

DOCKING AND ADMET EVALUATION OF ASTRAGALUS-DERIVED PHYTOCHEMICALS AGAINST GLYCOGEN SYNTHASE KINASE-3 β **E.M. Yergaliyeva¹, V.V. Vazhev², A.B. Uzakova^{3*}, D.B. Zhusupova¹, M.A. Gubenko¹, S.B. Abeuova⁴**¹ Akhmet Baitursynuly Kostanay Regional University, Kostanay, Kazakhstan² Kostanay Social-Technical University named after academician Zulkarnay Aldamzhar, Kostanay, Kazakhstan³ Abai Kazakh National Pedagogical University, Almaty, Kazakhstan⁴ Astana International University, Astana, Kazakhstan*Corresponding author e-mail: a.uzakova@abaiuniversity.edu.kz

Abstract. Glycogen synthase kinase-3 β (GSK-3 β) regulates cellular processes associated with inflammation, apoptosis, and neurodegeneration and is a validated therapeutic target. Interest in natural compounds capable of interacting with the GSK-3 β active site is driven by the toxicity and adverse effects associated with many existing kinase inhibitors. This study aimed to evaluate *Astragalus* phytocomponents as potential GSK-3 β ligands *in silico* using molecular docking and ADMET prediction. The docking methodology was validated by redocking the native ligand FKB501 from the cocrystallized X-ray structure, yielding an RMSD of 1.83 Å. To assess affinity for the GSK-3 β active site, a library of 96 *Astragalus* compounds was screened. Based on binding affinity and ADMET characteristics, six compounds were selected for detailed analysis: soyasapogenol B, soyasapogenol E, chlorogenic acid, neochlorogenic acid, isoliquiritigenin, and echinatin. Their binding energies were comparable to or exceeded, in absolute value, that of FKB501 (-7.546 kcal/mol), with the lowest values observed for soyasapogenol B (-8.523 kcal/mol) and soyasapogenol E (-8.176 kcal/mol). Interaction analysis revealed key active-site residues, including Ile62, Phe67, Val70, Ala83, Lys85, Val135, Gln185, Leu188, Cys199, and Asp200. ADMET prediction indicated that isoliquiritigenin and echinatin had the most balanced pharmacological and toxicological profiles, whereas sapogenins, despite their higher docking affinity, were limited by low solubility and high lipophilicity. The selected *Astragalus* phytocomponents are therefore promising candidates for further experimental evaluation as potential GSK-3 β inhibitors.

Keywords: GSK-3 β , *Astragalus*, molecular docking, ADMET, phytocomponents, soyasapogenol, chlorogenic acid, isoliquiritigenin, echinatin

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1. Introduction

The involvement of glycogen synthase kinase-3 β (GSK-3 β) in processes related to the regulation of glycogen synthase activity, insulin signaling, inflammation, apoptosis, and neurodegenerative processes makes GSK-3 β an important therapeutic target [1]. However, many known ATP-competitive inhibitors have limited use due to risks associated with low selectivity and safety concerns [2, 3]. Therefore, natural compounds remain a promising source in the search for new GSK-3 β ligands with favorable pharmacological and toxicological profiles.

The rich phytochemical composition and extensive study of *Astragalus membranaceus* and the genus *Astragalus* in general make them interesting targets for the above-mentioned research. The main groups of compounds found in *Astragalus* plants include triterpene saponins, flavonoids, isoflavonoids, and phenolic metabolites [4]. Also, according to sources, representatives of the genus exhibit inhibitory effects on α -glucosidase, α -amylase, cholinesterases, tyrosinase, β -glucuronidase, hCA II, COX-2, and bacterial targets. However, the type and intensity of activity depend on the plant species, organ, extract composition, and chemical class of compounds [4–7]. Therefore, we believe it would be appropriate to screen *Astragalus* phytocomponents for potential GSK-3 β inhibitors.

To prioritize such compounds, molecular docking and ADMET prediction are commonly used as complementary tools at the early stages of computer-aided drug discovery [8]. Docking makes it possible to evaluate the spatial orientation of a ligand within the protein active site and to compare its predicted affinity for the molecular target [9]. However, docking score alone is insufficient for selecting promising candidates, since compounds with favorable binding energy may still exhibit poor solubility, low permeability, undesirable interactions with CYP enzymes or hERG channels, or potential toxicity [10, 11]. Therefore, ADMET filtering provides an additional level of selection by assessing the predicted biopharmaceutical limitations and safety-related risks of candidate molecules. In the present study, this combined docking–ADMET strategy was applied to select *Astragalus*-derived phytocomponents capable of binding to the active site of GSK-3 β while retaining acceptable predicted properties for subsequent experimental investigation.

2. Experimental part

The crystal structure of GSK-3 β was downloaded from the Protein Data Bank, PDB ID: 6H0U, at 2.3 Å resolution [12]. During protein preparation in AutoDockTools 1.5.7, water molecules and ions, as well as the original ligand, were removed from the structure. The structure was saved in PDBQT after adding polar hydrogen atoms and Kollman charges.

Based on *Astragalus* phytocomponents described in the literature, a ligand library was created, comprising 96 compounds in SMILES format. The original structures of the compounds were converted to SDF format, and geometry was

optimized using Open Babel 3.1.1. Meeko 0.7.1 was used to add hydrogen atoms, calculate Gasteiger charges, and save the structure in PDBQT.

The active site of GSK-3 β was determined based on the position of the native ligand FKB501. The center of the calculation box was defined by the coordinates: X = -5.560 Å, Y = -28.948 Å, Z = -16.272 Å. The box size was 15 × 15 × 15 Å.

The docking protocol was validated by redocking the native ligand FKB501. The RMSD value between the experimental and predicted poses was 1.83 Å, which meets the generally accepted criterion for successful docking protocol validation: RMSD < 2.0 Å [13].

Molecular docking was performed in AutoDock Vina 1.2.3 [14] with an exhaustiveness setting of 32. For each ligand, the best binding energy was recorded, and the most favorable conformation was analyzed. Visualization of complexes and 2D interaction diagrams was performed in PyMOL and Discovery Studio Visualizer.

ADMETlab 3.0 [15] was used to evaluate molecular weight, the number of hydrogen bond donors and acceptors, TPSA, lipophilicity, drug-likeness, predicted absorption, distribution, metabolism, toxicity, and integrated indicators of compound suitability for further analysis. All 96 compounds were screened, and then, for a more in-depth analysis of binding parameters, bioavailability, and pharmacological and toxicological profiles, selection was performed based on a combination of high affinity, absence of Lipinski's rule violations, and absence of critical toxicological risks in ADMETlab 3.0.

3. Results and Discussion

The initial set of 96 *Astragalus*-associated compounds was ranked by docking affinity to the GSK-3 β active site and subsequently filtered according to predicted drug-likeness and toxicological parameters. Six compounds with the most favorable combination of docking score, phytochemical relevance, and ADMET profile were selected for detailed interaction analysis (Table 1).

Table 1 – Molecular docking scores and key interactions of selected *Astragalus*-derived compounds with GSK-3 β

Compound	Binding affinity, kcal/mol	Key interactions with GSK-3 β
FKB501	-7.546	Conventional H-bond: Gln185 (2.56 Å); π -donor H-bond: Phe67 (4.00 Å); π -sulfur interaction: Cys199 (4.03 Å); π - π stacked interactions: Phe67 (5.30–5.62 Å); alkyl interactions: Ala83 (3.77 Å), Leu188 (4.43 Å), Cys199 (5.11 Å); π -alkyl interactions: Phe67 (5.29 Å), Val70 (4.64 Å)
Soyasapogenol B	-8.523	Conventional H-bond: Val135 (2.61 Å); alkyl interactions: Ile62 (3.72–5.47 Å), Val70 (5.02 Å); π -alkyl interactions: Phe67 (5.05 Å), Tyr134 (4.62 Å)
Soyasapogenol E	-8.176	Conventional H-bonds: Lys183 (2.20 Å), Asn64 (2.40 Å); alkyl interactions: Ile62 (4.77 Å), Val70 (5.09 Å), Leu188 (5.22 Å), Cys199 (5.45 Å); π -alkyl interaction: Tyr134 (4.61 Å)

Chlorogenic acid	-7.739	Conventional H-bonds: Asp200 (2.13 Å), Asn64 (2.03 Å), Gln185 (2.88 Å); π -alkyl interactions: Ala83 (3.50 Å), Leu188 (4.99 Å)
Neochlorogenic acid	-7.675	Conventional H-bonds: Val135 (2.15 Å), Asp200 (2.64 Å), Lys85 (2.92 Å); π -alkyl interactions: Ala83 (3.57 Å), Leu188 (4.85 Å)
Isoliquiritigenin	-7.436	Conventional H-bonds: Val135 (1.87 and 2.15 Å), Asn186 (2.04 Å), Asp200 (2.63 Å); π -alkyl interactions: Ala83 (3.72 Å), Leu188 (4.99 Å), Val70 (5.43 Å)
Echinatin	-7.263	Conventional H-bond: Asp200 (2.37 Å); π -sulfur interaction: Cys199 (4.11 Å); π - π stacked interaction: Phe67 (4.52 Å); π -alkyl interactions: Ala83 (5.05 Å), Val70 (5.27 Å), Leu188 (5.36 Å)

Soyasapogenol B and Soyasapogenol E showed the most favorable docking scores among the selected phytocomponents. Soyasapogenol B formed one conventional hydrogen bond with Val135 (2.61 Å), a residue previously reported as important for the stabilization of ATP-competitive GSK-3 β inhibitors [2]. In addition to this polar contact, the complex was stabilized by several hydrophobic interactions involving Ile62, Val70, Phe67, and Tyr134. The predominance of alkyl and π -alkyl contacts is consistent with the triterpene structure of Soyasapogenol B, whose extended hydrophobic skeleton may favor anchoring in the nonpolar region of the GSK-3 β active site (Fig. 1). Soyasapogenol E formed two conventional hydrogen bonds with Lys183 and Asn64 and additional hydrophobic contacts with Ile62, Val70, Leu188, Cys199, and Tyr134. Compared to soyasapogenol B, the binding energy was less favorable, despite the higher number of hydrogen bonds. This may be due to the orientation of the ligand and the efficiency of the hydrophobic packing within the binding pocket.

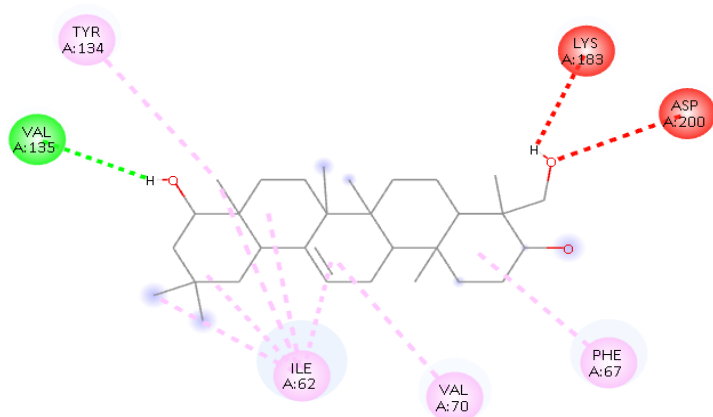


Figure 1 – 2D diagram of the interactions of Soyasapogenol B with the active site of GSK-3 β . Conventional hydrogen bonds are shown in green, π -alkyl hydrophobic interactions in pink, and unfavorable acceptor-acceptor contacts in red.

Chlorogenic acid formed three conventional hydrogen bonds with residues Asp200, Asn64, and Gln185. The shortest bonds were observed with Asn64 (2.03 Å) and Asp200 (2.13 Å), which may be the main contributor to complex stabilization. Additionally, the aromatic moiety of the ligand participated in hydrophobic π -alkyl interactions with Ala83 and Leu188. The contact with Gln185 is important, as this residue has already been noted to be important for binding of the native ligand FKB501 in the active site of GSK-3 β . Like chlorogenic acid, neochlorogenic acid formed hydrophobic π -alkyl interactions with Ala83 and Leu188, but instead of hydrogen contacts with Asn64 and Gln185, it was characterized by interactions with Lys85 and Val135.

Isoliquiritigenin formed an extensive network of conventional hydrogen bonds with residues Val135, Asn186, and Asp200. The shortest bond was observed between Val135 and the ligand oxygen atom (1.87 Å), indicating a significant contribution of this contact to complex stabilization. Additionally, the aromatic system of isoliquiritigenin participated in π -alkyl interactions with Ala83, Leu188, and Val70. Despite its less favorable docking affinity compared to sapogenins, the presence of several directional hydrogen bonds and hydrophobic contacts confirms stable fixation of the molecule in the GSK-3 β active site.

Echinatin formed one conventional hydrogen bond with Asp200 (2.37 Å), as well as several aromatic and hydrophobic contacts important for stabilizing the chalcone backbone in the GSK-3 β active site. Of particular significance are the π -sulfur interaction with Cys199 and π - π stacking with Phe67, as these residues are also noted to be important for ligand binding in the ATP-binding pocket of GSK-3 β . The molecule additionally formed π -alkyl contacts with Ala83, Val70, and Leu188. Despite its weaker docking affinity compared to sapogenins, the interaction profile of echinatin is qualitatively interesting due to the involvement of Cys199 and Phe67.

The native ligand FKB501 formed one conventional hydrogen bond with Gln185 (2.56 Å) and a π -donor hydrogen bond with Phe67 (4.00 Å). Aromatic and hydrophobic contacts significantly contributed to the stabilization of the complex: π -sulfur interaction with Cys199 (4.03 Å), π - π stacking with Phe67 (5.30–5.62 Å), and alkyl/ π -alkyl interactions with Val70, Ala83, Leu188, Cys199, and Phe67. Comparison with the native ligand FKB501 revealed that the selected phytocomponents are stabilized in the GSK-3 β active site through different mechanisms. Chlorogenic acid most clearly mimics the polar contact with Gln185 characteristic of FKB501. Echinatin, on the other hand, is closer to the native ligand in its aromatic-hydrophobic profile, interacting with Phe67 and Cys199. Soyasapogenol B and Soyasapogenol E exhibit the highest calculated affinities, but their binding is largely determined by the hydrophobic packing of the triterpene skeleton.

To assess the pharmacokinetic suitability of the selected compounds, a comparative analysis was conducted using ADMETlab 3.0. Table 2 lists the most informative parameters characterizing drug-likeness, solubility, lipophilicity,

polarity, predicted absorption, distribution, and toxicological risks; parameters that do not affect candidate ranking were omitted.

Table 2 – Comparative ADMET profile of selected *Astragalus*-derived compounds predicted by ADMETlab 3.0

Indicator	Soyasapogenol B	Soyasapogenol E	Chlorogenic acid	Neochlorogenic acid	Isoliquiritigenin	Echinatin
MW	458.38	456.36	354.10	354.10	256.07	270.09
QED	0.415	0.454	0.234	0.234	0.583	0.662
TPSA, Å ²	60.69	57.53	164.75	164.75	77.76	66.76
logP	4.27	3.73	1.04	0.84	2.52	2.83
logS	-5.25	-4.66	-2.96	-2.76	-3.46	-3.90
Caco-2	-5.39	-5.18	-6.43	-6.33	-4.84	-4.83
HIA	0.99	0.96	0.99	1.00	0.49	0.26
BBB	0.97	0.95	0.56	0.42	0.07	0.19
PPB, %	87.92	91.97	64.83	56.53	96.10	94.46
hERG	0.03	0.03	0.03	0.01	0.19	0.23
DILI	0.14	0.28	0.29	0.23	0.24	0.35
Ames	0.32	0.55	0.39	0.39	0.29	0.37
LD50 oral	0.657	0.739	0.597	0.584	0.923	0.883

Note - MW, molecular weight; QED, quantitative estimate of drug-likeness; TPSA, topological polar surface area; HIA, human intestinal absorption; BBB, blood-brain barrier penetration; PPB, plasma protein binding; DILI, drug-induced liver injury.

For the overall assessment, the quantitative estimate of drug-likeness (QED) metric provided by ADMETlab 3.0 was used, which integrally reflects a molecule's compliance with the typical properties of drug-like compounds. The highest QED values were calculated for the chalcones echinatin (0.662) and isoliquiritigenin (0.583). Isoliquiritigenin and echinatin, with moderate polarity (TPSA = 77.76 and 66.76 Å²) and acceptable lipophilicity (logP = 2.52 and 2.83), demonstrate the most balanced physicochemical profile.

Sapogenins demonstrated the most favorable docking scores; however, the low solubility and increased lipophilicity of Soyasapogenol B (logS = -5.25; logP = 4.27) and Soyasapogenol E (logS = -4.66; logP = 3.73) indicate limited bioavailability. In contrast, the hydrophilicity (logS = -2.96 and -2.76) and high polarity (TPSA = 164.75 Å²) of chlorogenic acid and neochlorogenic acid may limit their membrane permeability.

However, the toxicological predictors for all selected compounds remained within the acceptable range, consistent with the logic of preliminary ADMET filtration.

Thus, soyasapogenol B and soyasapogenol E demonstrated the highest affinity for the GSK-3β active site, while isoliquiritigenin and echinatin, whose binding energies are comparable to those of the native ligand, are preferred based on their pharmacological properties. Chlorogenic acid and its isomer, neochlorogenic acid, demonstrated acceptable affinity, but their high polarity may limit biopermeability.

4. Conclusion

Ninety-six phytocomponents of the genus *Astragalus* were evaluated *in silico* as potential GSK-3 β ligands, from which six compounds were selected for their combination of good affinity and favorable pharmacological and toxicological profiles. Molecular docking showed that soyasapogenol B and soyasapogenol E exhibited more favorable binding energies than the native ligand FKB501. Analysis of ligand-receptor interactions revealed the involvement of Phe67, Val70, Val135, Leu188, Cys199, and Asp200.

ADMET prediction allowed for refinement of the pharmacokinetic potential of the selected compounds. Sapogenins demonstrated the highest calculated affinity for GSK-3 β , but had limitations related to lipophilicity and solubility. Meanwhile, isoliquiritigenin and echinatin exhibited more balanced drug-like properties, making them interesting candidates for further research.

Thus, the obtained results confirm the feasibility of further studying *Astragalus* phytocomponents as potential GSK-3 β -targeting compounds. The results of this study can be used to select candidates for experimental testing, expand libraries of natural GSK-3 β inhibitors, and develop further research in the field of computer-aided discovery of biologically active compounds.

Conflict of Interest: The authors declare no conflict of interest.

АСТРАГАЛДАН АЛЫНҒАН ФИТОХИМИЯЛЫҚ ҚОСЫЛЫСТАРДЫ ГЛИКОГЕНСИНТАЗАКИНАЗА-3 β -ҒА ҚАТЫСТЫ ДОКИНГТІК ЖӘНЕ ADMET-БАҒАЛАУ

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Түйіндемесі. Гликогенсинтазакиназа-3 β (GSK-3 β) қабыну, апоптоз және нейродегенерациямен байланысты жасушалық үдерістерді реттейді және расталған терапиялық нысана болып табылады. GSK-3 β белсенді орталығымен әрекеттесуге қабілетті табиғи қосылыстарға қызығушылық осы киназаның көптеген қолданыстағы ингибиторларына тән уыттылық пен жанама әсерлерге байланысты. Зерттеудің мақсаты молекулалық докинг және ADMET қасиеттерін болжау әдістерін пайдалана отырып, астрагал фитокомпоненттерін GSK-3 β -ның әлеуетті лигандтары ретінде *in silico* бағалау болды. Докинг әдістемесі кокрystalданған рентгендік құрылымдағы FKB501 нативті лигандының қайта докингін жүргізу арқылы тексерілді; RMSD мәні 1,83 Å құрады. GSK-3 β белсенді орталығына аффинділікті бағалау үшін астрагалдың 96 қосылысынан тұратын кітапхана скринингтен өткізілді. Аффинділік және ADMET сипаттамалары негізінде егжей-тегжейлі талдау үшін алты қосылыс таңдалды: соясапогенол В, соясапогенол Е, хлороген қышқылы, неофлороген қышқылы, изоликиритигенин және эхинатин. Олардың байланысу энергиялары FKB501 байланысу энергиясымен (-7,546 ккал/моль) салыстырмалы болды немесе абсолюттік мәні бойынша одан жоғары болды, ал ең төмен мәндер соясапогенол В (-8,523 ккал/моль) және соясапогенол Е (-8,176 ккал/моль) үшін анықталды. Өзара әрекеттесулерді талдау белсенді орталықтың Ile62, Phe67, Val70, Ala83, Lys85, Val135, Gln185, Leu188, Cys199 және Asp200 негізгі қалдықтарын анықтады. ADMET болжамы бойынша изоликиритигенин мен эхинатиннің фармакологиялық және токсикологиялық профильдері ең теңгерімді болды, ал сапогениндер

докинг кезінде жоғары аффинділік көрсеткеніне қарамастан, төмен ерігіштігімен және жоғары липофильділігімен сипатталды. Осылайша, таңдалған астрагал фитокомпоненттері GSK-3 β әлеуетті ингибиторлары ретінде әрі қарай эксперименттік бағалау үшін перспективалы кандидаттар болып табылады.

Түйінді сөздер: GSK-3 β , астрагал, молекулалық докинг, ADMET, фитокомпоненттер, соясапогенол, хлороген қышқылы, изоликвиритигенин, эхинатин.

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ДОКИНГ И ADMET-ОЦЕНКА ФИТОХИМИЧЕСКИХ СОЕДИНЕНИЙ АСТРАГАЛА В ОТНОШЕНИИ ГЛИКОГЕНСИНТАЗАКИНАЗЫ-3 β

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Резюме. Гликогенсинтазакиназа-3 β (GSK-3 β) регулирует клеточные процессы, связанные с воспалением, апоптозом и нейродегенерацией, и является подтвержденной терапевтической мишенью. Интерес к природным соединениям, способным взаимодействовать с активным центром GSK-3 β , обусловлен токсичностью и побочными эффектами, характерными для многих существующих ингибиторов этой киназы. Целью исследования была *in silico* оценка фитокомпонентов астрагала как потенциальных лигандов GSK-3 β с использованием молекулярного докинга и прогнозирования ADMET. Методика докинга была валидирована путем редоккинга нативного лиганда FKB501 из кокристаллизованной рентгеновской структуры; значение RMSD составило 1,83 Å. Для оценки сродства к активному центру GSK-3 β была проведена проверка библиотеки из 96 соединений астрагала. На основании аффинности и ADMET-характеристик для детального анализа были выбраны шесть соединений: соясапогенол В, соясапогенол Е, хлорогеновая кислота, неохлаорогеновая кислота, изоликвиритигенин и эхинатин. Их энергии связывания были сопоставимы или превосходили по абсолютному значению энергию связывания FKB501 (-7,546 ккал/моль), при этом наиболее низкие значения отмечены для соясапогенола В (-8,523 ккал/моль) и соясапогенола Е (-8,176 ккал/моль). Анализ взаимодействий выявил ключевые остатки активного центра, включая Ile62, Phe67, Val70, Ala83, Lys85, Val135, Gln185, Leu188, Cys199 и Asp200. По результатам ADMET-прогнозирования наиболее сбалансированными фармакологическими и токсикологическими профилями обладали изоликвиритигенин и эхинатин, тогда как сапогенины, несмотря на более высокую аффинность при докинге, характеризовались низкой растворимостью и высокой липофильностью. Таким образом, выбранные фитокомпоненты астрагала являются перспективными кандидатами для дальнейшей экспериментальной оценки в качестве потенциальных ингибиторов GSK-3 β .

Ключевые слова: GSK-3 β , астрагал, молекулярный докинг, ADMET, фитокомпоненты, соясапогенол, хлорогеновая кислота, изоликвиритигенин, эхинатин

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