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"IN SILICO ADME AND DRUG-LIKENESS EVALUATION OF BERBERINE AND GLYCYRRHIZIN FOR GASTROPROTECTIVE POTENTIAL USING SWISS ADME"

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ABSTRACT

Peptic ulcer disease remains a serious gastrointestinal illness linked to increased gastric acid output, NSAID use, and Helicobacter pylori infection. Berberine and glycyrrhizin are two phytoconstituents that have shown promise as gastroprotective and anti-inflammatory agents. However, their pharmacokinetic appropriateness for oral medication development must be thoroughly evaluated. The current study used the Swiss ADME web tool to evaluate berberine and glycyrrhizin's absorption, distribution, metabolism, and excretion (ADME) properties.

The physicochemical features, lipophilicity, water solubility, pharmacokinetic parameters, medicinal chemistry filters, and BOILED-Egg model predictions were investigated. Berberine had good gastrointestinal absorption, blood-brain barrier permeability, and complied with Lipinski, Veber, Ghose, Egan, and Muegge criteria without exception. The bioavailability value of 0.55 indicates modest oral bioavailability. However, berberine inhibited the CYP1A2, CYP2D6, and CYP3A4 enzymes, indicating the possibility of drug-drug interactions. In contrast, glycyrrhizin exhibited low gastrointestinal absorption and a

lack of BBB permeability. It did not meet drug-likeness criteria due to its high molecular weight (822.93 g/mol), increased hydrogen bond donors and acceptors, and large topological polar surface area (267.04 Å²). The bioavailability score was low (0.11), indicating poor oral compatibility.

Overall, the in-silico research indicates that berberine has more favorable pharmacokinetic and drug-like properties than glycyrrhizin. While glycyrrhizin has pharmacological promise, formulation improvement or different delivery techniques may be required to increase its therapeutic efficacy.

KEYWORDS: In-silico ADME, SwissADME, Berberine, Glycyrrhizin, Drug-likeness, Gastroprotection.

1. INTRODUCTION

Peptic ulcer disease (PUD) is a chronic gastrointestinal disorder marked by mucosal erosion of the stomach or proximal duodenum caused by an imbalance between aggressive factors such as gastric acid, pepsin, non-steroidal anti-inflammatory drugs (NSAIDs), and Helicobacter pylori, and protective mechanisms such as mucus secretion, bicarbonate production, prostaglandins, and mucosal blood flow (1,2). Despite advancements in pharmacotherapy, such as proton pump inhibitors (PPIs) and H2-receptor antagonists, ulcer recurrence, drug resistance, and side effects continue to pose therapeutic problems (3). Long-term PPI use has been linked to nutrient malabsorption, renal damage, and an increased risk of infection, emphasizing the need for safer and more effective treatment options (4). As a result, natural products and phytoconstituents have received a lot of attention due to their gastroprotective, antioxidant, and anti-inflammatory characteristics (5).

Among plant-derived bioactive substances, berberine, an isoquinoline alkaloid predominantly isolated from Berberis aristata, and glycyrrhizin, a triterpenoid saponin produced from Glycyrrhiza glabra, have showed considerable pharmacological activity related to gastrointestinal protection. Berberine has antibacterial efficacy against H. pylori, inhibits NF-κB signaling, modulates oxidative stress pathways, and improves mucosal defense mechanisms (8,9). Glycyrrhizin, on the other hand, has anti-ulcer, anti-inflammatory, and cytoprotective properties, which are ascribed to prostaglandin activation, increased mucus secretion, and free radical scavenging (10,11). These pharmacodynamic features indicate that both compounds could be useful treatment candidates for ulcer care.

However, successful drug development is dependent not only on pharmacological action but also on desirable pharmacokinetic properties, which are typically defined as absorption, distribution, metabolism, and excretion (ADME) factors (12). A significant majority of medication candidates fail in clinical trials due to poor pharmacokinetic profiles, inadequate bioavailability, or toxicity concerns (13). As a result, early evaluation of ADME features by computer techniques has become an essential component of current drug research. In silico pharmacokinetic prediction methods allow for quick, cost-effective screening of compounds to identify their drug-likeness and oral compatibility before moving on to in vitro or in vivo studies (14).

SwissADME is a popular web-based tool for predicting physicochemical properties, lipophilicity, solubility, gastrointestinal absorption, blood-brain barrier (BBB) permeability, cytochrome P450 interactions, and adherence to established drug-likeness rules such as Lipinski, Veber, Ghose, Egan, and Muegge filters (15). Lipinski's Rule of Five, for example, estimates oral bioavailability using molecular weight, hydrogen bond donors and acceptors, and lipophilicity (16). Similarly, topological polar surface area (TPSA) and the BOILED-Egg model are useful for estimating membrane permeability and gastrointestinal absorption (15,17). These prediction models help to detect potential pharmacokinetic limits and optimize chemical structures for better therapeutic effectiveness.

Despite its potential pharmacological properties, berberine has been shown to have only modest oral bioavailability due to P-glycoprotein efflux and first-pass metabolism (18). It also has inhibitory activity against specific cytochrome P450 enzymes, which may affect drug-drug interactions (19). In contrast, glycyrrhizin has a large molecular weight and significant hydrogen bonding capacity, which may impede passive diffusion and oral absorption (20). Such structural properties frequently cause breaches of drug-likeness requirements, necessitating formulation techniques or structural alterations to improve bioavailability.

Given the increased interest in phytoconstituent-based gastroprotective treatments and the relevance of pharmacokinetic optimization, a thorough in silico study of berberine and glycyrrhizin is required. Comparative ADME studies can offer information about oral acceptability, metabolic stability, and potential drug-drug interactions. Furthermore, understanding these pharmacokinetic characteristics is especially important when contemplating combination therapy or synergistic herbal formulations, as absorption and metabolism have a substantial impact on therapeutic outcomes.

Therefore, the current work seeks to analyze and compare the in silico ADME features, drug-likeness factors, and medicinal chemistry characteristics of berberine and glycyrrhizin utilizing the SwissADME web server. This study aims to establish their eligibility as prospective oral gastroprotective medicines by integrating physicochemical, pharmacokinetic, and computational drug-likeness predictions, as well as identify any limits that may necessitate additional optimization [20].

2. MATERIALS AND METHODS

2.1 Retrieval of Chemical Structures

The three-dimensional (3D) chemical structure of berberine was obtained from the NCBI PubChem database (CID: 2353). The structure file was downloaded in SDF format for additional computational investigation.[21] The 3D structure of glycyrrhizin (the active component of Glycyrrhiza glabra) was derived from the ChemSpider database (CSID: 14263) [22]. Prior to ADME prediction investigations, all derived structures were rigorously validated and optimized. The downloaded molecular structures were then analyzed for pharmacokinetics and drug-likeness using the SwissADME web service [23].

2.2 In Silico ADME Prediction

Berberine and glycyrrhizin's pharmacokinetic and drug-likeness qualities were projected with the Swiss ADME web server (http://www.swissadme.ch), a verified online tool for estimating physicochemical descriptors, ADME parameters, medicinal chemistry properties, and drug-likeness criteria. The canonical SMILES of each compound were uploaded separately, and the default prediction parameters were used.

The characteristics tested were molecular weight, hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), topological polar surface area (TPSA), and the number of rotatable bonds. Lipophilicity was determined using several models, including iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT, as well as the estimated consensus LogP value. Water solubility was predicted with the ESOL, Ali, and SILICOS-IT models.

The pharmacokinetic parameters studied included gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate prediction, cytochrome P450 (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) inhibition potential, and skin permeability (LogKp). Drug-likeness was assessed using Lipinski, Ghose, Veber, Egan, and Muegge filters. Medicinal chemistry characteristics such as PAINS and Brenk warnings, bioavailability score, and synthetic accessibility were also evaluated. Furthermore, the

BOILED-Egg model was used to estimate passive gastrointestinal absorption and brain penetration using polarity and lipophilicity.

3. In Silico ADME Profile of Berberine (Swiss ADME)

3.1 Absorption

The chemical has high gastrointestinal (GI) absorption, indicating that it would be well absorbed in the intestine after oral administration. However, it is recognized as a P-glycoprotein (P-gp) substrate, implying that it may be actively effluxed from intestinal cells, potentially reducing its overall oral bioavailability. Caco-2 permeability values are not provided in the current output, hence its permeability across intestinal epithelial cell models cannot be calculated using this information. The chemical has moderate water solubility, with a Log S (ESOL) value of -4.55 (about 9.53×10^{-3} mg/mL), which may affect its dissolution rate and absorption profile.Additionally, the skin permeability (Log Kp) value of –5.78 cm/s indicates low transdermal penetration, suggesting that the compound is not suitable for transdermal delivery systems.

3.2 Distribution

The chemical has positive blood-brain barrier (BBB) permeability, indicating that it can penetrate the BBB and could be used to target the central nervous system (CNS). According to the BOILED-Egg model, **Fig.1** the chemical is classified as yellow (BBB permeation) and white (high human intestine absorption, HIA), showing both its ability to permeate the brain and its good intestinal absorption profile. Additionally, the topological polar surface area (TPSA) is 40.80 Å², which is significantly lower than the 90 Å² threshold often linked with good oral absorption and BBB permeability. This low TPSA promotes effective membrane permeability, increasing the compound's potential for CNS action.

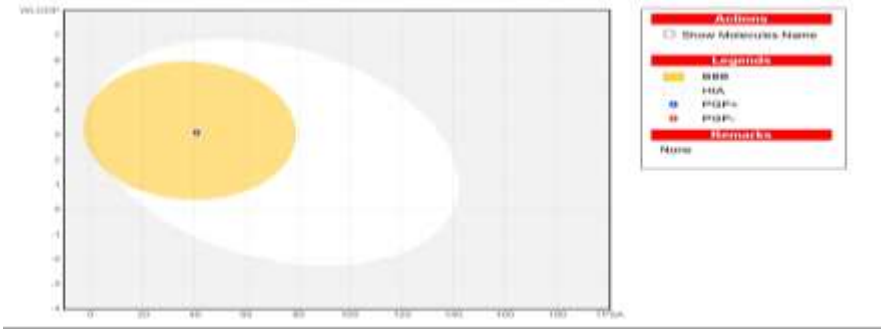

Fig.1 BOILED-Egg plot from SwissADME showing gastrointestinal absorption and blood–brain barrier (BBB) permeability prediction. The white region indicates high human intestinal

absorption (HIA), and the yellow region represents BBB permeation. The blue dot (test compound) lies in the yolk region, suggesting good BBB permeability with favorable absorption properties.

3.3 Metabolism

The molecule is projected to behave as a CYP1A2 inhibitor, implying that it may interfere with the metabolism of medicines that are substrates for this enzyme. It does not inhibit CYP2C19 or CYP2C9, implying a lesser likelihood of metabolic interactions via these pathways. However, it is expected to inhibit CYP2D6, which could result in clinically significant drug-drug interactions, especially with drugs largely processed by this isoenzyme. Furthermore, the chemical has been discovered as a CYP3A4 inhibitor, which raises concerns because CYP3A4 is a significant metabolic enzyme involved for the metabolism of a variety of medicines. Inhibition of CYP3A4 may result in altered plasma levels of co-administered medications, raising the risk of undesirable consequences.

3.4 Excretion

No direct renal clearance parameters (e.g., OCT2 substrate or total clearance) are provided in SwissADME, so additional tools (like pkCSM) may be needed for full excretion profiling.

3. 5 Toxicity Indicators

The molecule generates no PAINS (Pan-Assay Interference Compounds) alarms, indicating that it is unlikely to elicit false-positive findings in biological assays and lacks structural motifs often associated with assay interference. However, it raises one Brenk alarm, notably the existence of a quaternary nitrogen, indicating a potentially problematic substructure that may alter pharmacokinetic behavior or toxicity and necessitate careful investigation during drug development.

Concerning lead-likeness, the compound has one violation (XLOGP3 > 3.5), showing that its lipophilicity is slightly greater than the normal threshold for lead-like compounds. This shows that structural optimization may be required to increase its physicochemical qualities and match it more closely with the desired lead-like chemical space for future development.

3.6 Drug-Likeness

Table. 1 Drug-likeness evaluation indicates full compliance with major rules, moderate oral bioavailability (0.55), and acceptable synthetic accessibility (3.14).

Rule	Result	Interpretation
Lipinski's Rule	Yes (0 violations)	Fulfills oral drug-likeness criteria.
Veber's Rule	Yes	Good bioavailability prediction.
Ghose Filter	Yes	Acceptable physicochemical space.
Egan Rule	Yes	Favors absorption and permeability.
Muegge Rule	Yes	Drug-like features confirmed.
Bioavailability Score	0.55	Indicates moderate oral bioavailability.
Synthetic Accessibility	3.14	Moderate ease of synthesis (1 = easy, 10 = hard).

Berberine showed good oral bioavailability, with high GI absorption and blood-brain barrier penetration, implying that it has systemic and CNS effects. It moderately inhibits several CYP450 enzymes, particularly CYP1A2, CYP2D6, and CYP3A4, which may influence drug metabolism and interact with co-administered medications. The molecule satisfies all key drug-likeness standards (Lipinski, Veber, Ghose, and others), with a bioavailability score of 0.55 and synthetic accessibility of 3.14, indicating moderate drug-likeness and ease of synthesis.

Berberine's ADME profile, predicted using the SwissADME program, reveals positive pharmacokinetic features, including high gastrointestinal absorption and drug-likeness. Furthermore, the chemical does not break any important drug-likeness rules and exhibits no significant interactions with key cytochrome P450 enzymes, indicating a lower chance of drug-drug interactions. According to in silico projections, Berberine is regarded relatively safe with low toxicity potential, making it appropriate for further pharmacological study.

4. In Silico ADME Analysis of Glycyrrhizin (SwissADME)

4.1 Physicochemical Properties

The compound's molecular weight is 822.93 g/mol, exceeding the suggested limit of < 500 g/mol. This violates Lipinski's rule and may impact oral bioavailability. It has 16 hydrogen bond acceptors, which exceeds the permitted maximum of 10, and 8 hydrogen bond donors, which exceed the limit of 5. Both parameters indicate excessive polarity, which may affect membrane permeability. The topological polar surface area (TPSA) is 267.04 Å², exceeding the permitted threshold of < 140 Å². This suggests poor passive diffusion across biological membranes and limited oral absorption. The molecule possesses 7 rotatable bonds, which are

within the permissible range of ≤ 10, indicating sufficient molecular flexibility. Overall, multiple violations indicate that the compound does not comply with Lipinski's rule of five and may have poor oral drug-likeness without structural optimization.

4.2 Lipophilicity (LogP)

The chemical has moderate lipophilicity according to many predicted models. The iLOGP value of 1.89, XLOGP3 of 2.80, and WLOGP of 2.25 indicate balanced hydrophilic-lipophilic characteristics, whereas MLOGP (0.22) and SILICOS-IT (0.52) imply considerably reduced lipophilicity. The calculated consensus LogP of 1.49 is within the generally acceptable range for oral medication candidates, showing good membrane permeability without excessive hydrophobicity. Overall, the lipophilicity profile indicates a good mix of solubility and permeability, which is helpful to pharmacokinetic performance.

4.3 Water Solubility

The compound's anticipated water solubility varies depending on the computer model used. The ESOL model classifies the chemical as poorly soluble, with a Log S value of -6.24 indicating limited solubility in aqueous conditions. Similarly, the Ali model predicts an even lower Log S value of -8.06, implying poor solubility and raising concerns about dissolving and oral bioavailability. In contrast, the SILICOS-IT model predicts a Log S value of -1.39, designating the molecule as soluble. The variability among models indicates some uncertainty in the solubility prediction; however, with two out of three models indicating poor solubility, the compound may require formulation strategies or structural modification to improve its aqueous solubility and pharmacokinetic performance.

4.4 Pharmacokinetics

The chemical has low gastrointestinal (GI) absorption, implying restricted oral bioavailability and reduced systemic exposure after oral treatment. It is expected to have no blood-brain barrier (BBB) penetration, implying that it is unlikely to reach therapeutic concentrations in the central nervous system.

The molecule has been identified as a P-glycoprotein (P-gp) substrate, which suggests that it may be actively effluxed from intestinal epithelial cells, adding to its poor absorption. Importantly, it does not inhibit key CYP450 enzymes, indicating a lesser likelihood of drug-drug interactions via hepatic metabolic pathways.

Furthermore, the skin permeation value (Log Kp = -9.33 cm/s) suggests extremely low transdermal penetration, suggesting that the chemical is unsuitable for transdermal drug

delivery systems.Overall, the pharmacokinetic profile points toward limited permeability and absorption, although metabolic interaction risk appears minimal.

4.5 Drug likeness

Table.2 Drug-likeness assessment shows multiple rule violations (high MW, HBA/HBD, and TPSA), indicating poor oral drug-likeness potential.

Filter	Status
Lipinski	3 violations (MW>500, HBA>10, HBD>5)
Ghose	3 violations (MW>480, MR>130, heavy atoms>70)
Veber	TPSA > 140 Å²
Egan	TPSA > 131.6
Muegge	4 violations (MW>600, TPSA>150, HBA>10, HBD>5)

Bioavailability Score

- **0.11** → Very low (ideal score is 0.55 or higher)

4.6 BOILED-Egg Model

Glycyrrhizin is out of optimal range for both GI absorption and BBB permeability, as indicated by its location outside the white (HIA) and yellow (BBB) ellipses. **Fig.2**

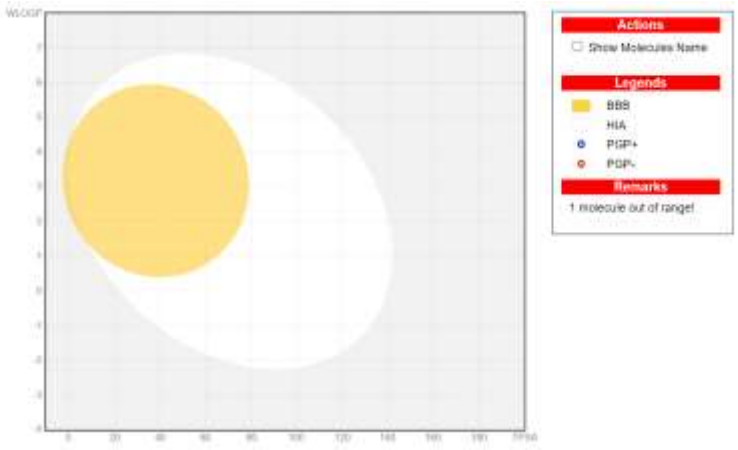

Fig. 2 BOILED-Egg plot showing the compound positioned outside the optimal BBB and HIA regions, indicating poor gastrointestinal absorption and lack of blood-brain barrier permeability, with one molecule out of the acceptable physicochemical range.

The in silico ADME analysis of Glycyrrhizin revealed poor oral bioavailability due to its high molecular weight (822.93 g/mol), high number of hydrogen bond donors (8) and acceptors (16), and an extremely large TPSA (267.04 Å²), violating multiple drug-likeness rules including Lipinski, Ghose, Veber, and Muegge filters. While lipophilicity (Consensus LogP =

1.49) is within acceptable limits, the chemical has low water solubility according to the ESOL and Ali models. Furthermore, the bioavailability score is low (0.11), and gastrointestinal absorption is expected to be inadequate. Glycyrrhizin is a P-glycoprotein substrate, although it does not inhibit key CYP450 isoenzymes, indicating a low risk of metabolic drug interactions. The chemical is also expected to be impermeable to the blood-brain barrier. Despite its pharmacological potential, the compound presents challenges for oral drug development.

4.7 Safety and Suitability Statement:

Based on the in silico ADME profile, Glycyrrhizin is expected to be pharmacologically safe, with little CYP-mediated interactions and no PAINS alarms. However, due to poor oral absorption and numerous drug-likeness violations, formulation improvement or alternate administration techniques may be required to assure therapeutic efficacy.

RESULT AND DISCUSSION

The current in silico ADME investigation found significant pharmacokinetic differences between berberine and glycyrrhizin, despite both substances' well-documented gastroprotective and anti-inflammatory effects. The success of drug development is heavily impacted by physicochemical properties and membrane permeability, which appear to favor berberine over glycyrrhizin.

Berberine showed excellent gastrointestinal absorption and met all of the major drug-likeness filters, including the Lipinski, Veber, Ghose, Egan, and Muegge criteria. The low topological polar surface area (TPSA = 40.80 $Å^2$) allows for effective passive diffusion across intestinal membranes, resulting in increased oral absorption. The consensus LogP value also suggests balanced lipophilicity, which is an important determinant of membrane permeability and systemic distribution. However, berberine was expected to be a P-glycoprotein substrate, which may account for its reported low plasma concentrations due to efflux-mediated transport. Furthermore, projected suppression of CYP1A2, CYP2D6, and CYP3A4 indicates a danger of drug-drug interactions, especially in polypharmacy settings. These data suggest that, while berberine has intriguing oral drug-like properties, careful dose adjustment and interaction assessment would be required in clinical applications.

In contrast, glycyrrhizin had several pharmacokinetic restrictions. The high molecular weight (822.93 g/mol), broad hydrogen bonding capability, and elevated TPSA (267.04 $Å^2$) significantly above accepted standards for optimum oral bioavailability. High polarity inhibits

passive diffusion across lipid membranes, explaining its limited gastrointestinal absorption and lack of blood-brain barrier permeability. Although glycyrrhizin has acceptable lipophilicity based on consensus LogP, it is insufficient to compensate for its large molecular size and polarity. The low bioavailability score (0.11) adds to its limited acceptability as a typical oral medication candidate.

Surprisingly, glycyrrhizin revealed no expected inhibition of major cytochrome P450 enzymes, indicating a lower likelihood of metabolic drug-drug interactions than berberine. This may indicate a relative pharmacokinetic advantage in combination treatments. However, a high synthetic accessibility score indicates structural complexity, which may provide difficulties in structural alteration or large-scale production.

Overall, the comparative analysis indicates that berberine has a better pharmacokinetic profile for oral development, whereas glycyrrhizin may require formulation enhancement strategies such as nanoparticle delivery, prodrug design, or alternative administration routes to overcome absorption limitations. These findings lay the groundwork for future optimization and experimental validation in gastroprotective medication development.

CONCLUSION

The current in silico ADME and drug-likeness study sheds light on the pharmacokinetic appropriateness of berberine and glycyrrhizin as possible gastroprotective drugs. According to comparative studies, berberine has positive physicochemical and pharmacokinetic properties, such as high projected gastrointestinal absorption, blood-brain barrier permeability, compliance with key drug-likeness norms, and a moderate bioavailability score (0.55). These characteristics contribute to its potential development as an orally active treatment candidate. However, its projected suppression of CYP1A2, CYP2D6, and CYP3A4 raises the possibility of drug-drug interactions, which should be carefully considered in future experimental and clinical research.

In contrast, glycyrrhizin violated numerous known drug-likeness criteria, owing to its high molecular weight, increased hydrogen bonding capability, and huge topological polar surface area. These characteristics lead to its anticipated low gastrointestinal absorption and poor oral bioavailability (bioavailability score = 0.11). Although glycyrrhizin demonstrated minor expected CYP450 inhibition, indicating a lower risk of metabolic interactions, its pharmacokinetic constraints indicate that formulation improvement or alternate delivery techniques are required to improve its therapeutic usefulness.

Overall, this computational study identifies berberine as a more attractive candidate for oral gastroprotective medication development, but glycyrrhizin may benefit from enhanced drug delivery methods. These findings provide a solid foundation for future in vitro, in vivo, and formulation-based investigations to evaluate and maximize their therapeutic potential.

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