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Research **OPEN ACCESS**

In silico prediction of ketamine as a janus kinase 1/2 inhibitor for systemic inflammatory response syndrome

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Abstract

Background Inhibition of Janus Kinase 1/2 (JAK1/2) may improve systemic inflammatory responses, signaling the need for the development of new treatments in the management of systemic inflammatory response syndrome (SIRS).

Objectives This study aimed to evaluate the potential of ketamine as a predicted inhibitor of the JAK1/2 signaling pathway using *in silico* molecular docking and toxicity profiling.

Methods Molecular docking simulations were conducted against JAK1 (PDB ID: 6N77) and JAK2 (PDB ID: 7Q7L) receptors. Ketamine served as the test ligand, while baricitinib was utilized as the reference comparator. Evaluation parameters included Root Mean Square Deviation (RMSD), binding affinity energy, percentage binding site similarity (%BSS), organ toxicity, carcinogenicity predictions, and visual interaction analysis (interaction profiling and ligand overlapping).

Results The RMSD validation values were within acceptable thresholds for JAK1 (=2.41Å or <3Å) and JAK2 (=1.66Å or <2Å). Ketamine's affinity energy was more negative than that of baricitinib at JAK 1 (-6.7; -3.3 kcal/mol) and JAK 2 (-6.9; -3.5 kcal/mol), respectively. Ketamine exhibited a %BSS ≥50%, whereas baricitinib <50%. Both compounds shared comparable predicted profiles for neurotoxicity and respiratory toxicity; however, ketamine was predicted to be non-carcinogenic in contrast to baricitinib. Structural visualization confirmed key binding interactions of ketamine within the JAK1/2 active sites and highlighted spatial overlap with baricitinib.

Conclusion *In silico* finding suggest that ketamine possesses strong binding interactions with the JAK1/2 pathway receptors, supporting its potential utility in managing SIRS-associated hyperinflammation.

Keywords Baricitinib | *in silico* | JAK1/2 pathway | ketamine | systemic inflammatory response syndrome

Introduction

Systemic inflammatory response syndrome (SIRS) is a systemic hyperinflammatory condition caused by an increase in pro-inflammatory cytokines in the body. The epidemiology of SIRS in dogs and cats has not been well reported, in contrast to reports in humans. The most reported SIRS in dogs and cats are caused by abdominal sepsis, pneumonia, pyothorax, and pyometra, which require high-level care, and are associated with high mortality rates (20% to 80%) (Babyak & Sharp, 2016; Aritonang, 2024). They release pro-inflammatory cytokines and mediators, which can contribute to systemic inflammation and subsequent multi-organ dysfunction (Sikora *et al.*, 2021; Wang & Wang, 2023).

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In SIRS, the activation of these immune cells is often dysregulated, leading to an excessive inflammatory response that damages host tissues, thereby exacerbating organ failure (Sikora *et al.*, 2021). Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are pro-inflammatory cytokines that are common in SIRS conditions. When these cytokines bind to receptors on the cell surface, they can activate Janus kinase (JAK) 1 and 2 to initiate signal transduction within the cell. The signal sent by JAK further triggers the activation of transcription factor signal transducer and activator of transcription (STAT), which affects the expression of inflammation-related genes. Inhibition of JAK1/2 may improve systemic inflammatory responses, signaling the development of new treatments in the management of SIRS (Gomez *et al.*, 2022; Pan *et al.*, 2020).

Ketamine is a common anesthetic drug that is often used in veterinary practice. The anesthetic effects of ketamine stem from its interaction with a variety of receptors. Ketamine disrupts excitatory neurotransmission by blocking N-methyl-D-aspartate receptors, which contributes to its anesthetic and analgesic properties (Ma *et al.*, 2023). Out of label studies of ketamine show its potential as an anti-inflammatory. Research has shown that ketamine has a powerful effect in reducing inflammation through several mechanisms involving cytokine regulation and signal transduction. Several studies have investigated its effecttiveness in lowering the levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, as well as other impacts of SIRS cases (Ince *et al.*, 2025). The assessment of the inhibitory activities of JAK1 and JAK2 lines has never been carried out before. This study aimed to analyze the ability of ketamine as a predicted inhibitor of the JAK1/2 pathway through in silico studies as an innovative treatment for SIRS. The results of this study can be a reference for the development of research and further development in using ketamine as an innovative therapy for SIRS.

Methods

Equipment, research application, and data sources

This is an experimental study using in silico molecular docking. The research was conducted at the Health Studies Complex Building of the of Universitas Riau in May 2026. The hardware used in the computational modeling was a Lenovo Thinkpad Intel core i5-8350U processor, 8 GB RAM, and 256 GB SDRAM. The software used included Autodocktools (v.1.5.6), Discovery studio (v7.6.14.149), Pymol (v.4.6.0), and the command prompt system. The structure of the receptor protein was downloaded from the RSCB Protein Data Bank (https://www.rcsb.org/). The molecular structures of the ketamine and baricitinib ligands were downloaded from Pubchem (https://pubchem.ncbi.nlm.nih.gov/).

Molecular docking techniques

Molecular docking modeling is divided into four stages; namely preparation of receptors and ligands, docking simulation and validation of native receptor-ligands, redocking of test ligands, and analysis of model goodness. The receptors used in this study were JAK1 (PDB ID 6N77) and JAK2 (PDB ID: 7Q7L). The selection of the receptor with the aforementioned PDB ID was based on the following considerations this structure corresponds to the JAK 1/2 kinase domain, which is the target of interest in this study, and the conformation of the protein in this structure represents the biologically active state relevant to JAK 1/2 inhibition. Preparation of JAK1 receptor with grid center size x= 6.262; y= -24.758 and z= 21.847 with dimensions x= 30; y= 30; and z= 30, space 1 Å.

The goodness of fit of the model was validated by analyzing the root mean square deviation (RMSD) value. The redocking page uses the same page as the native receptor-ligand docking. The affinity energy value used in native ligands is the first conformation value, whereas in ketamine and baricitinib it is the second conformation value. For the natural ligand, the first conformation was selected because it represented the pose with the lowest RMSD relative to the crystallographic structure, indicating that the docking protocol was able to reproduce the experimentally observed binding mode with good accuracy, which is consistent with common practice in docking validation. In contrast, for the test ligand, the second conformation was selected because its primary objective was not to reproduce the crystallographic pose, as in the case of the natural ligand, but rather to predict the binding mode that is most biologically relevant to the JAK 1/2 target (Hasibuan & Aritonang, 2025).

Research parameter and data analysis

The parameters of the model goodness test included the affinity energy value, percentage binding site similarity (%BSS), organ toxicity, carcinogenicity, and visualization (interaction of the receptor and ligand, and ligand overlapping). Organ toxicity and carcinogenicity tests were carried out through the Pro-Tox (https://tox.charite.de/protox3/index.php?site=home). The organs that are parameters of toxicity are the liver, neuro, kidneys, cardio, and respiratory organs. Carcinogenicity tests are divided into two categories, namely non and carcinogenic. The data of the model goodness parameters were descriptively analyzed.

Results

Preparation of JAK1 (PDB ID: 6N77) receptor with the native ligand N-[3-(5-chloro-2-methoxyphenyl)-1-methyl-1H-pyrazol-4-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (**Figure 1A**). JAK2 (PDB ID: 7Q7L) receptor with the native ligand 4-[2-azanyl-8-[[(2~{S})-1-oxidanylpropan-2-yl]amino] quinazolin-6-yl]-5-ethyl-2-fluoranyl-phenol (**Figure 1B**). The grid size of x= 33.257, y= 12.222, and z= 65.807 was obtained with dimensions of x= 30, y= 32, and z= 30, and a spacing of 1 Å. The x, y, and z dimensions correspond to the native ligand binding site on the JAK 1/2 receptor. The ligands are visualized in detail in the circles. The results showed RMSD values of JAK1 <3 Å and JAK2 <2 Å, indicating that the model was similar and identical to the original crystallographic structure. RMSD is an indicator that assesses the ability of ligand surface interactions before and after docking. An RMSD value of <2 Å indicates that the model has a validity of stability identical to its original crystallographic structure, whereas an RMSD value of <3 Å indicates that the model is close to the original position so that it can be used in redocking simula-

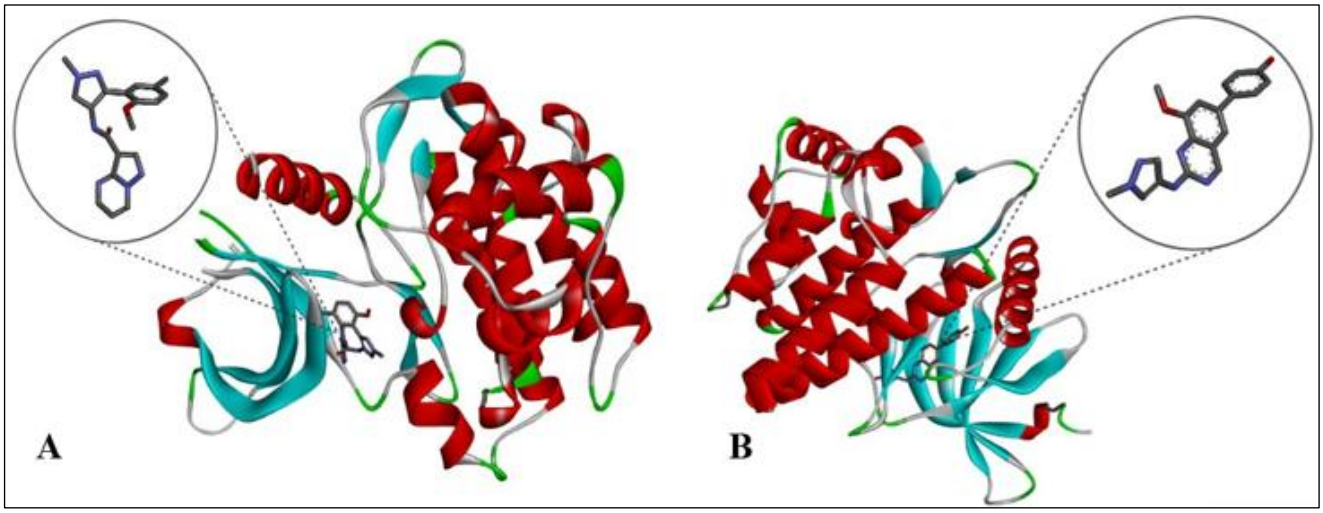


Figure 1 (A) Interaction of JAK1 and N-[3-(5-chloro-2-methoxyphenyl)-1-methyl-1H-pyrazol-4-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide; (B) interaction of JAK2 with 4-[2-azanyl-8-[[(2~{S})-1-oxidanylpropan-2-yl]amino]quinazolin-6-yl]-5-ethyl-2-fluoranyl-phenol

Table 1 Comparison of RMSD, affinity energy values, amino acid bond, and %BSS of JAK1/2 interacting with ketamine and baricitinib.

Parameters	JAK1			JAK2		
	Native	Baricitinib	Ketamine	Native	Baricitinib	Ketamine
RMSD (Å)	2,4063			1,6566		
Affinity energy (kcal/mol)	-8.3	-3.3	-6.7	-9.6	-3.5	-6.9
Hydrogenic bond	glu966	leu959*	arg1007	asp939	leu932	asp994*
	leu959	gly1020*		asp994		gly993
	gly1020					
Hydrophobic bond	kej1201		val889*	val863		val863*
	leu881		leu1010*	leu983		leu983*
	val889		leu881*	leu855		ala880*
	ala906		ala906*	ala880		val911*
	leu1010			lys882		met929*
				val911		leu855*
Electrostatic bond			met956	met929		
%BSS	100	25	50	100	0	77.7

* is a test or comparator amino acid ligand that has similarity to native ligand amino acids

tions on test ligands (Nursanti *et al.*, 2022; Syahputra *et al.*, 2022). A comparison of the RMSD is presented in **Table 1**.

Discussion

The ketamine's energy affinity was more negative than that of baricitinib, although it was not more negative than that of the native ligands. Baricitinib is a selective JAK inhibitor, particularly for commonly used JAK1/2. Baricitinib plays an important role in the transduction of signals from various cytokines that contribute to inflammatory processes in patients with SIRS. Baricitinib has also been shown to be effective in managing hyperinflammatory reactions associated with SARS-CoV-2 infection in humans, reflecting patients with SIRS (Kim *et al.*, 2021).

In molecular docking, binding affinity predictions are crucial for ranking potential ligands based on their interaction strength with the target protein. The use of both the native conformation for native ligands and alternative conformations for test ligands allows for a more comprehensive exploration of the ligand's binding behavior. This highlights the necessity of considering full ligand conformational flexibility for achieving accurate docking performances, reflecting the variability in binding observed with test ligands (Yang *et al.*, 2019). Increasingly negative affinity energy values indicate the ability of a ligand to bind to receptors (Aritonang *et al.*, 2024; Azzahra *et al.*, 2024).

Although the binding affinity of ketamine was better than that of baricitinib in this study, this result cannot be directly interpreted as evidence that ketamine is substantially superior. This is because molecular docking is merely an initial, predictive study of a molecular interactions. Methodological limitations inherent to docking, such as binding-site selection, ligand protonation, pose selection, scoring procedures,

and docking validation, indicate that further analysis is required. A comparison of the affinity energy values is presented in **Table 1**.

The results showed a hydrophobic bond between ketamine and the JAK1/2 receptor which was not found in baricitinib. This indicates that the interaction between ketamine and JAK1/2 receptors is much more stable than that of baricitinib. This threshold has practical implications for drug design, especially when exploring new compounds or derivatives. When test ligands can achieve at least a 50% match in binding stability to native ligands, this potentially indicates that further in vitro or in vivo studies could yield favorable therapeutic outcomes (Awoonor & Rowley, 2021). The results showed that %BSS for JAK2/JAK2 receptors was ≥ 50%, while %BSS for baricitinib was < 50%. Comparison of %BSS of JAK1 and JAK2 interacting with ketamine and baricitinib are presented in **Table 1**.

The gray area shown in **Figure 2** represents the JAK1/JAK2 receptor. The yellow area around the ligand indicatesthe active side of the receptor interacting with the ligand. The red area represents the ketamine ligand. The ligands are visualized in detail in the circles. Based on these results, it can be concluded that the ketamine ligand interacts via the JAK1/2 receptor with its various active sides. The overlap of ketamine ligands with native ligands JAK1/2 is shown in **Figure 3**. The green area represents the native ligand of JAK1/2, whereas the orange areарepresents ketamine. Based on these results, it can be seen that there is an overlap that occurs between native ligands and JAK1/2.

The development of drug candidates requires rigorous testing to evaluate their potential carcinogenic activity and organ toxicity to ensure patient safety. Given the advances in computational toxicology, in silico models play a significant role in predicting both the hepatotoxicity and nephrotoxicity of drug compounds. Techniques such as structure-activity relationship (SAR) modeling and machine learning approaches have been developed to predict the toxicity profiles of small molecules before conducting experimental assays. These models offer an efficient and ethical alternative to animal testing, providing early indicators of potential toxicity based on the chemical structures of the compounds (Banerjee *et al.*, 2018; Galati *et al.*, 2022; Gao *et al.*, 2023).

The results of this study showed that ketamine and baricitinib have similarities, namely toxic to two of the five organs analyzed, being neurotoxic and respiratory toxic. The liver and kidneys are two organs that are often used in the safety

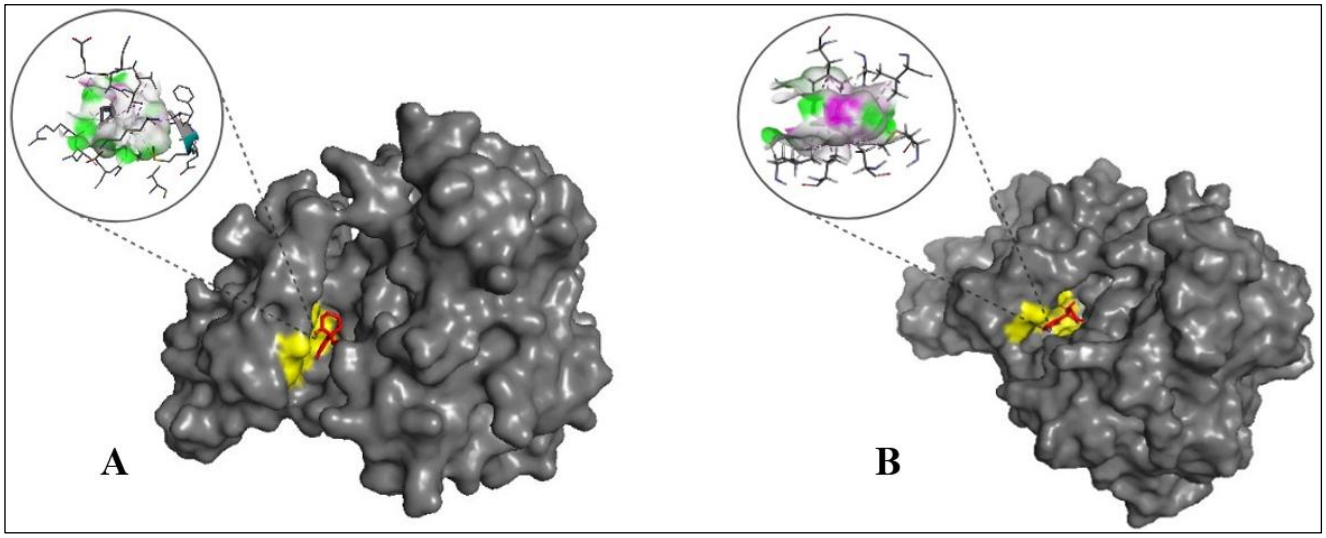


Figure 2 (A) Interaction of JAK1 with ketamine; (B) interaction JAK2 with ketamine. The details within the circle represent ligands bound to the receptor

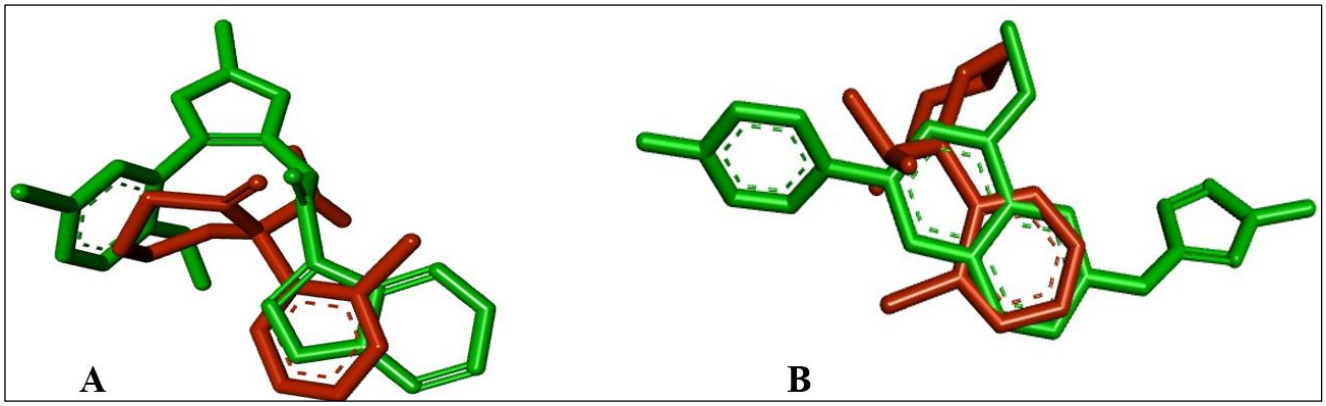


Figure 3 (A) Overlap of JAK1 native ligand with ketamine; (B) overlap of JAK2 native ligand with ketamine

analysis of a drug study because they, liver and kidneys are the main organs that play a role in metabolic processes in the body (Harahap *et al.*, 2025). Incorporating liver representatives into studies enhances the understanding of a drug's systemic efficacy and toxicity, providing a more accurate risk assessment profile. Factors such as specific organ drug metabolism and clearance rates contribute to the overall toxicity observed in the liver and kidney systems. This emphasizes the need for organ-specific models to accurately evaluate drug effects (Oleaga *et al.*, 2018; Rana *et al.*, 2020).

Carcinogenicity tests showed that ketamine was not carcinogenic, whereas baricitinib was carcinogenic. The development of therapies requires the potential for non-carcinogenic activity as the main condition including regulations issued by the Food and Drug Administration (FDA) Organization (Bacanlı, 2024). The potential carcinogenic activity of drugs can be dangerous because it can trigger the onset of cancer which can have negative post-treatment effects on patients.

The development of ligands as drug candidates requires testing for organ toxicity to minimize their effects in the body. Toxicity comparisons between ketamine and baricitinib are presented in **Table 2**. The limitation of this research is that the modeling was only carried out computationally in silico. Further in vivo studies in animal models are needed to validate its systemic anti-inflammatory activity.

Table 2 Comparison of toxicity prediction between ketamine and baricitinib

Condition	Baricitinib	Ketamine
Hepatotoxic	Nontoxic	Nontoxic
Nephrotoxic	Nontoxic	Nontoxic
Neurotoxicity	Toxic	Toxic
Cardiotoxicity	Nontoxic	Nontoxic
Respiratory toxicity	Toxic	Toxic
Carcinogenic	Carcinogenic	Noncarcinogenic
Predicted LD50 (mg/kg)	2200	447

Conclusion

In in silico molecular computing studies, ketamine was predicted to have a good ability to interact with the receptors of the JAK1/2 pathway. Ketamine also has a favorable safety profile as a candidate drug against systemic inflammatory response syndrome, which warrants further research and development.

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Conflict of interest All authors declare no conflict of interest in this research.

Author contribution EAA: Investigation, conceptualization analysis, and writing – original draft; RJ: analysis, and writing – review & editing; MFR: co-conceptualization, writing – review & editing.

Availability of data and materials The structure of the receptor protein was downloaded from the RSCB Protein Data Bank (https://www.rcsb.org/). The molecular structures of the ketamine and baricitinib ligands were downloaded from Pubchem (https://pubchem.ncbi.nlm.nih.gov/). Organ toxicity and carcinogenicity tests were carried out through the Pro-Tox (https://tox.charite.de/protox3/index.php?site=home).

Declaration of generative AI in writing process During the preparation of this work, the authors used DeepSeek to enhance the readability and language of the manuscript]. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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