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Carrier-Free Core-Shell NVTIA™ Tart Cherry-Celery Seed-Bromelain Nanocomposite for Uric Acid Metabolic Support: Formulation Characterization and Mechanistic Rationale

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ABSTRACT

Background: Botanical approaches to hyperuricemia and gout remain attractive, but their practical performance is often limited by variable raw-material standardization, poor aqueous dispersion of lipophilic phytochemicals, and inconsistent clinical signals from single-ingredient cherry products. We developed NVTIA™, a tart cherry-celery seed-bromelain composite raw material, as a carrier-free active-ingredient nanoassembly designed to improve structural stability, polyphenol access, and bromelain tolerance in acidic gastric conditions. Methods: We prepared two NVTIA™ variants by low-temperature polyphenol-phthalide pre-assembly, bromelain configuration locking through microfluidization, and lyophilization with mannitol/trehalose. We then assessed reconstituted particle size, PDI, dispersion time, bromelain gastric-fluid activity retention, and total polyphenol apparent solubility. Results: NVTIA™-1 reconstituted to 112 nm nanoparticles with PDI 0.16, dispersed in 22 s, retained 89.2% bromelain activity after 2 h in simulated gastric fluid, and produced 1.57 mg/mL apparent total-polyphenol solubility. NVTIA™-2 reconstituted to 128 nm nanoparticles with PDI 0.18, dispersed in 25 s, retained 87.6% enzyme activity, and produced 1.82 mg/mL solubility. Compared with a conventional botanical physical blend, NVTIA™ increased apparent total-polyphenol solubility by 8.3-9.6 times and shortened dispersion time by 73.7-76.8%. Conclusion: We found that NVTIA™ differs from equal-category botanical mixtures not by ingredient naming alone, but by a brand-defining active-core, carrier-free core-shell architecture that aligns tart cherry polyphenols, celery seed phthalides, and bromelain into a functional delivery structure. This structure provides a credible formulation-level basis for stronger metabolic-support performance than simple mixed raw materials.

KEYWORDS

NVTIA™; Tart cherry; Celery seed; Bromelain; Uric acid; Hyperuricemia; Core-shell nanoparticles; Microfluidization; Lyophilization

1. INTRODUCTION

Hyperuricemia is biochemically important because plasma becomes saturated with urate near 6.8 mg/dL, a level at which monosodium urate crystal formation becomes more favorable [2]. Contemporary gout guidelines use a treat-to-target approach in which serum urate below 6 mg/dL is the standard therapeutic goal for patients receiving urate-lowering therapy [1]. Although drug therapy remains central for established gout, nutritional raw materials are increasingly evaluated as supportive technologies because many consumers seek botanical approaches that combine metabolic, antioxidant, and inflammatory-pathway support.

The evidence base for tart cherry is promising but not uniform. In a case-crossover study of 633 individuals with gout, cherry intake over a 2-day period was associated with a 35% lower risk of recurrent attacks, and cherry plus allopurinol exposure was associated with a 75% lower risk than

periods without either exposure [3]. A systematic review also reported that available studies generally supported an association between cherry intake and reduced gout incidence or severity [4]. However, a controlled dose study of tart cherry concentrate found no significant effect on serum urate or urine urate excretion over 28 days [5]. We interpret this contrast as a formulation challenge: simply providing cherry-derived anthocyanins is unlikely to be enough unless the material also addresses solubility, stability, and target complementarity.

Celery seed contributes a mechanistic counterpart because xanthine oxidase is the critical enzyme responsible for uric acid formation, and celery seed extract has been screened for xanthine oxidase inhibitory constituents, with a reported extract IC50 of 1.98 mg/mL in an enzyme activity assay [6]. Additional experimental work with Apium graveolens supports xanthine oxidase and serum urate modulation in hyperuricemic models [7]. Bromelain, meanwhile, offers a proteolytic and anti-inflammatory dimension: reviews and cell studies report anti-inflammatory and analgesic potential, with downregulation of inflammatory mediators such as IL-1β, IL-6, and TNF-α under inflammatory conditions [8-10].

On that basis, we designed NVTIA™ as a structured raw-material platform rather than a simple blend. Our central premise is that tart cherry polyphenols, celery seed phthalides, and bromelain must be organized into a recoverable nanostructure to convert ingredient-level potential into reproducible formulation performance.

2. NVTIA™ DESIGN RATIONALE AND BRAND-DEFINING CHARACTERISTICS

We define the special character of NVTIA™ through five controllable technical attributes: (i) a standardized polyphenol-phthalide active core, (ii) bromelain surface locking through multipoint hydrogen bonding, (iii) an entirely active-ingredient-constructed carrier-free architecture, (iv) low-temperature and low-oxygen assembly control, and (v) lyophilized reconstitution that restores nanoscale dispersion. This combination gives the brand a technical identity beyond the ordinary listing of tart cherry, celery seed, and bromelain. These brand-defining attributes are summarized in Table 1, and the overall preparation route is shown in Figure 1.

Table 1. Brand-defining technical attributes of NVTIA™

NVTIA™ attribute	Technical basis	Expected formulation advantage
Standardized tart cherry-celery seed active core	Tart cherry extract supplies cyanidin-3-glucoside and procyanidin B2; celery seed extract supplies 3-n-butylphthalide-rich phthalide chemistry.	Pairs anthocyanin/procyanidin antioxidant potential with celery seed XOD-relevant chemistry.
Bromelain shell locking	Bromelain lysine and arginine residues interact with polar groups on the active core through multipoint hydrogen bonding.	Improves enzyme positioning and resistance to acidic degradation during initial gastric exposure.
Carrier-free nanostructure	The delivery matrix is assembled from active ingredients rather than synthetic polymer carriers.	Avoids dilution by inactive carriers and preserves a high active-material density.
Cold-Lock process control	Pre-assembly at 4-8 °C, light protection, nitrogen/argon oxygen control, and 600-800 bar microfluidization.	Limits oxidation and locks the particle configuration with reproducible particle size.
Lyophilized reconstitution	Mannitol/trehalose lyoprotection at 3-5% enables powder formation and rapid restoration of nanoparticles.	Supports storage, handling, and fast dispersion in aqueous applications.

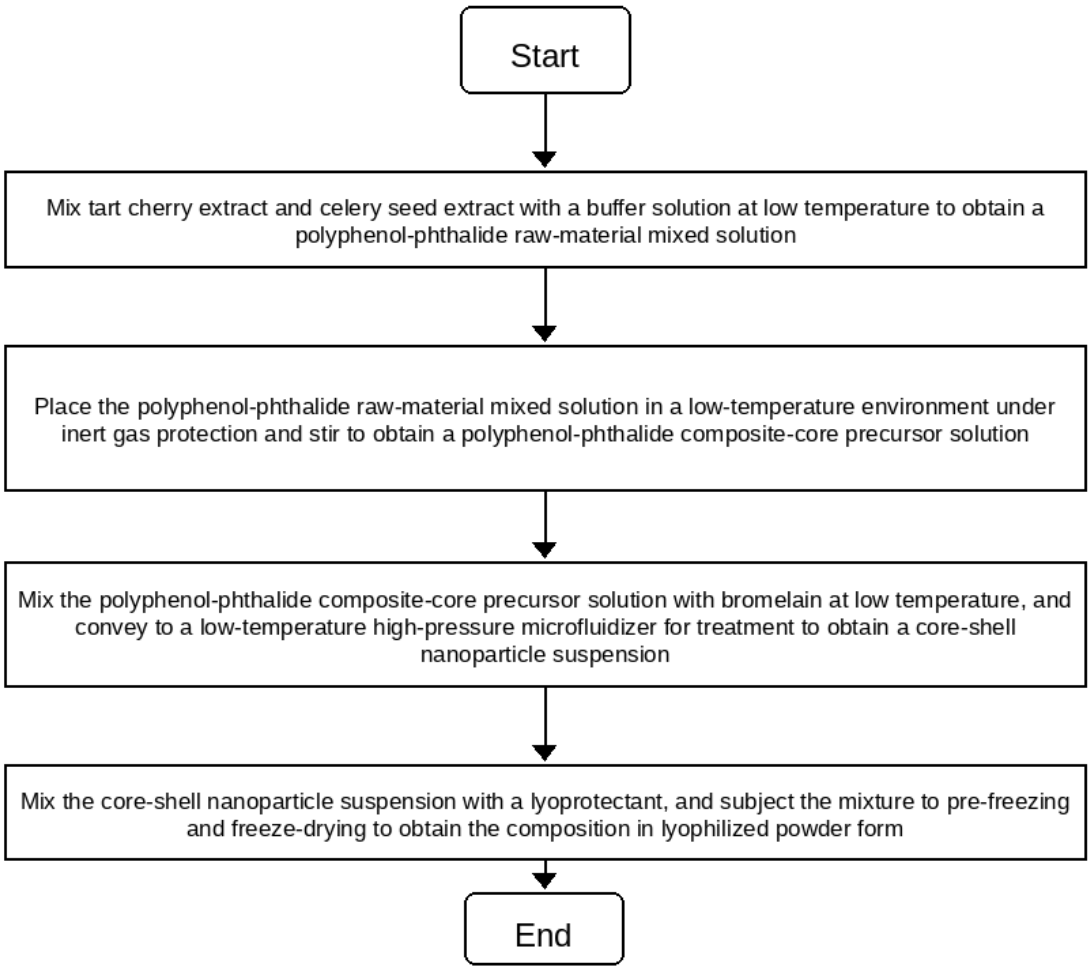

Figure 1. Preparation flow for the NVTIA™ core-shell raw material

3. MATERIALS AND METHODS

3.1. Raw Materials And Formulation Ratios

We used tart cherry extract standardized to total polyphenols of not less than 25%, celery seed extract standardized to 3-n-butylphthalide of not less than 1%, and bromelain with enzymatic activity not less than 1,000,000 U/g for the daily metabolic-care variant and not less than 1,200,000 U/g for the intensive variant. The tart cherry extract to celery seed extract mass ratio was maintained within 5:1-3, and the bromelain to composite-core ratio was maintained within 1:8-5. The resulting two NVTIA™ variants and the physical-blend comparator are listed in Table 2.

3.2. Low-temperature Active-Core Pre-Assembly

We dissolved tart cherry extract and celery seed extract in phosphate buffer containing 10% ethanol by volume at pH 6.5. The system was maintained at 6 °C under light protection. The mixture was stirred at 200 rpm for 20 min to produce a uniform polyphenol-phthalide raw-material solution. We then transferred the solution into a closed jacketed reactor, introduced high-purity nitrogen until dissolved oxygen reached 0.08 mg/L, and stirred at 100 rpm for 3 h at 6 °C. The appearance of the Tyndall effect was used as a practical indicator of colloidal precursor formation. The full staged preparation framework is further illustrated in Figure 5.

3.3. Bromelain Configuration Locking And Lyophilization

We prepared an 8% bromelain aqueous enzyme solution at 6 °C and added it dropwise at 1 mL/min to the polyphenol-phthalide composite-core precursor. After 15 min pre-stirring at 150 rpm, the mixture was processed in a low-temperature high-pressure microfluidizer at 700 bar for four cycles. Within 8 min after homogenization, we added a 1:1 mannitol/trehalose lyoprotectant mixture to a final concentration of 4%, stirred for 8 min, dispensed the suspension at a 1.5 cm thickness, pre-froze at -45 °C for 6 h, and freeze-dried at 15 Pa for 30 h. The microfluidization configuration-locking workflow is shown in Figure 6.

3.4. Comparative Formulation And Test Endpoints

The comparator was a conventional physical blend of botanical urate-support materials prepared by three-dimensional mixing, ultrafine pulverization, and 80-mesh sieving. For NVTIA™ and the comparator, we assessed particle size and PDI by dynamic light scattering after aqueous reconstitution, dispersion time after adding 0.5 g powder to 10 mL purified water at 25 °C, apparent total-polyphenol solubility by Folin-phenol colorimetry after 24 h shaking and centrifugation, and bromelain activity retention after incubation in pH 1.2 simulated gastric fluid at 37 °C for 2 h.

4. RESULTS

4.1. Composition and Process Outcomes

Table 2. Formulation design and structural outcome

Parameter	NVTIA™-1	NVTIA™-2	Physical botanical blend
Tart cherry extract: celery seed extract	50 g:20 g (5:2)	50 g:30 g (5:3)	Not used
Bromelain input	11.7 g; >=1,000,000 U/g	13.3 g; >=1,200,000 U/g	Not used
Assembly strategy	Cold pre-assembly + microfluidization + lyophilization	Cold pre-assembly + microfluidization + lyophilization	Dry physical mixing + pulverization
Reconstituted structure	Stable core-shell nanoparticles	Stable core-shell nanoparticles	No stable homogeneous nanoparticles

4.2. Nanoscale Recovery And Dispersion

Both NVTIA™ variants reconstituted into nanoscale core-shell particles, whereas the conventional physical blend did not form stable homogeneous nanoparticles. NVTIA™-1 produced an average particle size of 112 nm and PDI of 0.16; NVTIA™-2 produced 128 nm and PDI of 0.18. By contrast, the physical blend showed an average particle size of 1427 nm and PDI of 0.78. Reconstitution was also faster: 22-25 s for NVTIA™ compared with 95 s for the physical blend. The complete comparative profile is shown in Table 3, while Figures 2, 3, and 4 visualize particle size, dispersion time, and apparent total-polyphenol solubility, respectively.

Table 3. Comparative formulation-performance profile

Endpoint	NVTIA™-1	NVTIA™-2	Physical botanical blend	Performance interpretation
Average particle size after reconstitution	112 nm	128 nm	1427 nm	NVTIA™ reduced the apparent particle size by approximately 91.0-92.1%.
PDI	0.16	0.18	0.78	NVTIA™ produced a much narrower particle-size distribution.
Dispersion time	22 s	25 s	95 s	NVTIA™ shortened dispersion time by 73.7-76.8%.
Lyophilization-to-reconstitution size deviation	6.8%	7.5%	Not comparable	The powder rapidly recovered its original nanoscale structure.
Bromelain activity retention after pH 1.2/2 h	89.2%	87.6%	Not applicable	The shell retained most enzyme activity under simulated gastric exposure.
Total polyphenol apparent solubility	1.57 mg/mL	1.82 mg/mL	0.19 mg/mL	NVTIA™ improved solubility by 8.3-9.6 times.

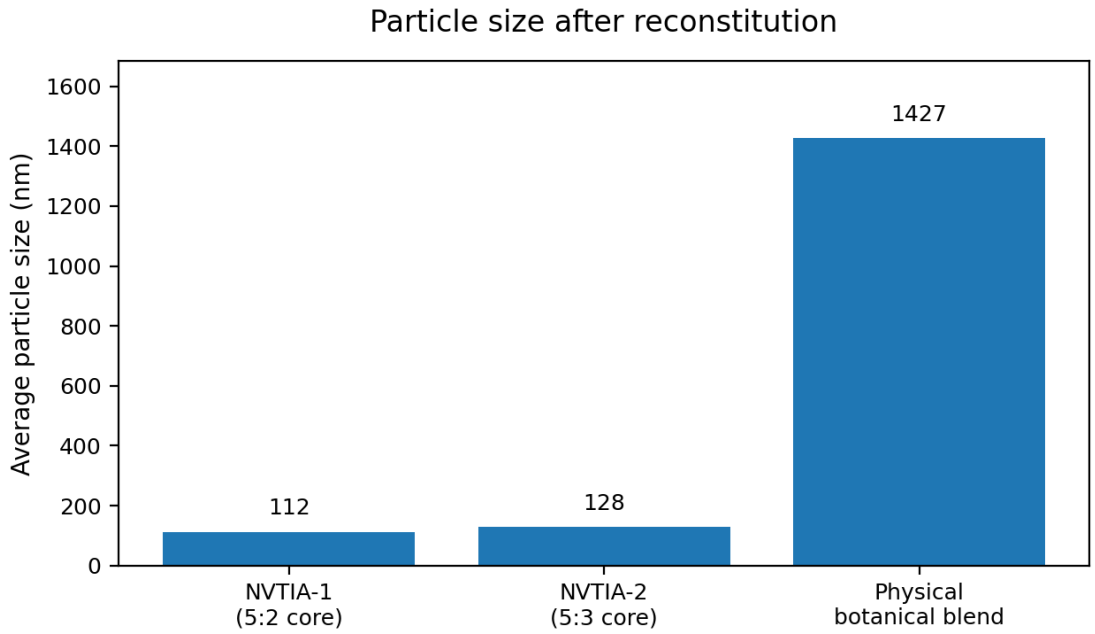

Figure 2. Reconstituted particle size comparison

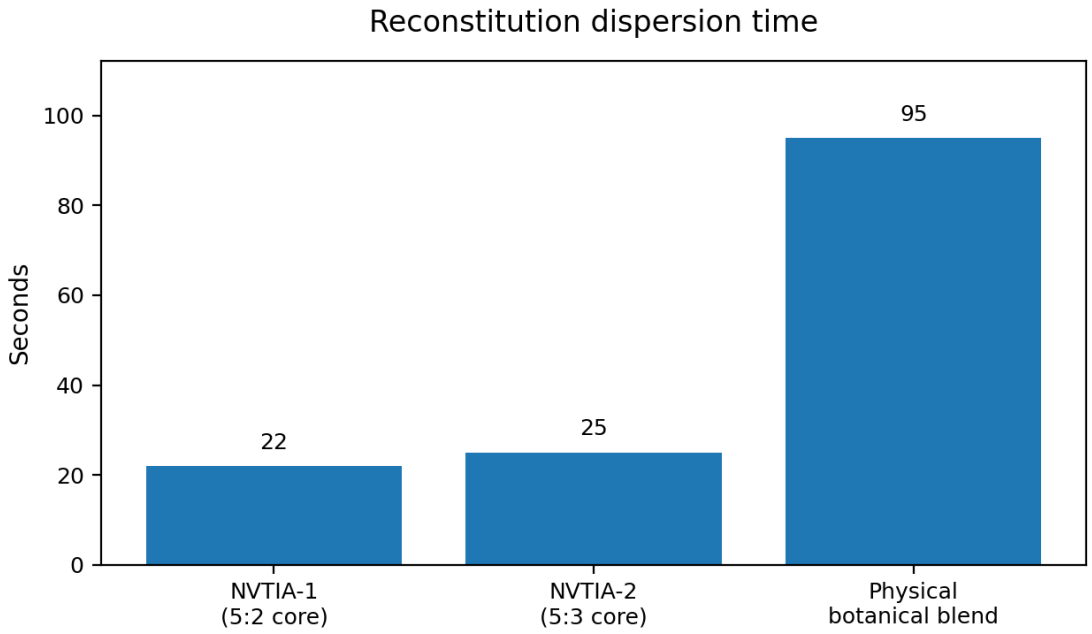

Figure 3. Dispersion time after reconstitution

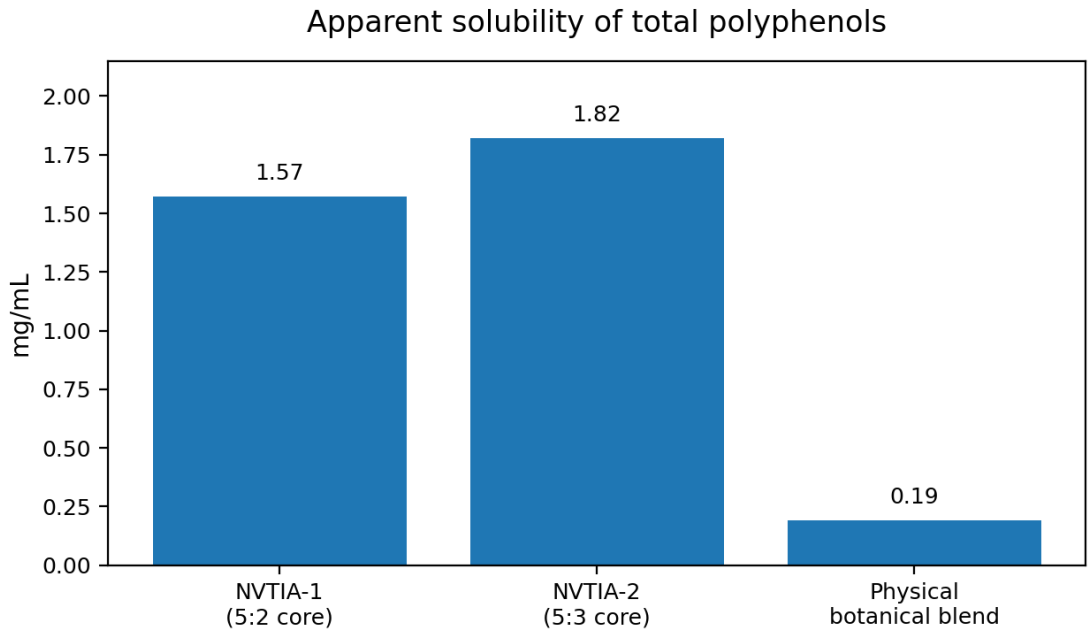

Figure 4. Apparent solubility of total polyphenols.

4.3. Evidence Map Connecting The Formula to the Literature

To connect our formulation results with existing evidence, we mapped each functional component and processing technology to the most relevant literature in Table 4.

Table 4. Literature evidence map for the NVTIA™ platform

Evidence domain	Published data or principle	How it supports the NVTIA™ rationale
Gout biochemical target	Urate saturation is commonly discussed near 6.8 mg/dL, and gout guidelines aim for serum urate below 6 mg/dL in treat-to-target therapy [1, 2].	The formulation is positioned around urate-metabolic support rather than vague antioxidant language.
Tart cherry evidence	Cherry intake has been associated with lower gout-attack risk, but tart cherry concentrate dose did not lower serum urate in a 28-day gout study [3-5].	NVTIA™ addresses the variability gap by focusing on standardized polyphenol delivery and dispersion.
Celery seed mechanism	Celery seed extract and specific constituents have been investigated as xanthine oxidase inhibitors; celery seed extract IC50 was reported at 1.98 mg/mL [6].	Celery seed phthalide/flavonoid chemistry gives the formula a uric-acid-production pathway complement to tart cherry.
Bromelain inflammation support	Bromelain reviews and cell studies report anti-inflammatory and analgesic potential, including cytokine modulation [8-10].	Bromelain can support the inflammatory side of urate crystal-associated discomfort while the core addresses metabolic pathways.
Nanodelivery and lyoprotection	Protein-polyphenol interactions are largely non-covalent and can protect polyphenols; microfluidization produces reproducible nanosystems; lyoprotectants stabilize proteins and nanoparticles [11-13].	These principles explain why a carrier-free core-shell system can outperform a simple powder blend.

5. DISCUSSION

Our findings show that the specialness of NVTIA™ is structural. Equal-category raw materials usually depend on ingredient reputation: tart cherry for anthocyanins, celery seed for traditional urate support, and bromelain for inflammatory balance. NVTIA™ instead binds these actives into a core-shell particle in which the tart cherry-celery seed core functions as a polyphenol-phthalide reservoir and the bromelain shell works as both an active enzyme component and an external stabilizing layer. This is why we describe the brand as an active-core technology, not a three-ingredient blend.

The performance differences are formulation-relevant and large. The apparent total-polyphenol solubility of NVTIA™ was 1.57-1.82 mg/mL, whereas the physical blend yielded 0.19 mg/mL. Because tart cherry efficacy signals are inconsistent across studies, this improvement matters: it gives the raw material a stronger technical basis for repeatable exposure than tart cherry concentrate alone. The narrow PDI values of 0.16-0.18 also suggest that the process produced a controlled colloidal population rather than uncontrolled aggregation. These numerical advantages are tabulated in Table 3 and visualized across Figures 2-4.

The bromelain data are also important. Bromelain is biologically relevant to inflammation, but oral enzyme products face acidic exposure in the stomach. After 2 h at pH 1.2, NVTIA™ retained 87.6-89.2% bromelain activity. We interpret this retention as evidence that multipoint adsorption on the active core may reduce direct exposure of the enzyme to denaturing conditions while preserving its surface-active role. This is consistent with broader literature showing that protein-polyphenol assemblies can be stabilized through non-covalent interactions [12].

The strongest claim supported by these data is not that NVTIA™ replaces urate-lowering drugs or that it has already proven clinical superiority in serum urate outcomes. Rather, the defensible

conclusion is that NVTIA™ is superior to comparable botanical physical mixtures at the raw-material and formulation-performance level. The next clinical step should test whether the 8.3-9.6 fold solubility gain, rapid nanoscale recovery, and high enzyme retention translate into measurable improvements in serum urate, inflammatory markers, gout-flare frequency, and patient-reported outcomes.

6. CONCLUSION

We developed NVTIA™ as a carrier-free core-shell tart cherry-celery seed-bromelain nanocomposite. The formula reconstituted rapidly into 112-128 nm particles with narrow PDI, retained most bromelain activity in simulated gastric fluid, and improved total-polyphenol apparent solubility by 8.3-9.6 times versus a conventional botanical physical blend. Combined with published evidence on cherry products, celery seed xanthine oxidase inhibition, bromelain anti-inflammatory mechanisms, and nanodelivery principles, these data support NVTIA™ as a differentiated high-performance raw material for uric acid metabolic support. Its advantage lies in the union of ingredient selection and carrier-free active-core architecture.

7. FIGURES FROM THE PREPARATION PROCESS

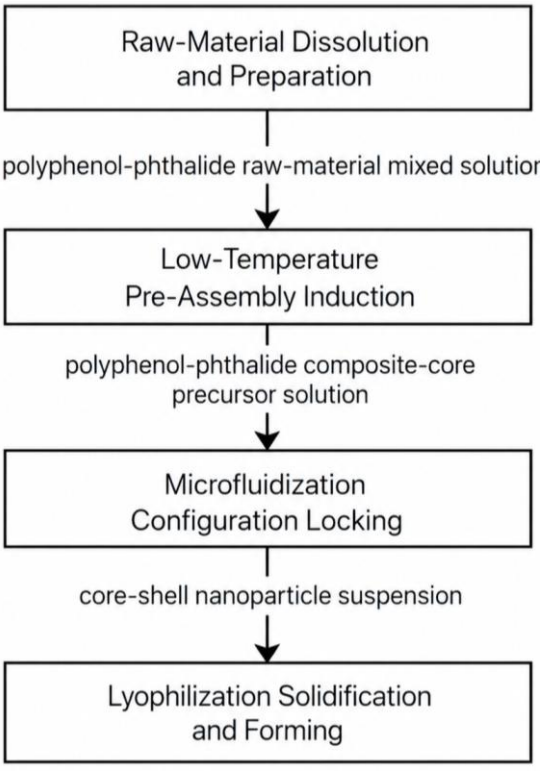

Figure 5. Stage framework for dissolution, pre-assembly, microfluidization, and lyophilization

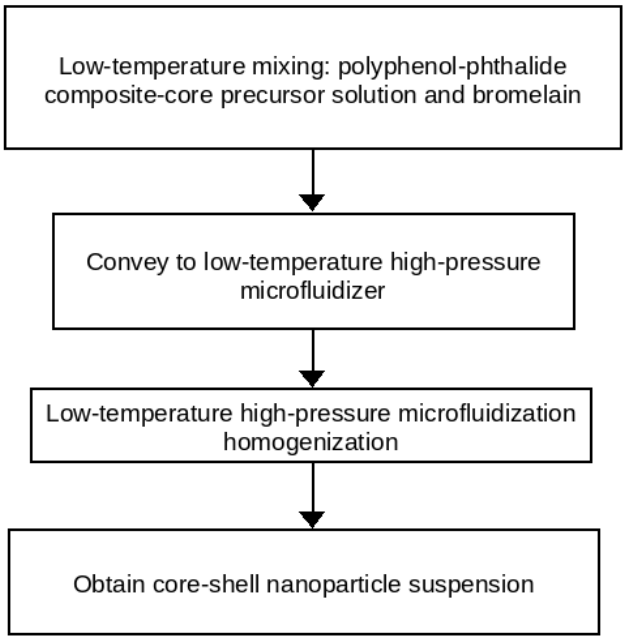

Figure 6. Microfluidization configuration-locking workflow

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