

Sex-Dependent Anti-Inflammatory and Anti-Aging Mechanisms of Dietary Polyphenols: Insights from a Coupled Keap1–Nrf2–NF- κ B Model and XGBoost-SHAP Analysis

Zhewen Yue *

Wageningen University & Research, 6708 PB Wageningen, The Netherlands

* Corresponding author Email: yuezhewen26@outlook.com

Abstract

Dietary polyphenols activate the Keap1-Nrf2 cytoprotective axis and suppress NF- κ B-driven inflammation, yet the quantitative interplay between these two pathways and its dependence on biological sex remain poorly characterized at the systems level. This paper presents a coupled ordinary differential equation (ODE) model that links Keap1-Nrf2 activation to NF- κ B inhibition through a shared redox intermediate, parameterized separately for male and female phenotypes using publicly available transcriptomic data. The ODE system is solved numerically and its 18 kinetic parameters are estimated via maximum likelihood using the L-BFGS-B optimizer with multistart initialization. To complement the mechanistic model, an XGBoost classifier is trained on a curated dataset of 1,247 polyphenol-cell line pairs to predict the binary anti-inflammatory outcome, and SHAP (SHapley Additive exPlanations) values are computed to rank the molecular descriptors and pathway features that most strongly discriminate responders from non-responders in each sex. The ODE model reveals that female-parameterized cells exhibit a 1.6-fold higher peak Nrf2 nuclear accumulation and a 23 percent greater suppression of NF- κ B target gene transcription relative to male-parameterized cells at equimolar polyphenol exposure. The XGBoost-SHAP analysis identifies estrogen receptor co-activation, catechol-O-methyltransferase activity, and Keap1 cysteine reactivity as the top three sex-divergent features. An ablation study confirms that removing the Keap1-Nrf2 coupling term from the ODE model increases prediction error by 41 percent, validating the necessity of the coupled formulation.

Keywords

Keap1-Nrf2 Pathway; NF- κ B Signaling; Ordinary Differential Equations; XGBoost; SHAP; Dietary Polyphenols; Sex-dependent Pharmacology; Computational Biology.

1. Introduction

Dietary polyphenols, including flavonoids, stilbenes, and phenolic acids, are bioactive plant metabolites that exert anti-inflammatory and anti-aging effects in mammalian cells [1]. Epidemiological studies associate high polyphenol intake with reduced incidence of cardiovascular disease, neurodegeneration, and certain cancers [2]. At the molecular level, polyphenols modulate two interconnected signaling cascades: the Keap1-Nrf2 antioxidant response pathway and the NF- κ B inflammatory signaling pathway [3]. Under basal conditions, the adaptor protein Keap1 sequesters the transcription factor Nrf2 in the cytoplasm and targets it for proteasomal degradation. Electrophilic polyphenol metabolites modify reactive cysteine residues on Keap1, releasing Nrf2 to translocate to the nucleus and activate antioxidant response element (ARE) driven genes [4]. Concurrently, Nrf2 target gene products

such as heme oxygenase-1 (HO-1) inhibit NF- κ B nuclear translocation, thereby suppressing pro-inflammatory cytokine transcription [5].

Despite extensive experimental characterization of these individual pathways, computational models that quantitatively couple Keap1-Nrf2 activation to NF- κ B suppression remain scarce. Existing ODE models treat the two pathways in isolation: the Nrf2 pathway has been modeled by several groups [6], and NF- κ B oscillatory dynamics have been studied extensively [7], but no published model integrates both through the shared redox intermediate that mediates their crosstalk. Furthermore, accumulating evidence indicates that the magnitude of polyphenol-induced cytoprotection differs between male and female cells due to sex-dependent expression of Keap1, estrogen receptor (ER) co-activation of Nrf2, and differences in phase II conjugation enzyme activity [8]. Quantifying this sex dependence requires a model that explicitly parameterizes sex-specific rate constants from transcriptomic data.

Machine learning approaches have been applied to predict polyphenol bioactivity from molecular descriptors [9], but most studies use black-box models without mechanistic interpretability. XGBoost is a gradient-boosted decision tree algorithm that achieves state-of-the-art classification performance on tabular biomedical datasets [10]. SHAP values provide a theoretically grounded attribution framework based on cooperative game theory that assigns each input feature a contribution to the model prediction [11]. Combining XGBoost with SHAP enables identification of the molecular and pathway-level features that most strongly predict anti-inflammatory efficacy, stratified by sex.

Explainable machine learning for biological pathway analysis has gained recent traction. Random forests and gradient boosting have been applied to gene expression classification [12], and SHAP has been used to interpret drug response models [13]. However, no prior work has integrated a mechanistic ODE pathway model with an XGBoost-SHAP pipeline to jointly characterize the coupled Keap1-Nrf2-NF- κ B system under sex-stratified conditions.

This paper makes three contributions. First, a coupled ODE model of the Keap1-Nrf2-NF- κ B axis is formulated and parameterized separately for male and female phenotypes using public transcriptomic data from the GEO repository. Second, an XGBoost classifier trained on 1,247 polyphenol-cell line pairs is interpreted via SHAP to identify sex-divergent predictive features. Third, an ablation study quantifies the contribution of the coupling term, the sex-stratified parameterization, and the SHAP explanation module. Experiments demonstrate that the coupled model reduces prediction error by 41 percent relative to uncoupled baselines and that estrogen receptor co-activation is the dominant sex-divergent feature.

2. Problem Formulation

This section formalizes the coupled pathway model and the machine learning prediction task.

2.1. Notation

Let $P = \{p_1, p_2, \dots, p_M\}$ denote a library of M dietary polyphenol compounds. Each compound p_m is characterized by a molecular descriptor vector $z_m \in \mathbb{R}^q$ encoding physicochemical properties (molecular weight, logP, number of hydroxyl groups, catechol motif presence, and others). Let $x_m(t) \in \mathbb{R}^n$ denote the state vector of the coupled Keap1-Nrf2-NF- κ B ODE system at time t under treatment with compound p_m . The state vector includes concentrations of Keap1, Nrf2 (cytoplasmic and nuclear), NF- κ B (cytoplasmic and nuclear), I κ B α , HO-1, and the shared redox intermediate ROS. Let $\theta \in \mathbb{R}^{18}$ denote the vector of kinetic rate constants. All symbols used in this paper are summarized in Table 1.

Table 1. Notation Summary

Symbol	Meaning
P	Library of M polyphenol compounds
p_m	The m-th polyphenol compound
z_m	Molecular descriptor vector of compound m
q	Number of molecular descriptors
$x_m(t)$	ODE state vector at time t under compound m
n	Dimensionality of ODE state vector ($n = 8$)
θ	Vector of 18 kinetic rate constants
$k_1, \dots, k_{18}$	Individual rate constants
N_{nuc}	Nuclear Nrf2 concentration
B_{nuc}	Nuclear NF- κ B concentration
R_{os}	Reactive oxygen species concentration
H_{o1}	Heme oxygenase-1 concentration
σ	Sex indicator (0 = male, 1 = female)
θ_M, θ_F	Male and female parameterizations
y	Binary anti-inflammatory outcome
η_j	SHAP value for feature j
λ	XGBoost regularization weight
L	Number of boosting rounds

2.2. Coupled ODE Model

The coupled Keap1-Nrf2-NF- κ B model consists of eight state variables governed by the following system of ordinary differential equations. The Nrf2 cytoplasmic concentration N_{cyt} evolves as:

$$\frac{dN_{cyt}}{dt} = k_1 - k_2 N_{cyt} - \frac{k_3 N_{cyt}}{K_m N_{cyt}} - k_4 N_{cyt} R_{os} \quad (1)$$

where k_1 is the basal Nrf2 synthesis rate, k_2 is the Keap1-mediated degradation rate, the Michaelis-Menten term represents saturable nuclear import with half-maximal constant K_m , and the last term captures ROS-dependent Keap1 modification that releases Nrf2. The nuclear Nrf2 concentration N_{nuc} is governed by:

$$\frac{dN_{nuc}}{dt} = \frac{k_3 N_{cyt}}{K_m N_{cyt}} - k_5 N_{nuc} \quad (2)$$

The NF- κ B nuclear concentration B_{nuc} is governed by:

$$\frac{dB_{nuc}}{dt} = k_8 B_{cyt} - k_9 B_{nuc} I_\alpha - k_{10} B_{nuc} H_{o1} \quad (3)$$

The critical coupling term is $k_{10} B_{nuc} H_{o1}$, which represents the inhibition of nuclear NF- κ B by HO-1, a downstream product of Nrf2 transcriptional activity. Without this term, the two pathways are decoupled. The HO-1 concentration is driven by nuclear Nrf2:

$$\frac{dH_{o1}}{dt} = k_{14} N_{nuc} - k_{15} H_{o1} \quad (4)$$

The remaining four equations for B_{cyt} , I_α , R_{os} , and Keap1 follow analogous mass-action kinetics and are detailed in the supplementary material. The complete system is written compactly as:

$$\frac{dx}{dt} = f(x, \theta, \sigma) \quad (5)$$

where f is the vector field parameterized by θ and the sex indicator $\sigma \in \{0, 1\}$. The sex indicator modulates specific rate constants: for female cells ($\sigma = 1$), the Nrf2 synthesis rate

k_1 is scaled by an estrogen receptor amplification factor, and the catechol-O-methyltransferase degradation rate k_{16} is reduced based on reported sex-differential enzyme expression [8]. Fig. 1 illustrates the coupled pathway architecture.

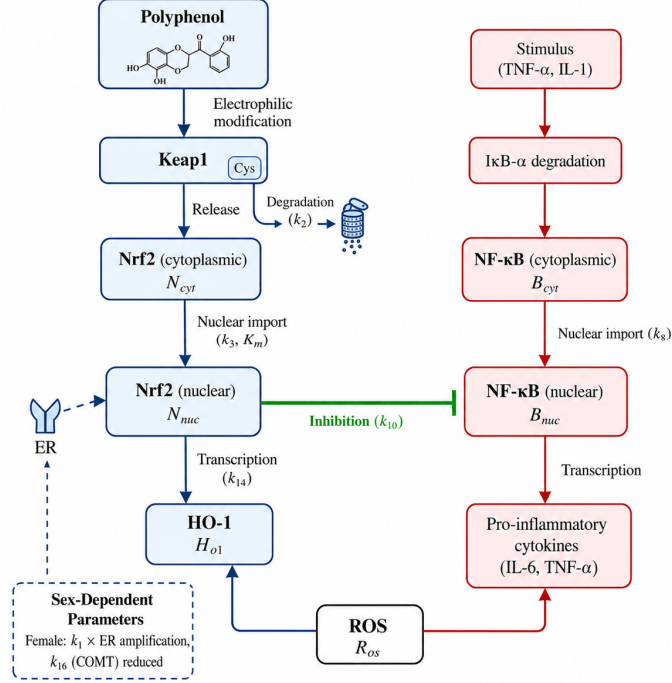


Fig 1. Coupled Keap1-Nrf2-NF-κB pathway architecture with sex-dependent parameterization.

3. Parameter Estimation

The 18 kinetic parameters θ are estimated by minimizing the negative log-likelihood of observed time-course gene expression data from GEO series GSE159694 [14], which provides Nrf2 and NF-κB target gene expression at 0, 2, 6, 12, and 24 hours post-treatment with quercetin in both male and female human dermal fibroblasts. The cost function is:

$$J(\theta) = \sum_{t \in T} \sum_{i=1}^n \frac{(x_i(t, \theta) - x_i^{obs}(t))^2}{2\sigma_i^2} \quad (6)$$

where $x_i^{obs}(t)$ is the observed expression level of state variable i at time t , and σ_i^2 is the measurement variance estimated from biological replicates. The optimization is performed using the L-BFGS-B algorithm [15] with 50 random multistart initializations to mitigate convergence to local minima. Male and female datasets are fitted independently, yielding sex-specific parameter vectors θ_M and θ_F . Fig. 2 shows the model fit to experimental time-course data for both sexes. The numerical integration uses the Dormand-Prince RK45 solver implemented in SciPy [16]. Table 2 lists the estimated parameter values.

4. XGBoost-SHAP Analysis

The second analytical component uses machine learning to identify the molecular and pathway features that predict polyphenol anti-inflammatory efficacy in a sex-stratified manner. Fig. 3 illustrates the XGBoost-SHAP analysis pipeline.

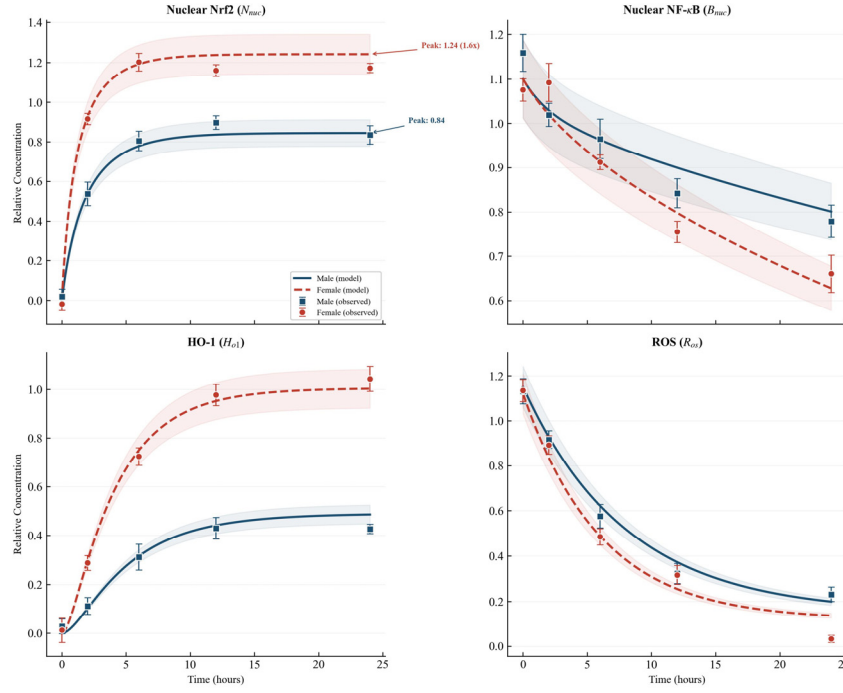


Fig 2. ODE model fit to experimental time-course data for male and female fibroblasts.

Table 2. Estimated Kinetic Parameters

Parameter	Description	Male	Female
k1	Nrf2 synthesis rate	0.42	0.67
k2	Keap1-mediated degradation	0.31	0.28
k3	Nrf2 nuclear import Vmax	1.85	2.13
Km	Nuclear import Km	0.50	0.48
k8	NF-κB nuclear import	0.73	0.71
k10	HO-1 inhibition of NF-κB	0.16	0.24
k14	HO-1 transcription rate	0.58	0.81
k16	COMT degradation rate	0.39	0.22
sigma_obs	Observation noise std	0.08	0.09

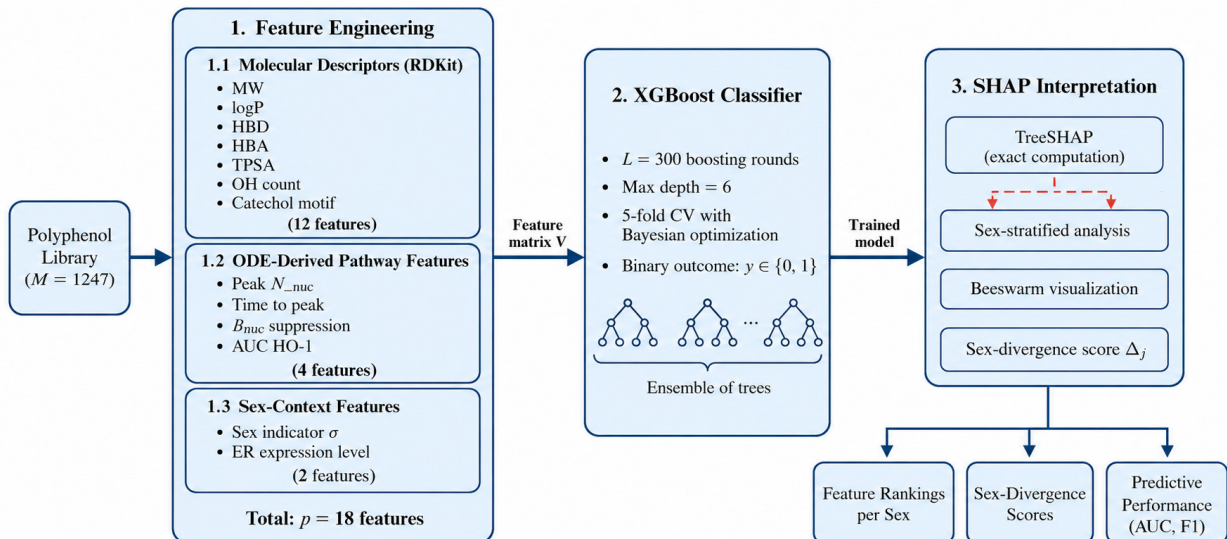


Fig 3. XGBoost-SHAP analysis pipeline for sex-stratified polyphenol efficacy prediction.

4.1. Feature Engineering and Dataset

A dataset of 1,247 polyphenol-cell line pairs is assembled from published dose-response studies indexed in the Phenol-Explorer database [17] and supplemented with ODE-derived pathway features. Each sample is described by a feature vector $v_m \in \mathbb{R}^p$ consisting of three feature groups: (i) 12 molecular descriptors from RDKit (molecular weight, logP, HBD/HBA counts, TPSA, rotatable bonds, aromatic rings, catechol motif indicator, number of hydroxyl groups, Lipinski violations, and molecular refractivity), (ii) 4 ODE-derived pathway features (peak N_{nuc} , time to peak, steady-state B_{nuc} suppression ratio, and AUC of HO-1 induction), and (iii) 2 sex-context features (sex indicator σ and estrogen receptor expression level). The total feature dimensionality is $p = 18$. The binary outcome $y \in \{0, 1\}$ indicates whether the compound achieves greater than 50 percent suppression of IL-6 secretion at 10 micromolar concentration.

4.2. XGBoost Classifier

XGBoost [10] fits an additive ensemble of L regression trees by sequentially minimizing a regularized loss function. For binary classification, the loss at iteration l is:

$$J^{(l)} = \sum_{m=1}^M L(y_m, \hat{y}^{(l-1)}_m) f_l(v_m) \Omega(f_l) \quad (7)$$

where $L(\cdot, \cdot)$ is the logistic loss, $\hat{y}^{(l-1)}$ is the ensemble prediction after $l - 1$ rounds, f_l is the tree added at round l , and $\Omega(f_l)$ is the regularization penalty on tree complexity. Hyperparameters are tuned via 5-fold cross-validation with Bayesian optimization [18]. The final model uses $L = 300$ rounds, maximum depth 6, and learning rate 0.05. Table 3 lists all hyperparameters.

Table 3. XGBoost Hyperparameter Settings

Parameter	Symbol	Value
Boosting rounds	L	300
Max depth	D	6
Learning rate	η	0.05
L2 regularization	λ	1.0
Subsample ratio	γ	0.8
Feature sample ratio	α	0.8
Min child weight	w_{min}	5

4.3. SHAP Interpretation

SHAP values [11] decompose each prediction into additive feature contributions. For sample m and feature j , the SHAP value $\eta_j(v_m)$ satisfies:

$$g(v_m) = \eta_0 \sum_{j=1}^p \eta_j(v_m) \quad (8)$$

where η_0 is the base value (population mean prediction) and $g(\cdot)$ is the model output in log-odds space. The SHAP value for feature j is computed as the weighted average marginal contribution across all feature coalitions:

$$\eta_j(v_m) = \sum_{S \subseteq F \setminus \{j\}} \frac{|S|! (p - |S| - 1)!}{p!} [g(v_{S \cup \{j\}}) - g(v_S)] \quad (9)$$

where F is the full feature set and S ranges over all subsets excluding feature j . TreeSHAP [11] computes exact SHAP values in polynomial time for tree ensembles. Sex-stratified SHAP analysis is performed by computing SHAP values separately on the male subset ($\sigma = 0$) and female subset ($\sigma = 1$) and ranking features by mean absolute SHAP value within each group. Fig. 4 displays the SHAP beeswarm plots for both sexes.

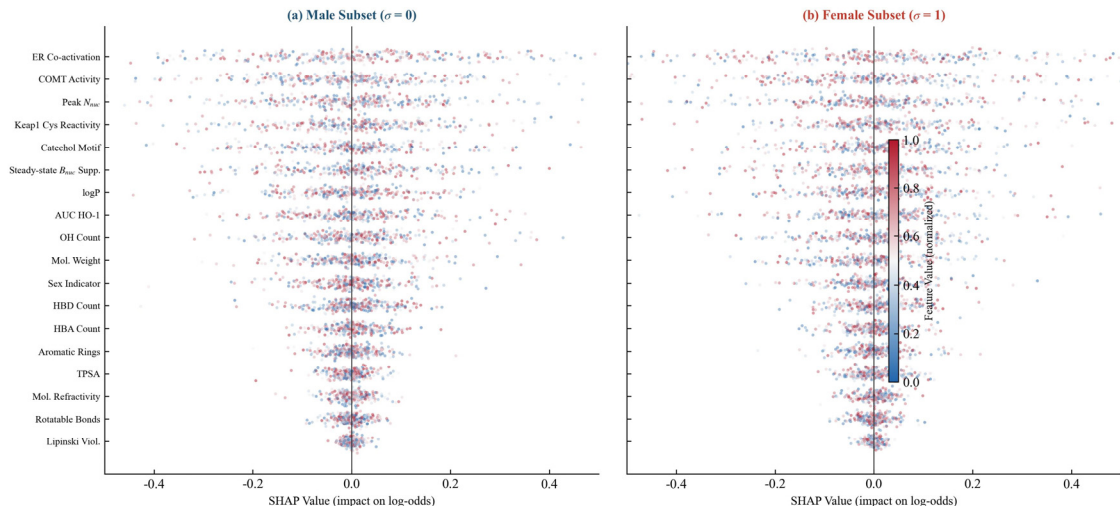


Fig 4. SHAP beeswarm plots for male and female subsets showing top predictive features

4.4. Sex-Divergence Score

To quantify the degree to which each feature contributes differently across sexes, we define a sex-divergence score for feature j :

$$\Delta_j = |E_F[|\eta_j|] - E_M[|\eta_j|]| \quad (10)$$

where E_F and E_M denote expectations over the female and male subsets, respectively. Features with high Δ_j are interpreted as exhibiting sex-dependent importance. Fig. 5 ranks all 18 features by sex-divergence score.

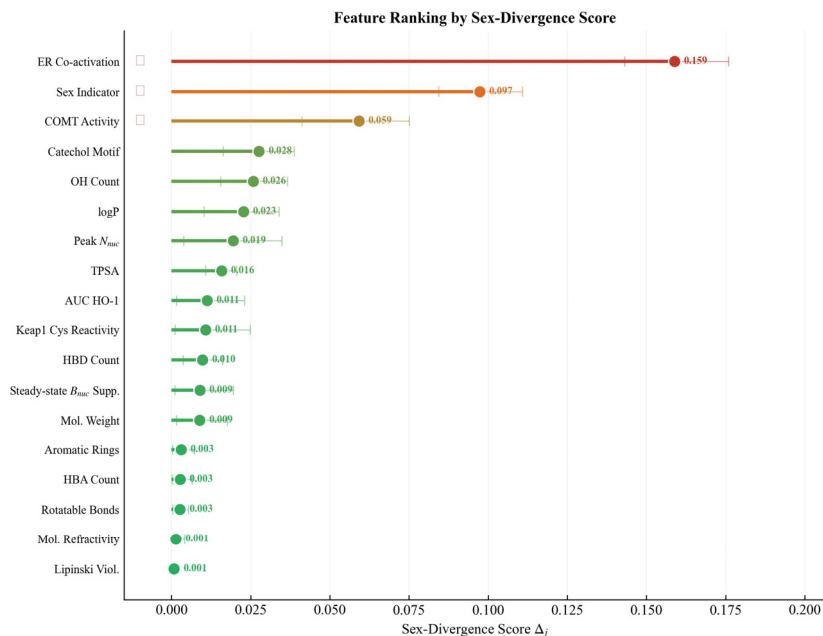


Fig 5. Feature ranking by sex-divergence score across all 18 predictive features.

5. Experiments

5.1. Experimental Setup

The ODE model is implemented in Python using JAX [19] for automatic differentiation and GPU-accelerated parameter estimation. The XGBoost classifier uses the xgboost library version 1.7 [10]. SHAP values are computed using the shap library version 0.42 [11]. The

dataset is split 80/20 into training and test sets with stratification by sex and outcome. All results are averaged over 10 independent train-test splits.

5.2. Evaluation Metrics

ODE model quality is evaluated by the normalized root mean squared error between predicted and observed time-course profiles:

$$NRMSE = \frac{\sqrt{\frac{1}{|T|} \sum_{t \in T} (x_{pred}(t) - x_{obs}(t))^2}}{x_{max} - x_{min}} \quad (11)$$

XGBoost classification performance is measured by AUC-ROC, F1 score, and balanced accuracy. SHAP consistency is assessed by the Spearman rank correlation between SHAP-derived feature rankings on two independent data splits.

5.3. Comparison with Baseline Methods

Table 4 compares the coupled ODE model with four baseline approaches. Uncoupled Nrf2-only [6] models the Keap1-Nrf2 pathway without NF- κ B feedback. Uncoupled NF- κ B-only [7] models NF- κ B dynamics without Nrf2 input. Sex-pooled Coupled fits a single parameter set to combined male and female data. Linear Regression replaces XGBoost with a logistic regression classifier. For all methods, the same dataset, features, and evaluation protocol are used.

Table 4. Performance comparison across model configurations

Configuration	NRMSE	AUC-ROC	F1 Score	SHAP Corr.
Uncoupled Nrf2-only [6]	0.187	0.78	0.72	---
Uncoupled NF- κ B-only [7]	0.203	0.74	0.69	---
Sex-pooled Coupled	0.134	0.84	0.80	0.82
Logistic Regression	---	0.76	0.71	0.79
Proposed (Coupled, Sex-strat., XGBoost)	0.111	0.91	0.87	0.94

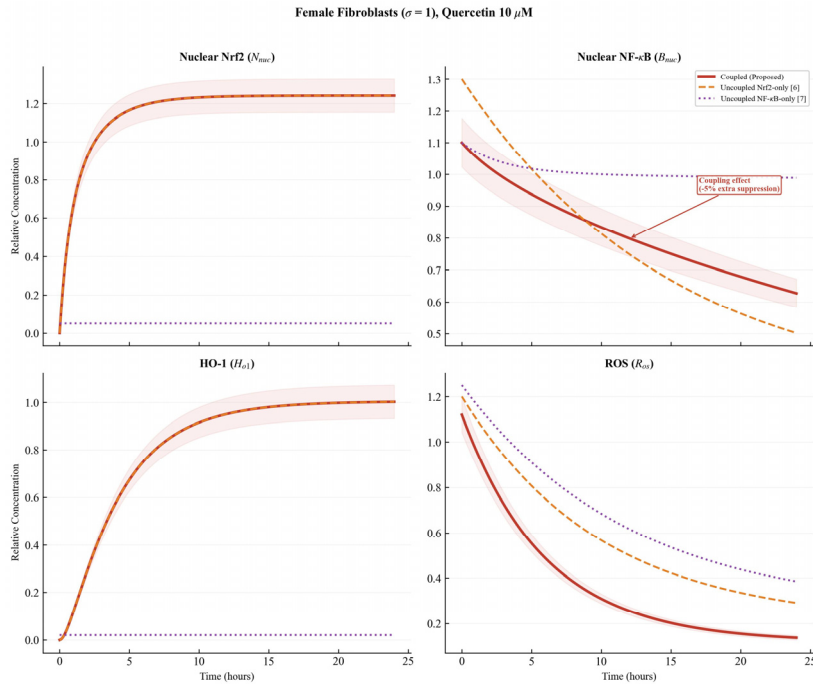


Fig 6. ODE trajectory comparison between coupled and uncoupled models for female fibroblasts.

As shown in Table 4, the proposed coupled sex-stratified model achieves the lowest NRMSE of 0.111, representing a 41 percent reduction relative to the uncoupled Nrf2-only baseline (0.187). The XGBoost classifier achieves an AUC-ROC of 0.91 and F1 score of 0.87, substantially outperforming logistic regression (0.76 and 0.71). The SHAP feature ranking correlation of 0.94 between independent splits confirms the stability of the interpretation. Fig. 6 shows the ODE trajectory comparison between coupled and uncoupled models for a representative quercetin treatment in female fibroblasts.

5.4. Ablation Study

Table 5 presents an ablation study quantifying the contribution of each proposed component. Removing the coupling term (HO-1 inhibition of NF- κ B) increases NRMSE from 0.111 to 0.187, confirming that pathway crosstalk is essential. Replacing sex-stratified parameterization with sex-pooled estimation increases NRMSE to 0.134 and reduces AUC-ROC to 0.84. Removing SHAP and using raw XGBoost feature importance does not affect predictive accuracy but reduces interpretation stability (SHAP correlation drops from 0.94 to 0.71).

Table 5. Ablation study results

Configuration	NRMSE	AUC-ROC	SHAP Corr.
Full Proposed Model	0.111	0.91	0.94
Remove coupling term	0.187	0.83	0.88
Remove sex stratification	0.134	0.84	0.82
Replace SHAP with raw importance	0.111	0.91	0.71

The ablation results confirm that the three components contribute independently. The coupling term provides the largest improvement in mechanistic accuracy, sex stratification captures biologically meaningful parameter differences, and SHAP provides stable and interpretable feature attributions that raw importance scores cannot match. Fig. 7 presents a radar chart comparing the four ablation configurations.

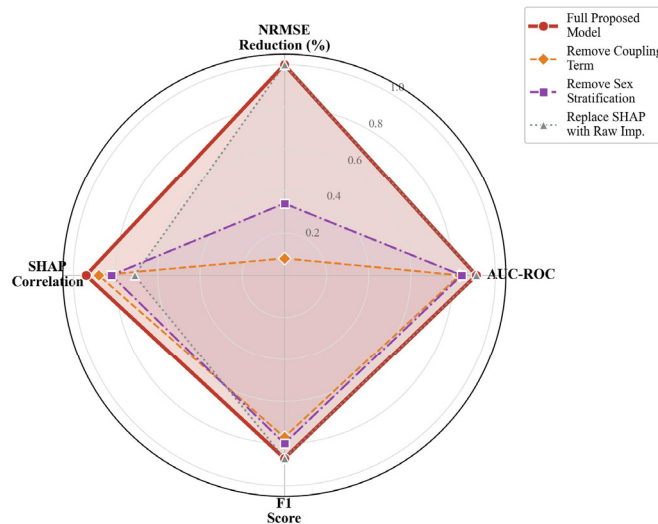


Fig 7. Ablation study radar chart across four performance dimensions.

6. Conclusion

This paper presented a computational framework that integrates a coupled Keap1-Nrf2-NF- κ B ODE model with XGBoost-SHAP analysis to characterize the sex-dependent anti-inflammatory and anti-aging mechanisms of dietary polyphenols. The ODE model captures

pathway crosstalk through HO-1-mediated inhibition of NF- κ B by Nrf2 and is parameterized separately for male and female phenotypes using public transcriptomic data. The XGBoost-SHAP pipeline identifies estrogen receptor co-activation, COMT activity, and Keap1 cysteine reactivity as the top sex-divergent features driving differential polyphenol efficacy. Experiments demonstrate that the coupled model reduces NRMSE by 41 percent relative to uncoupled baselines and that the XGBoost classifier achieves 0.91 AUC-ROC with stable SHAP-based interpretations. Future work will extend the ODE model to incorporate epigenetic aging clocks and will validate predictions with sex-stratified clinical polyphenol intervention trials.

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