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**Abstract**

Major depressive disorder (MDD) is a prevalent neuropsychiatric condition affecting approximately 280 million individuals worldwide, with women exhibiting a 50% higher likelihood of diagnosis than men. Despite significant advancements in treatment, MDD remains a chronic and relapsing disorder, necessitating the exploration of novel therapeutic interventions. This study focuses on the AKT1 gene, a key player in neuropsychiatric disorders, and investigates its interactions with natural phytochemicals as potential alternatives to conventional antidepressants. Molecular docking analysis was conducted using the AKT1 protein structure (PDB ID: 3O96) to evaluate the binding affinities of FDA-approved antidepressants and selected phytochemicals derived from Ayurvedic medicinal plants. Active site prediction using CASTpFold identified a binding pocket with a surface area of 1665.060 Å² and a volume of 1365.991 Å³. Docking studies revealed that Cannflavin A and Betulinic

Acid exhibited superior binding affinities (-10.6 and -10.3 kcal/mol, respectively) compared to Paroxetine (-10.2 kcal/mol) and Sertraline (-9.7 kcal/mol). Interaction analysis highlighted stronger hydrogen bonding, hydrophobic interactions, and van der Waals forces in Cannflavin A compared to Paroxetine, suggesting enhanced binding stability. Furthermore, ADMET analysis confirmed favorable pharmacokinetic properties for Cannflavin A, reinforcing its potential as a natural therapeutic agent for MDD. These findings underscore the promise of phytochemicals in modulating AKT1 activity and provide a foundation for future preclinical and clinical investigations into their antidepressant potential.

**Keywords**: MDD, Docking , AKT1, Cannflavin A, Betulinic Acid

## Introduction

Major depressive disorder (MDD) is a widespread neuropsychiatric condition with profound global implications, impacting millions of individuals and contributing to substantial economic and healthcare challenges [1]. Affecting approximately 280 million people worldwide, depression is a leading mental health concern, with over 5% of adults experiencing its effects. A notable gender disparity exists, with women exhibiting a higher prevalence rate (6%) compared to men (4%), reflecting a 50% greater likelihood of diagnosis. This disparity is particularly pronounced among pregnant women and postpartum mothers, with more than 10% affected by depressive symptoms [2]. MDD is clinically identified by a persistent feeling of sadness, loss of interest in activities, changes in weight or appetite, and an increased risk of suicidal tendencies. These characteristics align with the diagnostic guidelines outlined in the DSM-5 and are reinforced by the ICD-10 classification system[3]. Individuals diagnosed with MDD often report self-harm ideation, chronic sadness, cognitive impairments such as poor decision-making and reduced concentration, and other debilitating manifestations. While the precise etiology of MDD remains elusive, studies indicate that its development is influenced by a combination of environmental factors, gender-based differences, genetic vulnerabilities, epigenetic changes, and dysregulation in the nervous, endocrine, immune, and adrenal-pituitary systems. Importantly, MDD is frequently a chronic and relapsing condition, with many individuals experiencing recurrent episodes over their lifetime [4]. Despite advancements in treatment modalities, the prevalence of depression has remained unchanged since 1990, underscoring the complexity of its underlying mechanisms. Current research highlights four primary theoretical frameworks: monoamine deficiency, impaired neuroplasticity, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and microglial activation [5]. These areas collectively contribute to the ongoing exploration of the neural and biological pathways implicated in MDD.

In our study, we have focused on the AKT1 gene, which was identified as one of the key genes implicated in both major depressive disorder (MDD) and bipolar disorder in our previous research [6]. Given its critical role in these neuropsychiatric conditions, we have selected AKT1 for further exploration to identify natural phytochemical compounds that may interact with or modulate its activity.

The AKT1 gene, situated on chromosome 14q32.3, codes for a serine/threonine protein kinase and is a member of the AKT family, also known as protein kinase B. Originally linked to schizophrenia susceptibility, research has shown that individuals with the condition tend to

have lower levels of AKT1 protein in various tissues, including peripheral lymphocytes, frontal cortex, and hippocampus. While weak evidence links *AKT1* to bipolar disorder, its role in major depressive disorder (MDD) is supported by studies showing impaired neuroprotective mechanisms in MDD patients and reduced *AKT1* function in postmortem cortical regions. Dysregulation of *AKT1*, along with PTEN and PI3K, may disrupt lipid second messenger phosphorylation, contributing to MDD pathology[6]. Research has also underscored the significance of AKT and glycogen synthase kinase-3 (GSK-3) in psychiatric conditions, noting their complex interplay with dopamine and serotonin signaling pathways. The study also explored the effects of pharmacological treatments, including antipsychotics, antidepressants, and lithium, on these signaling mechanisms [7].

Molecular docking is a critical structural bioinformatics tool in drug discovery, enabling the prediction of optimal binding conformations and interactions between macromolecules (e.g., proteins) and small-molecule ligands. This method plays a pivotal role in identifying potential inhibitors for targeted therapeutic interventions. The molecular docking process typically involves three essential steps: (1) preparation of the macromolecular and small-molecule structures, (2) docking simulations to predict binding modes, and (3) evaluation of ligand-receptor binding affinity to assess interaction strength [8].

In Ayurvedic medicine, various herbs and natural compounds are utilized to mitigate symptoms of major depressive disorder (MDD). Ayurveda offers a rich repository of plant-based remedies, with around 80% of the global population depending on botanical medicines for primary healthcare needs, highlighting their significance in health management. Many of these herbs are integral to rasayana formulations, which aim to rejuvenate both physical and mental health. The rasayana approach promotes holistic well-being by enhancing digestive efficiency, optimizing metabolic processes, and ensuring effective nutrient delivery to essential tissues [9].

**Methodology:**

**Protein selection:**

The protein structure, identified by PDB ID 3O96, was retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/) for molecular docking studies. This structure, resolved at 2.70 Å, provides a high-resolution representation of the active site and inhibitor interactions, which is critical for ensuring the accuracy of docking simulations. Among available structures, 3O96 was chosen due to its superior resolution, enabling precise modeling of key protein-ligand interactions. The detailed insights into the active site offered by this structure enhance the reliability of predicting binding modes and affinities during docking studies.

**Active Site Prediction:**

To identify the protein-ligand binding site, we utilized CASTpFold [10] to predict specific amino acid residues involved in protein-ligand interactions. This targeted approach eliminated the need for blind docking and allowed for focused binding site identification. To confirm the precision and dependability of the predicted binding site, further validation was performed using the RCSB server. To confirm the consistency of the observed interactions, we cross-validated the results with the binding site residues predicted by CASTpFold. This comparison demonstrated a high degree of agreement between the predicted and observed ligand-protein interactions, reinforcing the reliability of our findings.

**Identification of Known Chemical Drugs:**

For interaction studies, we selected several FDA-approved drugs from various classes commonly used to treat Major Depressive Disorder (MDD). These included Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), and Monoamine Oxidase Inhibitors (MAOIs). All compounds were retrieved in SDF format from PubChem [11].Ensuring their structural accuracy for subsequent molecular docking and interaction analyses.

**Phytocompound selection:**

As part of our investigation into plant-derived natural compounds, we examined a range of phytochemicals sourced from Bacopa monnieri, Asparagus racemosus, Benincasa hispida, and Cannabis, with the aim of identifying potential alternatives to conventional pharmaceuticals. To this end, we compiled a dataset of bioactive compounds from various plant sources, utilizing publicly available databases and published research papers, which were retrieved in SDF format from PubChem.

**Docking Analysis:**

The protein structure (PDB ID: 3O96) was obtained from the Protein Data Bank. Using AutoDock 4.2.6, the structure was prepared by removing water molecules, adding polar hydrogen atoms, and assigning Kollman's charges. The processed structure was saved in PDBQT format. Molecular docking simulations were then performed to predict the preferred binding orientations of ligands with the 3D protein structure. Docking software, including AutoDock and AutoDock Vina [12], was employed for this purpose. The grid box dimensions for docking were set to 66 × 74 × 78 Å, with the maximum number of points in each dimension. The exhaustiveness parameter was set to 8.0 to ensure exhaustive conformational space sampling during docking analysis.

The docking protocol was optimized by leveraging AutoDock's capabilities to perform a thorough and flexible docking search within the protein's active site. By constraining the search space to the active site and increasing the exhaustiveness of the search, the likelihood of identifying optimal binding poses and orientations was significantly enhanced. This targeted approach facilitated an in-depth exploration of the conformational space, providing valuable insights into the molecular interactions governing the protein-ligand complex and enabling the elucidation of optimal binding modes.

**ADMET Analysis:**

The pharmacokinetic profile of a compound was evaluated through ADME (Absorption, Distribution, Metabolism, and Excretion) properties, which determine its drug-like behavior. In accordance with Lipinski's Rule of Five [13], ADME properties provide insight into a compound's bioavailability and accessibility throughout the body, facilitating the identification of promising lead candidates. We used admetSAR[14] and SwissADME[15] for identifying the AMDET properties.

**Visualization of Docking Results:**

The docking outcomes were visualized using Biovia Discovery Studio Visualizer 2024 and PyMol, facilitating the identification of the optimal binding configuration between the ligand

and AKT1 protein. A total of nine conformations were generated, from which those with the lowest root mean square deviation (RMSD) values were selected for further analysis. The docking affinity of the ligands was benchmarked against the protein's natural ligand and a positive control, enabling the identification of the top-performing ligand. The resulting ligand-protein complex was subsequently saved in PDB format, allowing for in-depth analysis and visualization of binding site interactions.

**Results and discussion**

**Prediction of active sites for AKT1:**

The identification of the active site of a protein is a crucial step in understanding its function and mechanism of action. In this case, CASTpFold was used to identify the active site, which revealed an area of 1665.060 $Å^2$ and a volume of 1365.991 $Å^3$. To further validate this finding, a comparison study was made with the active site features from the RCSB PDB structure (3O96), which provided information on interacting residues bound to the protein pocket. This comparison helped to confirm the accuracy of the active site identification, giving researchers a better understanding of the protein's structure and function. The use of AlphaFold2 models in CASTpFold also ensured high-accuracy structural predictions, making the results more reliable.

**Molecular Interaction between Ligands and active sites:**

The molecular docking simulations revealed promising results (Table 1,2), with certain phytochemicals exhibiting superior affinity scores compared to conventional medications for Major Depressive Disorder (MDD) treatment. Notably, Cannflavin A and Betulinic Acid, two natural compounds, demonstrated higher affinity scores than Paroxetine and Sertraline, which are FDA-approved antidepressant drugs. These findings suggest that these phytochemicals may have potential therapeutic benefits, and further investigation is warranted to explore their efficacy, safety, and pharmacokinetic profiles as alternative treatments for MDD. The analysis of the docking poses also provided valuable insights into the binding mechanisms, highlighting the importance of hydrophobic interactions, hydrogen bonding, and π-π stacking in stabilizing the ligand-protein complexes. Overall, the results of the molecular docking simulations offers a promising point for the development of novel, phytochemical-based treatments for MDD, and may ultimately lead to the discovery of more effective and safer therapeutic options for patients.

**Table 1. Molecular Docking Scores of Chemical Ligands with Protein Structure.**

| S.no | Pubchem CID | Ligands | Docking score(kcal/mol) |
|---|---|---|---|
| 1 | 43815 | Paroxetine | -10.2 |
| 2 | 68617 | Sertraline | -9.7 |
| 3 | 4543 | Nortriptyline | -9.6 |
| 4 | 2160 | Amitriptyline | -9.4 |
| 5 | 146570 | Escitalopram | -9.1 |
| 6 | 2771 | Citalopram | -9.1 |
| 7 | 3696 | Imipramine | -9 |
| 8 | 3386 | Fluoxetine | -8.8 |
| 9 | 60835 | Duloxetine | -8.7 |
| 10 | 125017 | Desvenlafaxine | -7.9 |
| 11 | 5656 | Venlafaxine | -7.9 |
| 12 | 3675 | Phenelzine | -6.3 |
| 13 | 19493 | Tranylcypromine | -6 |

**Table 2. Results shows the Interaction score of the natural compounds with protein structure.**

| S.no | Pubchem CID | Ligand Name | Binding Energy |
|---|---|---|---|
| 1 | 10071695 | Cannflavin A | -10.6 |
| 2 | 64971 | Betulinic Acid | -10.3 |
| 3 | 403815 | Cannflavin B | -9.8 |
| 4 | 16078 | Dronabinol | -9.8 |
| 5 | 5280343 | Quercetin | -9.7 |
| 6 | 5280863 | Kaempferol | -9.3 |
| 7 | 624971 | Racemosol | -9.3 |
| 8 | 160570 | Cannabidiolic Acid | -9.1 |
| 9 | 119287 | Cucurbitacin S | -8.5 |
| 10 | 644019 | Cannabidiol | -8.4 |
| 11 | 5281515 | Caryophyllene | -7.3 |
| 12 | 5280450 | Linoleic Acid | -7.2 |
| 13 | 6549 | Linalool | -5.6 |
| 14 | 54670067 | Ascorbic Acid | -5.4 |
| 15 | 119 | Gamma-Aminobutyric Acid | -4 |

**Interaction studies between Protein-ligands**

Examining the 3D structures of the docked protein-ligand complexes (Figure 1) revealed intricate details about the binding interactions between the protein target and ligands. This insight enabled the identification of potential drug candidates and elucidated their underlying

molecular mechanisms. To further elucidate protein-ligand interactions, 2D interaction studies (Figure 2) were conducted, examining hydrogen bonding, hydrophobic interactions, electrostatic interactions, and π-π stacking. These interactions were visualized using the Biovia Discovery Studio Visualizer and summarized in Table 3. This integrated analysis offered valuable insights into the binding patterns and key residues that stabilize the protein-ligand complexes, which are essential for structure-based design and optimization of prospective therapeutic agents. By elucidating the molecular mechanisms of protein-ligand interactions, researchers can rationally design novel inhibitors, optimize lead compounds, and predict potential off-target effects, ultimately laying the groundwork for the development of effective therapeutics targeting the identified protein.

**Figure 1. Figure depicts complex 3d structure of receptor protein-multicoloured structure and ligand (chemical, natural)- green coloured structure)**

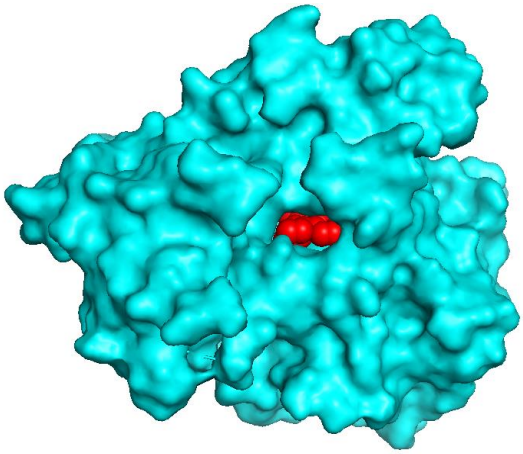
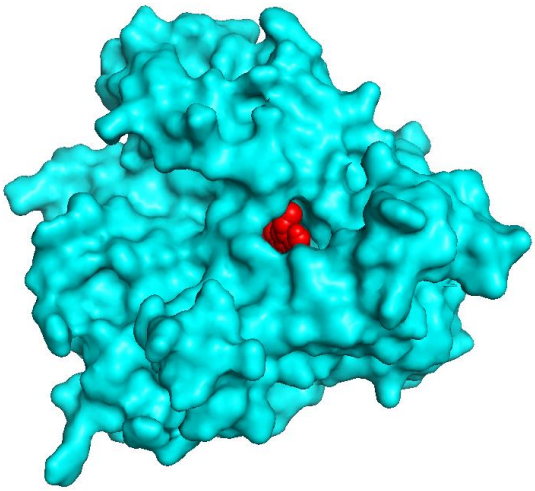
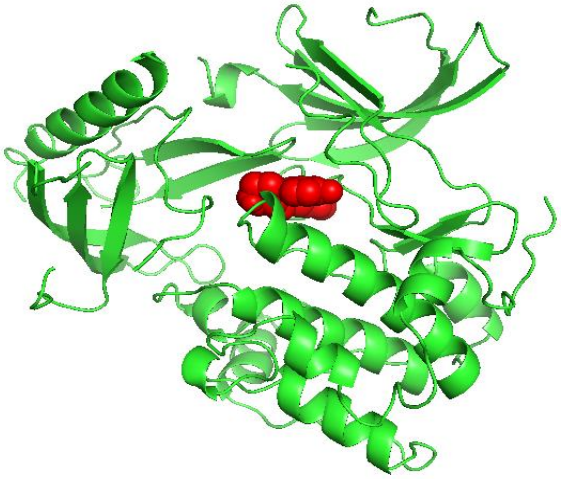
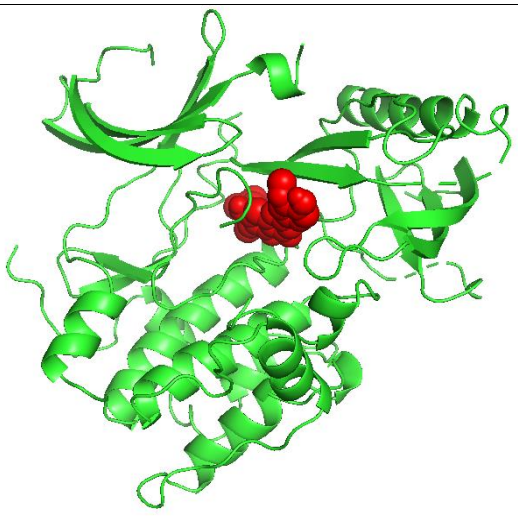
| **Protein(3O96)-ligand (Paroxetine) complex (Chemical)** | **Protein(3O96)-ligand (Cannflavin A) Complex (Natural)** |
|---|---|
|  |  |
|  |  |

**Figure. 2. Images depicts various 2d interactions between the protein and ligands (chemical, natural)**

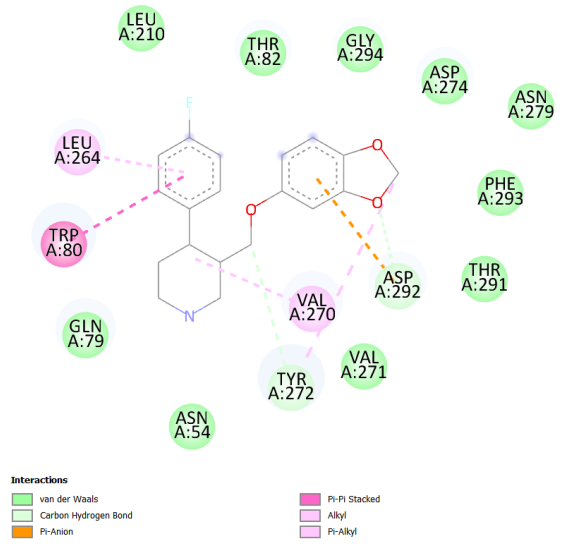
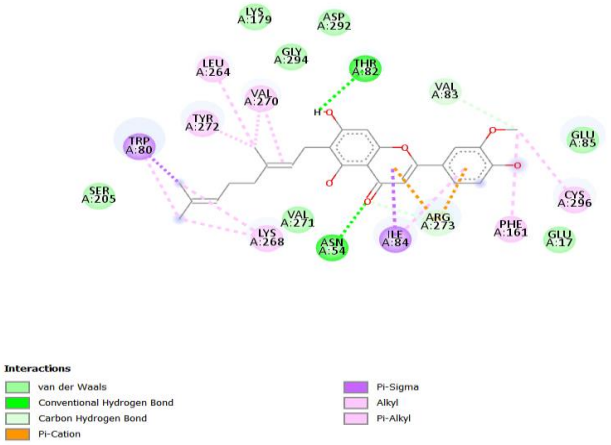
| 2D interaction between Protein (3O96)-ligand(Paroxetine) complex | 2D interaction between Protein(3O96)-ligand (Cannflavin A) Complex |
|---|---|
|  |  |





**Table.3. This table outlines the specific interactions observed between the protein residues/atoms and the ligands**

| S.no. | Ligands | Interaction bonds | | | |
|---|---|---|---|---|---|
| | | No. of Hydrogen bonds | Hydrogen binding interaction | Hydrophobic interaction | van der Waals Interactions |
| 1. | Cannflavin A | 3 | ASN A:54, THR A:82, ARG A:273 | TRP A:80, TYR A:272, PHE A:161, ILE A:84, LYS A:268, VAL A:270, CYS A:296, LEU A:264, ARG A:273 | LYS A:179, ASP A:292, GLY A:294, VAL A:83, GLU A:85, SER A:205, GLU A:17, VAL A:271 |
| 2. | Paroxetine | 2 | ASP A:292, TYR A:272, | TRP A:80, LEU A:264, VAL A:270, | LEU A:210, THR A:82, GLY A:294, ASP A:274, ASN A:279, PHE A:293, THR A:291, GLN |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | A:79, ASN A:54, VAL A:271, |

**Table.3. This table outlines the Comparison analysis between both the Compounds**

| Factor | Cannflavin A (Natural) | Paroxetine (Chemical) | Why Cannflavin A is Better |
|---|---|---|---|
| No. of Hydrogen Bonds | 3 | 2 | More hydrogen bonds = Stronger binding |
| Hydrophobic Interactions | 10 residues | 5 residues | More hydrophobic contacts = Better stability |
| van der Waals Interactions | 8 residues | 10 residues | Slightly higher for Paroxetine but weaker impact overall |
| Key Binding Residues | ARG A:273, PHE A:161, TYR A:272 | ASP A:292, TYR A:272 | ARG A:273 in Cannflavin A is crucial for binding |

Cannflavin A demonstrated stronger binding stability, forming three hydrogen bonds (ASN A:54, THR A:82, ARG A:273) compared to two for Paroxetine. Additionally, it showed more hydrophobic interactions (10 vs. 5), enhancing its anchoring within the active site. While Paroxetine had slightly more van der Waals interactions, Cannflavin A's key interactions with ARG A:273 and PHE A:161 suggest superior binding affinity.

**ADMET analysis of natural compounds**

The ADMET properties of Cannflavin A were evaluated to assess its potential as a therapeutic agent for targeting the AKT1 gene in Major Depressive Disorder (MDD). This evaluation, summarized in Table 4, examined the compound's absorption, distribution, metabolism, excretion, and toxicity to determine its drug-likeness. Analyzing these properties one can identify potential issues and determine the suitability of Cannflavin A as a treatment for MDD. The results provide valuable insights into the compound's pharmacokinetic and pharmacodynamic behavior, informing further development and optimization of Cannflavin A as a potential therapeutic agent for MDD.

**Table. 4. This table outlines the specific ADMET properties of natural compound.**

| S.no. | Ligands | AMES toxicity | BBB Penetration | Lipinski | Hepato toxicity | H-bond acceptors | H-bond donors |
|---|---|---|---|---|---|---|---|
| 1 | Cannflavin A | No | No | Yes | No | 6 | 3 |

Cannflavin A demonstrates promising drug-likeness and safety based on key pharmacokinetic and toxicity parameters. It is non-mutagenic, as indicated by a negative AMES toxicity test, ensuring that it does not pose risks for genetic mutations or carcinogenicity. Additionally, it does not cross the blood-brain barrier (BBB), suggesting its limited applicability for central nervous system (CNS) disorders but potential effectiveness in peripheral treatments. The compound complies with Lipinski's Rule of Five, indicating good oral bioavailability and drug-like properties. Importantly, Cannflavin A is non-hepatotoxic, meaning it poses no significant risk of liver damage, making it a safer candidate for long-term therapeutic use. With 6 hydrogen bond acceptors and 3 hydrogen bond donors, it has strong binding potential, further enhancing its pharmacological relevance. While its inability to penetrate the BBB limits direct CNS applications, formulation strategies or structural modifications could improve its neurological therapeutic potential.

## Discussion

The present study employed an in-depth computational approach to investigate the potential of phytochemicals in targeting AKT1, a key player in the pathophysiology of MDD. Molecular docking analysis revealed strong binding affinities of selected phytochemicals with the AKT1 protein, suggesting their potential as inhibitors. Among the screened compounds, Cannflavin A, a flavonoid derived from Cannabis sativa, demonstrated significant binding affinity with AKT1. Its interactions were stabilized by hydrogen bonding and hydrophobic interactions, which could contribute to its neuroprotective properties.

Additionally, Paroxetine, a well-known selective serotonin reuptake inhibitor (SSRI) and a standard antidepressant, was used as a reference compound. The docking results indicated that while Paroxetine binds effectively to AKT1, some phytochemicals, including Cannflavin A, exhibited comparable or even stronger binding affinities. This suggests the possibility of phytochemicals serving as natural alternatives or adjunctive therapies for MDD treatment. The pharmacokinetic analysis further highlighted the favorable ADMET properties of Cannflavin A, with good BBB permeability and low toxicity, making it a strong candidate for further investigation.

Despite promising results, the study has certain limitations. The in-silico approach, while highly informative, requires experimental validation through in vitro and in vivo studies to confirm the biological activity and therapeutic efficacy of these phytochemicals. Additionally, molecular dynamics simulations could provide further insights into the stability and dynamic behavior of phytochemical-AKT1 interactions over time.

## Conclusion

This study highlights the potential of phytochemicals as novel therapeutic agents targeting AKT1 in Major Depressive Disorder. The molecular docking and ADMET analyses suggest that selected compounds exhibit strong binding affinity, favorable pharmacokinetics, and low toxicity, making them promising candidates for further drug development. Future experimental validation through biochemical assays and preclinical studies will be essential to establish their efficacy and safety in treating MDD. The findings contribute to the growing interest in plant-derived compounds for neuropsychiatric disorders and pave the way for future research in natural product-based antidepressants.

## Authors' Contribution

Conceptualization: AC, CKJ. Data curation: AC. Formal analysis: AC, Methodology: AC, CKJ. Writing – original draft: AC. Writing – review & editing: AC, CKJ

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