

Type 2 Diabetes Mellitus

Candidate Formulation Hypothesis · Blueprint B2.3 · ICD-10 E11

Document class	Official demonstration example — full 12-stage pipeline trace
Framework	PhytoIntelligence v3.5.0 reference engine
Primary Driver Node	Node 2 (Metabolic)
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
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CONDITIONAL CANDIDATE — PATHWAY B (INVESTIGATIONAL BOTANICAL DRUG)

The synergy field and excipient screen pass, but two outcomes constrain deployment. First, the pharmacokinetic gate fails on Nodes 3 and 5 (early-peaking flavonoids misaligned against the late metabolic anchor), triggering a mandatory enteric-isolation / split-dosing directive. Second, the Safety Interaction Index of 0.1046 exceeds the 0.10 dietary-supplement ceiling — driven by the metabolic anchor's documented drug-interaction burden in a polypharmacy population — so the candidate qualifies only under Pathway B as an investigational botanical drug, not as a supplement.

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 ρ .
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

Type 2 diabetes mellitus is a chronic metabolic disorder defined by insulin resistance and progressive β -cell insufficiency, producing sustained hyperglycaemia. It was selected as the metabolic-dominant contrast case: the dominant therapeutic axis is energy-sensing and hepatic glucose handling rather than immune signalling.

Pathology	Type 2 Diabetes Mellitus (blueprint B2.3, ICD-10 E11)
Clinical endpoints	HbA1c, fasting plasma glucose, HOMA-IR, fasting lipid panel.
Comorbidity field	dyslipidaemia, hypertension, NAFLD, diabetic nephropathy; heavy polypharmacy.
Primary therapeutic axis	Dimension 2 — Metabolic (set as PDN)

§ 2 Step 02 — Intelligence Requirement & Target Deconvolution

Deconvolution centres on AMP-activated protein kinase (AMPK) — activated downstream of mitochondrial Complex-I inhibition — as the master metabolic switch, together with suppression of hepatic

gluconeogenesis and enhancement of PI3K/AKT/GLUT4 insulin signalling. Head-to-head human evidence against metformin anchors the Tier-1 metabolic entry.

Molecular target	Pathophysiological role	Evidence tier
AMPK (via Complex-I inhibition)	master metabolic energy switch	Tier 1
Hepatic gluconeogenesis / glycolysis	fasting glucose output	Tier 1
Insulin signalling (PI3K/AKT, GLUT4)	peripheral glucose uptake	Tier 2
Chronic low-grade inflammation (TNF-α, IL-6)	insulin resistance driver	Tier 2

Step 02a — Tier pre-screen. Gymnema sylvestre (gymnemic acids) and bitter-melon charantin cleared Tier-2 screening but were held in the auxiliary matrix: their dominant action (intestinal sugar-uptake blockade) duplicates the Node 2 metabolic axis without an orthogonal dimensional contribution, lowering marginal DMCF value.

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

The signature peaks sharply on Dimension 2 (Metabolic); the PDN is therefore Node 2, whose occupant carries a comparatively late absorption profile. This late anchor is the proximate cause of the pharmacokinetic flags raised downstream.

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 Gen	D2 Met	D3 Red	D4 Imm	D5 Epi	D6 Kin	Tier
Berberine	Coptis / Berberis spp.	6	9	5	5	4	2	1
Curcumin	Curcuma longa	7	6	7	6	5	2	1
Quercetin	Sophora / Allium spp.	5	6	8	6	5	3	2
Cinnamaldehyde	Cinnamomum spp.	5	7	5	6	3	4	2
Resveratrol	Polygonum cuspidatum	6	6	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
N2	Berberine	9	3.5	2.0	1.989	4.525
N3	Quercetin	8	2.0	2.0	1.778	4.499
N4	Cinnamaldehyde	6	3.0	1.5	1.821	3.295

Node	Compound	CES_raw	R	TCI	ρ	CES_final
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	insulin sensitisation; T2DM-incidence reduction in prediabetes RCT.
N2	Metabolic	Berberine PDN	AMPK activation; HbA1c reduction comparable to metformin (head-to-head RCT).
N3	Redox	Quercetin	redox / endothelial protection; aldose-reductase damping.
N4	Immune	Cinnamaldehyde	insulin-mimetic signalling; immune/inflammatory damping (cassia coumarin caveat).
N5	Epigenetic	Resveratrol	SIRT1 / AMPK epigenetic metabolic reprogramming (antiplatelet caveat).
N6	Kinetic	— vacant — VACANT	No candidate met the dimensional admission floor (raw DSV ≥ 5).
N7	Bioenhancer	Piperine NODE 7 LOCK	Node 7 bioenhancer: P-gp / UGT inhibition raising berberine + curcumin exposure.

§ 6 Step 07 — Pharmacokinetic Alignment (PKAS)

Each node is aligned against the Primary Driver Node’s peak-plasma time ($T_{\max} = 3.0\text{ h}$) under a tier-weighted tolerance:

PKAS(i) = 1 - (|T_{max,i} - T_{max,PDN}| / 4.0) · [1 + (1 - W_{tier})] pass ⇔ PKAS ≥ 0.50

Node	Compound	Tmax	Tier (W)	PKAS	Result
N1	Curcumin	2.0 h	1 (1.00)	0.750	PASS
N2	Berberine	3.0 h	1 (1.00)	1.000	ANCHOR
N3	Quercetin	1.0 h	2 (0.70)	0.350	FAIL — flag
N4	Cinnamaldehyde	1.5 h	2 (0.70)	0.512	PASS
N5	Resveratrol	1.0 h	2 (0.70)	0.350	FAIL — flag

PKAS DIRECTIVE. Node 3 (Quercetin), Node 5 (Resveratrol) fall below the 0.50 alignment floor: their early absorption is misaligned with the late primary-driver anchor. The framework does not discard them — it mandates **enteric isolation / temporal split dosing** (independent release compartment) so each agent reaches its own effective window. This conditions the formulation toward the investigational pathway.

§ 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	135.3 mg	18.0%
N2	Berberine	162.7 mg	21.7%
N3	Quercetin	161.8 mg	21.6%
N4	Cinnamaldehyde	118.5 mg	15.8%
N5	Resveratrol	161.8 mg	21.6%
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
Berberine	3.6	40.8	clear
Curcumin	3.2	93.1	clear
Quercetin	1.5	131.4	clear
Cinnamaldehyde	1.9	17.1	clear
Resveratrol	3.1	60.7	clear
Piperine	3.0	38.8	clear

Carrier retained: USP Microcrystalline Cellulose (USP-MCC). No constituent satisfies the joint adsorption trigger.

§ 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	0.93	ok
Node 1 ↔ 3	0.92	ok
Node 1 ↔ 4	0.91	ok
Node 1 ↔ 5	0.93	ok
Node 2 ↔ 3	0.93	ok

Interacting pair	Synergy index	Pass-1 status
Node 2 ↔ 4	0.81	floor watch
Node 2 ↔ 5	0.93	ok
Node 3 ↔ 4	0.93	ok
Node 3 ↔ 5	0.92	ok
Node 4 ↔ 5	0.93	ok

Pass 1 — minimum SI	0.810 (floor 0.80)	PASS
Pass 2 — NSI (geometric mean)	0.9133 (floor 0.90)	PASS
Synergy verdict	FIELD ACCEPTED	

The lowest-scoring pair clears the hard floor but is recorded for stability monitoring; it does not, by itself, reduce the aggregate below the 0.90 line.

§ 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	0.400	0.0180
N2	Berberine	0.55	0.60	0.800	0.2640
N3	Quercetin	0.15	0.35	0.512	0.0269
N4	Cinnamaldehyde	0.15	0.35	0.550	0.0289
N5	Resveratrol	0.20	0.40	0.550	0.0440
N7	Piperine ≥ 0.85 lock	0.85	0.55	0.750	0.3506
	Σ interaction terms				0.7324

Computed SII	0.1046
Pathway A — dietary supplement (SII ≤; 0.10)	NOT ELIGIBLE
Pathway B — investigational botanical drug (SII ≤; 0.50)	ELIGIBLE

PATHWAY BIFURCATION. The index clears the investigational ceiling but exceeds the supplement ceiling. Per §6.2 the candidate is routed exclusively to **Pathway B** — development as an investigational botanical drug under clinical-trial governance — and is **not** eligible for unsupervised dietary-supplement distribution.

§ 10 Steps 11-12 — Compilation & Epistemic Sealing

Final candidate formulation

Node	Component	Role	Mass / spec
N1	Curcumin	Genomic	135.3 mg
N2	Berberine	Metabolic — PDN	162.7 mg
N3	Quercetin	Redox	161.8 mg
N4	Cinnamaldehyde	Immune	118.5 mg
N5	Resveratrol	Epigenetic	161.8 mg
N7	Piperine	Bioenhancer (Node 7)	10.0 mg
	Excipient carrier	bulk-to-fill	USP Microcrystalline Cellulose (USP-MCC)

Pipeline verdict	CONDITIONAL CANDIDATE — PATHWAY B (INVESTIGATIONAL BOTANICAL DRUG)
Regulatory routing	Pathway B only — investigational botanical drug
Carrier	USP Microcrystalline Cellulose (USP-MCC)
Kinetic conditioning	enteric isolation of flagged nodes 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

10.1016/j.metabol.2008.01.013 | PMID:18442638 | 10.2337/db07-1552 | PMID:18285556 | 10.2337/dc12-0116 | PMID:22773702 | 10.1055/s-2006-957450 | PMID:9619120

SHA-256 = a014aa38ccc50c0945f1a88b750ffdc1e4c6104ac1d121bcae38b136725db1d1

§ 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	Yin J et al. Berberine vs metformin in T2DM (HbA1c 9.5->7.5%). Metabolism 2008. doi:10.1016/j.metabol.2008.01.013 · PMID 18442638
2	Turner N et al. Berberine inhibits Complex I -> AMPK activation. Diabetes 2008. doi:10.2337/db07-1552 · PMID 18285556
3	Chuengsamarn S et al. Curcumin prevents T2DM in prediabetes (9-mo RCT). Diabetes Care 2012. doi:10.2337/dc12-0116 · PMID 22773702
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.