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RESEARCH ARTICLE

Computational Analysis of Ginsenoside Rb1 and Gastrodin Analogues for Neurogenesis-Related Activity in Ischaemic Stroke

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ABSTRACT

At the global stage, ischemic stroke remains a leading cause of mortality and long-term disability, with a disproportionate portion of this burden being borne by low-and-middle-income nations, and increasingly, the young productive population bracket. Ischemic stroke's management has historically been constrained by considerable challenges in the form of narrow therapeutic windows, high treatment costs, and strict eligibility criteria for the institution of either of the only two treatment options available at the disposal of medics, with those being thrombolysis, and mechanical thrombectomy. Mounting evidence favourably positions pharmacological augmentation of endogenous neurogenesis as a compelling strategy capable of appreciably enhancing structural and functional brain repair following ischemic stroke. In this regard, a relatively unexplored source of neurorestorative agents is phytochemicals sourced from conventionally used traditional therapeutic plants. A computation-heavy framework integrating ligand-based virtual screening, target-based molecular docking, pharmacokinetic profiling, and in silico toxicology forecasting was employed in a bid to meet the study's principal objective, which was to identify novel phytochemical analogues possessing superior neurogenic potential, and favourable pharmacokinetic and toxicological profiles to ginsenoside Rb1, and gastrodin. Ginsenoside Rb1's structural complexity resulted in the compound only yielding 6 analogues from Swiss Similarity. For the most part, most of these analogues underperformed relative to the parent compound across critical parameters. The only parameters where some analogues managed to outperform ginsenoside Rb1 was GI (gastrointestinal) absorption, and Lipinski's violations. Gastrodin on the other hand typified a simpler chemical structure and returned some 400 analogues, several of which posted superior results to gastrodin's. A common challenge encountered with these analogues however was their inability to traverse the BBB (blood brain barrier). These findings highlight the potential of phytochemicals as candidates for further investigation into endogenous brain repair, though experimental validation is required before their neurorestorative relevance can be established.

Keywords: *Ginsenoside Rb1, Gastrodin, Ischemic Stroke, Neurogenesis.*

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INTRODUCTION

The American Stroke Association (ASA) defines an Ischemic Stroke (IS) as an episode of neurological dysfunction precipitated by focal cerebral, spinal cord or retinal infarction (Prabhakaran et al., 2026). The Global Stroke Fact Sheet 2025 (Feigin et al., 2025) reported that among non-communicable diseases, stroke ranks in as the second leading cause of death, and the third leading cause of mortality and disability combined. Lui et al. (2025) went further and noted that in 2021, an individual suffered a stroke every 40 seconds, and a stroke death occurred every 3 minutes 14 seconds. The same study observed that in the space of one year (2020-2021) the global stroke death rate increased from 38.8 per 100,000 to 41.1 per 100,000 people.

The African stroke statistics are markedly worse, with a 3-year fatality rate as high as 84% (Akinyemi et al., 2025). Akinyemi et al. (2025) further reported Sub-Saharan Africa (SSA) to have a mortality rate at least five times higher than that observed in high-income countries. To compound the troubles, a younger age of stroke onset has been noted across the African continent (Avan et al., 2025). Plant-derived compounds have been utilised in ischemic stroke management, with strong evidence coming from Traditional Chinese Medicine (TCM) where certain plants such as Gastrodia elata, Panax ginseng, Ginkgo biloba, & Rehmannia glutinosa have been observed to exemplify higher therapeutic effects on neurological ailments than on other medical conditions (Sowmiya et al., 2025). This is significant for us, as the present study probed the potential of compounds sourced from the first 2 plants, Gastrodia elata and Panax ginseng (Gastrodin & Ginsenoside Rb1 respectively) in promoting post ischemic stroke recovery via neurogenesis induction.

At present, the clinical management of ischemic stroke is confined to a pair of established treatment modalities: thrombolytic therapy, employing either intravenous alteplase or tenecteplase, and mechanical thrombectomy, leaving practitioners with a notably limited repertoire. Intravenous thrombolytic therapy is an intrinsically time-sensitive option, with administration typically confined to a narrow therapeutic window of up to 4.5 hours from stroke symptom onset. Moreover, eligibility is governed by stringent absolute contraindications as stipulated by the American Heart Association, 2021, with some of these including; CT (computed tomography) scans demonstrating subarachnoid haemorrhage, or intracranial haemorrhage, infective endocarditis, severe head trauma within the preceding 3 months, gastrointestinal bleeding within the last 21 days, INR [International Normalised Ratio] >1.7, platelet count<100,000, and reception of a full dose of LMWH (low molecular weight heparin) within the last 24 hours, among others. Mechanical thrombectomy while transformative for selected patients with large-vessel occlusions is similarly constrained by defined clinical criteria. Candidacy requires adult patients (older than 18 years of age) with substantial neurological deficits (NIHSS [National Institute of Health Stroke Scale] score of ≥ 6), favourable pre-stroke functional baseline (modified Rankin score of 0-1) and the capacity to initiate this intervention within 6 hours of symptom onset. The shortcomings of the current therapies underscore the need to expand our anti-stroke armamentarium with interventions bearing more permissive therapeutic windows.

A pivotal study by Eriksson et al. (1998) established that neurogenesis persists in the adult brain under physiological conditions. In the setting of an ischemic stroke, this process is amplified and now characterised by heightened proliferation of neural progenitor cells from the two principal neurogenic niches in the human brain; the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. These niches, however, exhibit a limited capacity to generate new neurons at a scale sufficient to independently drive meaningful functional recovery (Nagase et al., 2023). The existence of this glaring blemish has emerged as a compelling avenue for the designing of novel therapeutics capable of pharmacologically augmenting and sustaining endogenous neurogenesis in ischemic stroke settings, thus improving long-term functional recovery.

The campaign to identify these novel therapeutic compounds capable of inducing neurogenesis has unravelled some highly promising phytochemicals. Ginsenoside Rb1 for example has been reported to act through the regulation of the cAMP/PKA/CREB pathway (Zhao et al., 2022). In this pathway, ginsenoside Rb1 binds to and activates adenosine A2A receptors, leading to the activation of adenylyl cyclase which yields cAMP (cyclic adenosine monophosphate), that in turn activates protein kinase A (PKA). PKA then phosphorylates CREB (cAMP Response Element-Binding Protein) which finally promotes the expression of genes involved in neurogenesis (Gao et al., 2020).

Equally key in ginsenoside Rb1's effects on neurogenesis is the compound's ability to improve and potentiate the expression of vital neurotrophic factors such as BDNF (Brain-Derived Neurotrophic Factors), GDNF (Glial Cell Line-Derived Neurotrophic Factor) and GAP43 (Growth Associated Protein 43), while concomitantly reducing the expression levels of negative regulators of neurogenesis such as caspase 3 (Fan et al., 2014). Ginsenoside Rb1 can also scavenge free radicals, reduce the production of Reactive Oxygen Species (ROS), improve mitochondrial function and performance, dampen cerebral inflammation by downregulating the expression of pro-inflammatory factors like IL-6 (interleukin-6) and TNF-α (tumour necrosis factor-α), reduce reperfusion-induced apoptosis by inhibiting the inflammatory signals from HMGB1 (High Mobility Group Box 1 protein), protect the integrity of the Blood Brain Barrier (BBB), and reduce cerebral oedema (Zhao et al., 2022).

Gastrodin on the other hand operates through the inhibition of the phosphodiesterase-9 enzyme (PDE-9) an action that results in elevated cGMP (cyclic guanosine monophosphate) levels in the brain. Elevated cGMP levels promote proliferation and differentiation of neuronal stem cells (NSCs) (Gómez-Pinedo et al., 2011). The downstream effector of cGMP, protein kinase G (PKG), stimulates BDNF transcription. Activated PKG enhances the phosphorylation of CREB, which then binds to CRE (cAMP Response Element) in the promoter region of the BDNF gene. This action promotes the transcription of the BDNF gene, leading to increased production of BDNF mRNA and the subsequent translation into BDNF protein, which acts to promote nerve proliferation, survival and differentiation.

The adoption of a bioinformatics-driven discovery framework allowed for structured probing of the chemical space, thorough characterisation of the molecular interactions, and most crucially of all, the identification of structurally related analogues with enhanced neurogenic potential. Collectively, this study advances the rational design of next-generation therapeutics targeted at improving long term functional recovery following an ischemic stroke.

METHODS

PubChem, SwissSimilarity, PubChem Sketcher V2.4, Avogadro, RCSB PDB, UCSF Chimera, AutoDock Vina and BIOVIA Discovery Studio were used for structure preparation, screening, docking and visualisation. SwissADME and ProTox-III provided the principal pharmacokinetic and toxicity predictions. Additional sources used for ginsenoside Rb1 are described below. The materials, software and databases are summarised in Appendix A, Table A1.

Study Design

An in-silico study design, and a quantitative research methodology were employed for this project that was conducted at the School of Pharmacy, Kabarak University.

Ligand-based Virtual Screening

The canonical smiles of ginsenoside Rb1 (CID: 9898279) and gastrodin (CID: 115067) were retrieved from PubChem, then fed to SwissSimilarity, which concerned itself with screening the extensive ZINC database (RRID:SCR_006082) for molecules that are structurally similar to the keyed in ligands. From this screening process, 400 analogues were identified for gastrodin, while only 6 were obtained for ginsenoside Rb1. The canonical smiles of these analogues and their respective parent molecules were imported into the PubChem sketcher program (PubChem Sketcher V2.4) to reconstruct their respective two-dimensional molecular structures, then "cleaned", and the emanating structures downloaded as MDL molfiles. The so acquired structures were finally converted to their 3D formats, then optimised using the Avogadro software (RRID:SCR_015983), while employing MMFF94s as the force field of choice. These optimised structures were saved in the Sybyl Mol2 file format.

Target-based Virtual Screening

The structures of the parent molecules' targets (i.e. Adenosine A2A receptor (PDB: 5NM4) for ginsenoside Rb1 & phosphodiesterase-9 enzyme [PDE-9] (PDB: 3DYN) for gastrodin) were procured from the protein databank (RCSB PDB: Homepage) (RRID:SCR_012820) in PDB file format. Non-standard amino acids and residues present in these targets were then removed with the aid of UCSF Chimera (RRID:SCR_004097). Employing the AutoDock Vina (RRID:SCR_011958) tool embedded in UCSF chimera, surface binding analysis (docking) of the prepared analogues to their appropriate targets was executed in accordance with the procedure spelled out by Eberhardt et al., 2021 and Trott & Olson, 2010. The resultant docking scores were then accordingly recorded. Selected complexes born out of these surface binding analyses proceeded to be visualised, thanks to the BIOVIA Discovery Studio (RRID:SCR_015651).

To support reproducibility of the docking protocol, the search box used for each target was defined as follows.

For gastrodin and its analogues, docking to the phosphodiesterase-9 enzyme (PDE-9) was performed using a search box centred at x = 86.8185, y = 37.3821, z = 25.9725 (Å), with dimensions of 58.2511 × 81.4833 × 106.351 Å. For ginsenoside Rb1 and its analogues, docking to the adenosine A2A receptor was performed using a search box centred at x = -9.81609, y = 69.2629, z = 53.535 (Å), with dimensions of 56.6124 × 100.35 × 41.1827 Å. Docking was performed with an exhaustiveness setting of 8 and two independent docking runs per ligand-target pair, using an adenosine A2A receptor structure with PDB accession code 5NM4 and a PDE-9 structure with PDB accession code 3DYN.

Pharmacokinetic Analysis

This was achieved through feeding the canonical smiles of the analogues, and their parent phytochemicals onto the online tool SwissADME, which proceeded to forecast the pharmacokinetic profiles of the compounds. The results of this process were recorded in table format, and specifically, key parameters such as violations to Lipinski's rule of 5s, gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, susceptibility to efflux by p-glycoproteins (P-gp), Log-P, molecular weight, synthetic accessibility (SA) scores, as well as inhibitions of the cytochrome P-450 enzymes were analysed.

Toxicity Analysis

The toxicology profiles of the study compounds were unravelled thanks to the ProTox III server tool (ProTox-III). This was realised by keying in the compounds' canonical smiles onto the online tool and granting it time to make the predictions. Assessed components of these profiles included: the lethal dose (LD50) values, toxicity classes of the compounds, and their forecasted end organ toxicities e.g. hepatotoxicity, cytotoxicity, mutagenicity, and much more.

Additional Analyses for Ginsenoside Rb1

Because the primary SwissADME and ProTox-III workflow did not yield a complete profile for ginsenoside Rb1, additional available outputs were examined. DeepToxLab supplied supplementary toxicity predictions, including the endpoints shown in Appendix A, Figure A4. pkCSM supplied the physicochemical, permeability, CYP and toxicity outputs shown in Figure A5. ADMET-AI was consulted for additional ADMET predictions, and the DrugBank ginsenoside Rb1 record was consulted as a reference source rather than treated as a prediction generated in this study. These sources did not provide a complete, uniform endpoint panel. Their results were interpreted separately from the SwissADME and ProTox-III analogue outputs.

Ethical Consideration

Study approval was sought from Kabarak University, and this was granted via the approval number KUREC-040325 from Kabarak University's Institutional Scientific and Ethics Review Committee (KABU-ISERC). Permission to collect data and legally conduct the project in Kenya was solicited from the National Commission for Science, Technology and Innovation (NACOSTI). This was equally granted via the research license number NACOSTI/P/25/4175901.

RESULTS

Table 1: *Docking Score Analysis of Ginsenoside Rb1 and its Analogues*

	Ginsenoside Rb1	ZINC000514288119	ZINC000514288117	ZINC000514288120	ZINC000018193202	ZINC000005741940	ZINC000005742074
Similarity Index		0.492	0.489	0.483	0.599	0.591	0.581
Docking Scores	-8.2	-6.7	-6.8	-6.6	-5.6	-5.5	-5.2

Table 1 above arrays the similarity indices, and docking scores of ginsenoside Rb1, and its 6 analogues. The similarity indices range from 59.9% through to 48.3%. None of the analogues was modelled to have stronger docking strength to Adenosine A2A receptor than ginsenoside Rb1.

Table 2: *Docking Score Analysis of Gastrodin, and its Best Performing Analogues*

	Gastrodin	ZNC000012957061	ZNC000004521285	ZNC000031157466	ZNC000012957067	ZNC000033833283
Similarity Index		0.989	0.989	0.981	0.99	0.989
Docking Scores	-7	-9.2	-8.9	-8.8	-8.7	-8.5

Table 2 above shows the similarity indices and docking scores of ZINC analogues in comparison with gastrodin, the parent molecule. High similarity indices were noted, with their distribution ranging from 98.1% to 99% similarity. Docking score analysis revealed ZINC000012957061 demonstrated the most substantial superiority over gastrodin, with the compound posting the highest docking score (-9.2) across the entire compound class. Docking interaction visualisations are presented in Appendix A (Figures A1–A3). The reported interactions included van der Waals contacts, hydrogen bonding and hydrophobic contacts, with additional unfavourable interactions in some poses.

Table 3: *Analysis of the Pharmacokinetic and Toxicological Profiles of Ginsenoside Rb1, and its Analogues*

		Ginsenoside Rb1	ZNC000514288119	ZNC000514288117	ZNC000514288120	ZNC000018193202	ZNC000005741940	ZNC000005742074
Lipinski's Violations		* 5 out of 6 rules	1	1	1	0	0	0
BBB Penetration		No	No	No	No	No	No	No
GI Absorption		Low	Low	Low	Low	High	High	High
P-gp Substrate		Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP Inhibitions	CYP1A2	No	No	No	No	No	No	No
	CYP2C19	No	No	No	No	No	No	No
	CYP2C9	No	No	No	No	No	No	No
	CYP2D6	No	No	No	No	No	No	No
	CYP3A4	No	No	No	No	No	No	No

Synthetic Accessibility		-	6.32	6.32	6.32	5.4	5.4	5.4
LD50 (Toxicity Class)		-	190 (3)	190 (3)	190 (3)	648 (3)	648 (3)	648 (3)
Cardiotoxicity		*Active	Inactive	Inactive	Inactive	Active (0.8)	Active (0.8)	Active (0.8)
Nephrotoxicity		-	Active (0.59)	Active (0.59)	Active (0.59)	Active (0.7)	Active (0.7)	Active (0.7)
BBB Toxicity		-	Active (0.72)	Active (0.72)	Active (0.72)	Active (0.52)	Active (0.52)	Active (0.52)
NADH OX Toxicity		-	Active (0.79)	Active (0.79)	Active (0.79)	Active (0.76)	Active (0.76)	Active (0.76)
PXR Toxicity		-	Inactive	Inactive	Inactive	Active (0.63)	Active (0.63)	Active (0.63)

Table 3 reports the forecasted pharmacokinetic and toxicological profiles of ginsenoside Rb1, and its analogues. The following traits were noted to be shared by all seven compounds: inability to traverse the blood brain barrier (BBB), susceptibility to efflux action by being P-glycoprotein substrates, and complete absence of any cytochrome P-450 (CYP) enzyme inhibitions. Lipinski's rules were violated by the parent molecule, ginsenoside Rb1, as well as ZINC000514288119, ZINC000514288117 and ZINC000514288120. The same set of 4 compounds typified low gastrointestinal (GI) absorption, while the other 3 compounds were noted to have high absorption rates. Moderately demanding to challenging synthesis is to be anticipated for these compounds, given their structural complexity.
Ginsenoside Rb1 could not be processed by the primary SwissADME and ProTox-III workflow, so its supplementary predictions were obtained from other sources and should not be treated as directly equivalent to the analogue outputs. DeepToxLab results included low-confidence ototoxicity, haemolytic toxicity, hERG-related and nuclear-receptor flags (Figure A4). The available pkCSM results are retained in Figure A5. Both figures are provided in Appendix A.

Table 4: ***Analysis of the Pharmacokinetic and Toxicological profiles of Gastrodin, and its best analogues***

	Gastrodin	ZINC0000012957061	ZINC000004521285	ZINC000031157466	ZINC0000012957067	ZINC0000033833283
Lipinski's Violations	0	0	0	0	0	0
BBB Penetration	No	No	No	No	No	No
GI Absorption	Low	High	High	High	High	High
P-gp Substrate	No	Yes	Yes	No	Yes	No
CYP1A2	Yes	No	No	No	No	No
CYP2C19	No	No	No	No	No	No
CYP2C9	No	No	No	No	No	No
CYP2D6	No	No	No	No	No	No
CYP3A4	No	No	No	No	No	No
Synthetic Accessibility	4.1	4.32	4.32	4.14	4.32	4.25
LD50 (Toxicity Class)	3750 (5)	2500 (5)	2500 (5)	2190 (5)	2500 (5)	3750 (5)
Nephrotoxicity	Active (0.76)	Active (0.83)	Active (0.83)	Active (0.75)	Active (0.83)	Active (0.74)
BBB Toxicity	Active (0.94)	Active (0.75)	Active (0.75)	Active (0.56)	Active (0.75)	Active (0.64)
Clinical Toxicity	Active (0.51)	Active (0.50)	Active (0.50)	Active (0.52)	Active (0.50)	Active (0.56)

Table 5: *Analysis of the Pharmacokinetic and Toxicological Profiles of Gastrodin, and its Best Analogues*

Nutritional Toxicity	Inactive	Active (0.56)	Active (0.56)	Active (0.53)	Active (0.56)	Inactive
Transtyretin (TTR) Toxicity	Active (0.78)	Active (0.85)	Active (0.85)	Active (0.92)	Active (0.85)	Active (0.72)
Phosphoprotein p53 Toxicity	Inactive	Inactive	Inactive	Active (0.79)	Inactive	Inactive
Acetylcholinesterase Toxicity	Inactive	Inactive	Inactive	Active (0.57)	Inactive	Inactive
Immunotoxicity	Inactive	Active (0.52)	Active (0.52)	Inactive	Active (0.52)	Inactive
Mutagenicity	Inactive	Active (0.62)	Active (0.62)	Active (0.56)	Active (0.62)	Inactive
Respiratory Toxicity	Inactive	Active (0.58)	Active (0.58)	Active (0.56)	Active (0.58)	Inactive
Cardiotoxicity	Inactive	Active (0.54)	Active (0.54)	Inactive	Active (0.54)	Inactive

Table 4 above presents the anticipated pharmacokinetic and toxicological profiles of gastrodin, and its best performing analogues. Noted patterns across the entire class include zero violations to Lipinski's rules of 5s, inability to cross the BBB, and toxicity classification into class 5, though with mildly different LD50 values. Uncomplicated synthesis is to be expected for these compounds in light of their under 5 synthetic accessibility scores. All the analogues typified high GI absorption rates, and zero inhibition of any of the cytochrome P450 (CYP) enzymes. Gastrodin though was observed to register low absorption rates, and inhibit a single CYP enzyme, with that being CYP1A2. ZINC000012957061, ZINC000004521285 and ZINC000012957067 were noted to be the P-glycoprotein (P-gp) substrates in the cohort. On the toxicological front, all compounds were predicted to cause nephrotoxicity, BBB toxicity, clinical toxicity, and toxicity to the transport protein transthyretin (TTR), though with different activity confidence scores. Notable toxicities amongst the analogues included nutritional toxicity, mutagenicity, respiratory toxicity, immunotoxicity, and cardiotoxicity. It should be noted that ZINC000033833283 was forecasted not to bring about any of these adverse effects, unlike its colleagues. Interestingly, toxicities to the acetylcholinesterase enzyme, and phosphoprotein (tumour suppressor) p53 were only evidenced by ZINC000031157466.

Chemical structures of ginsenoside Rb1, gastrodin and the two illustrated gastrodin analogues are presented in Appendix A (Figures A6–A9). The gastrodin analogues contain extended, brominated aromatic systems and differ in the stereochemistry of their glucose moieties.

DISCUSSION

Neuronal death following an ischemic stroke is driven by excitotoxicity, whereby disrupted cerebral blood flow triggers glutamate-mediated calcium overload, mitochondrial dysfunction, and ultimately cell death (Nagase et al., 2023). Given this rapid and destructive cascade, therapeutic strategies capable of promoting neurogenesis after the acute injury phase, such as the phytochemical candidates examined in this study, are of particular clinical relevance.

Ginsenoside Rb1 outscored all six screened analogues at A2A, with ZINC000514288117 trailing by 1.4 kcal/mol (Table 1). Selected gastrodin analogues showed more favourable PDE-9 scores than gastrodin, with ZINC000012957061 scoring −9.2 kcal/mol compared with −7.0 kcal/mol for the parent compound (Table 2). These are model scores, not measurements of affinity or evidence of neurogenesis. The low structural similarity of the ginsenoside analogues and the extended aromatic systems of the gastrodin analogues may contribute to the differences, but these explanations require experimental testing. The relevant structures are retained in Appendix A, Figures A6–A9.

Considering the bonding interactions that mediated the docking of the compounds to their respective targets, the following are paramount with regard to ginsenoside Rb1 and its analogues; all compounds with the exception of ZINC000514288120 registered conventional hydrogen bonds with some residues of the adenosine A2A receptor. Some repeat residues that mediated these hydrogen bonds in more than one compound include phenylalanine 177 residue in ZINC000018193202 and ZINC000005741940 & glutamate 178 which was observed for ZINC000005741940 and ZINC000514288119's hydrogen bonding. Over and above these repeat residues, several other receptor residues were involved in facilitating hydrogen bonding between the receptor and the drug molecules e.g. histidine 369 and 383 for ZINC000514288117, and alanine 90 & isoleucine 89 for ZINC000005742074, among others. Van der Waal's bonds were the second key interactions for these molecules. They were present for all 7 molecules' docking, with a key residue, valine 93, notably mediating these bonds across all 6 analogues, but interestingly absent for ginsenoside Rb1. Several other different receptor residues were involved in these Van der Waal's bonds for the different molecules. Unfavourable acceptor-acceptor interactions were observed in four of the molecules' docking. These include ginsenoside Rb1 (at the asparagine 48 receptor residue), ZINC000514288119 (at lysine 162), ZINC000514288117 (at tyrosine 376) and ZINC000514288120 (at the phenylalanine 177 residue). Alkyl bonding was typified by ZINC000018193202, ZINC000005741940, ZINC000005742074 and ginsenoside Rb1. Two standout Pi-Sigma bonds were witnessed from ZINC000514288119 and ZINC000514288117's docking, with both bonds being mediated by the phenylalanine 177 residue of adenosine A2A receptor.

Docking interaction analysis of gastrodin and its analogues uncovered several key observations. These include conventional hydrogen bonding & Van der Waal's bonding were consistently noted to be present across all six compounds, the histidine residue 292 of phosphodiesterase-9 enzyme (PDE-9) mediated Van der Waal's bonding in all the selected compounds, aspartate 293 of PDE-9 was involved in hydrogen bonding across all the compounds save for ZINC000012957067. Among the analogues, Pi-Pi alkyl bonding was present in all except for ZINC000033833283 where a singular Pi-Pi T-shaped interaction was observed (courtesy of phenylalanine 251 residue of PDE-9). Methionine 365 served as the site of unfavourable donor-donor interactions for ZINC000004521285 and ZINC000012957067's docking. The very same residue (methionine 365) mediated Van der Waal's bonding in gastrodin, ZINC000012957061 & ZINC000033833283, and Pi-Alkyl bonding in ZINC000031157466.

Gastrodin analogues showed high predicted gastrointestinal absorption and no predicted inhibition of the CYP enzymes assessed, while gastrodin had low predicted absorption and a CYP1A2 inhibition flag (Table 4). ZINC000012957061, ZINC000004521285 and ZINC000012957067 were predicted P-glycoprotein substrates. These predictions motivate transporter studies, not dose increases or co-administration with transporter inhibitors. Liu et al. (2018) instead reported rapid oral absorption of gastrodin, illustrating a discrepancy requiring cautious interpretation. Both sources indicated that gastrodin was not a P-glycoprotein substrate.

Gastrodin, together with all its selected analogues, was noted to lack the ability to traverse the blood-brain barrier (BBB).This was a concerning observation as these molecules are intended to gain access to the brain so as to precipitate the desired outcome, i.e. neurogenesis stimulation. The in-silico predictions captured on row 3 of table 6 do not support this expectation.

It is therefore notable that (Lin et al., 2007, 2008; N. Liu et al., 2015; Y. Liu et al., 2018) reported a very interesting and nuanced observation, where gastrodin was able to pass through the BBB, and distribute in the brain quickly after entering the systemic circulation. Lin et al., 2008 noted gastrodin could be detected in the brains of mice in as little as 5 minutes following the intravenous administration of gastrodin at a dose of 50 mg/kg, and peak brain concentrations could be actualised in 15 minutes. A further finding from the Y. Liu et al., 2018 study is that the brain's exposure to gastrodin is notably low, with a brain-to-blood distribution ratio of 0.007 at an I.V dose of 100 mg/kg in mice. This detail was attributed to either the rapid metabolism of gastrodin into its main metabolite p-hydroxybenzyl alcohol (HBA), or gastrodin's poor BBB permeability. Gastrodin and its selected analogues returned synthetic accessibility (SA) scores (runs from 1 to 10 and gives a measure of how easy or hard it is to synthesise a given chemical structure) on the lower side of the scale (all under 5) thus relatively simple and straightforward synthesis is to be expected for these compounds.

Extending this in-silico pharmacokinetic analysis to ginsenoside Rb1 and its analogues, the following observations are noteworthy. Ginsenoside Rb1's entire pharmacokinetic and by extension toxicological profiles could not be revealed. The molecule's large and complex structure rendered it unprocessable via the project's primary PK and toxicity analysis tools, i.e. SwissADME, and Protox III respectively. A whole host of other in-silico tools [including ADMET-AI (ADMET-AI), pkCSM (pkCSM), drugbank (Ginsenoside Rb1: Uses, Interactions, Mechanism of Action | DrugBank Online), and DeepToxLab (deeptoxlab.scbdd.com)] were employed in a bid to unearth the parent drug's profiles, but even with this advanced armamentarium, ginsenoside Rb1's complete pharmacokinetic and toxicological profiles could not be unmasked.

Based on the available data, the following pharmacokinetic observations were noted across the class. All seven compounds registered zero proclivity for CYP enzyme inhibitions but absence of a modelled CYP inhibition flag does not exclude metabolic drug interactions. Other key patterns across the class include susceptibility to efflux action as a consequence of being P-glycoprotein substrates, inability to bypass the BBB, and as is to be expected, moderately hectic to challenging synthetic processes for the molecules. ZINC000018193202, ZINC000005741940 and ZINC000005742074 unlike their relative molecules exemplified high GI absorption, and zero violations to Lipinski's rules of 5. From the pkCSM results (Figure A5) ginsenoside Rb1 markedly deviated from Lipinski's rules of 5 and only managed to obey one of the rules with that exception coming from the LogP value which was indeed below the recommended value of 5. With a LogP value of -2.2026, ginsenoside Rb1 is 159 times more concentrated in water than in octanol. This profound hydrophilicity translates into poor passive diffusion across lipid membranes; hence the molecule is going to struggle to cross the intestinal epithelium (hereby explaining the very low absorption rates) and the BBB. Other key observation from the pkCSM results include the BBB and CNS permeability scores. A BBB permeability score of -2.652 (Interpretation: >0.3 [high BBB penetration] & <-1.0 [Poor BBB penetration]) predict the compound to very poorly traverse the blood brain barrier. -6.251 for a CNS permeability score (Interpretation: >-2 [High CNS permeability] &<-3 [Low CNS permeability]) suggests minimal ability of the molecule to penetrate brain tissue. Taken together, these findings suggest that ginsenoside Rb1 typifies negligible predicted brain exposure and generally lacks drug-like properties, based on the computational parameters assessed.

It is worth noting that, despite the nomenclature, Lipinski's rule of 5 comprises four primary physicochemical criteria, with those being: [1.] No more than 5 hydrogen bond donors, [2.] No more than 10 hydrogen bond acceptors, [3.] Molecular mass less than 500 Daltons, [4.] Partition coefficient (LogP) not greater than 5 (Drug Bank, 2026). Over and above these 4, there have been paramount extensions to the rules, with 2 notable ones including: No more than 10 rotatable bonds, & a total polar surface area (TPSA) under 140 $Å^2$ (Ivanović et al., 2020). It is from this pool of 6 rules that ginsenoside Rb1 managed to only obey one of them.

Karpagam et al., 2013 conducted a study on twelve ginsenosides (including ginsenoside Rb1) for their inhibitory action on BACE1 (β-site Amyloid precursor protein Cleaving Enzyme 1) for Alzheimer's disease treatment and noted that ginsenoside Rb1 lacked drug-like properties, including the ability to traverse the BBB. From the lot, only ginsenosides CK, F1, Rh1 and Rh2 typified drug-like properties. Y. Liu et al., 2024 further demonstrated ginsenoside Rb1's poor pharmacokinetics with the compound's dismal absorption and bioavailability scores after oral administration in humans. Ling et al., 2024 pointed out that ginsenoside Rb1's bioavailability can be boosted through co-administering the compound with verapamil, a P-glycoprotein inhibitor, because ginsenoside Rb1 serves as a substrate for P-gp.

Given ginsenoside Rb1's pharmacokinetic profile, intravenous (I.V) administration is the preferred route for its delivery for therapeutic purposes. Intratympanic (I.T) administration is a novel delivery approach that has been shown to achieve high drug concentrations in the inner ear and brain while circumventing both the Brain-Labyrinth Barrier (BLB) and the Blood-Brain Barrier (BBB) (Ling et al., 2024). Intranasal administration represents yet another alternative option for effectively delivering the drug to the Central Nervous System (CNS) while offering key advantages such as ease of use, avoidance of initial excretion, and high brain bioavailability. (Lu et al., 2011).

In-silico toxicological profiling predicted toxicity to the nephrons, the BBB, and the NADH-Quinone Oxidoreductase (NADHOX) enzyme across all six of ginsenoside Rb1's analogues. NADHOX (complex I) is central to mitochondrial ATP production (Grivennikova et al., 2024); were this predicted toxicity to be confirmed experimentally, it would be expected to compromise cellular energy production and increase reactive oxygen species generation, with potential downstream implications for organ function. Half of the analogues, namely ZINC000018193202, ZINC000005741940 and ZINC000005742074, were additionally predicted to cause cardiotoxicity (activity confidence score of 0.8) and toxicity to the pregnane X receptor (PXR), a nuclear receptor that regulates detoxification pathways and metabolic homeostasis (Ikeda et al., 2025). Should this prediction hold, disruption of PXR activity could plausibly compromise metabolic regulation, though this remains a computational forecast rather than a confirmed effect. All six analogues were placed in toxicity class 3 by Protox III, with predicted LD50 values of either 190 mg/kg or 648 mg/kg.

The toxicity results of the analogues cannot, however, be extrapolated onto ginsenoside Rb1 owing to the low similarity scores exemplified by the analogues. DeepToxLab analysis suggested ginsenoside Rb1 may be associated with several distinct toxicological effects not previously emphasised via table 3. These effects include ototoxicity, haemolytic toxicity, and potential cardiotoxicity linked to the inhibition of the potassium channel Kv11.1, encoded by the hERG II gene [i.e. human ether-á-go-go-related gene], which is critical for cardiac action potential repolarisation and rhythm regulation. Additionally, reproductive toxicities may arise from nuclear receptor-mediated mechanisms, particularly through activation of oestrogen receptors (NR-ER). It is important to note, however, that these toxicity predictions were generated with relatively low confidence (Figure A4). Significantly, toxicity to hERG II's channels by way of being an inhibitor was corroborated by results from the pkCSM online tool (Figure A5).

Attention is now directed towards gastrodin and its analogues' toxicity profiles as forecast by Protox III, where all compounds were predicted to cause nephrotoxicity, BBB toxicity, clinical toxicity, and toxicity to the transthyretin (TTR) transporter. The clinical toxicity endpoint is a binary prediction of resemblance to drugs that failed clinical trials due to toxicity, rather than a mechanistic toxicity measure (Banerjee et al., 2024), and across the series this prediction carried the lowest average confidence score (0.515), warranting cautious interpretation. TTR is a plasma and cerebrospinal fluid transport protein for thyroxine and retinol that also contributes to neuroprotection by limiting amyloid-β aggregation (Liz et al., 2020). Should the predicted TTR toxicity be confirmed, plausible downstream effects could include vitamin A deficiency, hypothyroidism-like symptoms, and reduced neuroprotective capacity, though these remain computational predictions requiring experimental verification rather than established outcomes.

Among the analogues, ZINC000033833283 exhibited a toxicity profile similar to the parent compound gastrodin, while the remaining four were predicted to carry additional toxicities, including nutritional toxicity, a contextual endpoint reflecting resemblance to toxic dietary chemicals rather than a mechanistic prediction (Banerjee et al., 2024), together with mutagenicity and respiratory toxicity. Immunotoxicity and cardiotoxicity were predicted for three of the four analogues, excluding ZINC000031157466, which was instead uniquely flagged for predicted toxicity to acetylcholinesterase (AChE) and the tumour-suppressor protein p53. Were these predictions confirmed, AChE inhibition could plausibly manifest as cholinergic toxicity, while interference with p53, a protein central to genomic stability (Xu et al., 2025), could theoretically compromise normal cell-cycle regulation. Given p53's fundamental role, this predicted liability is considered a meaningful limitation to ZINC000031157466's further development, pending experimental confirmation.

All things considered, ginsenoside Rb1 outperformed its Swiss Similarity analogues on most parameters. However, the molecule was constrained by poor pharmacokinetics and consequently lack of ideal drug-like properties. Still, the molecule's strong docking score is a solid advantage, that justifies further studies. Unlike ginsenoside Rb1, several of gastrodin's analogues managed to outperform their parent molecule.

Strong docking scores were a major plus for the analogues, though an analysis of their toxicity profiles tempered the analogues' promise.

LIMITATIONS

Reference-ligand redocking and pose RMSD validation were not performed. Docking scores therefore provide unvalidated comparisons within the selected protocol rather than confirmation of binding, selectivity or neurogenesis (Trott & Olson, 2010; Eberhardt et al., 2021). No in-vitro or in-vivo experiments were conducted, limiting biological interpretation and clinical application. Ginsenoside Rb1 could not be processed by the primary ADMET tools, and its supplementary results came from different platforms with different endpoints and applicability domains; direct parent–analogue comparisons are consequently limited. Only six low-similarity ginsenoside Rb1 analogues were retrieved, limiting generalisation to its wider chemical space. Predicted BBB permeability and toxicity differed from some cited experimental findings and require validation. Two docking runs per pair do not resolve these sources of uncertainty.

CONCLUSIONS

Ginsenoside Rb1 produced more favourable docking scores than its screened analogues but showed limitations in predicted disposition. Selected gastrodin analogues improved on the parent compound's docking score, although predicted brain permeability and toxicity remain concerns. These findings prioritise compounds for experimental evaluation; they do not demonstrate neurogenesis, therapeutic efficacy or safety. Further work should validate binding, functional activity, brain exposure and toxicity before therapeutic conclusions are drawn.

RECOMMENDATIONS

We recommend further studies on ginsenoside Rb1 in terms of identifying more structurally similar analogues, as well as a more robust evaluation of the molecule's pharmacokinetics, and the prudent strategies that could be employed to boost its drug-like properties. For gastrodin and its analogues, validation of the molecules' toxicity profiles is strongly advocated, coupled with concerted efforts aimed at enhancing the molecules' blood-brain barrier permeability.

DECLARATION

Availability of Data and Material

All data generated and analysed in this study are publicly available at the Harvard Dataverse and can be accessed via https://doi.org/10.7910/DVN/DC90SL

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

KT conceptualised, and designed the study, and was centrally involved in data acquisition, analysis, interpretation, and final approval of the submitted version.
RK was very key in the conceptualisation, design, analysis, and formatting of the manuscript, as well as giving the final approval.

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