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COMPARATIVE IN *Silico* ADMET ANALYSIS OF BERBERINE AND PIPERINE: A RATIONALE FOR COMBINATORIAL THERAPY TO OVERCOME P-GLYCOPROTEIN-MEDIATED EFFLUX

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ABSTRACT

Berberine, a bioactive isoquinoline alkaloid, exhibits diverse pharmacological activities including antimicrobial and anticancer effects; however, its clinical application is limited by poor oral bioavailability, largely attributed to efflux by P-glycoprotein (ABCB1). This study evaluates the pharmacokinetic and drug-likeness properties of berberine using in silico tools (SwissADME, ADMETLab, and pkCSM) to rationalize its limitations and support combinatorial therapeutic strategies. Predicted physicochemical parameters were consistent across platforms, with berberine demonstrating favorable drug-like properties, including moderate lipophilicity (logP 2.5–3.1), high gastrointestinal absorption, and compliance with Lipinski's rule of five. Despite these favorable attributes, berberine was consistently predicted to be a P-glycoprotein substrate, explaining its reduced intracellular accumulation and systemic availability. Additionally, berberine showed inhibitory potential toward CYP3A4, suggesting possible drug–drug interaction implications. These findings highlight that while berberine possesses strong drug-like characteristics, its therapeutic efficacy is compromised by efflux-mediated limitations. Therefore, co-administration with P-glycoprotein inhibitors such as piperine presents a promising strategy to enhance its bioavailability and pharmacological effectiveness. This study provides a computational basis for the rational design of combinatorial formulations targeting efflux transport mechanisms.

Keywords: Berberine, Piperine, P-Glycoprotein, ADMET, Bioavailability, Combinatorial Therapy

INTRODUCTION

Berberine (BBR), an isoquinolone alkaloid, is a yellow constituent of some plants including *Berberis*, *Coptis*, and *Hydrastis* species ((Pirillo & Catapano, 2015). It exhibits a wide range of pharmacological activities, including anti-diabetic, lipid-lowering, antimicrobial, and anticancer effects (Pirillo & Catapano, 2015; Ai *et al*., 2021; Shi *et al*., 2025). Despite these promising therapeutic properties, its clinical application remains limited by poor oral bioavailability**,** which is primarily attributed to low intestinal absorption, extensive first-pass metabolism, and active efflux mediated by P-glycoprotein (P-gp) (Cui *et al*., 2024). Susceptibility of BBR to P-gp is largely influenced by its aromatic and permanently cationic structure (Table 1) (Omote & Al-Shawi, 2006). Structural elucidation of P-glycoprotein reveal multiple stereoselective drug-binding sites within its internal cavity driven by hydrophobic and aromatic interactions, which explains the efficient recognition and efflux of aromatic alkaloids such as berberine (Aller *et al*., 2009).

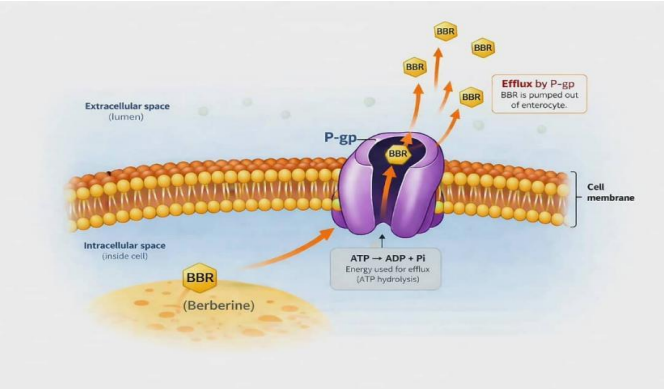


Figure 1: P-glycoprotein (P-gp)-Mediated Efflux of Berberine (BBR) from Enterocytes, Illustrating ATP-Dependent Transport and Reduced Intracellular Concentration

Experimental pharmacokinetic studies indicate that BBR exhibits extremely low systemic bioavailability (<1%) (Khoshandam *et al*., 2022) following oral administration, largely due to P-gp–mediated efflux and hepatic–intestinal metabolism (Cui *et al*., 2024). This efflux mechanism actively transports BBR out of intestinal cells, significantly reducing intracellular concentration and systemic bioavailability. As a result, relatively high oral doses (1000 – 1500 mg/day divided into doses) are typically required to achieve therapeutic effects. However, higher doses have been associated with gastrointestinal discomfort, further emphasizing its pharmacokinetic limitations (Moon *et al*., 2021).

Piperine (PIP), an amide alkaloid, a major bioactive compound of *Piper nigrum(black pepper)*, has emerged as a

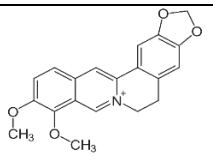
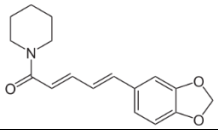
potent bioavailability enhancer. Recent studies demonstrate that piperine improves drug absorption by modulating intestinal permeability, inhibiting metabolic enzymes such as Cytochrome P450 3A (CYP3A4), and reducing efflux transporter activity, including P-gp (Jan *et al*., 2025; Li *et al*., 2025). Additionally, PIP has been shown to increase the systemic bioavailability (C_max and AUC) of co-administered compounds, highlighting its role in improving pharmacokinetic performance (Jan *et al*., 2025). Human studies and regulatory safety assessments indicate that piperine is typically administered at relatively low doses, especially when compared to compounds such as berberine. Clinical and toxicological evaluations suggest that PIP is safe at doses ranging from approximately 5 to 20 mg per day when used as a dietary supplement or bioenhancer (EFSA Panel on Food Additives and Flavourings, 2015; Ziegenhagen *et al*., 2021).

Therefore, a comparative *in silico* Absorption, Distribution, Metabolism and Toxicity (ADMET) analysis of berberine and piperine is essential to elucidate their pharmacokinetic characteristics and support the rationale for combination therapy targeting efflux-mediated drug limitations.

MATERIALS AND METHODS

SwissADME (Daina *et al*., 2017, ADMETLab 3.0 (Fu *et al*., 2024), and pkCSM (Pires *et al*., 2015) were employed to predict the pharmacokinetic properties and drug-likeness of BBR. The canonical SMILES of BBR and PIP were retrieved from PubChem database. Key physicochemical properties and drug-likeness (Table 2) obtained from the tools were compiled and compared to evaluate the pharmacokinetics of the alkaloid compounds.

Table 1: Chemical Formula, Chemical Structure, and Molecular Weight of BBR and PIP

Compound	PubChem CID	Chemical Formula	Chemical Structure	Molecular Weight (g/mol)
Berberine	2353	$C_{20}H_{18}NO_4^+$		336.36
Piperine	638024	$C_{17}H_{19}NO_3$		285.34

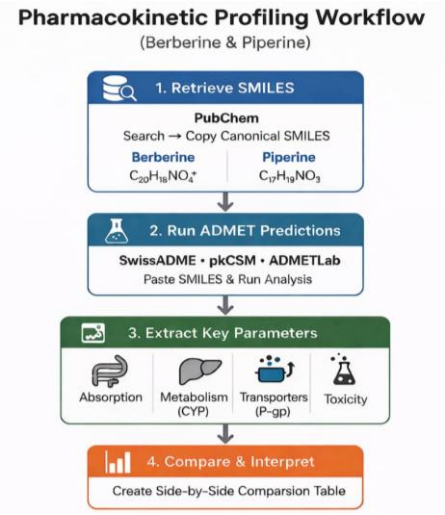


Figure 2: Workflow for *in Silico* Pharmacokinetic Profiling of Berberine and Piperine using ADMET Prediction Tools

RESULTS AND DISCUSSION

A summary of the predicted pharmacokinetics and drug-likeness properties of BBR and PIP are presented in Table 2.

Table 2: Predicted Drug Properties and Drug-Likeness of BBR and PIP

Property	Berberine			Piperine		
	SwissADME	ADMETLab	pkCSM	SwissADME	ADMETLab	pkCSM
Molecular weight (g/mol)	336.36	336.12	336.37	285.34	285.14	285.34
H-bond acceptors	4	—	4	3	4	3
H-bond donors	0	—	0	0	0	0
TPSA (Å²)	40.80	40.80	—	38.77	—	—
LogP	2.53	3.12	3.10	3.03	2.51	3.00
LogS	-4.55 (ESOL)	-5.06	−3.97	−3.74 (ESOL)	−3.91	−3.5

Property	Berberine			Piperine		
	SwissADME	**ADMETLab**	**pkCSM**	**SwissADME**	**ADMETLab**	**pkCSM**
GI absorption	High	—	97.15%	High	—	—
P-gp substrate	Yes	+ + +	Yes	No	− − −	Yes
P-gp inhibitor	—	− − −	No/Yes	—	+ + +	Yes/No
CYP3A4 inhibition	Yes	+ + +	—	No	+ + +	—
Lipinski rule	Pass	—	—	Pass	—	—
Veber rule	Pass	—	—	Pass	—	—
Ghose filter	Pass	—	—	Pass	—	—
Bioavailability score	0.55	—	—	0.55	—	—

ESOL, estimated solubility model used to predict logS by swissADME; LogS, predicted aqueous solubility expressed as log mol/L; — (not predicted by the respective prediction tool); LogP, octanol/water partition coefficient, a measure of compound lipophilicity indicating its distribution between hydrophobic and aqueous phases; Yes/No corresponds to pkCSM P-glycoprotein (P-gp) inhibition Model I and Model II predictions, respectively; classification probabilities are expressed as: 0.0–0.1 (− − −), 0.1–0.3 (− −), 0.3–0.5 (−), 0.5–0.7 (+), 0.7–0.9 (+ +), and 0.9–1.0 (+ + +), where increasing symbols indicate increasing prediction confidence.

Discussion

Evaluating the physicochemical and drug-likeness properties of a bioactive compound gives insight into its therapeutic potential. Results of the physicochemical properties of BBR and PIP across three platforms is largely consistent, and the results suggest that BBR and PIP possess physicochemical properties consistent with drug-like molecules. The comparative ADMET analysis clearly shows a contrast between BBR and PIP, which supports their potential use in combination therapy.

The partition coefficient (logP) of BBR ranges between 2.5 and 3.1, which indicates moderate lipophilicity. Compounds with logP values within this range generally exhibit balance between water solubility and membrane permeability. A strong evidence for this is the predicted high intestinal absorption as predicted by swissADME and pkCSM. However, across the three platforms, BBR was predicted to be a substrate of P-glycoprotein. Efflux by P-glycoprotein may partly explain the low oral bioavailability of BBR despite its predicted high gastro-intestinal absorption (Kwon *et al*., 2020; Pan *et al*., 2002; Shan *et al*., 2013). Inhibition of P-glycoprotein

increased the absorption and bioavailability of BBR (Pan *et al*., 2002; Murakami *et al*., 2023; Zha *et al*., 2013). In addition, BBR has exhibited potential of upregulating the activity and expression of P-glycoprotein (Maeng *et al*., 2002; Jing *et al*., 2018). In contrast, the predictions suggest that PIP is not a substrate of P-gp, rather, it is an inhibitor of P-gp, strongly supported by ADMETLab and partially supported by pkCSM. This distinction is mechanistically important because PIP can inhibit the efflux of P-gp substrates (such as BBR), thereby improving the intracellular concentration and systemic availability. The mechanism of inhibition involves the stabilization of ligands within the drug-binding cavity of P-gp through a combination of hydrogen bonding and hydrophobic interactions. PIP has been reported to form hydrogen bond with Tyr307 and hydrophobic contacts with Met69, Phe72, Phe336, Leu339, Phe728, Tyr953, Val982, Phe983, and Met986 (Syed *et al*., 2017).

Predictions by swissADME and ADMETLab suggest that BBR inhibits CYP3A4 enzyme. High concentrations of BBR downregulated the expression of CYP3A4 (Tang *et al*., 2015). In another study, berberine inhibits CYP3A4 by suppressing PXR-mediated transcription and promoting polyubiquitination-dependent degradation of the CYP3A4 protein (Feng *et al*., 2021). Repeated administration of BBR inhibits CYP3A4 enzyme (Guo *et al*., 2012). In addition to P-gp modulation, it has been widely reported that PIP inhibits a wide range of drug-metabolizing enzymes, including CYP3A4, thereby reducing first-pass metabolism of co-administered drugs (Jan *et al*., 2025; Pradeepa *et al*., 2023).

BBR and PIP exhibited very high drug-likeness properties. They passed all drug-likeness parameters including Lipinski's rule of five (Lo5). Lo5 predicts the likelihood that a drug candidate will be orally bioavailable. Lo5 suggests that drug-like compounds typically possess a molecular weight below 500 g/mol, no more than ten hydrogen bond acceptors, no more than five hydrogen bond donors, and exhibit moderate lipophilicity (partition coefficient (LogP) ≤5) (Lipinski *et al*., 2001; Singh & Singh, 2024). Compounds with more than one violation of these criteria are generally considered less likely to demonstrate optimal permeability and absorption. In addition to Lipinski's criteria, the Ghose filter further evaluates drug-likeness by suggesting that orally active compounds typically possess a molecular weight between 160–480 Da, logP between −0.4 and 5.6, molar refractivity between 40–130, and a total atom count between 20–70, reflecting favorable molecular size, lipophilicity, and polarizability for biological interaction (Ghose *et al*., 1999). The Veber rule complements these filters by emphasizing molecular flexibility and polarity, proposing that compounds with 10 or fewer rotatable bonds and a topological polar surface area (TPSA) of 140 Å² or less are more likely to demonstrate good membrane permeability and oral bioavailability (Veber *et al*., 2002). Furthermore, a predicted bioavailability score of 0.55, as estimated by SwissADME, indicates a reasonable probability that the compound possesses acceptable oral bioavailability (Martin, 2005), further supporting its suitability as a candidate for oral therapeutic development.

CONCLUSION

This study provides a comparative in silico evaluation of the pharmacokinetic and drug-likeness profiles of BBR and PIP, highlighting key differences that support their combinatorial therapeutic usage. Although BBR demonstrates favorable physicochemical properties and predicted high gastrointestinal absorption, its effectiveness is significantly limited by P-glycoprotein-mediated efflux and hepatic metabolic enzymes. In contrast, PIP exhibits properties consistent with a bioenhancer, which include predicted inhibition of P-glycoprotein and metabolic enzymes such as CYP3A4. The complementary pharmacokinetic profiles observed suggest that PIP may enhance the intracellular retention and systemic availability of BBR by blocking efflux and first-pass metabolism. Both compounds satisfy major drug-likeness criteria, reinforcing their suitability for oral administration. Together, these findings provide a

mechanistic basis for the rational design of BBR-PIP combination strategies aimed at overcoming the pharmacokinetic limitations associated with efflux transporters, potentially allowing for a reduction in the therapeutic dose of BBR. While the present study is based on computational predictions, it establishes a strong foundation for further experimental validation and formulation development to optimize the therapeutic potential of this combination.

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