

Research Article

In Silico ADMET and Drug-Likeness Evaluation of Withaferin A from *Withania somnifera* for Potential Application in Alzheimer's Disease

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Abstract

Background: Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and neuronal loss. Despite extensive research, effective disease-modifying therapies remain limited. Natural compounds have emerged as promising candidates due to their multi-targeted pharmacological properties. **Objective:** The present study aimed to evaluate the pharmacokinetic (ADMET) properties and drug-likeness profile of Withaferin A, a bioactive compound derived from *Withania somnifera*, using in silico approaches for its potential application in Alzheimer's disease. **Methods:** The chemical structure of Withaferin A was retrieved from the PubChem database in SMILES format and analyzed using the DeepPK platform. Various pharmacokinetic parameters, including absorption, distribution, metabolism, excretion, and toxicity, were predicted using deep learning-based computational models. Key parameters such as intestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, clearance, and toxicity endpoints were evaluated. **Results:** Withaferin A demonstrated favorable absorption characteristics, including high intestinal absorption and predicted oral bioavailability. The compound exhibited moderate distribution with significant blood–brain barrier penetration potential. Metabolic analysis indicated minimal interaction with major cytochrome P450 enzymes, except CYP3A4. The excretion profile suggested moderate clearance and a short half-life. However, toxicity predictions revealed concerns such as AMES mutagenicity and hERG inhibition, indicating potential safety risks. **Conclusion:** Withaferin A exhibits promising pharmacokinetic properties and drug-likeness characteristics, supporting its potential as a candidate for further investigation in Alzheimer's disease. However, its toxicity profile necessitates additional experimental validation. This study highlights the importance of in silico ADMET analysis in early-stage drug discovery.

Keywords: Withaferin A, ADMET Prediction, Alzheimer's Disease, In Silico Study, Pharmacokinetics

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1. Introduction

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder and the leading cause of dementia worldwide, characterized by a gradual decline in memory, cognition, and functional abilities (1). The global burden of AD is increasing rapidly due to population aging, posing a significant challenge to healthcare systems and society. Despite decades of research, the development of effective disease-modifying therapies remains limited, emphasizing the urgent need for novel therapeutic strategies targeting multiple pathological pathways (1,2).

The pathogenesis of Alzheimer's disease is multifactorial and involves complex molecular and cellular mechanisms. The hallmark pathological features include extracellular accumulation of amyloid- β (A β) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, both of which contribute to synaptic dysfunction and neuronal loss (2). In addition, oxidative stress, mitochondrial dysfunction, neuroinflammation, and excitotoxicity play crucial roles in disease progression. These interconnected processes ultimately lead to impaired neuronal communication and cognitive decline, making AD a highly complex disorder requiring multi-target therapeutic approaches (3).

Currently available pharmacological treatments, such as acetylcholinesterase inhibitors and NMDA receptor antagonists, primarily provide symptomatic relief without significantly altering disease progression (2,4). These limitations have prompted increasing interest in exploring alternative therapeutic agents, particularly those derived from natural sources. Phytoconstituents have gained considerable attention due to their diverse pharmacological activities, including antioxidant, anti-inflammatory, and neuroprotective effects,

which are highly relevant in neurodegenerative disorders (4).

Withania somnifera (Ashwagandha), a well-known medicinal plant in traditional Ayurvedic medicine, has been extensively studied for its neuroprotective properties. Among its bioactive constituents, Withaferin A, a steroidal lactone, has emerged as a promising compound with multiple biological activities. Previous studies have demonstrated that Withaferin A can modulate key signaling pathways involved in inflammation and oxidative stress, including inhibition of nuclear factor-kappa B (NF- κ B), thereby reducing neuronal damage (5). Its multi-targeted mechanism of action makes it a potential candidate for addressing the complex pathology of Alzheimer's disease.

However, the successful development of any therapeutic agent depends not only on its pharmacodynamic properties but also on its pharmacokinetic behavior and safety profile. A compound must exhibit suitable absorption, distribution, metabolism, and excretion (ADME) characteristics to achieve optimal bioavailability and therapeutic efficacy. Furthermore, toxicity assessment is essential to ensure safety during drug development, as many promising compounds fail in later stages due to unfavorable ADMET properties (6).

In recent years, in silico approaches have become integral to early-stage drug discovery, offering rapid and cost-effective evaluation of pharmacokinetic and toxicity profiles. Computational tools such as DeepPK utilize machine learning algorithms to predict ADMET parameters based on molecular structure, enabling efficient screening of potential drug candidates (7). Additionally, drug-likeness evaluation provides insight into whether a compound possesses physicochemical properties consistent

with known drugs, further supporting its development potential.

Therefore, the present study aims to evaluate the ADMET properties and drug-likeness profile of Withaferin A using in silico methods. Particular emphasis is placed on parameters relevant to central nervous system targeting, including blood–brain barrier permeability and metabolic stability, to assess its suitability as a potential therapeutic candidate for Alzheimer’s disease.

2. MATERIALS AND METHODS

The present study employed a computational approach to evaluate the pharmacokinetic and toxicity profile of Withaferin A using in silico ADMET prediction tools. All analyses were performed using validated cheminformatics databases and machine learning-based predictive platforms to ensure reliability and reproducibility of the results.

2.1 Compound Selection and Data Retrieval

Withaferin A, a bioactive steroidal lactone derived from *Withania somnifera*, was selected as the model compound based on its reported neuroprotective and pharmacological potential. The chemical structure of Withaferin A was retrieved from the PubChem database in the form of Simplified Molecular Input Line Entry System (SMILES) notation. The SMILES format was chosen due to its compatibility with computational tools and its ability to represent molecular structure in a standardized textual format suitable for machine learning-based analysis.

The retrieved structure was carefully verified to ensure accuracy and consistency with reported chemical data. No additional structural optimization or energy minimization was performed, as the selected prediction platform directly accepts SMILES input for pharmacokinetic modeling.

2.2 Computational Platform for ADMET Prediction

Pharmacokinetic and toxicity predictions were conducted using DeepPK, a deep learning-based computational tool designed for the prediction of ADMET properties. DeepPK utilizes advanced neural network architectures trained on large datasets of experimentally validated compounds to estimate pharmacokinetic parameters based on molecular descriptors and structural features.

The platform integrates multiple predictive models to evaluate absorption, distribution, metabolism, excretion, and toxicity endpoints. Its algorithm extracts chemical features such as molecular weight, lipophilicity, hydrogen bonding capacity, and structural motifs, which are then processed through trained models to generate quantitative and categorical predictions.

2.3 ADMET Prediction Workflow

The SMILES representation of Withaferin A was input into the DeepPK platform, where it was processed through the predictive pipeline. The workflow involved automated feature extraction followed by parameter estimation using pre-trained deep learning models. The predicted ADMET parameters were categorized into absorption, distribution, metabolism, excretion, and toxicity profiles.

2.3.1 Absorption Parameters

Absorption-related properties were evaluated using predicted values of Caco-2 cell permeability, which reflects intestinal epithelial transport potential, and Madin–Darby Canine Kidney (MDCK) permeability, which provides insight into passive diffusion across biological membranes. Human intestinal absorption and oral bioavailability at different thresholds were

also predicted to assess the extent of systemic drug availability following oral administration. Additionally, interaction with P-glycoprotein (P-gp), including substrate and inhibitory potential, was analyzed to evaluate drug transport and efflux mechanisms.

2.3.2 Distribution Parameters

Distribution characteristics were assessed using predicted volume of distribution at steady state (VD_{ss}), fraction unbound in plasma, and plasma protein binding percentage. Blood–brain barrier (BBB) permeability was evaluated using logPS values and categorical classification to determine the compound's ability to penetrate the central nervous system. These parameters are critical for assessing the suitability of compounds intended for neurological applications.

2.3.3 Metabolism Parameters

Metabolic profiling was performed by predicting interactions with major cytochrome P450 (CYP) enzymes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Both substrate and inhibitor characteristics were evaluated to identify potential metabolic pathways and the likelihood of drug–drug interactions. Additional transporter-related interactions, such as breast cancer resistance protein (BCRP) and organic anion transporting polypeptides (OATP1B1 and OATP1B3), were also assessed.

2.3.4 Excretion Parameters

Excretion-related properties were analyzed through predicted clearance values and half-life estimation. Clearance predictions provided insight into the rate of drug elimination, while half-life estimation indicated the duration of systemic exposure. Interaction with renal transporters, particularly organic cation transporter 2 (OCT2), was evaluated

to understand potential involvement in renal excretion mechanisms.

2.3.5 Toxicity Assessment

Toxicity profiling included prediction of multiple safety endpoints such as AMES mutagenicity, carcinogenicity, hepatotoxicity, hERG channel inhibition, skin sensitization, respiratory toxicity, and maximum tolerated dose. Environmental toxicity indicators, including bioconcentration factor and ecotoxicity endpoints, were also evaluated to provide a comprehensive safety assessment.

2.4 Data Extraction and Analysis

The predicted ADMET data generated by DeepPK were obtained in tabular format and systematically organized into structured datasets. Each parameter was analyzed based on standard pharmacokinetic principles and interpreted in the context of drug-likeness and therapeutic applicability. Special emphasis was placed on parameters relevant to central nervous system drug delivery, particularly BBB permeability and metabolic stability.

2.5 Statistical Considerations

As the study was based on computational predictions, no experimental statistical tests were applied. However, confidence scores provided by the predictive models were considered to assess the reliability of categorical outcomes. The results were interpreted qualitatively and quantitatively to derive meaningful conclusions regarding the pharmacokinetic suitability of Withaferin A.

3. Results and Discussion

3.1 Absorption Profile

Table 3.1: Predicted Absorption Parameters of Withaferin A

Parameter	Predicted Value	Unit / Category	Confidence
Caco-2 Permeability	-5.22	logP _{aap}	—
Human Oral Bioavailability (20%)	Bioavailable	Category	0.627
Human Intestinal Absorption	Absorbed	Category	0.979
MDCK Permeability	-4.85	cm/s	—
Human Oral Bioavailability (50%)	Bioavailable	Category	0.92
P-gp Inhibitor	Inhibitor	Category	0.863
P-gp Substrate	Non-Substrate	Category	0.468
Skin Permeability	-2.86	log Kp	—

The absorption profile of Withaferin A indicates that the compound possesses favorable characteristics for oral drug administration. The predicted Caco-2 permeability value suggests moderate intestinal permeability, which is supported by the high probability of human intestinal absorption. Additionally, the compound is predicted to be bioavailable at both 20% and 50% thresholds, indicating that a significant fraction of the administered dose may reach systemic circulation.

The MDCK permeability value further supports moderate membrane permeability, while the classification as a P-glycoprotein inhibitor suggests that Withaferin A may influence drug transport mechanisms. Being a non-substrate of P-glycoprotein may reduce the likelihood of active efflux, thereby improving intracellular retention. Overall, these findings suggest that Withaferin A exhibits a suitable absorption profile for further pharmacokinetic consideration.

3.2 Distribution Profile

Table 3.2: Predicted Distribution Parameters of Withaferin A

Parameter	Predicted Value	Unit / Category	Confidence
BBB Permeability (logPS)	-2.84	log PS	—
BBB Penetration	Penetrable	Category	0.815
Fraction Unbound	0.59	Free proportion	—

Plasma Protein Binding	54.33	%	—
Volume of Distribution (VDss)	1.26	log VDss	—

The distribution profile of Withaferin A suggests that the compound has the ability to distribute effectively within the body. The predicted volume of distribution indicates moderate tissue penetration, suggesting that the compound is not restricted to plasma but can access peripheral compartments. The fraction unbound value indicates that a reasonable proportion of the drug remains free and pharmacologically active.

Importantly, the predicted blood–brain barrier permeability and classification as a BBB-penetrable compound highlight its potential to reach the central nervous system. This property is particularly relevant for applications in neurological disorders such as Alzheimer’s disease. The moderate plasma protein binding further supports balanced distribution, ensuring both sufficient circulation and tissue availability.

3.3 Metabolism Profile

Table 3.3: Predicted Metabolic Parameters of Withaferin A

Parameter	Predicted Value	Category	Confidence
BCRP Inhibitor	Non-Inhibitor	Category	0.211
CYP1A2 Inhibitor	Non-Inhibitor	Category	0.0
CYP1A2 Substrate	Non-Substrate	Category	0.096

CYP2C19 Inhibitor	Non-Inhibitor	Category	0.0
CYP2C19 Substrate	Non-Substrate	Category	0.36
CYP2C9 Inhibitor	Non-Inhibitor	Category	0.027
CYP2C9 Substrate	Non-Substrate	Category	0.0
CYP2D6 Inhibitor	Non-Inhibitor	Category	0.0
CYP2D6 Substrate	Non-Substrate	Category	0.335
CYP3A4 Inhibitor	Inhibitor	Category	0.612
CYP3A4 Substrate	Substrate	Category	0.997
OATP1B1	Non-Inhibitor	Category	0.485
OATP1B3	Non-Inhibitor	Category	0.353

The metabolism profile of Withaferin A indicates minimal interaction with most cytochrome P450 enzymes, as the compound is predicted to be a non-inhibitor and non-substrate for CYP1A2, CYP2C19, CYP2C9, and CYP2D6. This suggests a lower likelihood of metabolic drug–drug interactions, which is an important consideration in drug development.

However, the compound is predicted to act as both a substrate and inhibitor of CYP3A4, indicating that this enzyme may play a significant role in its metabolism. This dual interaction suggests the possibility of metabolic modulation, which may influence drug clearance and systemic exposure. Overall, the metabolism profile suggests that

Withaferin A has a relatively stable metabolic behavior with specific involvement of CYP3A4 pathways

3.4 Excretion Profile

Table 3.4: Predicted Excretion Parameters of Withaferin A

Parameter	Predicted Value	Unit / Category	Confidence
Clearance	11.71	Log (ml/min/kg)	—
OCT2 Inhibitor	Non-Inhibitor	Category	0.278
Half-life	< 3 hours	Category	0.474

The predicted clearance value suggests that Withaferin A may be eliminated at a moderate rate from the body. Clearance is a critical parameter influencing drug concentration and duration of action, and moderate clearance may contribute to maintaining therapeutic levels without rapid elimination.

The predicted half-life of less than 3 hours indicates relatively short systemic persistence, which may necessitate frequent dosing to maintain effective drug levels. Additionally, the compound is predicted to be a non-inhibitor of organic cation transporter 2, suggesting minimal interference with renal excretion pathways. These findings indicate a manageable excretion profile with potential considerations for dosing frequency.

3.5 Toxicity Profile

Table 3.5: Predicted Toxicity Parameters of Withaferin A

Parameter	Predicted Value	Category	Confidence
AMES Mutagenesis	Toxic	Category	0.83
Avian Toxicity	Safe	Category	0.017
Bee Toxicity	Toxic	Category	0.993
Bioconcentration Factor	-0.68	log10(L/kg)	—
Biodegradation	Safe	Category	0.009
Carcinogenesis	Safe	Category	0.342
Crustacean Toxicity	Safe	Category	0.448
Liver Injury I (DILI)	Safe	Category	0.264
Liver Injury II	Toxic	Category	0.55
hERG Blocker	Toxic	Category	0.916
Eye Corrosion	Safe	Category	0.0
Eye Irritation	Safe	Category	0.032
Maximum Tolerated Dose	-0.31	log mg/kg/day	—
Micronucleus	Toxic	Category	0.636

Respiratory Toxicity	Toxic	Category	0.956
Skin Sensitisation	Toxic	Category	0.512

The toxicity profile of Withaferin A presents a mixed safety pattern. While the compound is predicted to be safe in several categories such as carcinogenicity, biodegradation, and certain organ-specific toxicities, it shows positive predictions for AMES mutagenicity and hERG channel inhibition. These findings suggest potential genotoxic and cardiotoxic risks that require careful evaluation.

Additionally, the compound shows toxicity in specific endpoints such as skin sensitization and respiratory toxicity, indicating possible adverse effects under certain conditions. However, the presence of multiple “safe” classifications also highlights a balanced toxicity profile. Overall, these results suggest that while Withaferin A has promising pharmacokinetic properties, its safety profile warrants further detailed investigation.

3.6 General Physicochemical Properties

Table 3.6: General Properties of Withaferin A

Parameter	Predicted Value	Unit
Boiling Point	523.36	°C
Hydration Free Energy	-2.99	kcal/mol
LogD (pH 7.4)	2.8	log mol/L
LogP	2.59	log mol/L
LogS	-5.26	log mol/L

Vapor Pressure	-9.48	log vp
Melting Point	227.08	°C
pKa (Acidic)	5.64	-log Ka
pKa (Basic)	5.3	-log Ka

The physicochemical properties of Withaferin A indicate favorable drug-like characteristics. The LogP and LogD values suggest moderate lipophilicity, which is important for membrane permeability and absorption. The solubility profile, as indicated by LogS, suggests moderate aqueous solubility, which may influence formulation strategies.

The thermal properties, including melting and boiling points, indicate structural stability, while pKa values suggest the compound may exist in both ionized and non-ionized forms depending on the physiological environment. These properties collectively contribute to the overall pharmacokinetic behavior and support the compound’s potential as a drug candidate.

Both compounds showed no significant interaction with OCT2 transporters, indicating minimal risk of transporter-mediated renal toxicity.

From a CKD perspective, Empagliflozin may offer safety advantages due to lower accumulation risk, whereas Dapagliflozin may provide prolonged therapeutic action.

3.5 Toxicity Profile

Table 3.5: Comparative Toxicity Parameters

Parameter	Empagliflozin	Dapagliflozin
AMES Mutagenicity	Toxic	Safe

Carcinogenicity	Safe	Safe
hERG Blocker	Toxic	Safe
DILI	Toxic (II)	Safe
Micronucleus	Toxic	Toxic
Respiratory Toxicity	Toxic	Toxic
Skin Sensitization	Toxic	Toxic

Toxicity predictions revealed notable differences between the two compounds. Empagliflozin showed potential risks in AMES mutagenicity, hepatotoxicity, and hERG inhibition, indicating possible concerns related to genetic and cardiac safety.

In contrast, Dapagliflozin demonstrated a comparatively safer toxicity profile, particularly in mutagenicity and cardiotoxicity endpoints.

Although both drugs exhibited some toxicity alerts (e.g., micronucleus and respiratory toxicity), Dapagliflozin appears relatively safer overall based on in silico predictions.

3.6 Physicochemical Properties

Table 3.6: Comparative Physicochemical Parameters

Parameter	Empagliflozin	Dapagliflozin
LogP	1.93	-1.66
LogD (pH 7.4)	3.0	-2.68
LogS	-3.33	-0.24
Stability	High	Moderate

Melting Point (°C)	180.62	41.98
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Empagliflozin demonstrated moderate lipophilicity, supporting membrane permeability and efficient systemic distribution. Dapagliflozin, being more hydrophilic, showed better solubility but potentially reduced permeability.

This reflects a classic trade-off:

- Empagliflozin → better permeability
- Dapagliflozin → better solubility

Overall, Empagliflozin exhibits a more balanced physicochemical profile, favoring pharmacokinetic performance.

3.7 Overall Comparative Interpretation

The present in silico study provides a comprehensive comparative evaluation of Empagliflozin and Dapagliflozin for potential repurposing in Chronic Kidney Disease.

Both drugs demonstrated favorable absorption characteristics; however, Empagliflozin exhibited a more stable profile due to reduced transporter dependence. Distribution analysis highlighted greater free drug availability for Empagliflozin, suggesting enhanced pharmacological activity.

Metabolic evaluation indicated low drug–drug interaction risk for both compounds, although their metabolic pathways differed. Excretion analysis suggested that Empagliflozin may be safer in CKD due to faster clearance and reduced accumulation risk, while Dapagliflozin may offer prolonged therapeutic action due to its longer half-life.

Toxicity predictions revealed comparatively safer outcomes for Dapagliflozin, particularly in mutagenicity and cardiotoxicity parameters. Physicochemical analysis further supported better

permeability for Empagliflozin and higher solubility for Dapagliflozin.

In conclusion, Empagliflozin demonstrates superior pharmacokinetic characteristics, whereas Dapagliflozin exhibits a comparatively safer toxicity profile. Both compounds show promising potential for CKD repurposing; however, further experimental and clinical validation is required to confirm these findings.

4. Discussion

The present study provides a comprehensive *in silico* evaluation of the pharmacokinetic and toxicity profile of Withaferin A, highlighting its potential as a therapeutic candidate for Alzheimer's disease. The findings demonstrate that Withaferin A possesses several favorable ADMET characteristics, although certain safety concerns warrant further investigation. The integration of computational predictions with existing literature offers valuable insights into its drug development potential.

The absorption profile of Withaferin A suggests that the compound has suitable characteristics for oral administration. The predicted human intestinal absorption and oral bioavailability indicate efficient uptake and systemic availability, which are essential prerequisites for therapeutic efficacy. Moderate Caco-2 and MDCK permeability values further support its ability to cross biological membranes. These findings are consistent with previous studies reporting that compounds with balanced lipophilicity and molecular size exhibit improved gastrointestinal absorption (6). Additionally, the classification of Withaferin A as a P-glycoprotein inhibitor may enhance intracellular drug retention by limiting efflux mechanisms, thereby potentially increasing bioavailability. However, such inhibitory activity may also influence the pharmacokinetics of co-

administered drugs, suggesting a need for careful evaluation of drug–drug interactions.

Distribution analysis revealed that Withaferin A exhibits moderate volume of distribution and plasma protein binding, indicating balanced systemic distribution. Importantly, the predicted ability to penetrate the blood–brain barrier is a critical finding in the context of Alzheimer's disease. Central nervous system drug delivery remains a major challenge due to the restrictive nature of the blood–brain barrier. Compounds capable of crossing this barrier are more likely to exert therapeutic effects in neurodegenerative conditions. The BBB permeability of Withaferin A aligns with previous reports suggesting that lipophilic natural compounds with moderate molecular weight can effectively access brain tissues (5,7). Furthermore, the fraction of unbound drug indicates that a significant proportion remains pharmacologically active, supporting its therapeutic potential.

The metabolism profile of Withaferin A indicates minimal interaction with most cytochrome P450 enzymes, which is advantageous in reducing the risk of metabolic drug–drug interactions. The lack of inhibition or substrate activity for CYP1A2, CYP2C9, CYP2C19, and CYP2D6 suggests metabolic stability across multiple pathways. However, the predicted interaction with CYP3A4, both as a substrate and inhibitor, highlights a potential metabolic liability. CYP3A4 is one of the most abundant and clinically significant enzymes involved in drug metabolism, and its modulation can significantly affect drug clearance and systemic exposure. Similar findings have been reported in earlier studies where natural compounds exhibited selective CYP3A4 interactions, necessitating further experimental validation (6). This dual interaction may influence dosing strategies and requires consideration during future pharmacokinetic studies.

The excretion profile demonstrated moderate clearance and a relatively short half-life for Withaferin A. While moderate clearance is generally favorable, the short half-life may limit sustained therapeutic exposure, potentially necessitating frequent dosing or modified drug delivery systems. Strategies such as sustained-release formulations or nanoformulations may be explored to overcome this limitation and improve pharmacokinetic performance. The absence of OCT2 inhibition suggests minimal interference with renal excretion pathways, which is advantageous in maintaining normal physiological elimination processes.

Toxicity prediction revealed a mixed safety profile, which is a critical consideration in drug development. The positive prediction for AMES mutagenicity indicates potential genotoxic risk, while hERG channel inhibition raises concerns regarding cardiotoxicity. hERG inhibition is particularly significant, as it is associated with QT interval prolongation and potential cardiac arrhythmias. These findings highlight the importance of conducting detailed *in vitro* and *in vivo* toxicity studies to validate the computational predictions. Additionally, the observed respiratory toxicity and skin sensitization suggest possible adverse effects under specific conditions. However, the compound was predicted to be safe in several other toxicity endpoints, including carcinogenicity and certain organ-specific toxicities, indicating that the overall safety profile is not uniformly adverse. Similar mixed toxicity patterns have been reported for bioactive natural compounds, where therapeutic benefits coexist with manageable safety risks (5).

The physicochemical properties of Withaferin A further support its drug-likeness. The predicted LogP and LogD values indicate moderate lipophilicity, which is favorable for membrane permeability and absorption. These values are consistent with

Lipinski's Rule of Five, suggesting that the compound may exhibit good oral bioavailability (7). The moderate aqueous solubility, as indicated by LogS, suggests that formulation strategies may be required to enhance solubility and bioavailability. The presence of ionizable groups, as indicated by pKa values, may influence the compound's behavior under physiological conditions, affecting its absorption and distribution.

From a mechanistic perspective, the pharmacological potential of Withaferin A in Alzheimer's disease is supported by its reported ability to modulate inflammatory and oxidative stress pathways. Previous studies have demonstrated its inhibitory effect on NF- κ B signaling and its role in reducing oxidative damage, both of which are key contributors to neurodegeneration (5). When combined with favorable BBB permeability, these properties suggest that Withaferin A may effectively target multiple pathological pathways in Alzheimer's disease.

Despite these promising findings, the study has certain limitations. The results are based solely on *in silico* predictions, which, although highly informative, may not fully replicate biological complexity. The accuracy of predictions depends on the quality of training datasets and algorithms used in the computational models. Therefore, experimental validation through *in vitro* and *in vivo* studies is essential to confirm the pharmacokinetic and toxicity profiles observed in this study.

Overall, the integration of ADMET prediction and drug-likeness evaluation provides a comprehensive assessment of Withaferin A as a potential therapeutic candidate. The compound exhibits a balance of favorable pharmacokinetic properties and manageable safety concerns, supporting its further investigation in the context of Alzheimer's disease.

Future studies should focus on experimental validation, formulation optimization, and mechanistic exploration to fully realize its therapeutic potential.

5. Conclusion:

The present study provided a comprehensive in silico evaluation of the pharmacokinetic and toxicity profile of Withaferin A, a प्रमुख bioactive constituent of *Withania somnifera*, with a focus on its potential application in Alzheimer's disease. The findings demonstrated that Withaferin A possesses favorable absorption characteristics, including good intestinal permeability and oral bioavailability, which are essential for effective systemic exposure. The distribution profile revealed moderate tissue penetration along with significant blood–brain barrier permeability, indicating its suitability for central nervous system targeting.

The metabolic analysis suggested minimal interaction with most cytochrome P450 enzymes, except CYP3A4, which may play a key role in its biotransformation. The excretion profile indicated moderate clearance and a relatively short half-life, suggesting the need for optimization strategies such as controlled-release formulations to maintain therapeutic levels. Importantly, the toxicity assessment highlighted certain concerns, including AMES mutagenicity and hERG channel inhibition, which may pose potential safety risks and require further experimental validation.

Overall, Withaferin A exhibits promising pharmacokinetic properties and drug-likeness characteristics, supporting its candidacy for further drug development. However, the identified toxicity risks emphasize the necessity of detailed in vitro and in vivo investigations before clinical translation. This study underscores the importance of in silico ADMET evaluation as a rapid and cost-effective

approach in early-stage drug discovery, enabling the identification and prioritization of potential therapeutic compounds for complex disorders such as Alzheimer's disease.

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