

# Knee Osteoarthritis

Candidate Formulation Hypothesis · Blueprint B3.5 · ICD-10 M17

|                     |                                                                  |
|---------------------|------------------------------------------------------------------|
| Document class      | Official demonstration example — full 12-stage pipeline trace    |
| Framework           | PhytoIntelligence v3.5.0 reference engine                        |
| Primary Driver Node | Node 4 (Immune)                                                  |
| Epistemic standard  | 1 = 1 = 1 (Retrieve = Store = Cite) — Seshat's Axiom             |
| Integrity protocol  | LHFP-II / CCHP cryptographic citation seal                       |
| Capsule basis       | 750 mg unit, 6+1 molecular stack                                 |
| Prepared by         | Marie-Soleil Seshat Landry (ORCID 0009-0008-5027-3337)           |
| Date of run         | 10 June 2026                                                     |
| CCHP fingerprint    | 756d6391939b3fc97f49d374227ccc005d1ec30e5a4bd0ab9bc7e225b024a12c |

VALIDATED CANDIDATE — EXCIPIENT-CORRECTED (HAP)

All therapeutic gates pass. The decisive event is at Step 08a: the Hydrophobic Adsorption Probability screen fires on the  $\beta$ -boswellic-acid constituent (logP 7.0 with polar surface area 57.5 Å<sup>2</sup>, satisfying the joint logP>4.5 AND PSA<60 trigger), indicating a high risk of irreversible adsorption onto cellulose excipient. The formulation is automatically corrected by substituting the default USP-MCC carrier with non-adsorbing USP dicalcium phosphate. The corrected candidate is dual-pathway eligible (SII 0.0323).

**SYSTEM OPERATIONAL WARNING.** This document is a **hypothetical research-and-development model output**. It has received **no clinical, pre-clinical or bench validation** and is **not medical advice**. The formulation described is a computational hypothesis only and must **not be compounded, administered or consumed** by any person under any circumstances without formal bench-scale validation and qualified medical, toxicological and regulatory oversight. Doses are deliberately constrained within established over-the-counter supplement envelopes as a precautionary margin and do not constitute a therapeutic recommendation.

Generated as one of three reference exemplars (Plaque Psoriasis B1.7 · Type 2 Diabetes B2.3 · Knee Osteoarthritis B3.5) demonstrating the PI 3.5.0 pipeline across distinct disease-signature topologies (immune-, metabolic- and inflammatory-dominant).

§ 0 Pipeline Overview

The PhytoIntelligence pipeline is a deterministic, gate-sequenced screen: each stage can reject or constrain the candidate before the next is reached. The full trace for this diagnostic follows. Stages 11-12 are not enumerated in the source specification table and are mapped here, transparently, to the compilation and cryptographic-sealing operations described in §1.2 of the specification.

| Step | Stage                         | Function                                                                     |
|------|-------------------------------|------------------------------------------------------------------------------|
| 01   | Anomaly Observation           | Define the pathological state, clinical endpoints and comorbidity field.     |
| 02   | Intelligence Requirement      | Deconvolute molecular targets and assign source-evidence tiers.              |
| 02a  | Tier Pre-Screen               | Reject non-botanical / out-of-envelope substrates before scoring.            |
| 03   | 6-Dimensional DSV Mapping     | Score the disease and each candidate across the six biological dimensions.   |
| 04   | Vector Convergence            | Match candidate dimensional vectors to the disease signature.                |
| 05   | Deconvolution Scoring (CES)   | Compute composite evidence scores under the calibrated risk penalty $\rho$ . |
| 06   | Node Assignment (6+1)         | Place compounds into dimensional nodes; resolve ties via DMCF.               |
| 07   | Pharmacokinetic Filter (PKAS) | Test tier-weighted Tmax alignment against the primary-driver anchor.         |
| 08   | Mass Allocation (CWMA)        | Distribute capsule mass by penalised evidence weight with a 5 mg floor.      |
| 08a  | Excipient Screen (HAP)        | Flag hydrophobic adsorption risk and select the carrier.                     |
| 09   | Synergy Verification (NSI)    | Two-pass pairwise synergy gate (hard floor, then aggregate).                 |
| 10   | Safety Interaction Gate (SII) | Normalised interaction burden; regulatory-pathway bifurcation.               |
| 11   | Formulation Compilation       | Lock the final node table, masses and excipient (inferred stage).            |
| 12   | Epistemic Sealing (CCHP)      | SHA-256 fingerprint over the ordered citation array (inferred stage).        |

§ 1 Step 01 — Anomaly Observation

Knee osteoarthritis is a degenerative joint disorder in which mechanical and inflammatory stress drive progressive cartilage matrix breakdown, subchondral remodelling and synovial inflammation. It was selected to exercise the excipient-adsorption machinery, because its strongest evidence-tier agent is a highly lipophilic triterpene acid.

|                          |                                                                               |
|--------------------------|-------------------------------------------------------------------------------|
| Pathology                | Knee Osteoarthritis (blueprint B3.5, ICD-10 M17)                              |
| Clinical endpoints       | WOMAC pain/stiffness/function, VAS pain, Lequesne index, hs-CRP.              |
| Comorbidity field        | obesity, chronic NSAID/PPI co-use, GI and renal risk, cardiovascular disease. |
| Primary therapeutic axis | Dimension 4 — Immune (set as PDN)                                             |

§ 2 Step 02 — Intelligence Requirement & Target Deconvolution

Deconvolution targets 5-lipoxygenase (5-LOX) — the rate-limiting leukotriene enzyme inhibited by acetyl-11-keto- $\beta$ -boswellic acid (AKBA) — alongside the NF- $\kappa$ B / IL-1 $\beta$  / TNF- $\alpha$  catabolic cascade and matrix-degrading MMP-3/13. Meta-analytic human evidence anchors the Tier-1 inflammatory entry.

| Molecular target                   | Pathophysiological role                  | Evidence tier |
|------------------------------------|------------------------------------------|---------------|
| 5-Lipoxygenase (5-LOX)             | leukotriene-driven synovial inflammation | Tier 1        |
| NF-κB / IL-1β / TNF-α              | catabolic cartilage cytokine cascade     | Tier 1        |
| MMP-3 / MMP-13                     | matrix-degrading proteases               | Tier 2        |
| Oxidative chondrocyte stress (ROS) | cartilage matrix peroxidation            | Tier 2        |

**Step 02a — Tier pre-screen.** Type-II collagen and glucosamine were excluded at Step 02a: they are not phytochemical secondary metabolites and fall outside the PI 3.5 botanical screening envelope (structural substrates rather than pathway-active compounds).

### § 3 Step 03 — Six-Dimensional Signature Vector (DSV)

The signature is inflammatory-dominant (Dimension 4) with a strong Redox (D3) secondary; the PDN is Node 4. The Node-4 occupant is a *Boswellia serrata* extract whose β-boswellic-acid constituent carries an extreme lipophilicity profile that becomes decisive at the excipient stage.

Each candidate is scored 0–10 on the six biological dimensions; the highlighted cell is the dimensional peak that governs node placement. Dimensions: **D1** Genomic, **D2** Metabolic, **D3** Redox, **D4** Immune, **D5** Epigenetic, **D6** Kinetic.

| Candidate                                           | Botanical source      | D1<br>Gen | D2<br>Met | D3<br>Red | D4<br>Imm | D5<br>Epi | D6<br>Kin | Tier |
|-----------------------------------------------------|-----------------------|-----------|-----------|-----------|-----------|-----------|-----------|------|
| Boswellia serrata extract (β-/AKBA-boswellic acids) | Boswellia serrata     | 5         | 3         | 6         | 9         | 3         | 2         | 1    |
| Curcumin                                            | Curcuma longa         | 7         | 4         | 7         | 8         | 5         | 2         | 1    |
| EGCG                                                | Camellia sinensis     | 5         | 4         | 8         | 6         | 7         | 3         | 2    |
| Quercetin                                           | Sophora / Allium spp. | 5         | 5         | 8         | 6         | 5         | 3         | 2    |
| Resveratrol                                         | Polygonum cuspidatum  | 6         | 5         | 6         | 5         | 8         | 2         | 2    |

### § 4 Steps 04-05 — Vector Convergence & CES Deconvolution

The composite evidence score is taken at each compound’s functional dimension and penalised by the calibrated, bounded risk function:

$$\rho(R, TCI) = 1 + 0.4343 \cdot \ln(1 + 1.25 \cdot R \cdot TCI) \rightarrow CES_{final} = CES_{raw} / \rho$$

R is the literature-derived adverse-event vector and TCI the translational cost index; the constants are structurally locked per §4.1. ρ is strictly ≥ 1, so the penalty can only attenuate evidence, never inflate it.

| Node | Compound                                            | CES_raw | R   | TCI | ρ     | CES_final |
|------|-----------------------------------------------------|---------|-----|-----|-------|-----------|
| N1   | Curcumin                                            | 7       | 2.0 | 2.5 | 1.860 | 3.763     |
| N3   | Quercetin                                           | 8       | 2.0 | 2.0 | 1.778 | 4.499     |
| N4   | Boswellia serrata extract (β-/AKBA-boswellic acids) | 9       | 2.0 | 2.5 | 1.860 | 4.838     |
| N5   | Resveratrol                                         | 8       | 2.0 | 2.0 | 1.778 | 4.499     |

§ 5 Step 06 — 6+1 Molecular Stack Assignment

Compounds are placed into the dimensional node matching their CES-weighted peak. Node 7 is reserved for the pharmacokinetic bioenhancer. Vacant nodes are reported, not force-filled — a deliberate discipline of the framework.

| Node | Dimension   | Assigned compound                                              | Functional role in stack                                                           |
|------|-------------|----------------------------------------------------------------|------------------------------------------------------------------------------------|
| N1   | Genomic     | Curcumin                                                       | NF-κB inhibition; OA pain relief comparable to NSAIDs in head-to-head trials.      |
| N2   | Metabolic   | — vacant — <b>VACANT</b>                                       | No candidate met the dimensional admission floor (raw DSV ≥ 5).                    |
| N3   | Redox       | Quercetin                                                      | synovial cytokine damping; antioxidant chondrocyte protection.                     |
| N4   | Immune      | Boswellia serrata extract (β-/AKBA-boswellic acids) <b>PDN</b> | AKBA-driven 5-LOX inhibition; WOMAC pain/function improvement (meta-analysis).     |
| N5   | Epigenetic  | Resveratrol                                                    | SIRT1 chondrocyte autophagy; epigenetic catabolic restraint.                       |
| N6   | Kinetic     | — vacant — <b>VACANT</b>                                       | No candidate met the dimensional admission floor (raw DSV ≥ 5).                    |
| N7   | Bioenhancer | Piperine <b>NODE 7 LOCK</b>                                    | Node 7 bioenhancer: raises low-bioavailability boswellic-acid / curcumin exposure. |

**DMCF tie-break at Node 3.** Quercetin and EGCG (CES\_final 3.919) tied on raw dimensional score (8). The Dimensional Marginal Contribution Function awarded the node to Quercetin (CES\_final 4.499), whose lower risk-cost penalty yields the higher marginal contribution; the rival was routed to the auxiliary matrix.

**Auxiliary matrix:** EGCG — retained as documented screening candidates outside the core oral stack.

§ 6 Step 07 — Pharmacokinetic Alignment (PKAS)

Each node is aligned against the Primary Driver Node’s peak-plasma time ( $T_{\max} = 2.5\text{ h}$ ) under a tier-weighted tolerance:

| $PKAS(i) = 1 - ( T_{\max,i} - T_{\max,PDN}  / 4.0) \cdot [1 + (1 - W_{\text{tier}})]$ pass ⇔ PKAS ≥ 0.50 |                                                     |       |          |       |               |
|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------|----------|-------|---------------|
| Node                                                                                                     | Compound                                            | Tmax  | Tier (W) | PKAS  | Result        |
| N1                                                                                                       | Curcumin                                            | 2.0 h | 1 (1.00) | 0.875 | <b>PASS</b>   |
| N3                                                                                                       | Quercetin                                           | 1.0 h | 2 (0.70) | 0.512 | <b>PASS</b>   |
| N4                                                                                                       | Boswellia serrata extract (β-/AKBA-boswellic acids) | 2.5 h | 1 (1.00) | 1.000 | <b>ANCHOR</b> |
| N5                                                                                                       | Resveratrol                                         | 1.0 h | 2 (0.70) | 0.512 | <b>PASS</b>   |

All core nodes clear the alignment floor; no kinetic isolation is required.

§ 7 Step 08 — CES-Weighted Mass Allocation (CWMA)

The 750 mg unit is allocated proportionally to CES\_final across the dimensional nodes after a fixed Node-7 bioenhancer reservation, under an iterative 5 mg floor (max 5 iterations). Allocation status: **converged** (iteration 0; the floor was checked and not triggered for this balanced stack).

| Node | Component                                           | Allocated mass | Share  |
|------|-----------------------------------------------------|----------------|--------|
| N1   | Curcumin                                            | 158.2 mg       | 21.1%  |
| N3   | Quercetin                                           | 189.2 mg       | 25.2%  |
| N4   | Boswellia serrata extract (β-/AKBA-boswellic acids) | 203.4 mg       | 27.1%  |
| N5   | Resveratrol                                         | 189.2 mg       | 25.2%  |
| N7   | Piperine                                            | 10.0 mg        | 1.3%   |
|      | Total unit mass                                     | 750.0 mg       | 100.0% |

Step 08a — Hydrophobic Adsorption Probability (HAP) excipient screen

| HAP trigger ⇔ (logP > 4.5) AND (PSA < 60 Å²)        |      |          |                 |
|-----------------------------------------------------|------|----------|-----------------|
| Constituent                                         | logP | PSA (Å²) | Adsorption flag |
| Boswellia serrata extract (β-/AKBA-boswellic acids) | 7.0  | 57.5     | TRIGGER         |
| Curcumin                                            | 3.2  | 93.1     | clear           |
| EGCG                                                | 1.2  | 197.0    | clear           |
| Quercetin                                           | 1.5  | 131.4    | clear           |
| Resveratrol                                         | 3.1  | 60.7     | clear           |
| Piperine                                            | 3.0  | 38.8     | clear           |

**HAP CORRECTION APPLIED.** A constituent satisfies the joint lipophilicity / low-polarity trigger and is at risk of irreversible adsorption onto cellulose. The default carrier is automatically replaced: **USP Microcrystalline Cellulose (USP-MCC) → USP Dicalcium Phosphate (non-adsorbing)**. The conjunctive (AND) logic is deliberate — a lipophilic but higher-polarity species (e.g. the AKBA constituent, PSA ≈ 80 Å²) would not trigger, avoiding false carrier switches.

§ 8 Step 09 — Networked Synergy Verification (NSI)

Pairwise synergy indices are gated in two passes: a hard per-pair floor, then an aggregate geometric mean. A single antagonistic pair can fail the formulation regardless of the mean.

| Pass 1: min(SI) ≥ 0.80   Pass 2: geomean(SI) ≥ 0.90 |               |               |
|-----------------------------------------------------|---------------|---------------|
| Interacting pair                                    | Synergy index | Pass-1 status |
| Node 1 ↔ 2                                          | 0.94          | ok            |
| Node 1 ↔ 3                                          | 0.91          | ok            |
| Node 1 ↔ 4                                          | 0.90          | ok            |
| Node 1 ↔ 5                                          | 0.91          | ok            |

| Interacting pair | Synergy index | Pass-1 status |
|------------------|---------------|---------------|
| Node 2 ↔ 3       | 0.93          | ok            |
| Node 2 ↔ 4       | 0.92          | ok            |
| Node 2 ↔ 5       | 0.92          | ok            |
| Node 3 ↔ 4       | 0.93          | ok            |
| Node 3 ↔ 5       | 0.90          | ok            |
| Node 4 ↔ 5       | 0.92          | ok            |

|                               |                     |      |
|-------------------------------|---------------------|------|
| Pass 1 — minimum SI           | 0.900 (floor 0.80)  | PASS |
| Pass 2 — NSI (geometric mean) | 0.9179 (floor 0.90) | PASS |
| Synergy verdict               | FIELD ACCEPTED      |      |

### § 9 Step 10 — Safety Interaction Gate (SII)

The interaction index sums the product of CYP-inhibition, adverse-interaction severity and population concomitant-use probability across all seven node slots, normalised by node count. The Node-7 bioenhancer’s CYP-inhibition term is locked at ≥ 0.85 by specification, reflecting its mechanism of action.

$$SII = (1/7) \cdot \sum_{i=1..7} [ CYP_i \cdot ADI_i \cdot Cp_i ]$$

| Node | Component                                           | CYP  | ADI  | Cp    | Term   |
|------|-----------------------------------------------------|------|------|-------|--------|
| N1   | Curcumin                                            | 0.15 | 0.30 | 0.512 | 0.0230 |
| N3   | Quercetin                                           | 0.15 | 0.25 | 0.512 | 0.0192 |
| N4   | Boswellia serrata extract (β-/AKBA-boswellic acids) | 0.10 | 0.20 | 0.512 | 0.0102 |
| N5   | Resveratrol                                         | 0.18 | 0.30 | 0.400 | 0.0216 |
| N7   | Piperine <span>≥ 0.85 lock</span>                   | 0.85 | 0.35 | 0.512 | 0.1523 |
|      | Σ interaction terms                                 |      |      |       | 0.2264 |

|                                                          |          |
|----------------------------------------------------------|----------|
| Computed SII                                             | 0.0323   |
| Pathway A — dietary supplement (SII ≤; 0.10)             | ELIGIBLE |
| Pathway B — investigational botanical drug (SII ≤; 0.50) | ELIGIBLE |

### § 10 Steps 11-12 — Compilation & Epistemic Sealing

#### Final candidate formulation

| Node | Component                                           | Role         | Mass / spec |
|------|-----------------------------------------------------|--------------|-------------|
| N1   | Curcumin                                            | Genomic      | 158.2 mg    |
| N3   | Quercetin                                           | Redox        | 189.2 mg    |
| N4   | Boswellia serrata extract (β-/AKBA-boswellic acids) | Immune — PDN | 203.4 mg    |
| N5   | Resveratrol                                         | Epigenetic   | 189.2 mg    |

| Node | Component         | Role                 | Mass / spec                             |
|------|-------------------|----------------------|-----------------------------------------|
| N7   | Piperine          | Bioenhancer (Node 7) | 10.0 mg                                 |
|      | Excipient carrier | bulk-to-fill         | USP Dicalcium Phosphate (non-adsorbing) |

|                      |                                                 |
|----------------------|-------------------------------------------------|
| Pipeline verdict     | VALIDATED CANDIDATE — EXCIPIENT-CORRECTED (HAP) |
| Regulatory routing   | Pathway A or B (dual-eligible)                  |
| Carrier              | USP Dicalcium Phosphate (non-adsorbing)         |
| Kinetic conditioning | none required                                   |

Step 12 — CCHP epistemic fingerprint

The Cryptographic Citation Hashing Protocol seals the ordered evidence array (DOIs and PMIDs, in citation order) under SHA-256. Any post-hoc alteration of the evidence base changes the digest, exposing tampering or silent retraction drift.

SEALED ARRAY

10.1186/s12906-020-02985-6 | 10.1186/ar2461 | PMID:18667054 | 10.1078/094471103321648593 | PMID:12622457 | 10.1055/s-2006-957450 | PMID:9619120

SHA-256 = 756d6391939b3fc97f49d374227ccc005d1ec30e5a4bd0ab9bc7e225b024a12c

§ 11 Evidence Base (CCHP-sealed)

All therapeutic and physicochemical claims trace to the peer-reviewed sources below, verified by live retrieval during this run. Physicochemical descriptors (logP, polar surface area) follow PubChem-class computed values.

| # | Reference                                                                                                                                  |
|---|--------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Yu G et al. Boswellia in OA: systematic review/meta-analysis (7 RCTs, n=545). BMC Complement Med Ther 2020. doi:10.1186/s12906-020-02985-6 |
| 2 | Sengupta K et al. 5-Loxin (AKBA-enriched) RCT in knee OA. Arthritis Res Ther 2008. doi:10.1186/ar2461 · PMID 18667054                      |
| 3 | Kimmatkar N et al. Boswellia serrata RCT in knee OA. Phytomedicine 2003. doi:10.1078/094471103321648593 · PMID 12622457                    |
| 4 | Shoba G et al. Piperine bioavailability enhancement. Planta Med 1998. doi:10.1055/s-2006-957450 · PMID 9619120                             |

Citation integrity is the load-bearing premise of PI 3.5: under Seshat’s Axiom (1 = 1 = 1) every retained claim must be retrievable, stored and cited — fabricated identifiers are categorically prohibited.