



In silico analysis of *Ziziphus mauritiana* Lam. bioactive compounds targeting GABA receptor and ADMET profiles for potential postpartum depression treatment

[Análisis *in silico* de compuestos bioactivos de *Ziziphus mauritiana* Lam. dirigidos al receptor GABA y perfiles ADMET para el posible tratamiento de la depresión posparto]

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Abstract

Context: Postpartum depression (PPD) affects 10–20% of women and has been associated with disruptions in neurotransmitter systems, neuroinflammation, and oxidative stress. *Ziziphus mauritiana* contains several bioactive compounds, including quercetin, which have demonstrated neuroprotective potential.

Aims: To predict the binding interactions of *Z. mauritiana* bioactive compounds with the GABA receptor, analyze their ADMET properties to evaluate their pharmacokinetic and toxicity profiles, and explore their therapeutic potential for PPD through *in silico*-based drug discovery methodologies.

Methods: Molecular docking simulations were performed to assess the interaction of quercetin and other *Z. mauritiana* compounds with key PPD-related targets, including the GABA_A receptor, BDNF, IL-6, and TNF- α . Fluoxetine and diazepam were used as reference drugs. Docking reliability was validated using RMSD analysis. ADMET profiling was conducted to evaluate drug-likeness, pharmacokinetics, and safety based on Lipinski's Rule of Five.

Results: Quercetin exhibited strong binding affinity to the GABA_A receptor (-7.0 kcal/mol), comparable to diazepam (-7.2 kcal/mol), and showed interactions with other neuroinflammatory markers. ADMET predictions supported its potential for good oral bioavailability and a favorable safety profile.

Conclusions: The findings suggest that *Z. mauritiana* bioactive compounds, particularly quercetin, hold promise as natural therapeutic agents for PPD via multi-target mechanisms. Their ability to modulate neurotransmission and inflammation supports further *in vivo* and clinical research to validate efficacy and safety in postpartum depression treatment.

Keywords: drug design; flavonoids; protein interaction maps; puerperal disorders; *Ziziphus*.

Resumen

Contexto: La depresión posparto (DPP) afecta al 10-20% de las mujeres y se ha asociado a alteraciones en los sistemas neurotransmisores, neuroinflamación y estrés oxidativo. *Ziziphus mauritiana* contiene varios compuestos bioactivos, entre ellos la quercetina, que han demostrado potencial neuroprotector.

Objetivos: Predecir las interacciones de unión de los compuestos bioactivos de *Z. mauritiana* con el receptor GABA, analizar sus propiedades ADMET para evaluar sus perfiles farmacocinéticos y de toxicidad, y explorar su potencial terapéutico para la PPD a través de metodologías de descubrimiento de fármacos *in silico*.

Métodos: Se realizaron simulaciones de acoplamiento molecular para evaluar la interacción de la quercetina y otros compuestos de *Z. mauritiana* con dianas clave relacionadas con la PPD, incluyendo el receptor GABA_A, BDNF, IL-6 y TNF- α . La fluoxetina y el diazepam se utilizaron como fármacos de referencia. La fiabilidad del acoplamiento se validó mediante el análisis RMSD. Se realizó un perfil ADMET para evaluar la similitud con el fármaco, la farmacocinética y la seguridad según la regla de los cinco de Lipinski.

Resultados: La quercetina mostró una fuerte afinidad de unión al receptor GABA_A (-7,0 kcal/mol), comparable a la del diazepam (-7,2 kcal/mol), y mostró interacciones con otros marcadores neuroinflamatorios. Las predicciones ADMET apoyaron su potencial para una buena biodisponibilidad oral y un perfil de seguridad favorable.

Conclusiones: Los hallazgos sugieren que los compuestos bioactivos de *Z. mauritiana*, en particular la quercetina, son prometedores como agentes terapéuticos naturales para la PPD a través de mecanismos multiobjetivo. Su capacidad para modular la neurotransmisión y la inflamación respalda la realización de nuevas investigaciones *in vivo* y clínicas para validar la eficacia y la seguridad en el tratamiento de la depresión posparto.

Palabras Clave: diseño de fármacos; flavonoides; mapas de interacción de proteínas; trastornos puerperales; *Ziziphus*.

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Abbreviations: 3D: Three-dimensional; ADMET: Absorption, distribution, metabolism, excretion, and toxicity; BBB: Blood-brain barrier; CNS: Central nervous system; FDA: Food and Drug Administration; GABA_A: Gamma-aminobutyric acid type A; GABA-AT: γ -Aminobutyric acid aminotransferase; Hacc: Hydrogen bond acceptors; Hdon: Hydrogen bond donors; HIA: Human intestinal absorption; MW: Molecular weight; Pa: Probability to be active; PPD: Postpartum depression; RCSB PDB: Research Collaboratory for Structural Bioinformatics Protein Data Bank; RMSD: Root mean square deviation; SAR: Structure-activity relationship; THR: Threonine (amino acid); TYR: Tyrosine (amino acid); VAL: Valine (amino acid).

INTRODUCTION

Postpartum depression (PPD) is a severe neuropsychiatric disorder that affects a significant proportion of women following childbirth. This condition not only compromises maternal mental health but also disrupts mother-infant bonding, leading to long-term developmental consequences for the child. The global prevalence of PPD is estimated to range between 10% and 20% of postpartum women, with variations influenced by genetic predisposition, hormonal fluctuations, environmental stressors, and socioeconomic factors. Despite its high prevalence and profound impact, PPD remains underdiagnosed and undertreated due to social stigma, limited awareness, and inadequate treatment options. Recent research suggests that PPD is driven by complex neurobiological mechanisms, including dysregulation of neurotransmitter systems, neuroinflammation, and oxidative stress, all of which contribute to mood disturbances and cognitive dysfunction (Suryawanshi and Pajai, 2022).

One of the key pathophysiological mechanisms underlying PPD is the dysfunction of the γ -aminobutyric acid (GABA)ergic system, which plays a crucial role in maintaining inhibitory neurotransmission in the central nervous system. The GABA receptor regulates mood stability, stress responses, and neural excitability, making it a critical target for neuropsychiatric interventions. Disruptions in GABAergic signaling have been directly linked to increased susceptibility to depressive and anxiety-related disorders, including PPD (Zhang et al., 2024). Current pharmacological treatments, such as selective serotonin reuptake inhibitors (SSRIs), primarily target serotonergic pathways but often fail to address the underlying GABAergic dysfunction in PPD, leading to suboptimal therapeutic outcomes. This limitation underscores the urgent need for alternative treatment strategies that directly target GABA receptors to restore neurochemical balance and alleviate depressive symptoms.

Natural bioactive compounds with anxiolytic and neuroprotective properties present a promising avenue for novel PPD therapeutics. *Ziziphus mauritiana* Lam. (family *Rhamnaceae*), commonly known as jujube, has been traditionally used in ethnomedicine for its sedative, anxiolytic, and neuroprotective effects. Phytochemical studies have identified a variety of

bioactive compounds in *Z. mauritiana*, including flavonoids, triterpenoids, and alkaloids, which have demonstrated potential interactions with GABA receptors. Among these, quercetin, rutin, and betulinic acid have been reported to modulate GABAergic activity, enhance neuroplasticity, and reduce oxidative stress, making them potential candidates for PPD treatment (Butt et al., 2021). However, despite the promising pharmacological profile of *Z. mauritiana*, the precise molecular mechanisms by which its bioactive compounds interact with GABA receptors remain largely unexplored.

In silico approaches offer a powerful computational framework to predict ligand-receptor interactions, providing critical insights into the binding affinity, molecular interactions, and structural stability of bioactive compounds within therapeutic targets. Molecular docking serves as a key tool to assess the potential of natural compounds to interact with the GABA receptor, guiding the discovery of novel anxiolytic and antidepressant agents. Additionally, comprehensive absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling is essential to evaluate the pharmacokinetic properties and safety profiles of these compounds. A rigorous assessment of their bioavailability and toxicity risks is crucial to determine their feasibility for drug development (Zhu et al., 2022).

Despite the importance of using clinically established reference drugs for comparative analysis, a universally recognized GABAergic-targeted drug for PPD remains absent from clinical guidelines. To address this limitation, this study employs a ligand-based molecular docking approach to predict the binding interactions of *Z. mauritiana* bioactive compounds with the GABA receptor. By using diazepam as a control ligand, this research aims to establish a comparative binding profile, enabling the identification of promising therapeutic candidates.

This study aims to (1) predict the binding interactions of *Z. mauritiana* bioactive compounds with the GABA receptor, (2) analyze their ADMET properties to evaluate their pharmacokinetic and toxicity profiles, and (3) explore their therapeutic potential for PPD through *in silico*-based drug discovery methodologies. By integrating computational strategies, this research seeks to bridge the existing knowledge gap in natural product-based interventions for PPD and

lay the groundwork for future experimental and clinical validation. The findings of this study may contribute to the development of safer, more effective treatment options for PPD by leveraging GABAergic modulation.

MATERIAL AND METHODS

Ligand preparation

The ligand preparation process began with the identification of bioactive compounds present in *Ziziphus mauritiana* through an extensive literature review of previous studies (Butt et al., 2021; Memon et al., 2013). These studies highlighted that *Z. mauritiana* contains a diverse range of bioactive compounds with pharmacological potential, including flavonoids, alkaloids, fatty acids, and terpenoids (Fig. 1). To retrieve the molecular structures and simplified molecular-input line-entry system (SMILES) representations of these compounds, we utilized the PubChem

database (<https://pubchem.ncbi.nlm.nih.gov/>). From this dataset, we selected quercetin, palmitic acid, α -linolenic acid, α -tocopherol, and squalene for further analysis (as detailed in Table 1). These compounds were chosen based on their potential interaction with GABA receptors, which are implicated in PPD. Specifically, quercetin was chosen for its well-documented antioxidant and anti-inflammatory properties, while α -linolenic acid and squalene were included due to their reported ability to modulate metabolic and inflammatory pathways.

Additionally, diazepam (PubChem ID: 3016) was included as a positive control ligand to serve as a reference for evaluating the binding affinity and interaction patterns of the bioactive compounds with the GABA-A receptor. This approach ensures a direct comparison between the selected natural compounds and a clinically established GABA modulator in the context of PPD treatment.

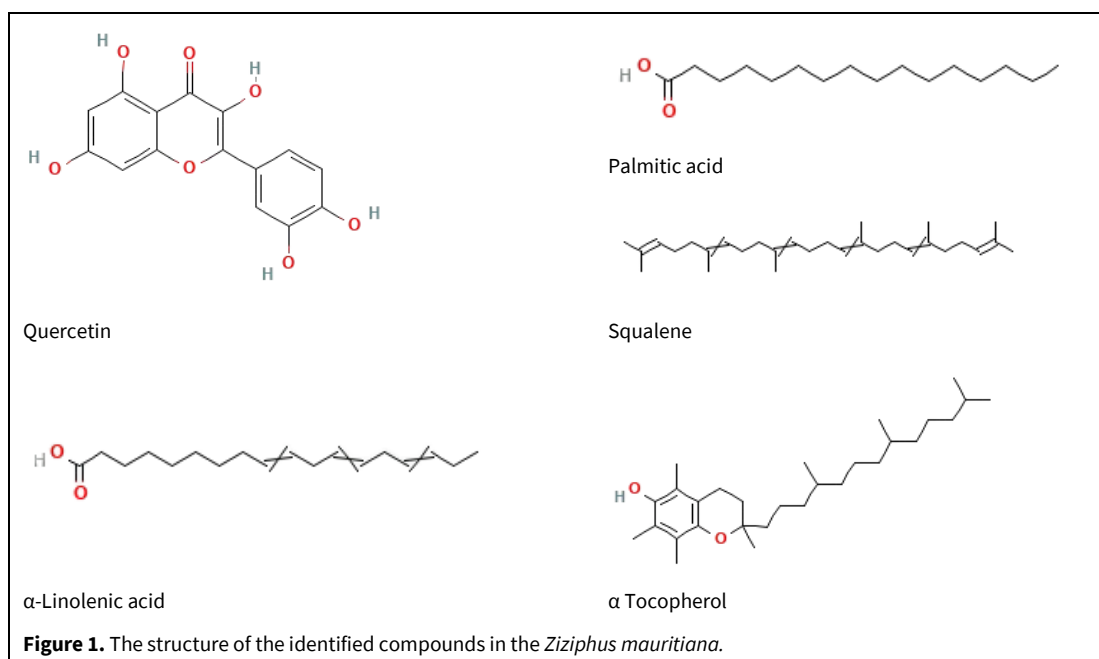


Figure 1. The structure of the identified compounds in the *Ziziphus mauritiana*.

Table 1. *Z. mauritiana* bioactive profile.

	Ligand	PubChem ID	Formula	Reference
1	Quercetin	5280343	C ₁₅ H ₁₀ O ₇	(Memon et al., 2013)
2	Palmitic acid	985	C ₁₆ H ₃₂ O ₂	(Butt et al., 2021)
3	α -Linolenic acid	5280934	C ₁₈ H ₃₀ O ₂	(Butt et al., 2021)
4	A-Tocopherol	2116	C ₂₉ H ₅₀ O ₂	(Butt et al., 2021)
5	Squalene	638072	C ₃₀ H ₅₀	(Butt et al., 2021)

The antioxidant and anti-inflammatory potential of bioactive compounds from *Ziziphus mauritiana* was evaluated using the prediction of activity spectra for substances PASS (WAY2DRUG) tool (<http://www.pharmaexpert.ru/passonline/predict.php>). This tool utilizes structure-activity relationship (SAR) analysis to compare the molecular structures of the selected compounds with known bioactive molecules, thereby predicting their potential pharmacological activities. The PASS predictions are expressed as a probability to be active (Pa) values, which range from 0 to 1, where higher values indicate a greater likelihood that the compound exhibits the predicted biological activity. The output provides insights into the potential antioxidant and anti-inflammatory properties of the selected compounds, which are relevant to PPD treatment due to their possible neuroprotective effects. The accuracy and reliability of the PASS prediction model have been well-documented in previous studies (Filimonov et al., 2014), making it a valuable tool for preliminary *in silico* bioactivity screening.

Prediction of ADMET

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of the selected bioactive compounds were assessed using the ADMETLab database (<https://admetmesh.scbdd.com/>) (Xiong et al., 2021). This *in silico* platform predicts a compound's pharmacokinetic behavior, including its intestinal absorption, plasma protein binding, blood-brain barrier permeability, metabolic stability, renal clearance, and potential toxicological risks. The analysis was performed to determine whether the selected compounds possess favorable pharmacokinetic properties and minimal toxicity, making them suitable for further drug development considerations.

Additionally, Lipinski's Rule of Five (Lipinski, et al., 2001) was applied to evaluate the oral bioavailability of the selected compounds. This rule suggests that an orally active drug candidate generally has a molecular weight of ≤ 500 Da, no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, and a log P value of ≤ 5 , indicating balanced lipophilicity for cellular permeability. While this rule provides a useful guideline for assessing drug-likeness, it does not guarantee biological efficacy. Instead, it helps predict whether a compound is likely to be absorbed and distributed effectively in the body following oral administration. Only compounds that exhibited promising ADMET characteristics and complied with Lipinski's Rule of Five were selected for further analysis, as detailed in Table 1. This comprehensive assessment ensures that the bioactive compounds possess favorable pharmacokinetic properties, sufficient bioavailability, and reduced toxicity

risks, reinforcing their potential for further *in vivo* validation and drug development targeting postpartum depression.

Molecular docking

Preparation of protein and ligand structures

The three-dimensional (3D) structures of the selected target proteins were retrieved from the RCSB Protein Data Bank (PDB) database (<https://www.rcsb.org/>). The target protein used in this study was 6X3X, a human GABAA receptor $\alpha 1$ - $\beta 2$ - $\gamma 2$ subtype complexed with GABA and diazepam. The interaction between GABA and diazepam plays a crucial role in modulating the GABA-A receptor, defining its active binding site, which is critical for docking analysis. The molecular structures of the selected bioactive ligands were obtained from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>), with the following PubChem IDs: Quercetin (5280343) and allopregnanolone (92786). Additionally, diazepam (PubChem ID: 3016) was used as a positive control ligand to provide a benchmark for evaluating the binding affinity and interaction profile of the bioactive compounds. Protein preparation was conducted using PyMOL 2.5.2, ensuring the removal of water molecules and non-essential heteroatoms to optimize docking accuracy. The selected ligands underwent energy minimization using the Universal Force Field (UFF) via Open Babel in PyRx v1.0, ensuring that all compounds were in their lowest energy conformations before docking simulations (Trott and Olson, 2010).

Molecular docking simulation

Molecular docking simulations were conducted using AutoDock Vina, integrated within PyRx v1.0 (Trott and Olson, 2010). The docking process followed a targeted docking (specific docking) approach, where the grid box size was carefully adjusted based on the binding residues of diazepam, which served as the control ligand. This strategy ensured that the bioactive compounds were docked into the same active site as diazepam, enabling a direct comparison of binding interactions and affinities. The binding site selection was further validated using the PrankWeb algorithm (<https://prankweb.cz/>), which employs a machine-learning approach to predict ligand-binding hotspots within the receptor structure. The docking results were expressed as binding affinity values (kcal/mol), representing the interaction energy between the ligand and the GABA-A receptor (6X3X), with more negative values indicating stronger binding affinities. To facilitate structural analysis, the ligand-protein

interactions were visualized using BioVia Discovery Studio 2024, which allowed for detailed inspection of key molecular interactions, including hydrogen bonds, hydrophobic interactions, and π - π stacking interactions.

Docking result validation

The reliability of the docking results was assessed using multiple validation parameters to ensure accuracy and reproducibility. One of the primary validation methods involved calculating the RMSD by comparing the redocking results with the experimental crystallographic structure. An RMSD value of less than 2 Å was considered indicative of strong conformational similarity between the docked structure and the experimentally determined complex, signifying accurate ligand placement within the active site. Further validation was conducted by comparing the docking positions of the reference ligand and the control ligand (diazepam) to confirm that both ligands were localized within the same binding cavity of the GABA-A receptor (6X3X). This ensured that the bioactive compounds occupied a pharmacologically relevant binding pocket similar to diazepam. Additionally, the analysis focused on the presence of identical protein residues interacting with both the bioactive ligands and diazepam, confirming whether the reference ligands exhibited a mechanism of action similar to that of the experimental control. The docking coordinates were further validated by referencing active site residues reported in previous studies (Kim et al., 2020) and binding site predictions from PrankWeb, which provided a confidence score of 0.911 on a scale of 0 to 1, reinforcing the reliability of the predicted binding interactions.

RESULTS AND DISCUSSION

Prediction of *Ziziphus mauritiana* activity using the SAR approach

The SAR analysis, conducted using the WAY2DRUG PASS platform (PASS Online v.2.0), provided insights into the pharmacological potential of bioactive compounds in *Z. mauritiana*. The *in silico* predictions indicated that these compounds exhibit a broad spectrum of biological activities, including the

inhibition of GABA aminotransferase, a key enzyme responsible for GABA metabolism and neurotransmitter regulation. This inhibitory activity suggests that bioactive constituents of *Z. mauritiana* may contribute to enhancing GABAergic neurotransmission, which is crucial for mood stabilization and the alleviation of postpartum depression symptoms.

Additionally, SAR analysis predicted that the selected bioactive compounds possess strong antioxidant and anti-inflammatory properties, which are essential in reducing oxidative stress and neuroinflammation—two major contributors to postpartum depression pathophysiology. These findings support the potential of *Z. mauritiana* compounds as natural therapeutic agents for neuropsychiatric disorders, particularly those associated with neurotransmitter dysregulation and oxidative stress, such as postpartum depression.

GABAergic modulation and neuroprotective potential

GABA is the primary inhibitory neurotransmitter in the central nervous system, playing a crucial role in regulating neuronal excitability and maintaining neural balance. Low levels of GABA have been implicated in various neurological disorders, including insomnia and depression (Fogaça and Duman, 2019). The enzyme γ -aminobutyric acid aminotransferase (GABA-AT) is responsible for the degradation of GABA in the brain. Inhibiting GABA-AT can increase GABA levels, promoting relaxation and potentially exerting antidepressant effects (Della Vecchia et al., 2022).

In silico predictions from SAR analysis revealed that quercetin, a prominent bioactive compound in *Z. mauritiana*, exhibited GABA aminotransferase inhibition potential with a score of 0.389. Allopregnanolone, another bioactive compound, showed a slightly lower score of 0.326. These findings suggest that quercetin may have a stronger potential for modulating GABAergic activity compared to allopregnanolone. Additionally, quercetin displayed anti-inflammatory (0.689) and antioxidant (0.872) activities, both of which are critical in reducing oxidative stress and neuroinflammation—two key contributors to the pathophysiology of postpartum depression (Table 2).

Table 2. SAR Prediction of quercetin and allopregnanolone using Way2Drug PASS Online.

Ligand	PubChem ID	Formula	GABA aminotransferase inhibitor	Anti-inflammatory	Antioxidant
Quercetin	5280343	C ₁₅ H ₁₀ O ₇	0.389	0.689	0.872
Allopregnanolone	92786	C ₂₁ H ₃₄ O ₂	0.326	0.528	0.177

The neuroprotective effects of quercetin are consistent with previous studies, which highlight its ability to regulate neurotransmitter balance and mitigate neuroinflammation (Bellavite, 2023). Furthermore, its higher antioxidant activity relative to allopregnanolone suggests that quercetin may serve a dual role in both GABAergic modulation and neuroprotection. Since oxidative stress has been increasingly recognized as a significant factor in the pathophysiology of depression (Bhatt et al., 2020), quercetin's combined ability to inhibit GABA-AT and provide antioxidant protection may offer a multifaceted approach to postpartum depression treatment.

However, the predicted values for GABA-AT inhibition are moderate, indicating that quercetin alone may not be sufficient as a standalone therapy. This limitation underscores the need for further *in vitro* and *in vivo* validation to better assess its clinical potential. Additionally, the bioavailability of quercetin in the central nervous system remains a concern, as flavonoids like quercetin often exhibit limited blood-brain barrier permeability (Batiha et al., 2020). Future research should explore formulation strategies to enhance quercetin's brain bioavailability, such as nanoparticle delivery systems or combination therapy with other bioactive compounds, to maximize its therapeutic efficacy.

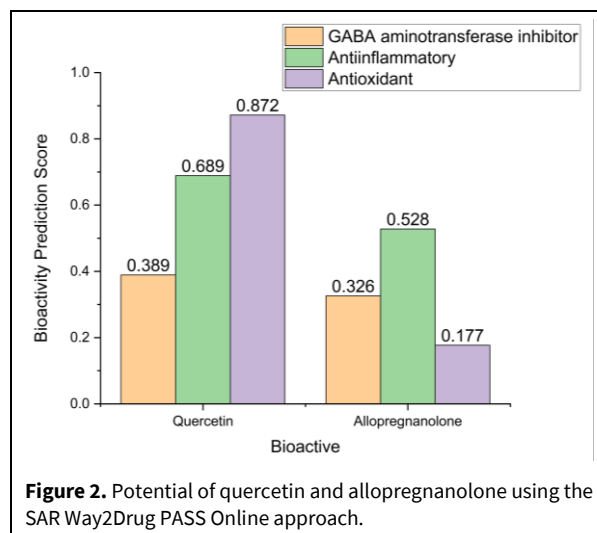
Therapeutic implications of *Ziziphus mauritiana*

The modulation of the GABAergic system through GABA aminotransferase inhibition presents a promising therapeutic strategy for neurological disorders, particularly postpartum depression (PPD). The bioactivity predictions indicate that quercetin, a key component of *Z. mauritiana*, exhibits moderate potential as a GABA aminotransferase inhibitor (0.389) while also demonstrating significant anti-inflammatory (0.689) and antioxidant (0.872) activities. These properties are essential in mitigating oxidative stress and neuroinflammation, which are crucial contributors to PPD pathophysiology.

As depicted in Fig. 2, quercetin outperforms allopregnanolone in antioxidant and anti-inflammatory activities, suggesting a broader pharmacological profile. While allopregnanolone is an FDA-approved neurosteroid for PPD treatment, its lower antioxidant activity (0.177) and only moderate anti-inflammatory effects (0.528) indicate that it primarily acts through GABAergic modulation rather than a multi-target approach (Boots et al., 2008). The higher antioxidant potential of quercetin supports its role in combating oxidative damage, a known trigger for neurodegenerative and psychiatric disorders, including depression. Recent studies have demonstrated that quercetin can

significantly improve depression-like behavior induced by chronic unpredictable mild stress (CUMS) by modulating key neurobiological pathways. Specifically, quercetin exerts its antidepressant effects by inhibiting the expression of NMDAR1 and $\alpha 2\delta$ -1, which play a role in neuronal excitability and stress response, ultimately leading to reduced hypothalamic-pituitary-adrenal (HPA) axis excitability. Quercetin alleviates chronic unpredictable mild stress-induced depression-like behavior by inhibiting NMDAR1 with $\alpha 2\delta$ -1 in rats (Wang et al., 2024).

Given these findings, *Z. mauritiana* appears to offer a multifaceted approach to PPD management, combining GABAergic modulation, anti-inflammatory action, and antioxidant defense. Research has shown that *Z. mauritiana* possesses significant antioxidant and anti-inflammatory properties, contributing to its therapeutic effects in various medical conditions. This multi-target potential aligns with recent trends in integrative medicine, where natural compounds with diverse mechanisms of action are explored for their ability to address complex neuropsychiatric conditions. Furthermore, the combined effects of these bioactive compounds may offer advantages over conventional single-target therapies, potentially reducing side effects and enhancing therapeutic efficacy (Nifolar et al., 2024).



However, despite these promising predictions, further *in vitro* and *in vivo* studies are required to validate the pharmacological potential of *Z. mauritiana* in clinical settings. Future research should focus on evaluating its bioavailability, metabolic stability, and synergistic interactions with other neuroactive compounds to optimize its therapeutic application. Moreover, clinical trials are essential to establish their safety profile and efficacy in comparison to existing pharmacotherapies for postpartum depression.

ADME prediction

The ADME analysis revealed that quercetin complies with Lipinski's Rule of Five and exhibits a favorable bioavailability score (Table 2). This score is comparable to that of allopregnanolone, a known post-depression treatment that targets the GABA A receptor modulator. Compounds that meet Lipinski's criteria—molecular weight (MW) ≤ 500 Da, $\log P \leq 5$, hydrogen bond acceptors (Hacc) ≤ 10 , and hydrogen bond donors (Hdon) ≤ 5 —are considered suitable for oral administration and systemic circulation. Both quercetin and allopregnanolone satisfy these conditions, reinforcing their pharmacokinetic viability.

The human intestinal absorption (HIA) score predicts a compound's ability to be absorbed in the gastrointestinal tract, where higher values indicate better absorption. Similarly, the blood-brain barrier (BBB) penetration score estimates a compound's potential to cross the BBB, with lower values suggesting limited CNS permeability. These metrics help assess a compound's pharmacokinetic profile, particularly in distinguishing peripherally and centrally active agents (Tong et al., 2022). As shown in Table 3, quercetin demonstrates a relatively low HIA score (0.014), indicating limited intestinal absorption, while its BBB penetration score (0.008) suggests restricted CNS permeability. In contrast, allopregnanolone, the reference compound, exhibits lower intestinal absorption (0.004) but significantly higher BBB permeability (0.331), aligning with its role as a CNS-active agent.

Despite its limited direct penetration into the central nervous system (CNS), quercetin remains a promising candidate due to its well-documented antioxidant, anti-inflammatory, and neuroprotective properties. Studies have shown that quercetin can activate AMP-activated protein kinase (AMPK), a cellular

energy sensor that modulates inflammation and oxidative stress, thereby offering neuroprotection (Chiang et al., 2023). To address its poor bioavailability, various formulation strategies, such as nanoencapsulation and lipid-based delivery systems, have been explored. These advanced drug delivery nanosystems can enhance quercetin's solubility, stability, and absorption, thereby improving its therapeutic efficacy (Tomou et al., 2023). Furthermore, although its direct CNS penetration may be limited, quercetin can exert indirect neuroprotective effects by modulating systemic inflammation and oxidative stress—two key factors implicated in neurodegenerative diseases. Its favorable safety profile further supports its potential for long-term therapeutic applications.

Molecular docking

The molecular docking study aimed to evaluate the binding affinity and interaction profiles of quercetin and allopregnanolone with the GABA_A receptor, providing insights into their potential as modulators of GABAergic neurotransmission. The docking simulations demonstrated that quercetin exhibited a binding affinity of -7.0 kcal/mol, slightly stronger than allopregnanolone (-6.5 kcal/mol) (Table 4). These values suggest a stable ligand-receptor interaction, with both compounds displaying affinities comparable to established GABA_A receptor modulators such as diazepam, which has been reported to bind with an affinity of approximately -7.2 kcal/mol (Kim et al., 2020). Given that binding energies lower than -5.0 kcal/mol are generally indicative of strong ligand-receptor interactions (Liu et al., 2021), these results highlight the potential of both quercetin and allopregnanolone as promising GABA_A receptor modulators.

Table 3. ADMET prediction score.

Bioactive compound	Molecular weight (Da)	Hydrogen bond acceptors	Hydrogen bond donors	logP (mol/L)	Human intestinal absorption prediction score	Blood-brain barrier penetration prediction score	Lipinski rule compliance
Quercetin	302.04	7	5	2.155	0.014	0.008	Accepted
Allopregnanolone (control)	318.26	2	1	4.707	0.004	0.331	Accepted

Table 4. Molecular docking results of bioactive compounds with GABA_A receptor.

Bioactive	Binding affinity (kcal/mol)
Quercetin	-7.0
Allopregnanolone	-6.5

Table 5. Amino acid residue interactions between GABA_A receptor and bioactive compounds.

Bioactive	Hydrophobic bond	Hydrogen bond
Quercetin	-	TYR160, THR207, TYR210
Allopregnanolone	VAL203	TYR160, TYR161

Based on the analysis of amino acid residue interactions, quercetin is predicted to interact with the active site of the GABA_A receptor, specifically at residues TYR160 and TYR210, through hydrogen bonding. Meanwhile, allopregnanolone is predicted to interact with TYR160 (Table 5). A previous study by Kim et al. (2020) identified several key residues involved in interactions with GABA_A receptor modulators such as diazepam and flumazenil, including F100, Y160, F77, N60, H102, Y210, S205, and Y58. Some of these residues also appear in the interaction analysis of quercetin and allopregnanolone in the present study, suggesting a potentially relevant interaction mechanism. However, further experimental studies are needed to confirm these interactions. The ability of quercetin to form multiple hydrogen bonds suggests a potentially stronger stabilization mechanism, which may enhance its modulatory effects on the GABAergic system.

As visualized in Fig. 3, allopregnanolone forms conventional hydrogen bonds with TYR160 and ALA161, which may contribute to its stabilization within the GABA_A receptor binding site. Additionally, a hydrophobic alkyl interaction with VAL203 is observed. These findings suggest potential interactions with key residues involved in GABA_A receptor modulation, though further validation is required to determine whether this binding profile aligns with classical benzodiazepine-site modulators like diazepam.

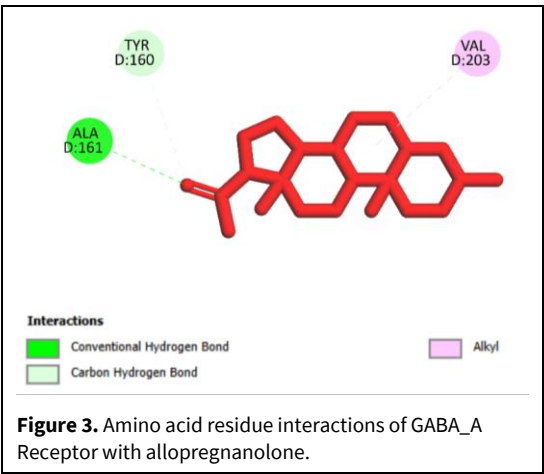


Figure 3. Amino acid residue interactions of GABA_A Receptor with allopregnanolone.

Molecular docking validation was conducted to assess the accuracy and reliability of the docking sim-

ulations. This process involved redocking diazepam, the positive control, into the GABA_A receptor binding site and comparing its conformation with the experimental crystallographic structure. The calculated RMSD value was below 2 Å, indicating a strong structural correlation between the docked and experimental conformations. These results support the validity of the docking protocol in predicting ligand-receptor interactions. Additionally, diazepam was redocked into the same binding cavity as observed in its crystallographic structure, further reinforcing the reliability of the docking method (Fig. 4).

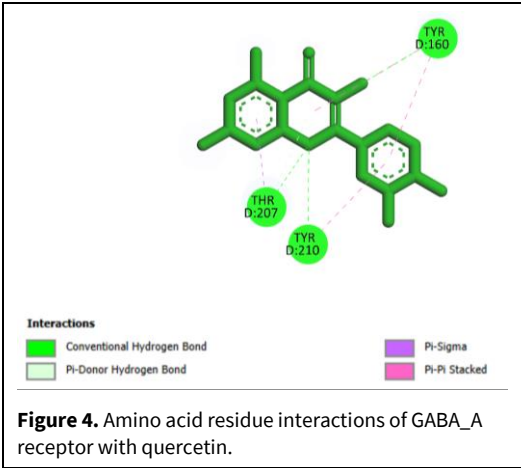
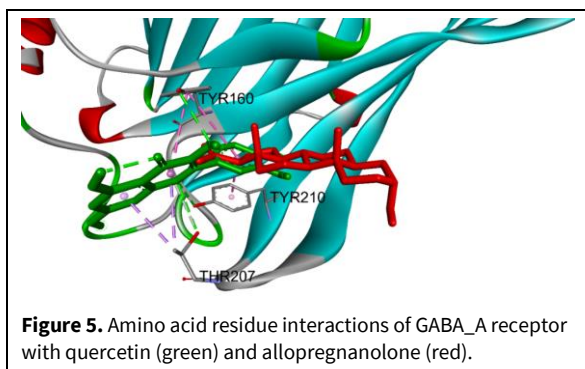


Figure 4. Amino acid residue interactions of GABA_A receptor with quercetin.

Following validation, quercetin was docked into the GABA_A receptor, and its interactions were analyzed. The docking results showed that quercetin occupied the same binding cavity as diazepam, suggesting a potential modulatory interaction with the receptor. Notably, key amino acid residues involved in diazepam binding, including Tyr160, Thr207, and Tyr210, were also identified as interacting with quercetin (Fig. 5). These interactions primarily consisted of conventional hydrogen bonds and π - π stacking, both of which are important for ligand stability and receptor engagement. The presence of these conserved interactions suggests that quercetin may influence GABAergic neurotransmission, although further studies are required to elucidate its precise mechanism of action.

Previous studies have suggested that flavonoids, including quercetin, can interact with GABA_A receptors and exhibit neuroactive properties (Goutman et al., 2003). The interaction patterns observed in this

study align with earlier findings indicating that certain flavonoids can bind to GABA_A receptors and potentially modulate inhibitory neurotransmission (Zhang et al., 2024). While diazepam functions as a benzodiazepine receptor agonist, the binding profile of quercetin suggests a possible modulatory role; however, its pharmacodynamic effects may differ due to variations in binding affinity and receptor kinetics.



Although this study provides valuable insights into the potential of quercetin as a GABA_A receptor modulator, several limitations must be acknowledged. First, while molecular docking is a widely accepted *in silico* method, it does not fully capture the dynamic and conformational changes that occur in a biological environment. The absence of molecular dynamics simulations limits our ability to assess the stability, flexibility, and potential allosteric effects of quercetin-receptor interactions over time. Incorporating such simulations in future studies would provide a more comprehensive understanding of quercetin's binding mechanism. Second, this study relies on docking validation through RMSD values and comparison with diazepam as a positive control. While these parameters strengthen the credibility of the findings, additional experimental validation, such as *in vitro* receptor binding assays, site-directed mutagenesis, and electrophysiological studies, would be necessary to confirm quercetin's functional effects on GABA_A receptor activity. These approaches would help determine whether quercetin induces receptor activation, potentiates GABAergic signaling, or exhibits its modulatory effects distinct from benzodiazepines. Finally, while quercetin's antioxidant and anti-inflammatory properties suggest broader therapeutic potential, the lack of *in vivo* or clinical evidence limits conclusions regarding its pharmacokinetics, bioavailability, and long-term efficacy in postpartum depression treatment. Previous studies indicate that quercetin has poor bioavailability due to rapid metabolism; therefore, future studies should explore formulation strategies to enhance its systemic absorption. Additionally, utilizing relevant animal models of postpartum depression and conducting clinical trials would

be crucial to bridging the gap between computational predictions and real-world therapeutic applications.

CONCLUSION

This study highlights quercetin as a promising compound for further investigation in postpartum depression treatment. Molecular docking analysis, validated through RMSD assessment and comparison with diazepam as a positive control, demonstrated that quercetin binds effectively to the GABA_A receptor, interacting with key residues Tyr160, Thr207, and Tyr210. These interactions suggest that quercetin may modulate GABAergic neurotransmission, although its mechanism of action may differ from benzodiazepines. Additionally, quercetin's antioxidant and anti-inflammatory properties support its potential role in mitigating oxidative stress and neuroinflammation, both of which are implicated in postpartum depression. While these findings provide valuable insights, further *in vivo* and clinical studies are essential to validate their pharmacokinetics, efficacy, and safety in a physiological setting.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Concepts or ideas	x					
Design			x	x		
Definition of intellectual content	x					
Literature search			x			x
Experimental studies	x					
Data acquisition			x			x
Data analysis	x				x	
Statistical analysis				x	x	
Manuscript preparation	x		x			x
Manuscript editing		x		x	x	
Manuscript review	x	x	x	x	x	x

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