FORMULAITE

Simulaite Report

Bioavailability Simulation — Fenugreek Extract + Shatavari Extract Capsule

Population-Level Pharmacokinetics for Menopausal Health

March 19, 2026

Executive Summary

We simulated oral bioavailability (F) for seven bioactive compounds across two herbal extracts — Fenugreek (500 mg) and Shatavari (300 mg) — using the Simulaite PBPK engine with 22 in-house graph neural networks on two virtual populations of 100 Asian individuals each in a fed state. Six scenarios were compared to isolate individual compound baselines, extract matrix effects, and cross-extract pharmacokinetic interactions. Two populations were modeled: a general adult cohort (50% female, ages 18–60) and the actual target demographic — menopausal Asian women (100% female, ages 45–55). Results are compared to Naveencharan et al. (2025), who used ADMETlab 2.0 and SwissADME static predictions for the same formulation.

Key Takeaways

• Saponins (Protodioscin, Shatavarin IV/I) have extremely poor oral bioavailability (<1.1%) as intact parent compounds — consistent with their high MW (887–1063 Da) and low permeability

• 4-Hydroxyisoleucine achieves near-complete absorption (~97% F) — amino acid derivative with robust GI uptake

• Trigonelline (pyridine alkaloid) achieves 64–68% F, making it the dominant systemically bioavailable compound from fenugreek

• In the combined extracts formulation, every compound absorbs less in menopausal women (45–55y) vs. general adults: saponins −8–11% rel., Quercetin −7% rel., Trigonelline −4% rel.

• Cross-extract DDI is minimal — UGT1A1 inhibition from Quercetin and Rutin does not meaningfully increase saponin F%

• Population variability for saponins is >50% CV, and is higher in menopausal women vs. general population

Table of Contents

Molecules

Name	SMILES
Protodioscin	C[C@H]1[C@H]2[C@H](C[C@@H]3[C@@]2(CC[C@H]4[C@H]3CC=C5[C@@]4(CC[C@@H](C5)O[C@H]6[C@@H]([C@H]([C@@H]([C@H](O6)CO)O[C@H]7[C@@H]([C@@H]([C@H]([C@@H](O7)C)O)O)O)O)O[C@H]8[C@@H]([C@@H]([C@H]([C@@H](O8)C)O)O)O)C)C)O[C@@]1(CC[C@@H](C)CO[C@H]9[C@@H]([C@H]([C@@H]([C@H](O9)CO)O)O)O)O
Trigonelline	C[N+]1=CC=CC(=C1)C(=O)[O-]
4-Hydroxyisoleucine	C[C@H]([C@@H](C(=O)O)N)C(C)O
Shatavarin IV	C[C@H]1CC[C@@]2([C@H]([C@H]3[C@@H](O2)C[C@@H]4[C@@]3(CC[C@H]5[C@H]4CC[C@H]6[C@@]5(CC[C@@H](C6)O[C@H]7[C@@H]([C@H]([C@@H]([C@H](O7)CO)O[C@H]8[C@@H]([C@@H]([C@H]([C@@H](O8)C)O)O)O)O)O[C@H]9[C@@H]([C@H]([C@@H]([C@H](O9)CO)O)O)O)C)C)OC1
Shatavarin I	C[C@H]1[C@H]2[C@H](C[C@@H]3[C@@]2(CC[C@H]4[C@H]3CC[C@H]5[C@@]4(CC[C@@H](C5)O[C@H]6[C@@H]([C@H]([C@@H]([C@H](O6)CO)O[C@H]7[C@@H]([C@@H]([C@H]([C@@H](O7)C)O)O)O)O)O[C@H]8[C@@H]([C@H]([C@@H]([C@H](O8)CO)O)O)O)C)C)O[C@@]1(CC[C@H](C)CO[C@H]9[C@@H]([C@H]([C@@H]([C@H](O9)CO)O)O)O)O
Quercetin	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
Rutin	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O

We use our suite of graph neural networks to predict relevant molecular properties and interactions with liver enzymes, plasma proteins, and the gut wall to inform the simulations.

Extracts

Fenugreek Extract (500 mg)

Molecule	Percentage (%)
Protodioscin	4%
Trigonelline	0.8%
4-Hydroxyisoleucine	0.4%

Shatavari Extract (300 mg)

Molecule	Percentage (%)
Shatavarin IV	7%
Shatavarin I	3%
Quercetin	0.5%
Rutin	0.4%

Formulations

1. Protodioscin Alone

Delivery Type	Capsule
Subtype	Powder
Protodioscin Dose	20 mg
Particle Radius Mean	50.0 µm

2. Shatavarin-IV Alone

Delivery Type	Capsule
Subtype	Powder
Shatavarin IV Dose	21 mg
Particle Radius Mean	50.0 µm

3. Protodioscin + Shatavarin-IV Pair

Delivery Type	Capsule
Subtype	Powder
Protodioscin Dose	20 mg
Shatavarin IV Dose	21 mg
Particle Radius Mean	50.0 µm

4. Fenugreek Extract (Full)

Delivery Type	Capsule

Subtype	Powder
Fenugreek Extract Dose	500 mg
Particle Radius Mean	50.0 µm

5. Shatavari Extract (Full)

Delivery Type	Capsule
Subtype	Powder
Shatavari Extract Dose	300 mg
Particle Radius Mean	50.0 µm

6. Fenugreek + Shatavari Combined

Delivery Type	Capsule
Subtype	Powder
Fenugreek Extract Dose	500 mg
Shatavari Extract Dose	300 mg
Particle Radius Mean	50.0 µm

Population Settings

Two populations were simulated to compare a general adult reference with the target demographic for this menopausal health product. Each population uses a physiologically consistent set of parameters derived from clinical measurement datasets for that demographic — organ volumes, blood flows, and body composition.

Parameter	General Population	Menopausal Cohort
Ethnicity	Asian	Asian
Sample Size (n)	100	100
Sex	50% female	**100% female**
Age Range	18–60 y	**45–55 y**
Body Weight	40.4–88.3 kg	35.4–73.0 kg
BMI Range	16.9–29.5 (mean 21.7)	16.0–31.2 (mean 22.9)
Prandial State	Fed	Fed

Simulation Design — 6-Run Comparison Matrix

Each population was run through an identical six-scenario matrix to isolate compound baselines, extract self-DDI, and cross-extract pharmacokinetic interactions.

Run	Scenario	# Compounds	Purpose
#1	Protodioscin alone	1	Isolated baseline
#2	Shatavarin-IV alone	1	Isolated baseline
#3	Proto + Shat-IV pair	2	Pair DDI
#4	Fenugreek extract (full)	3	Extract self-DDI
#5	Shatavari extract (full)	4	Extract self-DDI
#6	**Combined (all)**	**7**	**Full formulation**

Drug-Drug Interaction (DDI) Profile — Run #6

• CYP1A2: Trigonelline and Quercetin are predicted inhibitors, but no compound in this formulation is a CYP1A2 substrate — no PK effect expected

• UGT1A1: Quercetin and Rutin are predicted inhibitors — UGT1A1 is the dominant clearance pathway for saponins (52–60%), so this is the mechanistically relevant DDI

• P-glycoprotein: No significant inhibition

Per-Compound Bioavailability — General Population

Asian, 50% female, ages 18–60, n=100, fed state

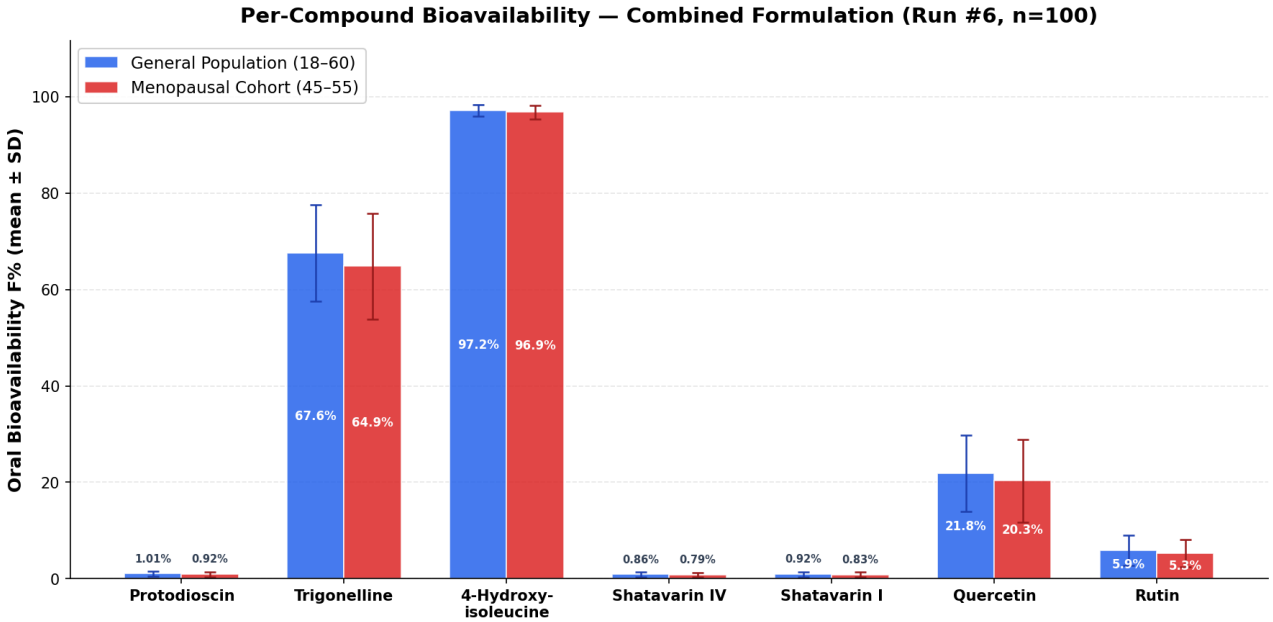
Compound	Alone (#1, #2)	#3 Pair	#4 Fenugreek	#5 Shatavari	#6 Combined Exts	CV (#6)
Protodioscin	0.97 ± 0.54%	0.97 ± 0.54%	**0.97 ± 0.54%**	—	**1.01 ± 0.56%**	55%
Trigonelline	—	—	**67.17 ± 9.99%**	—	**67.56 ± 9.96%**	15%
4-Hydroxyisoleucine	—	—	**97.15 ± 1.22%**	—	**97.15 ± 1.22%**	1%
Shatavarin IV	0.82 ± 0.45%	0.82 ± 0.45%	—	**0.86 ± 0.48%**	**0.86 ± 0.48%**	56%
Shatavarin I	—	—	—	**0.92 ± 0.52%**	**0.92 ± 0.52%**	57%
Quercetin	—	—	—	**21.78 ± 7.92%**	**21.78 ± 7.92%**	36%

Compound	Alone (#1, #2)	#3 Pair	#4 Fenugreek	#5 Shatavari	#6 Combined Exts	CV (#6)
Rutin	—	—	—	5.88 ± 3.12%	5.88 ± 3.12%	53%

Per-Compound Bioavailability — Menopausal Cohort

Asian, 100% female, ages 45–55, n=100, fed state

Compound	Alone (#1, #2)	#3 Pair	#4 Fenugreek	#5 Shatavari	#6 Combined Exts	CV (#6)
Protodioscin	0.89 ± 0.51%	0.89 ± 0.51%	0.89 ± 0.51%	—	0.92 ± 0.53%	58%
Trigonelline	—	—	64.45 ± 11.00%	—	64.85 ± 10.97%	17%
4-Hydroxyisoleucine	—	—	96.86 ± 1.42%	—	96.86 ± 1.42%	1%
Shatavarin IV	0.75 ± 0.44%	0.75 ± 0.44%	—	0.79 ± 0.47%	0.79 ± 0.47%	59%
Shatavarin I	—	—	—	0.83 ± 0.48%	0.83 ± 0.48%	58%
Quercetin	—	—	—	20.30 ± 8.58%	20.30 ± 8.58%	42%
Rutin	—	—	—	5.26 ± 2.82%	5.26 ± 2.82%	54%



Key Comparisons

General Population vs Menopausal Cohort (Combined Formulation, Run #6)

Compound	General F%	Menopausal F%	Δ (Relative)
Protodioscin	1.01 ± 0.56%	0.92 ± 0.53%	-8.9%
Trigonelline	67.56 ± 9.96%	64.85 ± 10.97%	-4.0%
4-Hydroxyisoleucine	97.15 ± 1.22%	96.86 ± 1.42%	-0.3%
Shatavarin IV	0.86 ± 0.48%	0.79 ± 0.47%	-8.1%
Shatavarin I	0.92 ± 0.52%	0.83 ± 0.48%	-9.8%
Quercetin	21.78 ± 7.92%	20.30 ± 8.58%	-6.8%
Rutin	5.88 ± 3.12%	5.26 ± 2.82%	-10.5%

Cross-Extract DDI Analysis (General Population)

Compound	Alone	In Own Extract	Combined	Fold Δ
Protodioscin	0.97%	0.97%	1.01%	1.04×
Shatavarin IV	0.82%	0.86%	0.86%	1.05×

Cross-extract pharmacokinetic enhancement is minimal (+4–6%). The UGT1A1 DDI from flavonoid co-constituents (Quercetin, Rutin) provides a modest uplift to saponin F% but does not fundamentally change their absorption profile.

Comparison with Naveencharan et al. (2025)

Reference: Naveencharan, R. et al. "Validation of combination of protodioscin and shatavarin IV from medicinal extracts for alleviating menopausal symptoms by computational deep learning models." *Talanta Open*, 2025, 100552. doi:10.1016/j.talo.2025.100552

Dimension	Naveencharan et al. (2025)	Simulaite PBPK
Molecular repr.	ECFP6 fingerprints (300-bit) — used for additivity prediction	**Full molecular graph to 22 GNNs**
Herbal extension	Fixed-bit hashing cannot accurately represent large molecular topologies and does not extend to herbal compounds with structures not in pharma molecule training data	**Learns from atomic connectivity at the quantum level, preserving ring systems and molecular structure — inherently extendable to herbal molecules**
Property prediction	ADMETlab 2.0, SwissADME	**In-house GNN suite**
PD modeling	**Molecular docking, Loewe additivity (FFNN), dose-response curves**	PD not modeled in this case study

Dimension	Naveencharan et al. (2025)	Simulaite PBPK
PK modeling	Static ADME flags only (ADMETlab)	**Full mechanistic PBPK**
Population	None	**n=100, two populations**
Compounds	2 (isolated)	**7 simultaneously, 6 scenarios**
Output	Probability flags, IC_{50}	**Absolute F% ± SD, CV%, profiles**
Dose anchoring	0.01–100 µM at receptor	**Oral dose to systemic conc.**
Target pop.	None	**Menopausal women quantified**

Naveencharan et al. present substantive pharmacodynamic modeling: a deep learning additivity model (4-layer FFNN on DrugComb, R^2=0.99 across MCF7 and 786-O cell lines), molecular docking against five KNDy pathway neuronal targets, and dose-response curves derived via Cheng-Prusoff from binding free energies. Their PD contribution is genuine. Our comparison focuses specifically on the pharmacokinetic gap: their ADME section uses static flags (ADMETlab 2.0, SwissADME) with no population, no oral dose anchoring, and no variability modeling. Our PBPK simulation complements their PD insight by answering what systemic concentrations are actually achievable from an oral dose.

Key PK Findings vs Naveencharan et al.

1. F% vs Probability Flag: Their F20% flag (Shatavarin-IV: 0.8% probability of ≥20% F) is directionally consistent with our absolute F of 0.70–0.87%, but ours provides a clinically actionable distribution, not a threshold probability.

2. Target Population Never Modeled: Their ADME predictions are systematically optimistic for menopausal women. Every compound F% drops 4–11% in the actual target demographic.

3. Variability Invisible: Saponins show >50% CV in both populations. CV is slightly higher in menopausal women — a meaningful fraction receive essentially zero systemic exposure. Their model cannot detect this.

4. Co-Constituents Missing: Their paper models only 2 compounds. The compounds actually reaching systemic circulation are Trigonelline (64–68% F) and 4-Hydroxyisoleucine (97% F) — which are not modeled in their paper. If these contribute to menopausal relief, their attribution is incomplete.

5. Cross-Extract DDI: Our 6-scenario matrix shows the combined formulation provides only +4–6% PK enhancement for saponins. The OVX rat superiority is unlikely driven by cross-extract PK — must be pharmacodynamic complementarity or metabolite effects.

6. Dose-Response Anchoring: Our bioavailability is calculated from the actual oral dose (20 mg Protodioscin from 500 mg extract), producing an absolute F% anchored in the real formulation. Their dose-response curves derive IC_{50} values from molecular docking free energies, which requires assumptions about what systemic concentrations are achievable — assumptions their static ADME flags cannot validate.

7. Trigonelline as Phytoestrogen: Our simulation reveals Trigonelline as the dominant bioavailable compound (64–68% F) from fenugreek. Allred et al. (2009) identified Trigonelline as a novel phytoestrogen with ER activity at picomolar concentrations via a non-classical mechanism — potentially relevant to menopausal symptom relief yet entirely absent from Naveencharan et al.

Metabolic Fingerprint

CYP and UGT enzyme contributions to total intrinsic clearance, plus P-glycoprotein efflux substrate status. Values

are compound properties, identical across populations. Enzyme contributions are derived from GNN predictions.

Substrate Profile — Enzymes & Transporters

Compound	CYP1A2	CYP3A4	CYP2D6	CYP2C9	UGT1A1	Influx Transporter	P-gp Efflux
Protodioscin	0.0%	41.5%	5.9%	0.0%	52.6%	—	Yes
Trigonelline	0.0%	29.7%	22.2%	20.8%	27.3%	—	—
4-Hydroxyisoleucine	—	—	—	—	—	Yes	—
Shatavarin IV	0.0%	35.1%	7.4%	0.0%	57.4%	—	Yes
Shatavarin I	0.0%	35.2%	5.1%	0.0%	59.7%	—	Yes
Quercetin	0.0%	25.3%	13.3%	13.7%	47.7%	—	—
Rutin	0.0%	31.8%	8.4%	1.5%	58.2%	—	—

Metabolic Insights

• UGT1A1 (glucuronidation) is the dominant metabolic pathway for all saponins and flavonoids — consistent with extensive Phase II conjugation of polyphenolic and glycosidic substrates

• Saponins are strong P-gp substrates: co-administration with a P-gp inhibitor (e.g., piperine) could increase absorption

• 4-Hydroxyisoleucine has zero CYP/UGT clearance (amino acid derivative, cleared renally) — no metabolic competition with other compounds

GNN predictions for enzyme inhibition. Inhibition magnitude is also predicted by our GNN suite and applied during simulation (not shown). Quercetin and Rutin inhibit UGT1A1, the dominant clearance pathway for saponins. CYP1A2 inhibition by Quercetin and Trigonelline has no PK effect in this formulation as no compound is a CYP1A2 substrate. The net DDI effect on co-formulated saponins is +4–6% F (see Key Comparisons).

Inhibition Profile — Enzymes & Transporters

Compound	CYP1A2	CYP3A4	CYP2D6	CYP2C9	UGT1A1	P-gp
Protodioscin	—	—	—	—	—	—
Trigonelline	Yes	—	—	—	—	—
4-Hydroxyisoleucine	—	—	—	—	—	—
Shatavarin IV	—	—	—	—	—	—

Compound	CYP1A2	CYP3A4	CYP2D6	CYP2C9	UGT1A1	P-gp
Shatavarin I	—	—	—	—	—	—
Quercetin	Yes	—	—	—	Yes	—
Rutin	—	—	—	—	Yes	—