**A Multi-scale Prediction Model Using Machine Learning and Dynamics Simulation for the Selection of Transdermal Penetration Enhancers**

**Ying Zheng**1,2,\*, Yidan Tang1, Zheng Wu1, Jianjia Su1, Defang Ouyang1,2,\*.

State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau1, Macao, China

Faculty of Health Sciences, University of Macau2, Macao, China

**Background and aims.** Penetration enhancers (PEs) are widely employed in transdermal drug delivery systems due to their cost-effectiveness and biocompatibility. However, two critical challenges persist: (i) high experimental costs and extended durations hinder traditional in vitro permeation tests (IVPT); (ii) existing quantitative structure-activity relationship (QSAR) models, predominantly constructed from limited datasets (n < 500), exhibit limited predictive accuracy for complex "drug-PE" interactions. To address these challenges, this study proposed a multi-scale modeling strategy that integrated machine learning, experimental validation, and mechanistic explanation, aiming to establish a rapid screening platform for transdermal formulations.

**Methods.** A comprehensive database of 1,022 transdermal flux records was constructed from literature. Four machine learning algorithms (LightGBM, RF, SVM, DNN) were evaluated, with LightGBM selected for its optimal predictive performance (R²test set = 0.79). Then, feature importance analysis identified key factors influencing transdermal flux. Experimental validation was conducted using berberine and ferulic acid with PEs (azone, menthol, and oleic acid). Molecular dynamics(MD) simulations elucidated mechanistic actions.

**Results.** Feature importance analysis demonstrated a dose-dependent correlation between PE concentration and transdermal efficiency (SHAP value > 0). At the same time, the drug’s log S exhibited a biphasic effect on transdermal flux: extremely low log S values impede permeation through the hydrophilic regions of the skin barrier, whereas excessively high log S values reduce compatibility with the stratum corneum’s lipid layer. Experimental validation using berberine and ferulic acid systems confirmed model predictions, with azone showing highest efficacy for BER (ER = 3.23) and oleic acid for FA (ER = 1.79). MD simulations highlighted distinct mechanisms: BER disrupts lipid bilayer order, while FA modulates polar headgroup interactions.

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**Figure 1**. The graphic abstract.

**Conclusion.** This study successfully integrated machine learning with molecular dynamics to select penetration enhancers for transdermal formulation design. The approach addressed critical limitations of traditional methods by: (i) establishing a robust database of drug-PE pairs; (ii) identifying key molecular determinants of transdermal flux; (iii) providing mechanistic explanations through MD simulations.

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