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Research Article

Potential of *Cymbopogon citratus* Terpenoids as GABA-A Receptor Modulators in Anxiety Disorders: In Silico Study

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This study evaluated the potential of bioactive lemongrass (Cymbopogon citratus) compounds geraniol, citral, neral, β-myrcene, and linalool as anti-anxiety candidates through in silico molecular docking against the human GABA-A receptor α1β2γ2 subtype (PDB ID: 6X3X). The workflow included Lipinski's Rule of Five analysis, molecular docking, interaction visualization, and ADMET prediction. All compounds satisfied Lipinski's criteria, indicating favorable physicochemical properties and oral bioavailability potential. Docking validation produced an RMSD of 0.89 Å, confirming protocol reliability. All compounds showed negative binding energies, indicating interaction with the target protein. Geraniol exhibited the strongest binding affinity among tested compounds (−4.57 kcal/mol), though lower than the reference ligand alprazolam (−6.28 kcal/mol). Citral, Neral and Linalool interacted with all amino acid residues involved in the native ligand binding, while Linalool also formed an additional interaction with THR207, suggesting comparable binding patterns. ADMET prediction revealed high human intestinal absorption (>90%), favorable Caco-2 permeability, no inhibition of CYP2C19, CYP2C9, CYP2D6, or CYP3A4, and non-mutagenic toxicity (Ames test). Overall, these terpenoid compounds exhibit promising drug-like properties, acceptable oral bioavailability, favorable pharmacokinetics, and preliminary safety. Overall, these findings support the potential of lemongrass bioactive terpenoids as candidates for further anti-anxiety drug development;.

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Anti-anxiety refers to efforts to reduce symptoms such as restlessness, tension, and excessive worry that interfere with daily activities. Persistent anxiety may develop into disorders such as Generalized Anxiety Disorder (GAD). Biologically, anxiety is associated with imbalances in neurotransmitters including serotonin, dopamine, and GABA, while genetic factors may also increase susceptibility. Anxiety disorders represent one of the most prevalent categories of psychiatric conditions globally, affecting individuals across different age groups and socioeconomic backgrounds. The lifetime prevalence of anxiety disorders is estimated to range between 15% and 20%. Among the different anxiety disorders, specific phobia has the highest 12-month prevalence at approximately 12.1%, followed by social anxiety disorder at 7.4%, generalized anxiety disorder at 2.9%, panic disorder at 2.7%, and agoraphobia at 2.5% [1].

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Receptors are specialized proteins that mediate cellular communication by interacting with neurotransmitters, hormones, endogenous ligands, and drugs [2]. The target protein used in this study was 6X3X from the RCSB Protein Data Bank, representing the human γ-aminobutyric acid type A (GABAA) receptor α1β2γ2 subtype complexed with GABA and diazepam. As the primary mediator of inhibitory neurotransmission in the brain, the GABAA receptor plays an important role in anxiety regulation and is therefore considered a promising target for anti-anxiety drug development [3].

Lemongrass (*Cymbopogon citratus*) was selected in this study due to its reported anxiolytic potential. Its essential oil contains geranial (52.1%) and neral (35.2%), the major constituents of the citral group. In addition to these major constituents, geraniol, β-myrcene, and linalool are also naturally occurring terpenoids in lemongrass essential oil and may contribute to its anxiolytic activity through synergistic interactions among multiple constituents. [4]. Previous studies have shown that inhalation of lemongrass essential oil significantly reduces anxiety scores, possibly through modulation of the GABA-A–benzodiazepine receptor complex, and may reduce long-term dependence on benzodiazepines [4]. Costa *et al*. (2011) demonstrated the anxiolytic-like effects of C. citratus essential oil in vivo[5], and Cortes-Torres *et al*. (2023) investigated the interaction of C. citratus constituents with several central nervous system targets however, neither study specifically evaluated their interaction with the GABA-A receptor [6]. Therefore, further investigation is needed to clarify the molecular basis of the anxiolytic activity of lemongrass terpenoids through modulation of the GABA-A receptor. This study aims to evaluate the binding interactions and potential modulatory effects of these terpenoids using an in silico approach.

To assess their suitability as drug candidates, the bioactive terpenoids were evaluated for drug-likeness using Lipinski's Rule of Five through the SwissADME web server [7]. In addition, ADMET prediction was performed using the pkCSM web server to estimate pharmacokinetic properties and safety profiles [8].

Results and Discussion

This study was conducted to evaluate the potential of bioactive compounds from Cymbopogon citratus (lemongrass) as anti-anxiety agents through an in silico approach. Anxiety disorders were selected because they are among the most prevalent mental health conditions and are closely associated with dysfunction of the γ-aminobutyric acid (GABA) neurotransmitter system. The human GABAA receptor alpha1-beta2-gamma2 subtype (PDB ID: 6X3X) was chosen as the molecular target because it plays a crucial role in inhibitory neurotransmission and serves as the primary target of clinically used anxiolytic drugs such as diazepam, alprazolam, and zolpidem. The bioactive compounds Citral, Neral, Geraniol, Linalool, and β-myrcene were selected due to their presence in lemongrass essential oil and their reported neuropharmacological activities. The compounds were subsequently evaluated through Lipinski's Rule of Five analysis, molecular docking studies, and ADMET prediction to assess their potential as drug candidates.

Protein Preparation

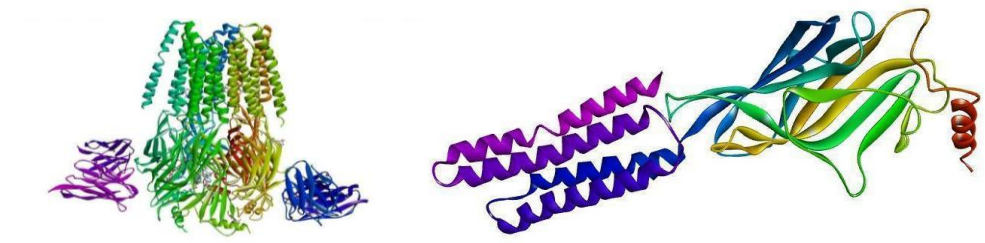


Figure 1. Target Protein (PDB ID: 6X3X) Before (Left) And After (Right) Protein Preparation

The target protein used in this study was the human gamma-aminobutyric acid type A (GABAA) receptor alpha1-beta2-gamma2 subtype (PDB ID: 6X3X), obtained from the RCSB Protein Data Bank (PDB) database in .pdb format. The crystal structure of 6X3X consists of the GABAA receptor complexed with gamma-aminobutyric acid (GABA) and diazepam as the co-crystallized ligand. Prior to molecular docking analysis, the protein structure was prepared to optimize the receptor and improve the reliability and accuracy of docking predictions, As shown in **Figure 2.1**, The crystal structure of 6X3X consists of the GABAA receptor complexed with gamma-aminobutyric acid (GABA) and diazepam as the co-crystallized ligand. Protein preparation was performed using AutoDockTools through removal of water molecules, separation of the co-crystallized ligand from the receptor, and addition of polar hydrogen atoms [14]. Water molecules were removed because they may interfere with ligand–receptor interactions, whereas polar hydrogen atoms are necessary to accurately represent hydrogen-bonding interactions and charge distribution [15]. The prepared receptor was saved in .pdbqt format for method validation and docking studies [13].

Ligand Preparation

Ligand preparation was performed as an essential step prior to molecular docking to ensure that each ligand possessed an optimized three-dimensional structure suitable for interaction analysis with the target protein. This process involved obtaining the chemical structures, optimizing their geometry, and converting them into the appropriate file format required for docking simulations. Proper ligand preparation is crucial because the quality of the ligand structure directly affects the accuracy and reliability of molecular docking results.

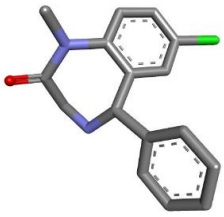


Figure 2. Visualization of native ligand preparation before method validation

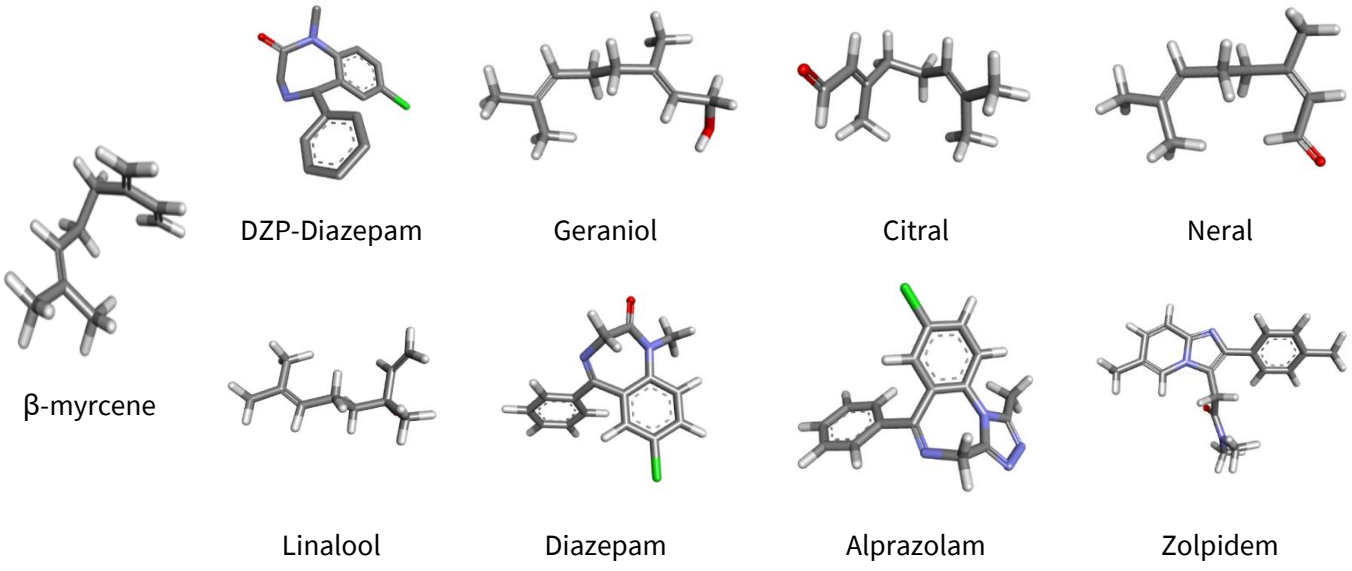


Figure 3. Chemical Structures

Ligand preparation involved obtaining chemical structures of Geraniol, Citral, Neral, β-myrcene, and Linalool from PubChem and MolView in .mol format[16], followed by geometric optimization using Avogadro to obtain the most stable conformation prior to docking, then conversion to .pdb format. Proper ligand preparation significantly influences the validity and accuracy of molecular docking results [17].

Method Validation

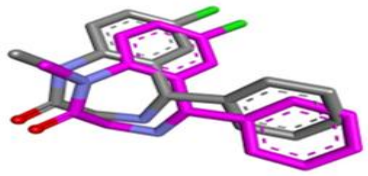


Figure 4. 3D Visualization After Method Validation

In Figure 2.4, the pink structure represents the ligand conformation obtained after docking validation, whereas the gray structure represents the prepared ligand before validation. The overlap between both structures was used to calculate the RMSD value and assess the accuracy of the docking protocol. An RMSD value of 0.89 Å indicates good agreement between the two conformations and confirms the validity of the docking method [18].

Validation of molecular docking using the native ligand diazepam against the 6X3X target protein yielded a free binding energy of −5.37 kcal/mol and an inhibition constant (Ki) of 115.86 µM. A negative binding energy indicates that the ligand can spontaneously interact with the receptor and form a stable complex; the more negative the value, the stronger the binding affinity. The native ligand interacted with key residues TYR210, TYR160, VAL203, SER205, PHE100, and HIS102, consistent with residues reported in previous studies on the same receptor (TYR58, PHE77, PHE100, HIS102, TYR160, VAL203, SER205, TYR210), supporting the reliability of the docking model [9]. The grid parameters (spacing 0.375 Å, box size 25×25×25) are standard AutoDock parameters known to produce optimal docking results [18].

The validation produced an RMSD value of 0.89 Å (run 38) with 100 docking runs, well below the 2 Å threshold required for a valid docking protocol, and within the range indicating high accuracy (<1 Å). Although a previous study on the same receptor system reported a lower RMSD of 0.49 Å, the value obtained here confirms that the docking protocol is reliable and capable of accurately reproducing native ligand binding orientations [9]. Together with the negative binding energy and consistent amino-acid residue interactions, this confirms the method is suitable for the subsequent docking of test compounds [19].

Table 1. Method Validation Results

Native ligand	Protein Target	Free Binding Energy (kkal/mol)	Ki (pM)	Grid Scale (X,Y,Z)	Spacing (Å)	Box Size	RMSD (Å)	Run ke-
(DZP-Diazepam)	6X3X	-5.37	115.86 uM	89.59, 125.888, 105.542	0.375	25x25x25	0.89	38

Note : Ki : Inhbition Constant; RMSD : Root Mean Square Deviation; TYR : Tyrosine; VAL : Valine; SER : Serine; PHE : Phenylalanine; HIS : Histidine

Lipinski's Rule of Five Analysis Study

Lipinski's Rule of Five analysis was performed as an initial screening step before molecular docking studies to evaluate the drug-likeness properties of the investigated compounds. This analysis is necessary because compounds with favorable physicochemical characteristics are more likely to exhibit good oral bioavailability and can therefore be considered potential drug candidates. The evaluated parameters included molecular weight, LogP, hydrogen-bond acceptors, and hydrogen-bond donors. These parameters were selected because they influence the ability of a compound to be absorbed through biological membranes following oral administration. In addition, Diazepam, Alprazolam, and Zolpidem were selected as reference ligands because they are clinically used drugs that act on the GABAA receptor, allowing the bioactive compounds of lemongrass to

be compared with compounds that have established pharmacological activity.

Table 2. Lipinski's Rule of Five Analysis Study

Compound	Mw (≤ 500)	LogP (≤ 5)	Hydrogen Bonds	RO5 Description	Compound
			Acceptor (≤ 10)	Donor (≤ 5)	
(DZP Diazepam)	284.74	2.97	2	0	Met
Linalool	154.25	2.66	1	1	Met
Citral	152.23	2.71	1	0	Met
Beta-Myrcene	136.23	3.43	0	0	Met
Neral	152.23	2.71	1	0	Met
Geraniol	154.25	2.74	1	1	Met
Diazepam	284.74	2.97	2	0	Met
Alprazolam	308.76	2.99	3	0	Met

Based on **Table 2.2**, the native ligand, 7-Chloro-1-Methyl-5-Phenyl-1,3-Dihydro-2H-1,4 Benzodiazepin-2-One (Diazepam), fulfills the criteria of Lipinski's Rule of Five. The compound has a molecular weight of 284.74 Da, a LogP value of 2.97, two hydrogen-bond acceptors, and no hydrogen-bond donors, all of which fall within the acceptable limits of the RO5 criteria [19]. In addition, all bioactive compounds (Linalool, Citral, β-myrcene, Neral, and Geraniol) and reference compounds (Diazepam, Alprazolam, and Zolpidem) also satisfy the RO5 requirements. All evaluated compounds exhibit molecular weights below 500 Da, LogP values below 5, fewer than 10 hydrogen-bond acceptors, and fewer than 5 hydrogen-bond donors. These findings indicate favorable oral bioavailability properties and drug-like characteristics [20].

The molecular weight parameter influences membrane permeability, whereas LogP reflects lipophilicity and affects absorption and distribution. Furthermore, hydrogen-bond donors and acceptors contribute to solubility and membrane permeability, both of which are important determinants of oral bioavailability. Therefore, all evaluated compounds satisfy the initial requirements for ligand preparation and subsequent molecular docking studies [21]

Molecular Docking of ligands Against Target Proteins

Table 3. Results of Compound Binding to Target Proteins

Compound	Free Binding Energy (kcal/mol)	Ki uM	Amino Acid Residues	%	Run No.
Geraniol	-4.57	445.20	**VAL=203 HIS=102 TYR=160 PHE=100 TYR=210** THR=207	83%	27
Citral	-4.36	632.28	**TYR=160 PHE=100 TYR=210 HIS=102 VAL=203 SER=205**	100%	75
Neral	-4.08	1021,7	**TYR=160 SER=205 PHE=100 TYR=210 HIS=102 VAL=203**	100%	13
β-myrcene	-3.96	1251,1	**HIS=102 TYR=210 PHE=100 VAL=203 TYR=160**	83%	51
Linalool	-4.36	632.67	**VAL=203 HIS=102 TYR=210 PHE=100 TYR=160** THR=207 **SER=205**	100%	29
Diazepam	-5.51	91.68	**TYR=160 PHE=100 HIS=102 TYR=210 VAL=203 SER=205**	100%	27
Alprazolam	-6.28	24.91	**TYR=210 TYR=160 VAL=203 HIS=102 PHE=100**	83%	47
Zolpidem	-5.09	185.47	**HIS=102 VAL=203** PHE=101 **PHE=100 TYR=160 TYR=210**	83%	23

Note: Bold residues are **similar** with the native ligand; red indicates hydrogen bond interactions, while black indicates hydrophobic interactions.

All bioactive compounds were able to interact with the 6X3X target protein, as evidenced by their binding energy, Ki values, and amino acid residue interactions. More negative binding energy indicates stronger binding affinity and greater complex stability [15]. As presented in **Table 2.3**, the tested bioactive

compounds exhibited different binding affinities and interaction profiles toward the 6X3X receptor. Geraniol showed the strongest interaction among tested compounds (−4.57 kcal/mol), followed by Citral and Linalool (−4.36 kcal/mol), Neral (−4.08 kcal/mol), and β-myrcene, the weakest (−3.96 kcal/mol). Compared with reference ligands, the tested compounds showed lower binding affinities than Diazepam (−5.51 kcal/mol), Alprazolam (−6.28 kcal/mol, the strongest overall), and Zolpidem (−5.09 kcal/mol). Ki values were consistent with these results, with reference ligands showing lower Ki and thus stronger inhibitory potential [19].]

Visualization of Interaction

The visualization of ligand–protein interactions was performed to identify the binding orientation of each compound within the active site of the GABA-A receptor (PDB ID: 6X3X) and to evaluate the amino acid residues involved in the binding process. Analysis of the interaction patterns provides insight into the stability and strength of ligand binding, as well as the potential of each compound to occupy the receptor binding pocket. The interaction diagrams revealed that the tested compounds formed several hydrophobic and non-covalent interactions with key residues located within the receptor binding site.

Additionally, ligand–protein interactions involve several amino acid residues such as TYR160, TYR210, PHE100, HIS102, VAL203, THR207, and SER205. These residues are located within the binding pocket of the GABA-A receptor and are known to contribute to ligand recognition and stabilization. The interaction maps showed that all tested compounds were able to occupy the active site and establish favorable contacts with the receptor. Among the tested ligands, Geraniol exhibited the most favorable binding energy, suggesting a stronger interaction and greater binding affinity toward the target protein compared to the other compound

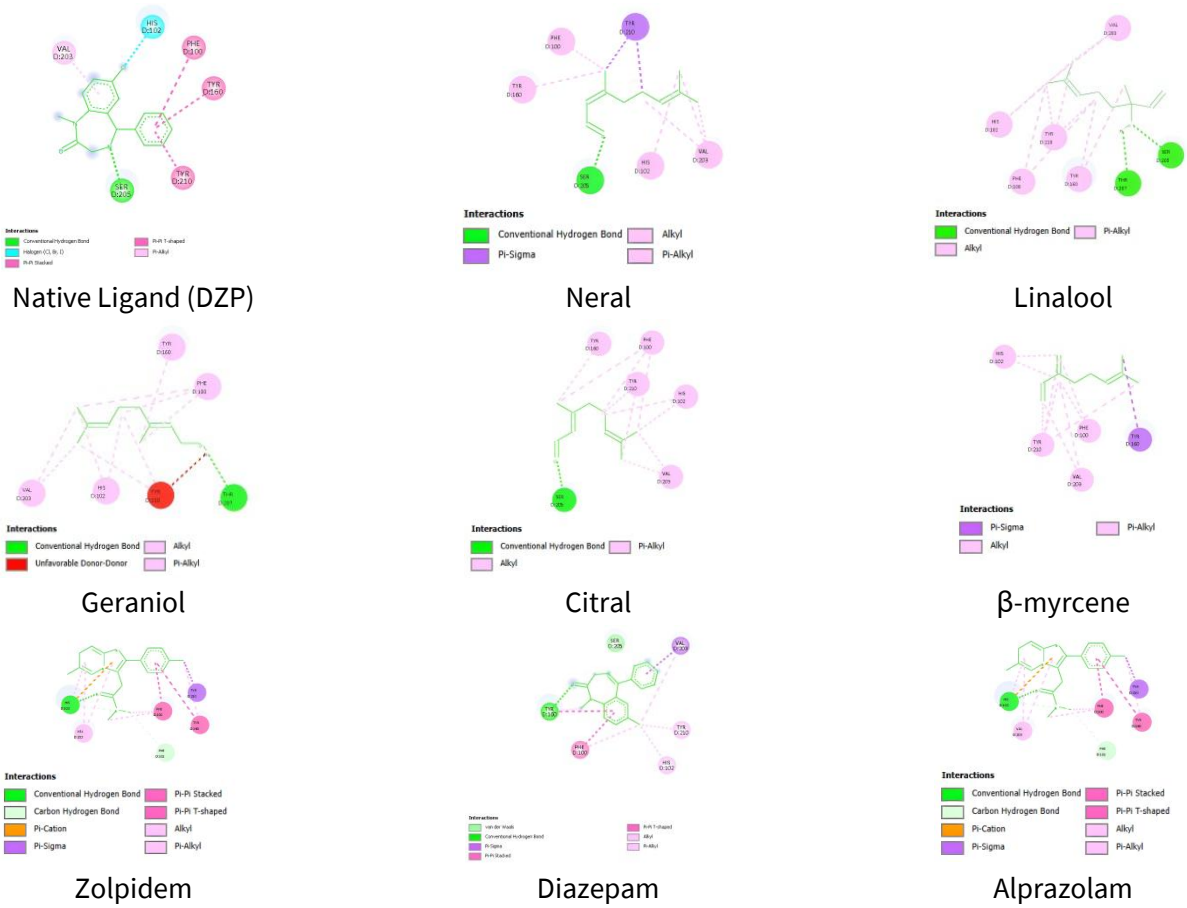


Figure 4. Visualization of interactions

Citral and Linalool showed 100% residue similarity to the native ligand, interacting with the same residues as Diazepam (TYR160, PHE100, TYR210, HIS102, VAL203, SER205), indicating binding patterns that closely resemble the native ligand. Geraniol, Neral, and β-myrcene showed 83% similarity due to

differences such as the presence of THR207 or absence of SER205, but still retained interactions with the major residues TYR160, TYR210, HIS102, VAL203, and PHE100 reported in the literature as key GABA-A receptor binding-site residues (Tyr58, Phe77, Phe100, His102, Tyr160, Val203, Ser205, Tyr210) [9],

ADMET Prediction Study

ADMET evaluation complements molecular docking by assessing pharmacokinetic behavior and toxicity, since docking alone cannot determine whether a compound has favorable absorption, distribution, metabolism, excretion, and safety characteristics [9]

All test compounds exhibited high Human Intestinal Absorption (HIA > 90%) and favorable Caco-2 permeability, supporting their potential for oral administration. Because the target (6X3X) is a CNS receptor, Blood–Brain Barrier (BBB) permeability is particularly important; Diazepam and other reference compounds showed better BBB permeability than the tested terpenoids. None of the test compounds were predicted to inhibit CYP2C19, CYP2C9, CYP2D6, or CYP3A4, suggesting a low risk of metabolic drug–drug interactions, and all were predicted non-mutagenic based on the Ames test. Overall, the ADMET results indicate promising pharmacokinetic characteristics and acceptable safety profiles, although CNS penetration remains lower than that of the reference ligands [20]

Table 5. ADMET Prediction Study

Ligand	Absorption		Distribution		Metabolism (CYP)				Excretion		Toxicity	
									Total	Renal OCT2		
	HIA	Caco2	VDss	BBB	2C19	2C9	2D6	3A4	Clearance	Sub	Mutagen	LD50
Citral	95,317	1,504	0,166	0,626	No	No	No	No	0,376	No	No	1,815
Geraniol	92,788	1,49	0,17	0,606	No	No	No	No	0,437	No	No	1,636
Neral	95,317	1,504	0,166	0,626	No	No	No	No	0,376	No	No	1,815
Beta-Myrcene	95,393	1,405	0,368	0,786	No	No	No	No	0,438	No	No	1,683
Linalool	93,163	1,493	0,152	0,598	No	No	No	No	0,446	No	No	1,704
Diazepam	97,42	1,554	0,365	0,331	Yes	Yes	No	No	0,294	Yes	No	2,404
Alprazolam	98,375	1,499	0,167	0,435	Yes	Yes	No	No	0,207	Yes	No	2,347
Zolpidem	88,512	1,959	-0,397	0,527	Yes	No	No	No	0,735	Yes	No	2,324

Conclusion

This in silico study demonstrates that bioactive terpenoid compounds from lemongrass (Cymbopogon citratus), Geraniol, Citral, Neral, β-myrcene, and Linalool show potential as anti-anxiety agents through interaction with the 6X3X target protein, supported by satisfactory docking validation (RMSD 0.89 Å) and compliance with Lipinski's Rule of Five for all compounds, indicating their suitability as oral drug candidates. Among the tested compounds, Geraniol exhibited the strongest binding affinity (−4.57 kcal/mol), although still lower than reference ligands Diazepam (−5.51 kcal/mol), Alprazolam (−6.28 kcal/mol), and Zolpidem (−5.09 kcal/mol), while Citral and Linalool showed 100% amino acid residue similarity to the native ligand, suggesting comparable binding patterns at the GABA-A receptor active site. ADMET predictions further revealed favorable pharmacokinetic properties, including high human intestinal absorption (HIA >90%), acceptable Caco-2 permeability, no inhibition of CYP2C19/2C9/2D6/3A4, and non-mutagenic toxicity, though predicted blood–brain barrier permeability was lower than that of the reference ligands. Overall, these findings suggest that lemongrass bioactive compounds hold promise as candidates for anti-anxiety therapy, though further in vitro and in vivo studies are required to confirm their biological activity and safety

Materials and Methods

This in silico study was conducted using a Lenovo IdeaPad Flex 5 14ALC05 laptop equipped with an AMD Ryzen 7 5700U processor with Radeon Graphics, operating on a 64-bit Windows 11 Pro system. The

software used included AutoDockTools version 1.5.6, Avogadro, BIOVIA Discovery Studio Visualizer 2025, the RCSB PDB website, PubChem, SwissADME, pkCSM, and MolView [3]. The materials used were bioactive terpenoid compounds from lemongrass Geraniol, Citral, Neral, β-myrcene, and Linalool [4]. The target receptor was the GABAA receptor alpha1-beta2-gamma2 subtype with PDB ID 6X3X [9].

Protein Preparation

The target protein, the human GABAA receptor alpha1-beta2-gamma2 subtype (PDB ID: 6X3X), was obtained from rcsb.org in .pdb format, containing the native ligand diazepam (DZP). Preparation was performed using AutoDockTools by separating the protein from its native ligand prior to docking analysis [9]

Method Validation

Method validation used the protein and its native ligand (DZP), converted into .pdbqt format using AutoDockTools, with a grid box size of 25×25×25, coordinates X=89.59, Y=125.888, Z=105.542, centered on the ligand. The docking parameters were deemed valid if the maximum RMSD value was ≤2.0 Å [10].

Analysis of Lipinski's Rule of Five

Lipinski's Rule of Five analysis evaluated the potential of the test compounds as oral drug candidates using the swissadme.ch web server with SMILES input. Parameters analyzed included molecular weight (≤500 g/mol), hydrogen bond donors (≤5), hydrogen bond acceptors (≤10), and LogP (≤5). A compound is considered to meet the rule if it does not exceed one violation [11].

Test Ligand Preparation

Test ligands consisted of terpenoid compounds from lemongrass Geraniol, Citral, Neral, β-myrcene, and Linalool [12]. Diazepam, Alprazolam, and Zolpidem served as reference ligands [5]. Three-dimensional structures of all ligands were retrieved from PubChem and MolView, geometrically optimized using Avogadro, and converted into .pdbqt files for docking.

Molecular Docking of Compounds to Target Protein

Molecular docking was performed using AutoDockTools version 1.5.6, with the grid box defined at the protein's active site based on the position of the native ligand diazepam with 100 docking runs. Results were analyzed based on binding affinity values and amino acid residue interactions [13]

Visualization of Interactions

Visualization of the interactions between the ligands and the protein resulting from the molecular docking process was performed using BIOVIA Discovery Studio Visualizer 2025 software. This software was used to analyze and illustrate the binding interactions formed between the ligand-protein complex [10]

ADMET Prediction Study

ADMET prediction was conducted using the pkCSM web server (https://biosig.lab.uq.edu.au/pkcsm/prediction) by inputting compound structures in SMILES format. Parameters analyzed included absorption, distribution, metabolism, excretion, and toxicity to evaluate each compound's potential as a safe and effective drug candidate [8].

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