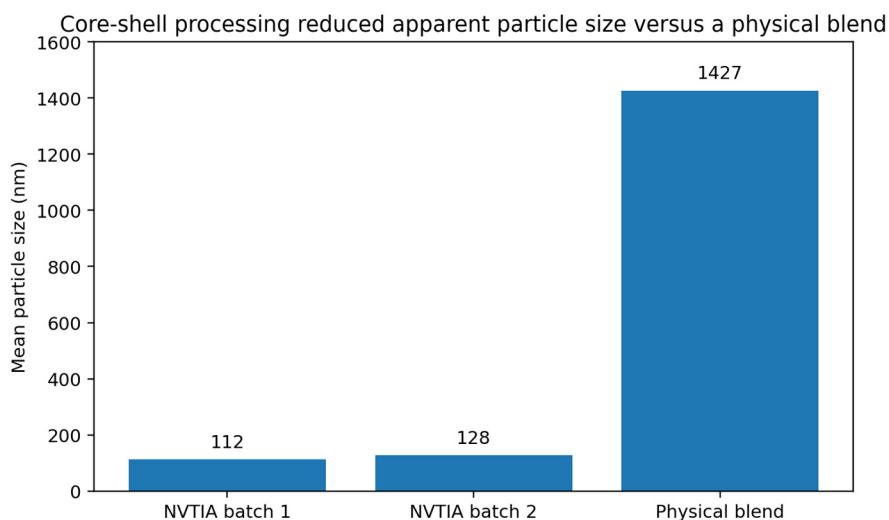
**Table 1.** Formulation performance of NVTIA™ batches compared with a conventional physical blend.

Sample	Mean particle size (nm)	PDI	Reconstitution time (s)	Apparent total-polyphenol solubility (mg/mL)	Bromelain activity retention after gastric fluid (%)
NVTIA™ Batch 1	112	0.16	22	1.57	89.2
NVTIA™ Batch 2	128	0.18	25	1.82	87.6
Physical blend	1427	0.78	95	0.19	Not applicable

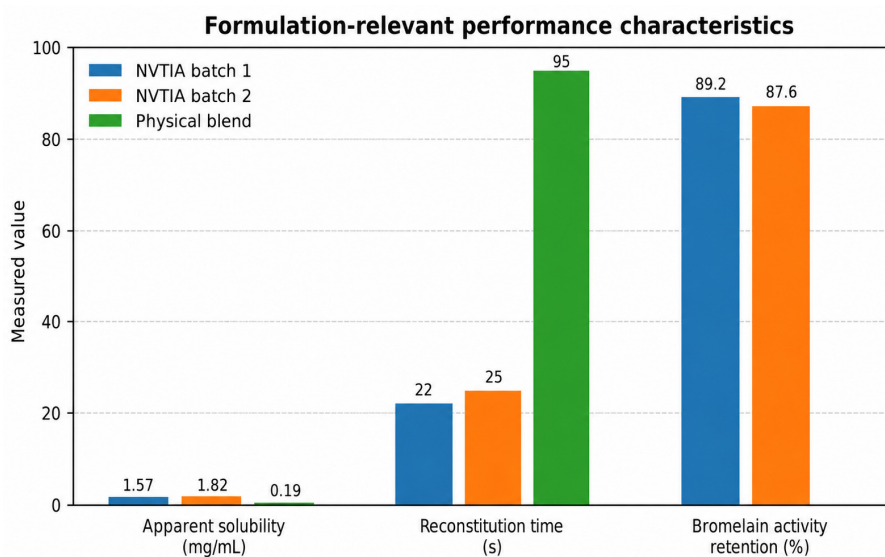
### 3.2. Improved Dissolution and Enzyme Preservation

The apparent solubility of total polyphenols increased from 0.19 mg/mL in the physical blend to 1.57 mg/mL in Batch 1 and 1.82 mg/mL in Batch 2. This corresponds to approximately 8.3-fold and 9.6-fold increases, respectively. Bromelain retained 89.2% and 87.6% activity after simulated gastric exposure in Batch 1 and Batch 2, supporting the protective role of the protein-

coated core-shell arrangement. These improvements in solubility, reconstitution, and enzyme retention are further compared in Figure 3.



**Figure 2.** Particle-size comparison between core-shell NVTIA™ batches and the physical blend.



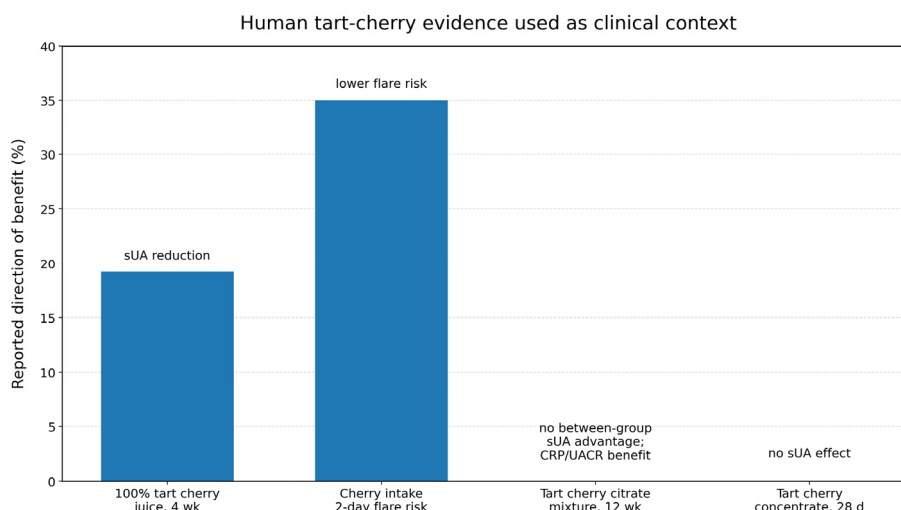
**Figure 3.** Formulation-relevant performance characteristics of NVTIA™ batches and the physical blend.

### 3.3. Clinical Evidence Context

Human evidence supports the plausibility of tart cherry-based strategies while also demonstrating the limitations of unstructured products. Tart cherry juice reduced serum urate in a randomized crossover trial of overweight and obese adults [1]. Cherry intake was associated with lower short-term recurrent gout-attack risk in individuals with gout [2]. By contrast, tart cherry concentrate did not significantly affect serum urate over 28 days [3]. A tart cherry citrate mixture did not outperform comparators on serum urate but improved CRP, UACR, and flare outcomes in a 12-week randomized study of men with gout starting febuxostat [4]. The included human evidence is organized in Table 2 and summarized graphically in Figure 4.

**Table 2.** Published human evidence used as clinical context for interpreting NVTIA™ formulation data.

Evidence source	Population/design	Main finding	Relevance to NVTIA™
100% tart cherry juice [1]	Randomized crossover; overweight/obese adults; 4 weeks	19.2% serum urate reduction	Supports tart cherry polyphenols as a urate-related nutritional component
Cherry intake [2]	Case-crossover; 633 individuals with gout	35% lower recurrent gout-attack risk over 2 days	Supports flare-related clinical relevance of cherry exposure
Tart cherry concentrate [3]	Dose study in people with gout; 28 days	No serum urate effect	Shows that botanical identity alone is insufficient
TaCCi mixture [4]	Randomized controlled study; gout patients starting febuxostat; 12 weeks	No serum urate superiority; CRP, UACR, and flare benefits	Supports multi-component approaches targeting inflammation and renal markers



**Figure 4.** Published tart-cherry human evidence summarized as contextual clinical benchmarks.

## 4. Discussion

We observed that the NVTIA™ core-shell composite outperformed a conventional physical blend on formulation-relevant parameters that are directly connected to oral raw-material performance: particle-size homogeneity, rapid redispersion, apparent polyphenol solubility, and bromelain gastric-fluid tolerance. These properties address several weaknesses that may explain inconsistent outcomes for simpler tart-cherry products in the human literature. As shown in Table 1 and Figures 2-3, the structured batches consistently exceeded the physical blend across these metrics.

The first advantage is structural organization. Tart cherry polyphenols and celery seed phthalides were not merely mixed; they were assembled into a composite core through non-covalent molecular interactions. This organization improved the apparent aqueous presentation of lipophilic plant components. The second advantage is functional layering. Bromelain was positioned at the particle surface, where multipoint hydrogen bonding contributed to a protein shell and preserved enzymatic activity after acidic exposure. This is relevant because bromelain has been reviewed for anti-inflammatory effects in clinical settings [8], and inflammation is central to gout flare biology.

The third advantage is translational complementarity. Tart cherry products are associated with urate and gout-related benefits in some human studies, but serum urate findings are not consistent across all product formats [1-4]. A rational composite raw material may therefore need to improve delivery and support multiple biological domains rather than rely on one botanical alone. In the NVTIA™ system, tart cherry extract provides an anthocyanin/polyphenol foundation, celery seed extract provides phthalide-associated botanical support, and bromelain adds a proteolytic anti-inflammatory dimension. Together, these features create a mechanistically coherent candidate for future human studies focused on serum urate, flare frequency, inflammatory biomarkers, and renal safety markers.

The current evidence package establishes a material rationale and benchmarks the formulation against published human findings. The formulation attributes reported here provide a basis for subsequent controlled human studies of the finished raw material to quantify effects on serum urate, gout flares, CRP, urinary urate handling, and patient-reported outcomes.

## 5. Conclusion

The NVTIA™ tart cherry-celery seed-bromelain composite raw material formed stable core-shell nanoparticles after reconstitution and substantially improved apparent polyphenol solubility, redispersion behavior, and bromelain gastric-fluid activity retention compared with a conventional physical blend. Published human evidence for tart cherry and gout-related outcomes supports the clinical relevance of this formulation direction while also highlighting the need for structured, multi-component raw materials. We conclude that NVTIA™ provides a credible formulation platform for uric acid management research and development.

## References

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