Targeting p38 MAPK: Molecular Docking and Therapeutic Insights for Alzheimer's Disease Management

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Abstract

Background: Alzheimer's disease (AD), a progressive neurodegenerative disorder, is closely linked to the p38 mitogen-activated protein kinase (MAPK) pathway, which regulates neuroinflammation, oxidative stress, apoptosis, and other key pathological processes. Developing selective inhibitors targeting p38 MAPK could offer novel therapeutic interventions for AD. Methods: Nine molecules, selected for their therapeutic potential based on literature, were docked against p38 MAPK (5MTX) using molecular docking. Binding affinities, hydrogen bonding, and hydrophobic interactions were analyzed to assess the strength and stability of ligand-receptor interactions. Residues contributing to selectivity and therapeutic potential were identified, and results were contextualized with in vitro and in vivo studies. Results: NJK14047 exhibited the highest binding affinity (-10.2 kcal/mol) due to hydrogen bonds with Asn115, Gly110, Met109, Asp168, and Glu71, contributing to enhanced stability and selectivity. Ginsenoside Rg1 (-7.9 kcal/mol) and Apigenin (-8.7 kcal/mol) demonstrated significant interactions with key residues, including Thr106 and Leu104, with Ginsenoside Rg1 supporting mitophagy and memory improvement in AD models. Skepinone-L showed high inhibitory activity with hydrophobic residues but lacked hydrogen bonding. In vivo studies supported the neuroprotective and anti-inflammatory effects of several candidates, with NJK14047 reducing microglial activation and promoting neuroprotection. Conclusion: The study underscores the therapeutic potential of p38 MAPK inhibitors in AD management. NJK14047, with its strong binding affinity and selectivity, emerges as a lead candidate for further exploration. These findings highlight the need for clinical trials to validate the efficacy of p38 MAPK inhibitors as a comprehensive approach to treating AD.

Keywords: Alzheimer's Disease (AD), p38 MAPK Inhibitors, Molecular Docking, Neuroinflammation, Therapeutic Targets

Significance | This study identifies potent p38 MAPK inhibitors, highlighting their potential in developing targeted therapies for Alzheimer's disease.

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Introduction

The prevalence of dementia is growing rapidly across the globe, driven largely by the aging population. Currently, an estimated 37 million individuals worldwide are living with dementia, a number that is expected to rise significantly in the coming decades (Hodges, 2017). Among the various forms of dementia, Alzheimer's disease

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(AD) stands as the most common and is the leading cause of disability and death among the elderly ((Ashwell, 2006)). Despite substantial advancements in our understanding of Alzheimer's over the past decade, it remains a condition without a cure. The search for effective treatments continues to be a critical challenge in medical research, with the focus on identifying potential therapeutic targets that could slow or halt disease progression (Avital et al., 2003). One such target that has garnered significant attention is p38 mitogen-activated protein kinase (MAPK), a protein involved in a variety of cellular processes, including inflammation (Bains & Oliet, 2007). In recent years, the role of p38 MAPK in AD has been explored in more detail, but most reviews on the subject have been limited to peripheral tissue inflammatory disorders, such as rheumatoid arthritis, and have been published mainly in the context of cellular models of neuroinflammation. Early reviews, dating back to 2003, focused almost exclusively on understanding how p38 MAPK signaling contributes to the pathology of Alzheimer's disease, especially in terms of inflammation within the brain (Barbieri et al., 2008). However, during this period, the investigation was largely confined to cell models, and there were no studies testing p38 MAPK inhibitors in animal models of Alzheimer's disease. This has changed in recent years, as scientists have deepened their focus on the molecular pathways involved in neurodegeneration and the decline of cognitive functions in AD (Barone et al., 2001).

The emerging role of p38 MAPK in Alzheimer's disease is becoming increasingly evident, particularly in its contribution to memory loss and the broader cognitive decline that characterizes the disease (Knutson et al., 2002). Recent studies have broadened our understanding of this pathway, highlighting its involvement in key aspects of the disease's progression. This updated understanding of p38 MAPK's role in Alzheimer's is crucial, as it may offer new avenues for therapeutic intervention (Bernardo & Minghetti, 2007). By modulating this pathway, it may be possible to slow down or even prevent the damage that occurs within the brain, potentially alleviating symptoms or delaying the onset of severe stages of the disease. Given its significance, p38 MAPK is now being investigated as a prime candidate for targeted therapeutic strategies that could slow Alzheimer's progression and perhaps improve the quality of life for those affected (Bhat et al., 1998).

In Alzheimer's disease, one of the critical steps in managing the condition is early detection and prevention. Identifying the disease in its initial stages offers the best opportunity to intervene before significant cognitive decline occurs. This emphasizes the importance of targeting molecular pathways, such as p38 MAPK, that are involved in the early stages of neuroinflammation (Bhat et al., 2002). Through understanding how these pathways work, researchers hope to find ways to intervene earlier in the disease process, potentially halting or slowing its progression. By focusing on p38 MAPK, which plays a central role in initiating neuroinflammation and interacts with multiple others signaling pathways, scientists hope to develop novel therapeutic approaches that address both the inflammatory and neurodegenerative components of the disease (Bliss & Collingridge, 1993).

The focus of this study is to examine p38 MAPK as a potential target for intervention in Alzheimer's disease. To move forward with this approach, the study aims to create a comprehensive list of ligands with enhanced activity in the central nervous system (CNS) that may effectively target p38 MAPK. A key step in this process will be conducting molecular docking studies to explore the interactions between these ligands and the p38 MAPK protein. Using advanced software tools such as Chemdraw Professional 16.0, PyMOL, and SWISS pdb viewer, the study will prepare the structures of both the selected ligands and the protein for docking simulations. By utilizing PyRx for the docking process and visualizing the protein-ligand interactions through Discovery Studio 2021 Client and to gain valuable insights into the potential of p38 MAPK-targeting therapies for Alzheimer's disease. This work will contribute to the broader effort to develop more effective treatments for Alzheimer's, with the hope of improving outcomes for those living with this devastating condition.

Materials and Methods

Preparation of Protein

The first step in this study involved retrieving the three-dimensional (3D) experimental tertiary structure of the p38 MAPK protein from the RCSB Protein Data Bank (PDB). The PDB ID 5MTX was selected (Figure 1), which corresponds to p38 MAPK with a resolution of 1.80 Å. The protein structure includes the following R-values: R-value Free: 0.233, R-value Work: 0.188, and R-value Observed: 0.191. After retrieving the protein structure from the database, the protein file was analyzed and processed for docking studies (Table 2).

Using PyMOL, the original ligand and water molecules present in the crystal structure were eliminated, as they are not relevant to the docking analysis. Following this, additional preparatory steps were carried out using Discovery Studio 2021, where the co-factors, water molecules, and metal ions that were bound to the protein were also removed to ensure the protein was in its purest form for the docking simulations. This step ensured that only the core structure of p38 MAPK was retained for further analysis.

To ensure the stability of the protein structure, energy minimization was performed using SWISS PDB Viewer. This process was essential to eliminate any steric clashes and optimize the geometry of the protein structure, thus preparing it for accurate docking interactions with the selected ligands.

Preparation of Ligands

Table 1. Binding affinity between the target protein and ligands.

	Molecules Name	Binding Affinity (Kcal/mol)
5MTX	Ginsenoside Rg1	-7.9
	Apigenin	-8.7
	Linalool	-5.6
	Skepinone-L	-9.2
	Triptolide	-8.4
	Glaucocalyxin b	-7.5
	NJK14047	-10.2
	SB202190	-8.3
	Geranylgeranyl Acetone	-7.3

Table 2. Analysis of the interaction between the protein 5MTX and target ligands using BIOVIA Discovery Studio

Target protein	Ligand name	Interacted Amino Acid Residues				
		Hydrogen Bond	Alkyl bond	Carbon H-bond	Pi sigma	Pi cation
5MTX	Ginsenoside Rg1	THR(A:106) LEU(A:104)	VAL(A:30), ALA(A:157), LEU(A:108), LEU(A:167)	GLY(A:31)		
	Apigenin	MET(A:109)	ILE(A:84), LYS(A:53), VAL(A:38), ALA(A:51) ALA(A:157)		LEU(A:167)	
	Skepinone-L		LYS(A:53), ILE(A:84) LEU(A:75), VAL(A:38) ALA(A:51), ALA(A:157) VAL(A:30)		LEU(A:167)	
	Triptolide	THR(A:106) ASN(A:115) ASP(A:112)	VAL(A:38), ALA(A:51) LEU(A:167), ALA(A:157)			
	Linalool	ASP(A:168)	LEU(A:171), PHE(A:169) LEU(A:74), LEU(A:75) LYS(A:53), LEU(A:167) LEU(A:104)			
	Glaucocalyxin b		VAL(A:38), LEU(A:167)	SER(A:154)		
	NJK1404	ASN(A:115) GLY(A:110) MET(A:109) ASP(A:168) GLU(A:71)	ALA(A:157), VAL(A:30) ALA(A:51), VAL(A:38) ILE(A:84), PHE(A:169) LEU(A:75)		LEU(A:167)	LYS(A:53)
	SB202190		VAL(A:30), ALA(A:157) LEU(A:108), ALA(A:51) LEU(A:167), LYS(A:53)	ALA(A:111)	VAL(A:38)	
	Geranylgeranyl Acetone	PHE(A:169)	LEU(A:75), LYS(A:53) VAL(A:38), LEU(A:167) ILE(A:84), ALA(A:157) ALA(A:51), LEU(A:108)			

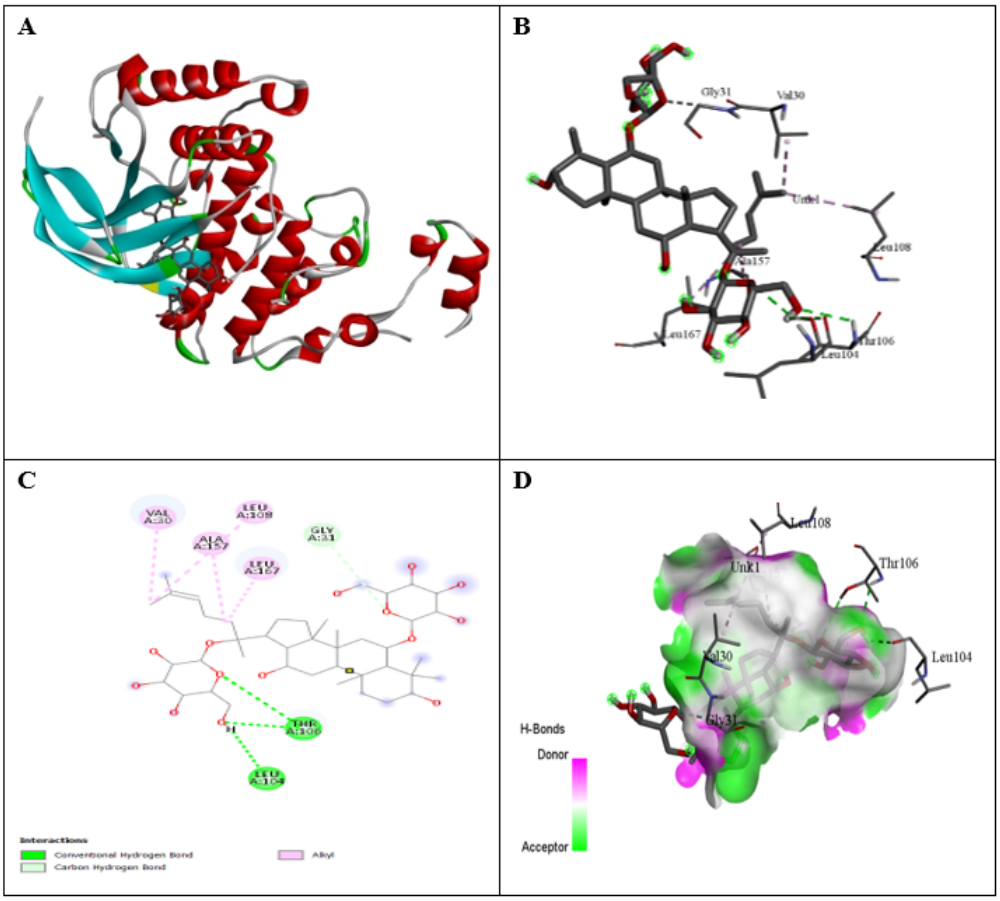

Figure 1. (A) and (B) The 3D conformation of ginsenoside Rg1 (ligand) and 5MTX (protein), (C) 2D diagram of ginsenoside Rg1 and 5MTX, (D) Hydrogen bond interaction between ginsenoside Rg1 and 5MTX.

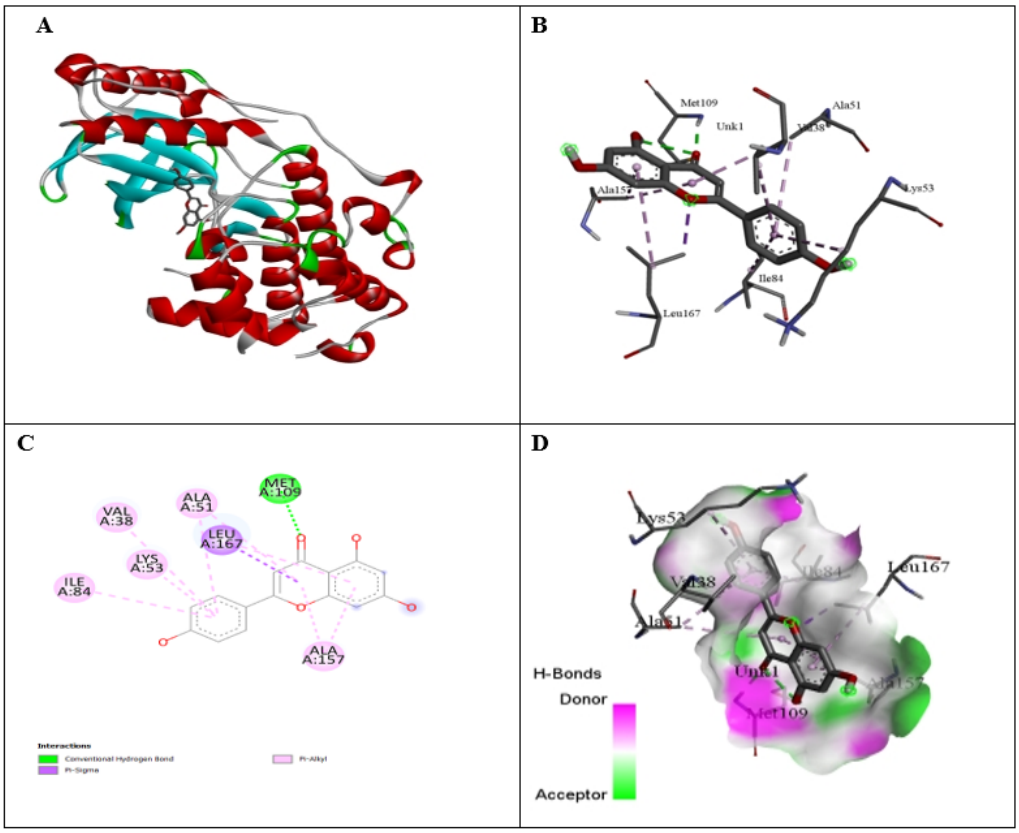

Figure 2. (A) and (B) The 3D conformation of Apigenin (ligand) and 5MTX (protein), (C) 2D diagram of Apigenin and 5MTX, (D) Hydrogen bond interaction between Apigenin and 5MTX.

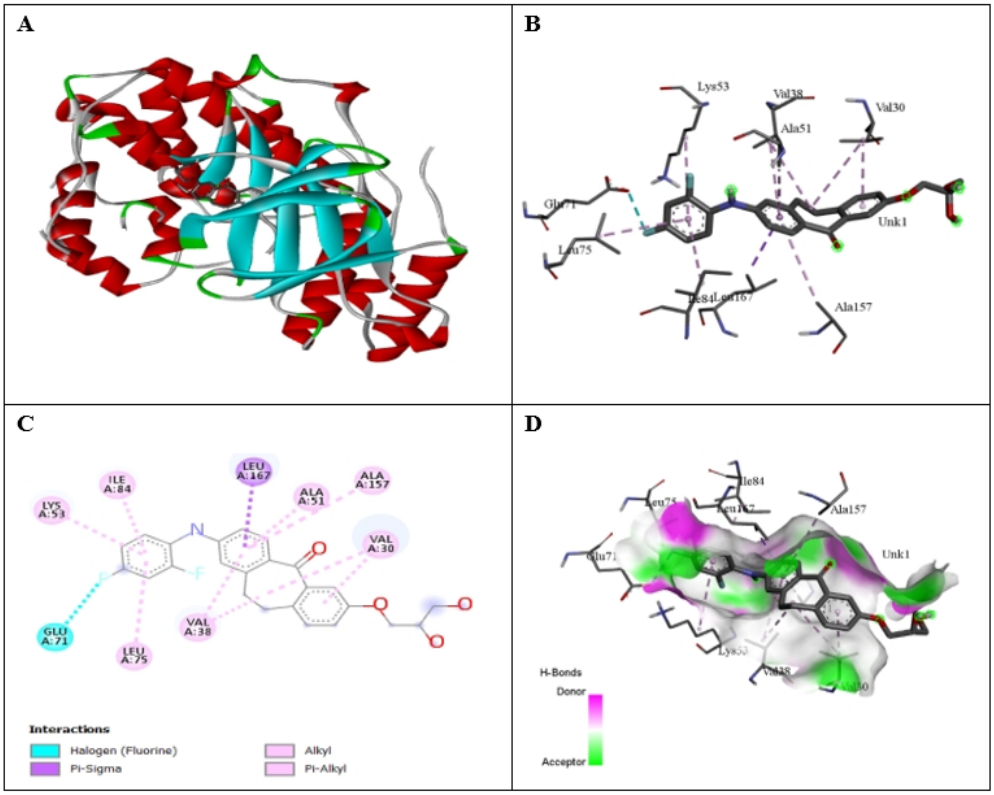

Figure 3. (A) and (B) The 3D conformation of Skepinone-L (ligand) and 5MTX (protein), (C) 2D diagram of Skepinone-L and 5MTX, (D) Hydrogen bond interaction between Skepinone-L and 5MTX.

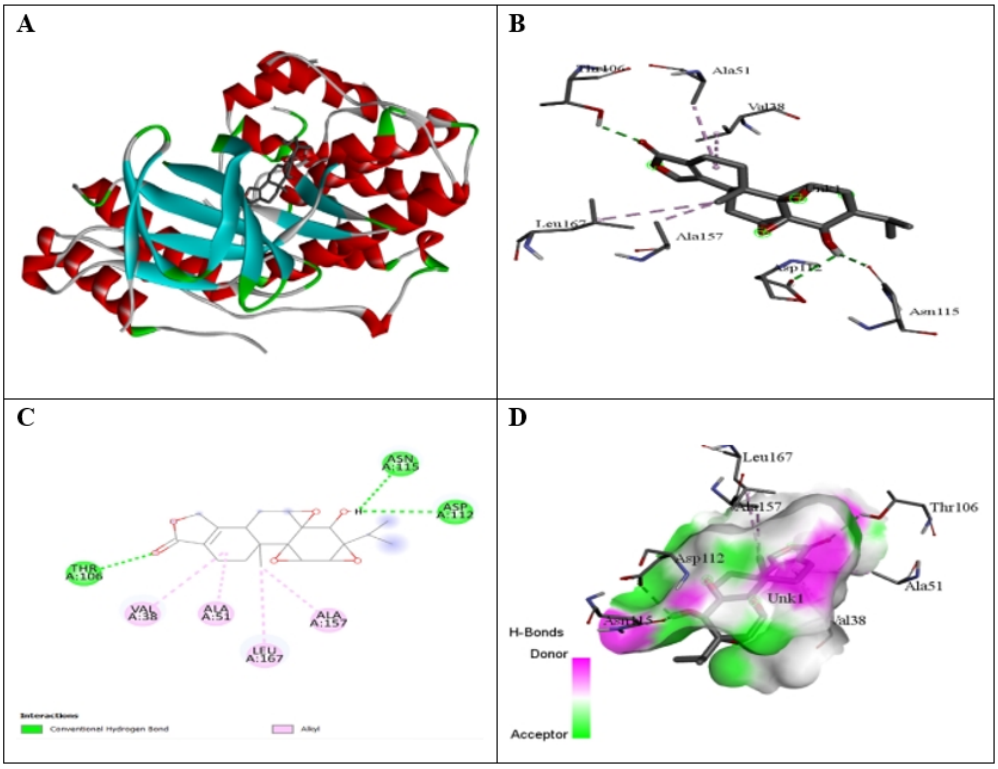

Figure 4. (A) and (B) The 3D conformation of Triptolide (ligand) and 5MTX (protein), (C) 2D diagram of Triptolide and 5MTX, (D) Hydrogen bond interaction between Triptolide and 5MTX.

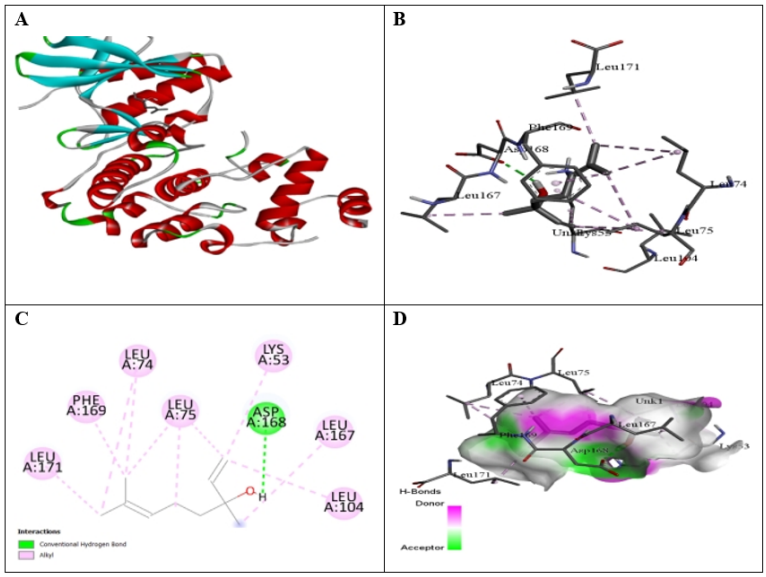

Figure 5. (A) and (B) The 3D conformation of Linalool (ligand) and 5MTX (protein), (C) 2D diagram of Linalool and 5MTX, (D) Hydrogen bond interaction between Linalool and 5MTX.

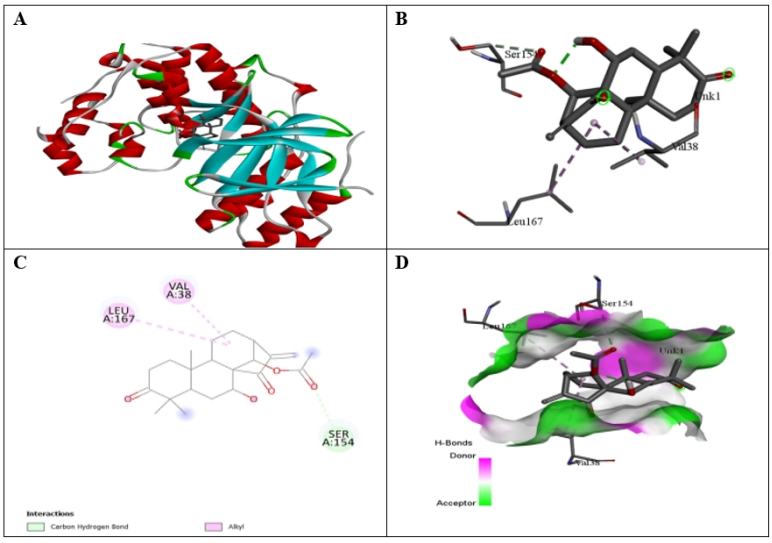

Figure 6. (A) and (B) The 3D conformation of Glaucocalyxin b (ligand) and 5MTX (protein), (C) 2D diagram of Glaucocalyxin b and 5MTX, (D) Hydrogen bond interaction between Glaucocalyxin b and 5MTX.

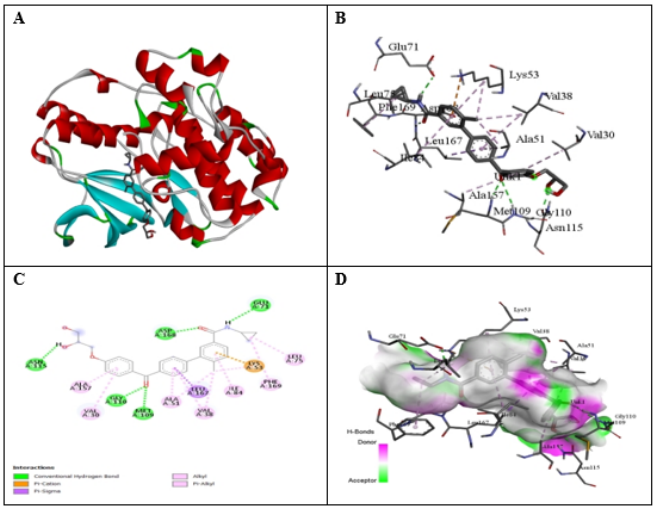

Figure 7. (A) and (B) The 3D conformation of NJK1404 (ligand) and 5MTX (protein), (C) 2D diagram of NJK1404 and 5MTX, (D) Hydrogen bond interaction between NJK1404 and 5MTX.

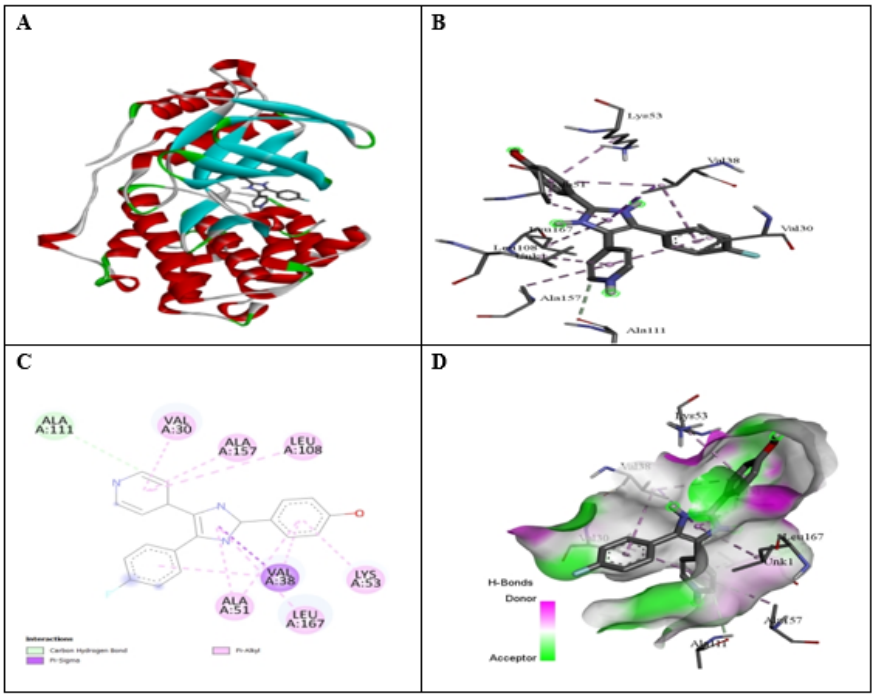

Figure 8. (A) and (B) The 3D conformation of SB202190 (ligand) and 5MTX (protein), (C) 2D diagram of SB202190 and 5MTX, (D) Hydrogen bond interaction between SB202190 and 5MTX.

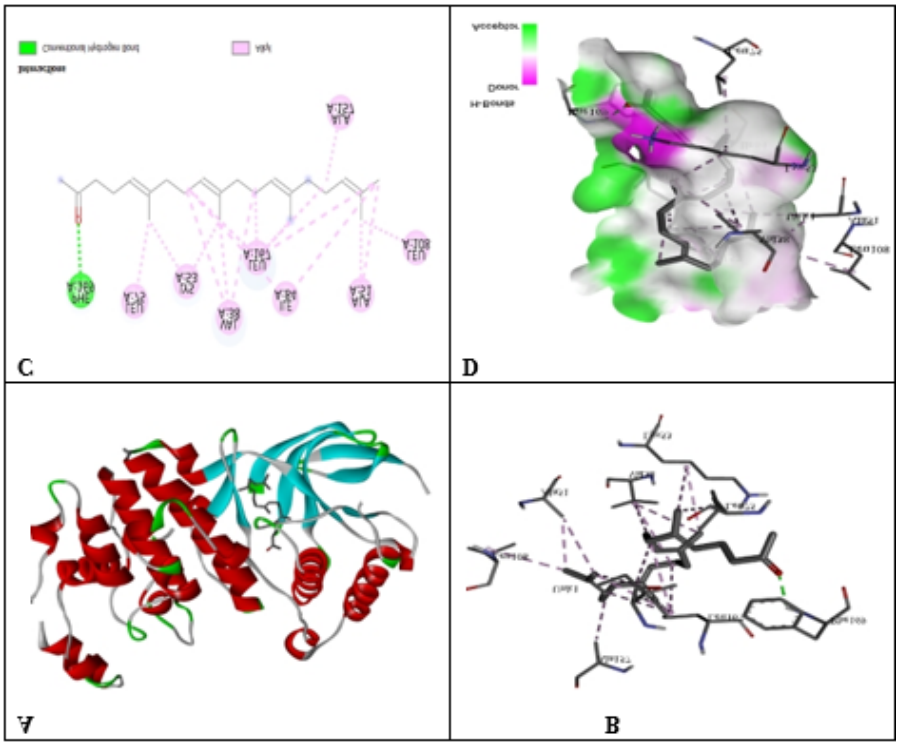

Figure 9. (A) and (B) The 3D conformation of Geranylgeranyl Aceton (ligand) and 5MTX (protein), (C) 2D diagram of Geranylgeranyl Aceton and 5MTX, (D) Hydrogen bond interaction between Geranylgeranyl Aceton and 5MTX.

A total of nine molecules were selected as potential ligands based on their known neurogenic activity and ability to reduce neuroinflammation and cognitive impairment, which are crucial aspects of Alzheimer's disease. The chemical structures of these ligands were obtained from the PubChem online database, a reliable source for chemical information, where their 3D structures were retrieved. To further prepare the ligands for docking, their 3D structures were drawn using Chemdraw Professional 16.0. This software allowed for precise modeling of the chemical structures. Subsequently, the ligands underwent geometrical optimization to ensure they adopted the most stable conformations. This optimization was done to improve the accuracy of the docking simulations. Once the ligands were optimized, their structures were saved in .sdf format, which is compatible with molecular docking software. For converting the 2D structures of the ligands into their 3D conformations, Open Babel, a molecule format converter, was used. This ensured that the ligands were in the proper 3D conformation for use in molecular docking.

Molecular Docking and Virtual Screening

Once both the protein and the ligands were prepared, the next step was to perform molecular docking to predict the binding interactions between the protein and the ligands. This was carried out using the AutoDock Vina wizard within the PyRx tool. Prior to docking, both the protein and ligands underwent energy minimization to ensure the accuracy and reliability of the docking results. The molecular docking was performed in a way that allowed the ligands to bind to the protein in the most favorable binding sites, simulating the natural interaction between the two. The results were then outputted as .pdb files, representing the protein-ligand complexes. To analyze and visualize the binding interactions, the protein-ligand complexes were examined using Discovery Studio 2016 and PyMOL. These software programs enabled detailed visualization of the interactions between the protein and ligands, specifically focusing on hydrophobic interactions, hydrogen bonds, and other complex binding interactions that may contribute to the overall stability of the protein-ligand complex. Finally, to identify the most promising ligands, the AutoDock Vina wizard in PyRx was utilized to assess the docking scores and interactions of the protein-ligand complexes. The results were further analyzed using BIOVIA Visualizer in Discovery Studio 2021 to observe the binding poses and to understand how the ligands interact with the protein's active sites. The comprehensive molecular docking and virtual screening procedures employed in this study helped identify potential inhibitors that could modulate p38 MAPK activity, offering insights into the possible therapeutic applications for Alzheimer's disease. Through this approach, a detailed understanding of protein-ligand interactions was obtained, facilitating the identification of the most effective compounds for further investigation.

Results

Molecular Docking Score between Ligand and Target Protein

The molecular docking score between the ligands and target protein (5MTX) determine the binding energy of all selected nine compounds that are represented in table 1.

Molecular Docking and Binding Interaction Analysis

Molecular Docking and binding interactions are analyzed through 2D and 3D diagrams of the selected compounds bound to their target protein using Discovery Studio 2021 that illustrates different binding poses of protein -ligand complex.

Binding Interaction of Ginsenoside Rg1 with 5MTX

In the interaction of Ginsenoside Rg1and target protein (5MTX), the amino acids of THR (A:106) and LEU(A:104) are involved in hydrogen bond interaction, VAL(A:30), ALA(A:157), LEU(A:108) and LEU(A:167) have formed alkyl interaction and GLY(A:31) has formed carbon hydrogen bond interaction respectively.

Binding Interaction of Apigenin with 5MTX

In the interaction of Apigenin and target protein(5MTX), the amino acids of ILE(A:84), LYS(A:53), VAL(A:38), ALA(A:51) and ALA(A:157) have formed pi-alkyl interactions, LEU(A:167) is involved in pi sigma and MET(A:109) has formed conventional hydrogen bond interaction.

Binding Interaction of Skepinone-L with 5MTX

In the interaction of Skepinone-L and target protein(5MTX), the amino acids of LYS(A:53), ILE(A:84), LEU(A:75), VAL(A:38), ALA(A:51), ALA(A:157) and VAL (A:30) are involved in alkyl interactions. LEU (A:167) has formed pi-sigma interaction and GLU(A:71) has formed Halogen (Fluorine)interaction (Figure 3).

Binding Interaction of Triptolide with 5MTX

In the interaction of Triptolide and target protein (5MTX), the amino acids of THR(A:106), ASN(A:115) and ASP(A:112) are involved in conventional hydrogen bond. VAL(A:38), ALA(A:51), LEU(A:167) and ALA(A:157) have formed alkyl bond interactions (Figure 4).

Binding Interaction of Linalool with 5MTX

In the interaction of Linalool and target protein(5MTX), the amino acids of LEU(A:171), PHE(A:169), LEU(A:74), LEU(A:75), LYS(A:53), LEU(A:167) and LEU(A:104) have formed alkyl bond interactions. ASP(A:168) is involved in conventional hydrogen bond formation.

Binding Interaction of Glaucocalyxin b with 5MTX

In the interaction of Glaucocalyxin b and target protein(5MTX), the amino acids of VAL(A:38) and LEU(A:167) are involved in alkyl bond interactions.SER(A:154) has formed carbon hydrogen bond (Figure 6).

Binding Interaction of NJK1404 with 5MTX

In the interaction of NJK1404 and target protein(5MTX), the amino acids of ASN(A:115), GLY(A:110,) MET(A:109), ASP(A:168) and GLU(A:71) are involved in formed carbon hydrogen

bond.ALA(A:157), VAL(A:30), ALA(A:51), VAL(A:38), ILE(A:84), PHE(A:169) and LEU(A:75) are involved in alkyl bond interactions. LEU(A:167) has formed pi-sigma and LYS(A:53) has formed pi-cation bond interactions (Figure 7).

Binding Interaction of SB202190 with 5MTX

In the interaction of SB202190 and target protein(5MTX), the amino acids of VAL(A:30), ALA(A:157), LEU(A:108), ALA(A:51), LEU(A:167) and LYS (A:53) are involved in pi alkyl bond interaction. VAL(A:38) has formed pi-sigma and ALA(A:111) has formed carbon hydrogen bond (Figure 8).

Binding Interaction of Geranylgeranyl Aceton with 5MTX

In the interaction of Geranylgeranyl Aceton and target protein(5MTX), the amino acids of PHE(A:169) is involved in conventional hydrogen bond and LEU(A:75) LYS(A:53), VAL(A:38), LEU(A:167), ILE(A:84), ALA(A:157), ALA(A:51) and LEU(A:108) are involved in alkyl bond interactions (Figure 9).

Molecular interaction of 5MTX protein with Ligands

In Ginsenoside Rg1 two amino acid residues THR(A:106) and (LEU(A:104) are involved in Hydrogen bond. Moreover, hydrophobic interaction is formed for VAL(A:30), ALA(A:157), LEU(A:108) and LEU(A:167) amino acid residues. Only one amino acid GLY(A:31) has formed carbon hydrogen bond interaction respectively.

In Apigenin MET(A:109) is involved in hydrogen bond formation, ILE(A:84), LYS(A:53), VAL(A:38), ALA(A:51), ALA(A:157) and LEU(A:167) are involved in hydrophobic interaction.

In Skepinone-L there are eight amino acid LYS(A:53), ILE(A:84), LEU(A:75), VAL(A:38), ALA(A:51), ALA(A:157), VAL(A:30) and LEU(A:167) involved in alkyl interaction.

In Triptolide THR(A:106), ASN(A:115) and ASP(A:112) are involved in hydrogen bond interaction. The amino acid residues of VAL(A:38), ALA(A:51), LEU(A:167) and ALA(A:157) are involved in alkyl bond interaction

In Linalool, the amino acids of LEU(A:171), PHE(A:169), LEU(A:74), LEU(A:75), LYS(A:53), LEU(A:167) and LEU(A:104) have formed alkyl bond interactions. ASP(A:168) is involved in conventional hydrogen bond (Figure 5).

In Glaucocalyxin b the amino acids of VAL(A:38) and LEU(A:167) are involved in alkyl bond interactions.SER(A:154) has formed carbon hydrogen bond. There is absence of hydrogen bond formation.

In NJK14047 the amino acids of ASN(A:115), GLY(A:110), MET(A:109), ASP(A:168) and GLU(A:71) are involved carbon hydrogen bond.ALA(A:157), VAL(A:30), ALA(A:51), VAL(A:38), ILE(A:84), PHE(A:169) and LEU(A:75) are involved in alkyl bond interactions. LEU(A:167) has formed pi-sigma and LYS(A:53) has formed pi-cation bond interactions.

In SB202190 the amino acids of VAL(A:30), ALA(A:157), LEU(A:108), ALA(A:51), LEU(A:167) and LYS (A:53) are involved in pi alkyl bond interaction. VAL(A:38) has formed pi-sigma and ALA(A:111) has formed carbon hydrogen bond.

In Geranylgeranyl Aceton the amino acids of PHE(A:169) is involved in conventional hydrogen bond and LEU(A:75) LYS(A:53), VAL(A:38), LEU(A:167), ILE(A:84), ALA(A:157), ALA(A:51) and LEU(A:108) are involved in alkyl bond interactions

Discussion

The molecular docking study of nine selected molecules targeting p38 MAPK (5MTX) reveals their potential for therapeutic application, particularly in addressing Alzheimer's disease (AD) (Welch et al., 2014). These molecules were chosen based on their reported therapeutic activity and docked against the target protein to assess binding affinities and interactions (Xu et al., 2012).

Molecular Docking Results and Observations

Ginsenoside Rg1 demonstrated a binding affinity of -7.9 kcal/mol, engaging in two hydrogen bonds with Thr106 and Leu104 residues. Additionally, hydrophobic interactions with Val30, Leu108, Ala157, and Leu167 stabilize the ligand-receptor complex. Notably, a covalent bond with Gly31 further enhances binding stability (Yan et al., 2020). (Figure 2), Apigenin, with a higher binding affinity of -8.7 kcal/mol, displayed hydrophobic interactions with residues like Ile84, Lys53, Val38, Ala51, Ala157, and Leu167 (Yang et al., 2020) (Table 1). The hydrogen bond formed by Met109 contributes to binding stability, although the absence of carbon-hydrogen bond interactions limits reversible interactions (Yang et al., 2013). Skepinone-L exhibited predominant hydrophobic interactions with residues such as Lys53, Ile84, Leu75, Val38, Ala51, Ala157, Val30, and Leu167 (Yang et al., 2018). Its binding affinity was robust, but the absence of hydrogen and carbon-hydrogen bonds may reduce receptor binding stability (Yasuda et al., 2011). Triptolide, with a binding affinity of -8.4 kcal/mol, formed conventional hydrogen bonds with Asn115, Asp112, and Thr106, and hydrophobic interactions with Val38, Ala51, Leu167, and Ala157. This indicates a stable and specific binding profile (Yokota & Wang, 2016).

Glaucocalyxin B formed hydrophobic interactions with Val38 and Leu167, achieving a binding affinity of -7.5 kcal/mol. The presence of a hydrogen bond with Ser154 contributes to binding stability, although fewer interaction sites may limit its overall efficacy (Yuan et al., 2016). NJK14047 exhibited the highest binding affinity (-10.2 kcal/mol) among the studied ligands. Its interaction profile includes five hydrogen bonds with Asn115, Gly110, Met109, Asp168, and Glu71, alongside hydrophobic interactions with Ala157, Val30, Ala51, Val38, Ile84, Phe169, and Leu75 (Yue et al., 2022). These comprehensive interactions ensure high selectivity and stability, emphasizing its therapeutic potential. SB202190, with a binding affinity of -8.3 kcal/mol, interacts hydrophobically with Val30, Ala157, Leu108, Ala51, Leu167, and Lys53. A single hydrogen bond with Ala111 contributes to stability (Yusufzai et al., 2018).

Geranylgeranyl acetone exhibited hydrophobic interactions with residues like Leu75, Lys53, Val38, Leu167, Ile84, Ala51, Leu108, and Ala157, alongside a hydrogen bond with Phe169. Its binding affinity was also high, showcasing its potential for p38 MAPK inhibition (Zarubin & Han, 2005).

Common Interaction Patterns

Several residues were consistently involved in ligand binding across multiple molecules, including Val30, Ala157, Ile84, Lys53, Val38, and Leu167 (Zetterberg et al., 2016). These residues define critical binding sites on p38 MAPK, crucial for ligand interactions. Hydrogen bond-forming residues such as Met109 and Asn115 appear selective for ligands like NJK14047 and Apigenin, contributing to higher binding stability and therapeutic potential ((Zhang & Jiang, 2014).

Therapeutic Implications

Numerous studies support the therapeutic potential of the selected molecules:

Ginsenoside Rg1 modulates the PINK1-Parkin pathway to promote mitophagy and alleviate memory impairments in AD models, reducing β-amyloid accumulation and enhancing neuroprotection (Zhang et al., 2017). Apigenin exhibits anti-inflammatory and neuroprotective properties by mitigating oxidative stress, neuronal calcium disturbances, and apoptosis, demonstrating efficacy in human-derived AD models (Zhang et al., 2019). Skepinone-L has shown high selectivity for p38 MAPK, achieving potent inhibition in cellular assays, particularly in reducing TNF-α release (Zhang, 2016). Triptolide inhibits amyloidogenic pathways and exhibits antioxidative and anti-inflammatory effects, conferring neuroprotection in AD transgenic mouse models (Zhang et al., 2013). Glaucocalyxin B reduces neuroinflammation by inhibiting p38 MAPK, NF-kB pathways, and reactive oxygen species generation, showcasing anti-neuroinflammatory activity (Zhao et al., 2013). NJK14047 demonstrates potent binding to p38 MAPK, with high selectivity and efficacy in reducing neuroinflammation, as evidenced by significant reductions in proinflammatory mediators in cellular and animal models. SB202190 effectively reduces hippocampal apoptosis and ameliorates spatial memory deficits by inhibiting the p38 MAPK pathway (Zheng et al., 2022). Geranylgeranyl Acetone (GGA) enhances heat shock protein (HSP)-70 expression, ameliorating cognitive impairment and AD-related phenotypes via the ERK/p38 MAPK pathway.

Conclusion

This study demonstrated the potential of selected molecules as inhibitors of p38 MAPK, a critical pathway in Alzheimer's disease (AD) pathology. Among the nine candidates, NJK14047 exhibited the highest binding affinity (-10.2 kcal/mol) and superior stability due to its glycine flip induction and double hydrogen bonding, making it a promising therapeutic agent. Other molecules, including Ginsenoside Rg1, Apigenin, and Skepinone-L, also demonstrated significant neuroprotective and anti-inflammatory properties, supported by in vitro and in vivo studies. Key residues like Val30, Ala157, and Met109 were identified as critical for ligand interaction. These inhibitors collectively address neuroinflammation, oxidative stress, and apoptosis, offering a comprehensive approach to AD management. Further investigations, including clinical trials, are essential to validate their efficacy and safety for clinical application, with NJK14047 standing out as a lead candidate for AD treatment.

Author contributions

M.A.B.S. and A.D. conceptualized, conducted lab and field works, analysed data, wrote the original draft, reviewed, and edited; M.S.U., M.S.A. and A.R. conducted research design, validated methodology, analysed, visualized the data, reviewed, and edited; M.A.M., M.A.R.B., M.S.A. and M.S.B.N.T. validated the methodology, analysed data, investigated, visualized, reviewed, and proof-read; B.A., A.A.N., and M.H.S. conceptualization, conducted research design, validated methodology, conducted analysis, investigated, visualized the data, reviewed, obtained grant, supervised and edited the paper. All authors read and approved the paper for publication.

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Competing financial interests

The authors have no conflict of interest.

References

Ashwell, J. D. (2006). The many paths to p38 mitogen- activated protein kinase activation in the immune system. 6(July), 532–540. https://doi.org/10.1038/nri1865

Avital, A., Goshen, I., Kamsler, A., Segal, M., Iverfeldt, K., Richter-Levin, G., & Yirmiya, R. (2003). Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus, 13(7), 826–834. https://doi.org/10.1002/hipo.10135

Bains, J. S., & Oliet, S. H. R. (2007). Glia: they make your memories stick! Trends in Neurosciences, 30(8), 417–424. https://doi.org/10.1016/j.tins.2007.06.007

Barbieri, R., Alloisio, S., Ferroni, S., & Nobile, M. (2008). Differential crosstalk between P2X7 and arachidonic acid in activation of mitogen-activated protein kinases. Neurochemistry International, 53(6–8), 255–262. https://doi.org/10.1016/j.neuint.2008.05.001

Barone, F. C., Irving, E. A., Ray, A. M., Lee, J. C., Kassis, S., Kumar, S., Badger, A. M., White, R. F., McVey, M. J., Legos, J. J., Erhardt, J. A., Nelson, A. H., Ohlstein, E. H., Hunter, A. J., Ward, K., Smith, B. R., Adams, J. L., & Parsons, A. A. (2001). SB 239063, a second-generation p38 mitogen-activated protein kinase inhibitor,

reduces brain injury and neurological deficits in cerebral focal ischemia. Journal of Pharmacology and Experimental Therapeutics, 296(2), 312–321.

Bernardo, A., & Minghetti, L. (2007). PPAR-γ Agonists as Regulators of Microglial Activation and Brain Inflammation. Current Pharmaceutical Design, 12(1), 93–109. https://doi.org/10.2174/138161206780574579

Bhat, N. R., Feinstein, D. L., Shen, Q., & Bhat, A. N. (2002). p38 MAPK-mediated transcriptional activation of inducible nitric-oxide synthase in glial cells: Roles of nuclear factors, nuclear factor κB, cAMP response element-binding protein, CCAAT/enhancer-binding protein-β, and activating transcription factor-2. Journal of Biological Chemistry, 277(33), 29584–29592. https://doi.org/10.1074/jbc.M204994200

Bhat, N. R., Zhang, P., Lee, J. C., & Hogan, E. L. (1998). Extracellular signal-regulated kinase and p38 subgroups of mitogen- activated protein kinases regulate inducible nitric oxide synthase and tumor necrosis factor-α gene expression in endotoxin-stimulated primary glial cultures. 18(5), 1633–1641.

Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. Nature, 361(6407), 31–39. https://doi.org/10.1038/361031a0

Hodges, J. (2017). Pick's disease: Its relationship to progressive aphasia, semantic dementia and frontotemporal dementia. In Dementia, Fifth Edition (Vol. 21). https://doi.org/10.1201/9781315381572

Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., Beattie, E. C., Stellwagen, D., Morishita, W., Bresnahan, J. C., Ha, B. K., & Zastrow, M. Von. (2002). <Beattie Science 2002.pdf>. 295(March), 2282–2285.

Welch, L., Lewitter, F., Schwartz, R., Brooksbank, C., Radivojac, P., Gaeta, B., & Schneider, M. V. (2014). Bioinformatics curriculum guidelines: Toward a definition of core competencies. Computational Biology, 10(3). https://doi.org/10.1371/journal.pcbi.1003496

Xu, Y., Yan, J., Zhou, P., Li, J., Gao, H., Xia, Y., & Wang, Q. (2012). Neurotransmitter receptors and cognitive dysfunction in Alzheimer's disease and Parkinson's disease. Progress in Neurobiology, 97(1), 1–13. https://doi.org/10.1016/j.pneurobio.2012.02.002

Yan, Z., Zhou, Z., Wu, Q., Chen, Z. B., Koo, E. H., & Zhong, S. (2020). Presymptomatic increase of an extracellular RNA in blood plasma associates with the development of Alzheimer's disease. Current Biology, 30(10), 1771-1782.e3. https://doi.org/10.1016/j.cub.2020.02.084

Yang, C., Zhu, Z., Tong, B. C. K., Iyaswamy, A., Xie, W. J., Zhu, Y., Sreenivasmurthy, S. G., Senthilkumar, K., Cheung, K. H., Song, J. X., Zhang, H. J., & Li, M. (2020). A stress response p38 MAP kinase inhibitor SB202190 promoted TFEB/TFE3-dependent autophagy and lysosomal biogenesis independent of p38. Redox Biology, 32. https://doi.org/10.1016/j.redox.2020.101445

Yang, S., Zhou, G., Liu, H., Zhang, B., Li, J., Cui, R., & Du, Y. (2013). Protective effects of p38 MAPK inhibitor SB202190 against hippocampal apoptosis and spatial learning and memory deficits in a rat model of vascular dementia. BioMed Research International, 2013. https://doi.org/10.1155/2013/215798

Yang, T. T., Liu, C. G., Gao, S. C., Zhang, Y., & Wang, P. C. (2018). The serum exosome derived microRNA-135a, -193b, and -384 were potential Alzheimer's disease biomarkers. Biomedical and Environmental Sciences, 31(2), 87–96. https://doi.org/10.3967/bes2018.011

Yasuda, S., Sugiura, H., Tanaka, H., Takigami, S., & Yamagata, K. (2011). p38 MAP kinase inhibitors as potential therapeutic drugs for neural diseases. Central Nervous System Agents in Medicinal Chemistry, 11.

Yokota, T., & Wang, Y. (2016). P38 MAP kinases in the heart. Gene, 575(2), 369–376. https://doi.org/10.1016/j.gene.2015.09.030

Yuan, H., Ma, Q., Ye, L., & Piao, G. (2016). The traditional medicine and modern medicine from natural products. Molecules, 21(5). https://doi.org/10.3390/molecules21050559

Yue, Q., Song, Y., Liu, Z., Zhang, L., Yang, L., & Li, J. (2022). Receptor for advanced glycation end products (RAGE): A pivotal hub in immune diseases. Molecules, 27(15). https://doi.org/10.3390/molecules27154922

Yusufzai, S. K., Khan, M. S., Sulaiman, O., Osman, H., & Lamjin, D. N. (2018). Molecular docking studies of coumarin hybrids as potential acetylcholinesterase, butyrylcholinesterase, monoamine oxidase A/B, and β-amyloid inhibitors for Alzheimer's disease. Chemistry Central Journal, 12(1). https://doi.org/10.1186/s13065-018-0497-z

Zarubin, T., & Han, J. (2005). Activation and signaling of the p38 MAP kinase pathway. Cell Research, 15(1).

Zetterberg, H., Skillbäck, T., Mattsson, N., Trojanowski, J. Q., Portelius, E., Shaw, L. M., Weiner, M. W., & Blennow, K. (2016). Association of cerebrospinal fluid neurofilament light concentration with Alzheimer disease progression. JAMA Neurology, 73(1), 60–67. https://doi.org/10.1001/jamaneurol.2015.3037

Zhang, F., & Jiang, L. (2014). Neuroinflammation in Alzheimer's disease. Neuropsychiatric Disease and Treatment, 11, 243–256. https://doi.org/10.2147/NDT.S75546

Zhang, N., Zhang, L., Li, Y., Gordon, M. L., Cai, L., Wang, Y., Xing, M., & Cheng, Y. (2017). Urine AD7c-NTP predicts amyloid deposition and symptom of agitation in patients with Alzheimer's disease and mild cognitive impairment. Journal of Alzheimer's Disease, 60(1), 87–95. https://doi.org/10.3233/JAD-170383

Zhang, R., Zhu, X., Bai, H., & Ning, K. (2019). Network pharmacology databases for traditional Chinese medicine: Review and assessment. Frontiers in Pharmacology, 10(February). https://doi.org/10.3389/fphar.2019.00123

Zhang, W. (2016). Network pharmacology: A further description. Network Pharmacology, 1(1).

Zhang, Y., Yang, S., Jiao, Y., Liu, H., Yuan, H., Lu, S., Ran, T., Yao, S., Ke, Z., Xu, J., Xiong, X., Chen, Y., & Lu, T. (2013). An integrated virtual screening approach for VEGFR-2 inhibitors. Journal of Chemical Information and Modeling, 53(12), 3163–3177. https://doi.org/10.1021/ci400429g

Zhao, L., Wang, J. L., Liu, R., Li, X. X., Li, J. F., & Zhang, L. (2013). Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model. Molecules, 18(8), 9949–9965. https://doi.org/10.3390/molecules18089949

Zheng, S., Xue, T., Wang, B., Guo, H., & Liu, Q. (2022). Application of network pharmacology in the study of mechanism of Chinese medicine in the treatment of ulcerative colitis: A review. Frontiers in Bioinformatics, 2. https://doi.org/10.3389/fbinf.2022.928116