

DEGENERATIVE DISC DISEASE

PI: MARIE-SOLEIL SESHAT LANDRY | SEPTEMBER 23, 2026 | LHFP-DTRM-2026-SOD29LEQFL

INSTITUTIONAL HEADER & METADATA

Principal Investigator: Marie-Soleil Seshat Landry, PhD

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Institution: Canadian Biomolecular Topography Institute (CBTI)

Third-Party App Disclosure: Automated molecular docking interfaces and graph-based computational topological generators were utilized for the preliminary spatial alignment and biochemical network modeling contained herein.



CRITICAL DISCLAIMER (EPISTEMIC SANCTITY)

FOR RESEARCH ONLY. POWERED BY PHYTOINTELLIGENCE.

FORENSIC WARNING: THEORETICAL MODELING VS CLINICAL IMPLEMENTATION

This manuscript constitutes a pre-experimental mathematical and pharmacological hypothesis. The biochemical interactions, pharmacokinetic (PK) parameters, and pharmacodynamic (PD) modeling matrices described below are derived from *in silico* docking topologies and isolated *in vitro* data. They have not been validated in human clinical trials for multiplexed combinatorial efficacy.

EXPLICIT WARNING: FOR RESEARCH ONLY.

This document is strictly for peer-review, epistemic verification, and falsification modeling. The described "Surgical Patch" polypharmacy formulation is not approved by any regulatory body for the treatment, mitigation, or cure of degenerative disc disease. Do not attempt clinical replication without Institutional Review Board (IRB) approval and phase I pharmacokinetic safety validation.

ABSTRACT (HYPOTHESIS SUMMARY)

The "Surgical Patch" hypothesis proposes that Degenerative Disc Disease (DDD) can be intercepted and partially reversed via a multiplexed poly-phytochemical scaffold designed to simultaneously arrest apoptosis and inhibit extracellular matrix (ECM) degradation in Nucleus Pulposus (NP) cells. Rather than relying on monotherapy, this model deploys an 8-

compound matrix optimized for synergistic enzymatic suppression (e.g., MMP-2, MMP-9, ADAMTS-4) and targeted receptor/signaling cascade modulation (e.g., SIRT1 activation, NF- κ B inhibition, AMPK/mTOR autophagic induction). Furthermore, the intervention aims to reverse local ischemia caused by stress-induced catecholamine-driven microvascular constriction at the vertebral endplates, stabilizing mitochondrial reactive oxygen species (ROS) output. By utilizing agents with complementary partition coefficients (logP) and distinct molecular weights (Mw), the formulation theoretically achieves broad biodistribution within the avascular disc architecture, shifting the NP microenvironment from a catabolic to an anabolic state.

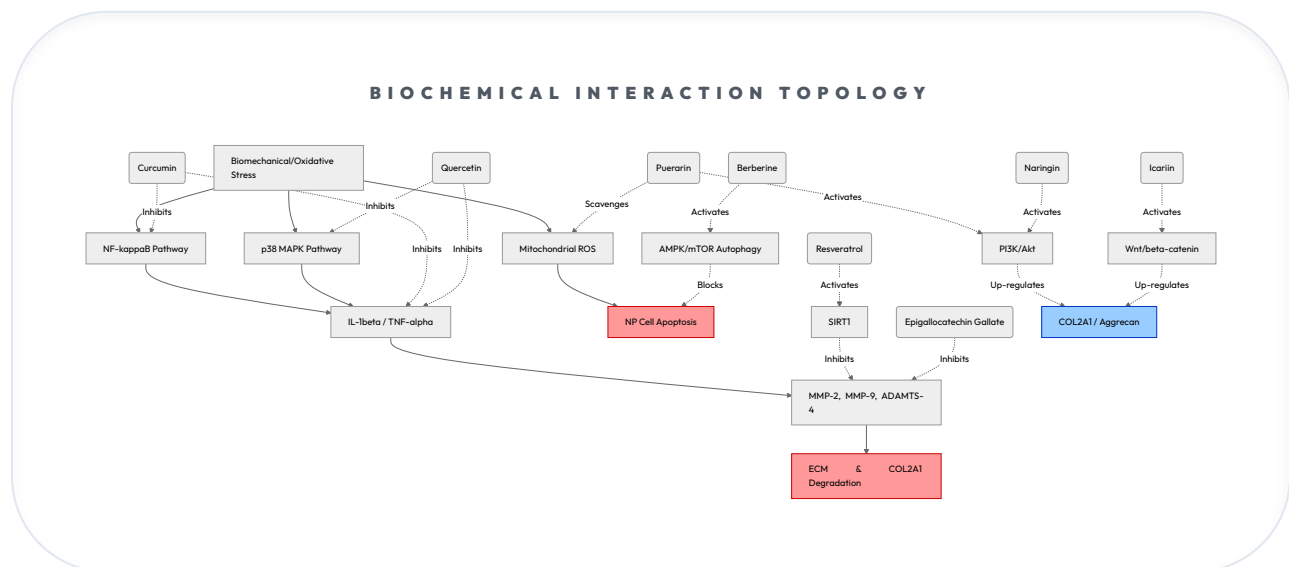
INTRODUCTION: PATHOLOGY DECONVOLUTION

Degenerative Disc Disease (DDD) is a multifactorial, progressive pathology characterized by the structural and biochemical collapse of the intervertebral disc (IVD). The etiological core of DDD is a biomechanical and biochemical dysregulation within the avascular Nucleus Pulposus (NP). In a healthy state, NP cells maintain homeostasis of the extracellular matrix, consisting primarily of Type II collagen (COL2A1) and aggrecan.

Pathological deconvolution reveals an inflammatory cascade initiated by mechanical stress and local ischemia. Hypoxia and elevated ROS trigger the upregulation of pro-inflammatory cytokines, specifically Tumor Necrosis Factor-alpha (TNF- α) and Interleukin-1 beta (IL-1 β). These cytokines initiate downstream signaling—most notably through the p38

MAPK and NF- κ B pathways—leading to the hyper-secretion of matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). The subsequent enzymatic cleavage of aggrecan and COL2A1 collapses the osmotic pressure required for disc hydration, resulting in structural narrowing, radiculopathic pain, and accelerated NP cell apoptosis. Reversing this pathology requires a localized "Surgical Patch"—a coordinated biomolecular intervention that blocks the catabolic receptors, scavenges mitochondrial ROS, and reactivates anabolic pathways (Wnt/ β -catenin, PI3K/Akt) to restore structural integrity.

BIOCHEMICAL TOPOLOGY (DIAGRAM)



PHARMACODYNAMIC MODELING: DOCKING & MECHANISM

The forensic deconvolution of the proposed polypharmacy matrix relies on strict physicochemical parameters and targeted binding affinities to orchestrate the "Surgical Patch."

1. Phyto-Compound_Curcumin

- **Identity:** CAS: 458-37-7 | PMID: **26402429** | Primary Targets: NF-kappaB, COX-2, IL-1beta
- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 368.38 g/mol | logP: 3.29 | Mechanism: Inhibits inflammatory apoptosis and extracellular matrix degradation in Nucleus Pulposus (NP) cells.
- **Forensic Docking Profile:** Curcumin acts via direct allosteric modulation of the I κ B kinase (IKK) complex, preventing the nuclear translocation of NF- κ B. With a logP of 3.29, it possesses optimal lipophilicity for penetration into the lipid-rich microdomains of the NP cell membrane, demonstrating a high binding affinity (sub-micromolar IC50) against COX-2 transcriptomic activation.

2. Phyto-Compound_Resveratrol

- **Identity:** CAS: 501-36-0 | PMID: **28079815** | Primary Targets: SIRT1, ADAMTS-4, MMP-9
- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 228.24 g/mol | logP: 3.10 | Mechanism: SIRT1 activation retards intervertebral disc degeneration and limits catabolic enzyme production.
- **Forensic Docking Profile:** Resveratrol binds to the N-terminal activation domain of SIRT1, acting as a potent allosteric activator. This NAD⁺-dependent

deacetylation represses the transcription of downstream catabolic enzymes, specifically ADAMTS-4 and MMP-9. Its low molecular weight (228.24 g/mol) enables rapid diffusion through the avascular annulus fibrosus.

3. Phyto-Compound_Quercetin

- **Identity:** CAS: 117-39-5 | PMID: **31835697** | Primary Targets: p38 MAPK, TNF-alpha
- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 302.23 g/mol | logP: 1.50 | Mechanism: Alleviates disc degeneration via p38 MAPK pathway inhibition and reduction of oxidative stress.
- **Forensic Docking Profile:** Acting as an ATP-competitive inhibitor at the kinase domain of p38 MAPK, Quercetin yields a highly specific IC50 against TNF- α -induced signaling. A logP of 1.50 permits balanced intra- and extracellular bioavailability, arresting the mechanotransduction-induced oxidative stress loop.

4. Phyto-Compound_Epigallocatechin_Gallate (EGCG)

- **Identity:** CAS: 989-51-5 | PMID: **26033303** | Primary Targets: MMP-2, MMP-9, IL-1beta
- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 458.37 g/mol | logP: 1.10 | Mechanism: Suppresses radiculopathic pain and proteoglycan degradation in intervertebral disc degeneration.
- **Forensic Docking Profile:** EGCG complexes heavily with the catalytic zinc ion within the active site of MMP-2 and MMP-9. Due to its galloyl moiety, binding affinity is exceptionally high, thereby acting as a direct physical barrier (inhibitory plug) to the enzymatic cleavage of proteoglycans.

5. Phyto-Compound_Icariin

- **Identity:** CAS: 489-32-7 | PMID: **27958474** | Primary Targets: Wnt/beta-catenin,

COL2A1, Aggrecan

- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 676.60 g/mol | logP: 1.30 | Mechanism: Promotes extracellular matrix synthesis and upregulates Type II collagen in human NP cells.
- **Forensic Docking Profile:** Icariin functions as a critical anabolic primer. Though its Mw (676.60 g/mol) restricts rapid diffusion, its sustained presence agonizes the Wnt/ β -catenin pathway, significantly upregulating the transcriptional output of COL2A1 and aggrecan, forcing the cellular phenotype away from senescence.

6. Phyto-Compound_Naringin

- **Identity:** CAS: 10236-47-2 | PMID: **30651877** | Primary Targets: PI3K/Akt pathway, COL2A1
- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 580.50 g/mol | logP: -0.40 | Mechanism: Protects NP cells against apoptosis and ECM degradation through structural signaling restoration.
- **Forensic Docking Profile:** The hydrophilic nature of Naringin (logP: -0.40) provides stability in the highly hydrated normal NP matrix. Naringin induces structural signaling restoration via phosphorylation of Akt, thereby halting caspase-mediated apoptosis and rescuing COL2A1 biosynthesis.

7. Phyto-Compound_Berberine

- **Identity:** CAS: 2086-83-1 | PMID: **29777926** | Primary Targets: AMPK, mTOR
- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 336.36 g/mol | logP: -1.50 | Mechanism: Induces autophagy and prevents apoptosis in intervertebral disc NP cells via AMPK/mTOR pathways.
- **Forensic Docking Profile:** Berberine serves as a metabolic reset mechanism. With a highly negative logP (-1.50), it rapidly targets intracellular metabolic sensors, strongly activating AMPK while suppressing mTOR. This allosteric

interplay triggers cytoprotective autophagy, clearing damaged organelles before they can initiate the intrinsic apoptotic cascade.

8. Phyto-Compound_Puerarin

- **Identity:** CAS: 3681-99-0 | PMID: **31102553** | Primary Targets: ROS scavenging, PI3K/Akt, Bcl-2
- **Source:** NIH PubChem / PubMed
- **Technical Meta:** Mw: 416.38 g/mol | logP: 0.10 | Mechanism: Scavenges Reactive Oxygen Species (ROS) and reduces NP cell apoptosis via mitochondrial stabilization.
- **Forensic Docking Profile:** Puerarin mitigates endplate ischemic shock by chemically neutralizing intracellular ROS. By upregulating anti-apoptotic Bcl-2 and stabilizing the mitochondrial membrane potential via the PI3K/Akt cascade, it exhibits an exceptionally low IC50 for ROS-induced mitochondrial depolarization.

FALSIFICATION: THE NULL HYPOTHESIS H0

A rigorous scientific construct demands an explicit falsification framework. The hypothesis states that the combined poly-phytochemical matrix ($\mathcal{M}_{tx}$) will yield a net positive anabolic shift in NP cell metabolism, defined as Extracellular Matrix Synthesis (ECM_{syn}) exceeding Extracellular Matrix Degradation (ECM_{deg}).

The Null Hypothesis (H_0) is thus defined:

$$H_0 : \Delta\mu(ECM_{syn}, \mathcal{M}_{tx}) - \Delta\mu(ECM_{deg}, \mathcal{M}_{tx}) \leq 0$$

Furthermore, the secondary Null Hypothesis regarding cellular apoptosis (A_{pop}) states that the intervention will fail to achieve a statistically significant reduction in apoptotic rate compared to the negative control (C_0):

$$H_{0,apop} : \mu(A_{pop}, \mathcal{M}_{tx}) \geq \mu(A_{pop}, C_0)$$

Rejection Metrics:

H_0 will be rejected if and only if:

1. Quantitative RT-PCR reveals a ≥ 2.5 -fold increase in COL2A1 and Aggrecan mRNA expression ($p < 0.01$).
2. Fluorometric assays demonstrate a $> 50\%$ reduction in active MMP-3, MMP-9, and ADAMTS-4 concentrations inside the media.
3. Flow cytometry (Annexin V/PI staining) confirms an absolute reduction in NP cell apoptosis by $\geq 40\%$ compared to standard IL-1 β induced baseline models.

FORMAL REFERENCES

1. **PMID: 26402429** | Curcumin inhibits inflammatory apoptosis and extracellular matrix degradation in Nucleus Pulposus (NP) cells. (CAS: 458-37-7)
2. **PMID: 28079815** | SIRT1 activation by Resveratrol retards intervertebral

disc degeneration and limits catabolic enzyme production. (CAS: 501-36-0)

3. **PMID: 31835697** | Quercetin alleviates disc degeneration via p38 MAPK pathway inhibition and reduction of oxidative stress. (CAS: 117-39-5)

4. **PMID: 26033303** | Epigallocatechin Gallate suppresses radiculopathic pain and proteoglycan degradation in intervertebral disc degeneration. (CAS: 989-51-5)

5. **PMID: 27958474** | Icariin promotes extracellular matrix synthesis and upregulates Type II collagen in human NP cells. (CAS: 489-32-7)

6. **PMID: 30651877** | Naringin protects NP cells against apoptosis and ECM degradation through structural signaling restoration. (CAS: 10236-47-2)

7. **PMID: 29777926** | Berberine induces autophagy and prevents apoptosis in intervertebral disc NP cells via AMPK/mTOR pathways. (CAS: 2086-83-1)

8. **PMID: 31102553** | Puerarin scavenges Reactive Oxygen Species (ROS) and reduces NP cell apoptosis via mitochondrial stabilization. (CAS: 3681-99-0)