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Neuroprotective Potential of Oleic Acid and Alpha Tocopherol on Memory Function: In-Silico Docking and ADMETox

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Abstract. *Introduction: Decreased levels of brain-derived neurotrophic factor (BDNF) are closely related to neurodegenerative diseases such as Alzheimer's. This causes a decrease in cognitive function, memory and behavior due to a decrease in the BDNF protein which has the main function of protecting nerve growth, plasticity, nerve resilience, as well as being an important shield against nerve degeneration. Objective: of this research is to analyze the interaction between the oleic acid and alpha tocopherol ligands with the BDNF protein by molecular docking, as well as to analyze the ADMETox compounds of oleic acid and alpha tocopherol. Methods: This research is descriptive analytical. Molecular docking uses the Autodock tools, LigandScout, Discovery Studio, and Marvin Sketch applications. ADMETox analysis uses the SwissADME, ADMETlab 2.0, and ProTox-II sites. Results: the binding energy of oleic acid compounds to BDNF, TrkB, and CREB is -3.13 kcal/mol, -6.13 kcal/mol, and -3.70 kcal/mol. The binding energy results for alpha tocopherol compounds on BDNF, TrkB, and CREB are -5.67 kcal/mol, -8.04 kcal/mol, and -7.04 kcal/mol. ADMETox found that alpha tocopherol and oleic acid compounds fulfill Lipinski's rule of five and do not inhibit cytochrome P450 enzymes. Conclusion: Oleic acid and alpha tocopherol bind to BDNF, TrkB and CREB proteins and are safe for oral consumption.*

Keywords: *Alpha-Tocopherol; ADMETox; Brain-Derived Neurotrophic Factor (BDNF); Molecular Docking; Oleic Acid.*

1. INTRODUCTION

The global burden of neurodegenerative diseases continues to rise significantly, with Alzheimer's disease and other dementias increasing by 160.84% from 1990 to 2019, affecting over 51 million people, while Parkinson's disease affects approximately 10 million individuals worldwide with a 4% annual increase. (Ou et al., 2021) This trend highlights the urgent need for effective neuroprotective strategies.

Brain-derived neurotrophic factor (BDNF) deficiency is strongly associated with neurodegenerative diseases. Reduced BDNF levels contribute to amyloid plaque accumulation in Alzheimer's disease, degeneration of dopaminergic neurons in Parkinson's disease, and neuronal death in Huntington's disease (Gao et al., 2022).

BDNF plays a crucial role in neuronal survival, growth, plasticity, and memory formation, making it essential for maintaining optimal brain function (Colucci-D'amato et al., 2020).

BDNF expression can be enhanced through lifestyle interventions and pharmacological approaches, including antioxidant intake. (Mudjihartini, 2021) Alpha-tocopherol, a form of vitamin E, exhibits strong antioxidant and neuroprotective properties and has been shown to increase BDNF levels.(Ionescu-Tucker & Cotman, 2021).

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Similarly, oleic acid, commonly found in olive oil and avocados, demonstrates anti-inflammatory and neuroprotective effects and may enhance BDNF expression, thereby supporting cognitive function and reducing the risk of neurodegenerative diseases (Jeon et al., 2014).

2. RESEARCH METHOD

The main materials used are ligand structures, namely active substances like alpha-tocopherol, oleic acid, BDNF, TrkB, and CREB proteins obtained from PDB (https://www.rcsb.org/). The applications used are Autodock tools, Mgl tools, LigPlot+, Marvin Sketch, Pymol, and Notepad++.

Ligand Structure Search and Target Protein

The ligand structure was obtained from https://pubchem.ncbi.nlm.nih.gov/, namely Tocopherol (86472) and Oleic Acid (445639). Furthermore, the 3D structure of the various compounds is in the form of *.sdf file format. The amino acid sequences of the BDNF protein (1B8M), TrkB (4AT5), and CREB (2JAM) were obtained from Uniprot (https://www.uniprot.org/) and PDB (https://www.rcsb.org/) in the form of *.pdb.

Protein 3D Structure Modeling

The 3D structure of the target protein is predicted using the X-ray method, namely by removing water molecules, adding charges, removing solvents, and removing native ligands using Autodock tools**.**

Molecular Docking

Docking simulation between alpha-tocopherol and oleic acid with BDNF, TrkB, and CREB proteins using Autodock tools software. The docking protocol consists of three stages: ligand and protein preparation, imaginary box creation, and docking.

Analysis of binding interactions between proteins and ligands

The results of the docking analysis will then be visualized using Ligandscout software. Interactions between proteins and ligands are analyzed to see the amount of binding energy and inhibition constants.

Analysis of Absorption, Distribution, Metabolism, Excretion and Toxicity

ADMETOX analysis was conducted by searching for ligand compound data on the SwissADME, ADMETlab 2.0, and ProTox-II sites. The resulting data were then interpreted based on toxicity analysis, compound pharmacology, cytochrome P450 (CYP) enzyme inhibition, and fulfillment of the Lipinski rule of five.

Data Analysis

The results of the docking analysis were visualized using Autodock tools, Mgl tools, LigPlot+, and Marvin Sketch software. Protein-ligand interaction analysis was carried out to determine the number and type of bonds formed, including hydrogen bonds, hydrophobic bonds, and van der Waals bonds. Bond energy and bond points between the ligand and the active compound were evaluated.

3. RESULT

ADMETOX analysis results of Alpha Tocopherol, Oleic Acid, and Donepezil compound.

Table 1. Druglikeness Analysis Results.

Compounds	MW (g/mol)	HBA	HBD	Log P	Lipinski	Class
Alpha Tocopherol	430.71	2	1	8.29	Yes	Class 5
Oleic Acid	282.46	2	1	5.65	Yes	Class 2
Donepezil	379.49	4	0	4.191	Yes	Class 4

Description: MW: Molecular Weight; HBA: Hydrogen Bond Acceptor; HBD: Hydrogen Bond Donor.

Donor

Molecular weight is the sum of the masses of all atoms in one compound molecule.(Putra, 2016) HBA refers to the number of atoms in a molecule that can accept hydrogen bonds from a hydrogen bond donor, which refers to the number of atoms in a molecule that can donate hydrogen bonds to a hydrogen bond acceptor (HBA). (Opo et al., 2021a) Log P is a term used to describe the partition coefficient of a compound between two immiscible solvents. Log P is the logarithm of the ratio of the concentrations of the compound in these two phases. This is an important measure of the compound's lipophilicity (tendency to dissolve in fat) (Nusantoro & Fadlan, 2020).

The class table refers to the category or classification used to assess the extent to which a compound meets certain criteria to be considered a potential drug candidate. This classification is often used to screen and prioritize compounds in drug development (Brunton et al., 2023).

Table 2. Pharmacokinetic Analysis Results.

Compounds	Gastrointestinal Absorption	Blood Brain Barrier	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Alpha Tocopherol	*Low*	*No*	*No*	*No*	*No*	*No*	*No*
Oleic Acid	*High*	*No*	*No*	*No*	*No*	*No*	*No*
Donepezil	*High*	*Yes*	*No*	*No*	*No*	*Yes*	*Yes*

Tocopherol

Description: CYP: Cytochrome P450

Gastrointestinal absorption involves analyzing several important parameters that determine how a compound or drug is absorbed through the gastrointestinal tract and enters systemic circulation (Shannon et al., 2007).

The blood-brain barrier is a protective structure in the central nervous system consisting of tightly bound endothelial cells, which limits the movement of substances from the blood to the brain. The blood-brain barrier plays a crucial role in determining the extent to which drugs or chemical compounds can reach the brain and interact with neural tissue (Paulson, 2002).

CYP inhibitors are Cytochrome P450, a large family of enzymes that play a role in metabolizing various chemical compounds, including drugs and environmental chemicals (Zhao et al., 2021).

The results of the pharmacokinetic analysis of the active compound show that high oleate is absorbed in the gastrointestinal analysis, but this compound still cannot penetrate the Blood-Brain Barrier. In the analysis of cytochrome P450 (CYP) enzyme inhibition, alpha-tocopherol and oleic acid compounds did not inhibit CYP enzymes, while donepezil inhibited CYP2D6 and CYP3A4 enzymes.

Table 3. Toxicity Analysis Results.

Compound	Acute Oral Toxicity	Skin Sensitization	Carcinogenicity	Pulmonary Toxicity	LC50 FM	LC50 DM-
Alpha Tocopherol	--	+++	---	--	6.279	6.342
Oleic Acid	---	+++	---	++	3.702	4.393
Donepezil	--	--	---	+++	5.338	6.367

Description: LC50FM: Lethal Concentration 50% for Fish Models; LC50DM : Lethal Concentration 50% for.

Daphnia Models

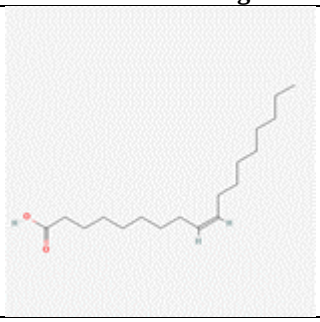
The "+" and "-" signs in toxicity analysis are simple but important indicators that show whether a compound has or does not have the potential for toxicity or other specific effects. Interpretation of these results helps develop and safely assess chemical compounds or drugs. For the classification endpoint, the predicted probability values were converted into six symbols: 0-0.1(---), 0.1-0.3(--), 0.3-0.5(-), 0.5-0.7(+), 0.7-0.9(++), and 0.9-1.0(+++) (Wang et al., 2024).

LC50FM refers to the lethal concentration that causes 50% mortality of fathead minnows within 96 hours (-log10 [(mg/L)/(1000xMw)]. A low LC50 value indicates that the compound is highly toxic to fish, while a higher value indicates lower toxicity (Renantha et al., 2022). LC50DM indicates the lethal concentration that causes 50% mortality of Daphnia magna

within 48 hours (-log10 [(mg/L)/(1000xMw)]. A low LC50 indicates that the compound is highly toxic to Daphnia, while higher values indicate lower toxicity (Boros et al., 2022).

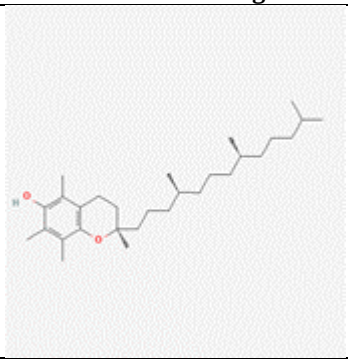
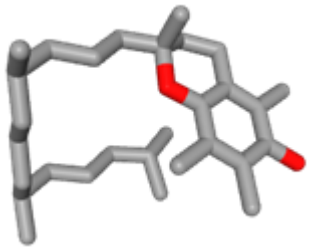
Results for the structure of alpha-tocopherol and Oleic Acid compounds

Table 4. Oleic Acid Ligand Structure.

Name of Ligand	2D Structure of Ligand	3D Structure of Ligand
Oleic Acid		

Search results for the structure of the oleic acid compound with ID number 445639. The oleic acid compound has Isomeric SMILES: CCCCCCCC/C=C\CCCCCCCC(=O)O with the formula C18H34O2. This compound has a molecular weight of 282.5g/mol. This compound has the name International Union of Pure and Applied Chemistry (IUPAC), namely (Z)-octadec-9-enoic acid, and the results of this search were obtained on the website (https://pubchem.ncbi.nlm.nih.gov/compound/445639).

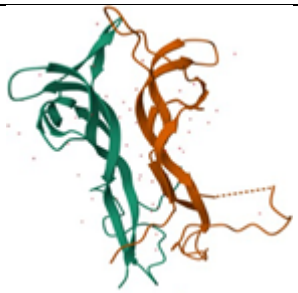
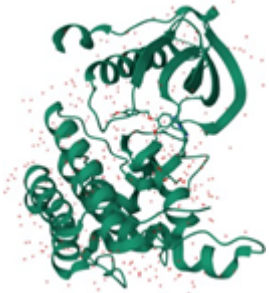
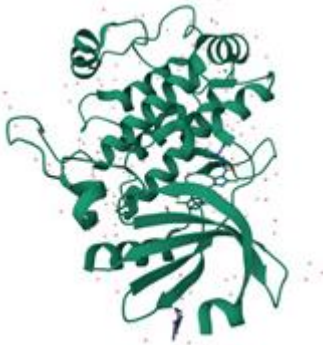
Table 5. Alpha Tocopherol Ligand Structure.

Name of Ligand	2D Structure of Ligand	3D Structure of Ligand
Alpha Tocopherol		

The search results for the structure of the alpha-tocopherol compound with ID number 14985. The alpha tocopherol compound has Isomeric SMILES: CC1=C(C2=C(CC[C@@](O2)(C)CCC[C@H](C)CCC[C@H](C)CCCC(C)C)C(=C1O)C)C with the formula C29H50O2. This compound has a molecular weight of 430.7g/mol. This compound has the International Union of Pure and Applied Chemistry (IUPAC) name, namely (2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol and the search results were obtained on the website (https://pubchem.ncbi.nlm.nih.gov/compound/14985) *Results for the structure of BDNF, TrkB, and CREB proteins.*

BDNF protein with ID number 1B8M was published on February 9, 1999, and is not mutated. This protein has chains A and B with a resolution of 2.75 Å that do not have a native ligand. BDNF can be accessed through the website (https://www.rcsb.org/structure/1B8M)

Table 6. Structure of BDNF, TrkB, and CREB Proteins.

Name of Protein	3D Structure of Protein
Brain Derived Neurotropic Factor	
Tropomyosin-Related Kinase B	
cAMP Response Element-Binding Protein	

Results of Analysis of Interactions Between Proteins and Ligands

The molecular docking simulation's results were obtained in the form of Binding Energy (EP) and Inhibition Constant (KP).

Table 7. Molecular Docking Simulation Results.

Bioactive	BDNF		TrkB		CREB	
Components	**EP**	**KP**	**EP**	**KP**	**EP**	**KP**
	(kcal/mol)	(uM)	(kcal/mol)	(uM)	(kcal/mol)	(uM)
Oleic Acid	-3.13	5080	-6.13	32.23	-3.70	1930
Alpha Tocopherol	-5.67	69.46	-8.04	1.27	-7.04	6.94

The highest binding energy for proteins against oleic acid is TrkB with oleic acid with a value of -6.12 kcal/mol. Furthermore, the highest protein energy against alpha-tocopherol is TrkB with alpha-tocopherol with a value of -8.04.

Visualization of the interaction of Oleic Acid with BDNF

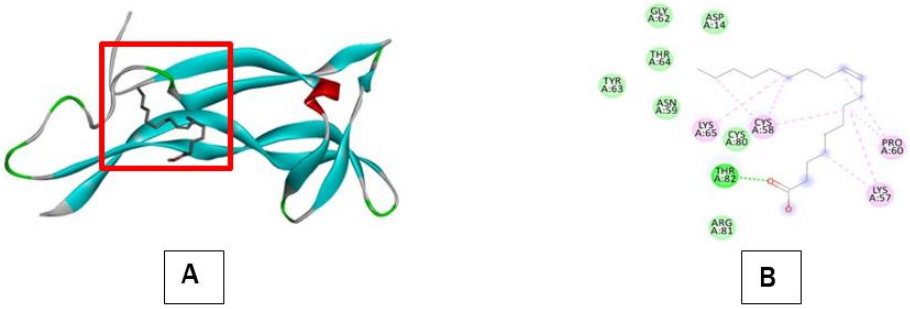


Figure 1. (A) 3D Visualization of Oleic Acid with BDNF, (B) 2D Visualization of Oleic Acid with BDNF. Conventional Hydrogen Bond van der Waals Alkyl.

The 2D visualization results of the interaction of Oleic Acid with BDNF protein show three interactions: van der Waals interactions, hydrogen bonds, and alkyl bonds. Van der Waals interactions are amino acids Glycine (GLY) 62, Aspartic Acid (ASP) 14, Threonine (THR) 64, Tyrosine (TYR) 63, Asparagine (ASN) 59, Cysteine (CYS) 80, Arginine (ARG) 81. Hydrogen bonds are THR 82, and Alkyl bonds are Lysine (LYS) 65, CYS 58, Proline (PRO) 60, and LYS 57. Furthermore, the amino acid residues in the interaction of oleic acid and BDNF compounds that have H-O bonds are in amino acids THR 82, then those that have H-R bonds are in amino acids LYS 65, CYS 58, Proline (PRO) 60, and LYS 57.

Visualization of Alpha Tocopherol Interaction with BDNF

Figure 2. (A) 3D Visualization of Alpha Tocopherol with BDNF, (B) 2D Visualization of Alpha Tocopherol with BDNF. van der Waals Conventional Hydrogen Bond Pi-Sigma Alkyl Pi-Alkyl.

The 2D visualization results of the interaction of alpha-tocopherol with BDNF protein show that there are five interactions: van der Waals interactions, hydrogen bonds, pi-sigma bonds, pi-alkyl bonds, and alkyl bonds. Van der Waals interactions are TYR 86, THR 107, Tryptophan (TRP) 100, Valine (VAL) 42, Glutamine (GLN) 51, Alanine (ALA) 89, TYR 52, TYR 54. Hydrogen bonds are ARG 88, Pi-Sigma Bonds Phenylalanine (PHE) 53 and VAL 87,

Alkyl and Pi Alkyl Bonds are PHE 102, Isoleucine (ILE) 105, TRP 19. Furthermore, the amino acid residues in the interaction of alpha-tocopherol and BDNF compounds that have H-O bonds are in ARG 88 and VAL 87 acids, then those that have H-R bonds are in amino acids PHE 102 and PHE 53.

Visualization of Oleic Acid Interaction with TrkB

Figure 3. (A) 3D Visualization of Oleic Acid-TrkB, (B) 2D Visualization of Oleic Acid-TrkB. Conventional Hydrogen Bond Unfavorable Donor-Donor Alkyl Pi-Alkyl.

The 2D visualization results of the interaction of Oleic Acid with the TrkB protein show four interactions: hydrogen bonds, unfavorable donor-donor bonds, pi-alkyl bonds, and alkyl bonds. Hydrogen Bonds, namely LYS 618, Unfavorable Donor-Donor Bonds, namely, Histidine (HIS) 613 Alkyl and Pi Alkyl Bonds, namely HIS 690, VAL 617, Leucine (LEU) 683, PHE 633, ILE 616, LEU 608, and PHE 619. Furthermore, the amino acid residues in the interaction of oleic acid and TrkB compounds that have H-O bonds are in amino acids HIS 613 and LYS 618, then those that have H-R bonds are in amino acids HIS 690, VAL 617, LEU 683, PHE 633, ILE 616, LEU 608, and PHE 619.

Visualization of Alpha Tocopherol Interaction with TrkB

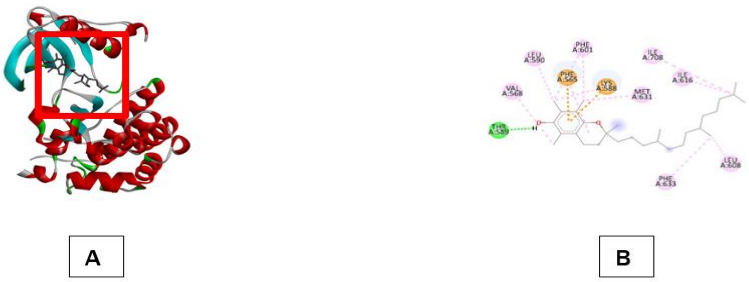


Figure 4. (A) 3D Visualization of Alpha Tocopherol-TrkB, (B) 2D Visualization of Alpha Tocopherol-TrkB. Conventional Hydrogen Bond Pi-Cation Alkyl Pi-Alkyl.

In the 2D visualization results of the interaction of alpha-tocopherol with the TrkB protein, there are four interactions: hydrogen bonds, pi-cation bonds, pi-alkyl bonds, and alkyl bonds. Hydrogen bonds are THR 589, Pi-cation bonds PHE 565, and LYS 588. Alkyl and Pi Alkyl bonds are VAL 568, LEU 590, PHE 601, ILE 708, ILE 616, Methionine (MET) 631, PHE 633, LEU 608. Furthermore, the

amino acid residues in the interaction of alpha-tocopherol and TrkB compounds that have H-O bonds are in amino acid THR 589, then those that have H-R bonds are in amino acid.

Visualization of the Interaction of Oleic Acid with CREB

Figure 5. (A) 3D Visualization of Oleic Acid-CREB, (B) 2D Visualization of Oleic Acid-CREB. Conventional Hydrogen Bond.

In the 2D visualization results of the interaction of Oleic Acid with CREB protein, there is one interaction, namely, hydrogen bond. Hydrogen bonds are THR 164, PHE 166, and LYS 52. Furthermore, the amino acid residues in the interaction of oleic acid and CREB compounds only have H-O bonds, namely in amino acids THR 164, PHE 166, and LYS 52.

Visualization of Alpha Tocopherol Interaction with CREB

Figure 6. (A) Alpha Tocopherol-CREB, (B of Alpha Tocopherol-CREB. Conventional Hydrogen Bond.

In the 2D visualization results of the interaction of alpha-tocopherol with protein, there is one interaction: a hydrogen bond. Hydrogen bonds are THR 164, PHE 166, and LYS 52. Furthermore, the amino acid residues in the interaction of alpha-tocopherol and CREB compounds only have H-O bonds, namely in amino acids THR 164, PHE 166, and LYS 52.

Visualization of Donepezil Interaction with BDNF

Figure 7. (A) 3D visualization of donepezil-BDNF, (B) 2D visualization of donepezil-CREB. Conventional Hydrogen Bond Carbon Hydrogen Bond P i -Sigm Pi-Alkyl.

In the 2D visualization results of the interaction of donepezil with BDNF protein, there are four interactions: hydrogen bonds, pi-sigma bonds, and pi-alkyl bonds. Hydrogen bonds are TYR 54, Pi Alkyl bonds are VAL 42, Pi-Sigma bonds are GLN 51, and Carbon Hydrogen Bonds are LYS 50, THR 107, and ASP 106.

Visualization of Donepezil Interaction with TrkB

Figure 8. (A) 3D Visualization of Donepezil-TrkB, (B) 2D Visualization of Donepezil-TrkB. Van der Waals Conventional Hydrogen Bond Pi-sigma Alkyl.

The 2D visualization results of the donepezil interaction with BDNF protein show four interactions: hydrogen bonds, pi-sigma bonds, and pi-alkyl bonds. Hydrogen bonds are TYR 54, Pi Alkyl bonds are VAL 42, Pi-Sigma bonds are GLN 51, and Carbon Hydrogen Bonds are

LYS 50, THR 107, and ASP 106.

Visualization of Donepezil Interaction with CREB

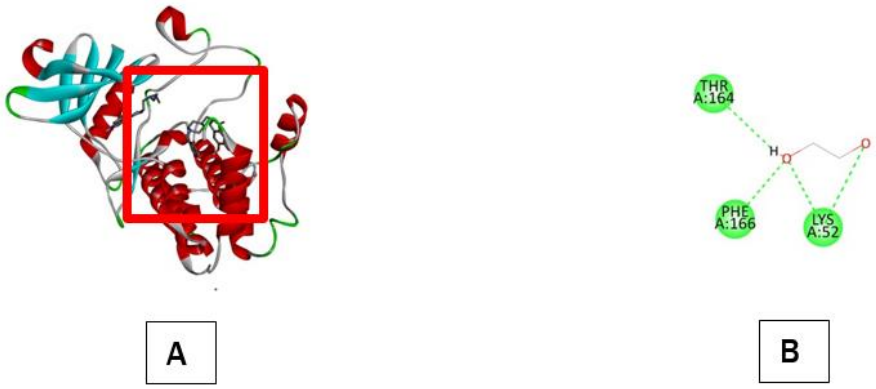


Figure 9. (A) 3D Visualization of Donepezil-CREB, (B) 2D Visualization of Donepezil-CREB. Conventional Hydrogen Bond.

In the 2D visualization results of the interaction of donepezil with CREB protein In the 2D visualization results of the interaction of donepezil with CREB protein, there is one interaction, namely, a hydrogen bond. Hydrogen bonds are THR 164, PHE 166, and LYS 52. Furthermore, the amino acid residues in the interaction of donepezil and CREB compounds only have H-O bonds, namely in the amino acids THR 164, PHE 166, and LYS 52.

4. DISCUSSION

From the results of drug-likeness, tocopherol, and oleic acid compounds fall into the Lipinski rule of five so that both compounds can be drug candidates.

The drug-likeness analysis showed that alpha-tocopherol and oleic acid fulfill Lipinski's rule of five, indicating their potential as drug candidates. In terms of toxicity, alpha-tocopherol is classified as class 5, suggesting low toxicity. Pharmacokinetic analysis revealed that oleic acid has high gastrointestinal absorption but is unable to penetrate the blood-brain barrier (BBB), likely due to its large molecular size. The BBB is a selective barrier that limits the entry of compounds into the brain (Paulson, 2002). and this limitation may be overcome through structural modification or advanced delivery systems such as nanoparticles or liposomes (Kadry et al., 2020).

Alpha-tocopherol is widely available in foods such as vegetable oils, nuts, and green vegetables, with a recommended daily intake of up to 100 mg (Huang et al., 2023). while oleic acid is commonly found in olive oil, avocados, and meat and is considered safe as part of a balanced diet (Marcelino et al., 2019). Both compounds do not inhibit cytochrome P450

enzymes, indicating a favorable safety profile compared to donepezil, which inhibits CYP2D6 and CYP3A4 and may accumulate in the body (Salvatore et al., 2017).

Molecular docking results showed that both compounds interact with BDNF, TrkB, and CREB proteins, with more negative binding energy indicating stronger interactions . (Kezia et al., 2023) Alpha-tocopherol demonstrated stronger binding affinity and can be categorized as a potent inhibitor. Oleic acid showed the strongest interaction with TrkB, a protein involved in learning and memory processes (Numakawa & Odaka, 2022). According to Sakurai et al. (2021) and has been associated with beneficial effects on cognitive decline.

Analysis of amino acid residues revealed that both compounds share binding sites in TrkB (PHE633, ILE616, LEU608) and CREB (THR164, PHE166, LYS52), while no similarity was found in BDNF. Amino acid residues play an important role in ligand binding and molecular simulations (Boittier et al., 2020).

Docking studies help predict binding sites and ligand orientation, which are essential for modulating protein activity (Pinzi & Rastelli, 2019).

5. CONCLUSION

Based on the research that has been conducted and the discussion that has been presented regarding the relationship between alpha-tocopherol and oleic acid on BDNF, TrkB, and CREB proteins, it can be concluded:

Oleic acid has interactions with BDNF, TrkB, and CREB proteins. Alpha-tocopherol has interactions between alpha-tocopherol and BDNF, TrkB, and CREB proteins. In the ADMETox analysis, it was found that the compounds alpha-tocopherol and oleic acid fulfill the Lipinski rule of five and do not inhibit the cytochrome P450 enzyme, so these two compounds are safe to be used as oral drug preparations.

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REFERENCE

Boittier, E. D., Tang, Y. Y., Buckley, M. E., Schuurs, Z. P., Richard, D. J., & Gandhi, N. S. (2020). Assessing molecular docking tools to guide targeted drug discovery of CD38 inhibitors. *International Journal of Molecular Sciences*, *21*(15), 1–19. https://doi.org/10.3390/ijms21155183

Boros, B. V., Dascalu, D., Ostafe, V., & Isvoran, A. (2022). Assessment of the effects of chitosan, chitooligosaccharides and their derivatives on *Lemna minor*. *Molecules*, *27*(18). https://doi.org/10.3390/molecules27186123

Brunton, L. L., Dandan, R. H., & Knollmann, B. C. (2023). *Goodman & Gilman's: The pharmacological basis of therapeutics* (14th ed.). McGraw-Hill Education.

Colucci-D'Amato, L., Speranza, L., & Volpicelli, F. (2020). Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *International Journal of Molecular Sciences*, *21*(20), 1–29. https://doi.org/10.3390/ijms21207777

Gao, L., Zhang, Y., Sterling, K., & Song, W. (2022). Brain-derived neurotrophic factor in Alzheimer's disease and its pharmaceutical potential. *Translational Neurodegeneration*, *11*(1). https://doi.org/10.1186/s40035-022-00279-0

Huang, Y., He, C., Hu, Z., Chu, X., Zhou, S., Hu, X., Deng, J., Xiao, D., Tao, T., Yang, H., Chen, A. F., Yin, Y., & Yang, X. (2023). The beneficial effects of alpha-tocopherol on intestinal function and the expression of tight junction proteins in differentiated segments of the intestine in piglets. *Food Science & Nutrition*, *11*(2), 677–687. https://doi.org/10.1002/fsn3.3103

Ionescu-Tucker, A., & Cotman, C. W. (2021). Emerging roles of oxidative stress in brain aging and Alzheimer's disease. *Neurobiology of Aging*, *107*, 86–95. https://doi.org/10.1016/j.neurobiolaging.2021.07.014

Jeon, S., Lee, C. H., Liu, Q. F., Kim, G. W., Koo, B. S., & Pak, S. C. (2014). Alteration in brain-derived neurotrophic factor (BDNF) after treatment of mice with herbal mixture containing *Euphoria longana*, *Houttuynia cordata* and *Dioscorea japonica*. *DARU Journal of Pharmaceutical Sciences*, *22*(1). https://doi.org/10.1186/s40199-014-0077-2

Kadry, H., Noorani, B., & Cucullo, L. (2020). A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids and Barriers of the CNS*, *17*(1). https://doi.org/10.1186/s12987-020-00230-3

Kezia, I., Erlina, L., Mudjihartini, N., & Fadilah, F. (2023). Molecular simulation for screening bioactive compounds as potential candidate for Alzheimer's disease. *Eksakta: Berkala Ilmiah Bidang MIPA*, *24*, 179–192. https://doi.org/10.24036/eksakta/vol24-iss02/401

Marcelino, G., Hiane, P. A., Freitas, K. de C., Santana, L. F., Pott, A., Donadon, J. R., & Guimarães, R. de C. A. (2019). Effects of olive oil and its minor components on cardiovascular diseases, inflammation, and gut microbiota. *Nutrients*, *11*(8). https://doi.org/10.3390/nu11081826

Mudjihartini, N. (2021). Brain-derived neurotrophic factor (BDNF) dan proses penuaan: Sebuah tinjauan. *Jurnal Biomedika dan Kesehatan*, *4*(3), 120–129. https://doi.org/10.18051/JBiomedKes.2021.v4.120-129

Numakawa, T., & Odaka, H. (2022). The role of neurotrophin signaling in age-related cognitive decline and cognitive diseases. *International Journal of Molecular Sciences*, *23*(14). https://doi.org/10.3390/ijms23147726

Nusantoro, Y. R., & Fadlan, A. (2020). Analisis sifat mirip obat, prediksi ADMET, dan penambatan molekular isatinil-2-aminobenzoilhidrazon dan kompleks logam transisi Co(II), Ni(II), Cu(II), Zn(II) terhadap BCL2-XL. *Akta Kimia Indonesia*, *5*(2), 114. https://doi.org/10.12962/j25493736.v5i2.7881

Opo, F. A. D. M., Rahman, M. M., Ahammad, F., Ahmed, I., Bhuiyan, M. A., & Asiri, A. M. (2021). Structure-based pharmacophore modeling, virtual screening, molecular docking and ADMET approaches for identification of natural anti-cancer agents targeting XIAP protein. *Scientific Reports*, *11*(1). https://doi.org/10.1038/s41598-021-83626-x

Ou, Z., Pan, J., Tang, S., Duan, D., Yu, D., Nong, H., & Wang, Z. (2021). Global trends in the incidence, prevalence, and years lived with disability of Parkinson's disease in 204 countries/territories from 1990 to 2019. *Frontiers in Public Health*, *9*. https://doi.org/10.3389/fpubh.2021.776847

Paulson, O. B. (2002). Blood-brain barrier, brain metabolism and cerebral blood flow. *European Neuropsychopharmacology*, *12*, 495–501. https://doi.org/10.1016/S0924-977X(02)00098-6

Pinzi, L., & Rastelli, G. (2019). Molecular docking: Shifting paradigms in drug discovery. *International Journal of Molecular Sciences*, *20*(18). https://doi.org/10.3390/ijms20184331

Putra, A. M. J. (2016). Sifat-sifat substansi pangan fungsional yang aman. *Indonesia Natural Research Pharmaceutical Journal*, *1*(1).

Renantha, R. R., Liga, A. R., Tanugroho, C. B., Denovian, L. X., Budiyanto, S. L. A. Z., & Parikesit, A. A. (2022). Flavonoids as potential inhibitors of dengue virus 2 (DENV2) envelope protein. *Journal of Pharmacy and Pharmacognosy Research*, *10*(4), 660–675. https://doi.org/10.56499/jppres22.1375_10.4.660

Sakurai, K., Shen, C., Shiraishi, I., Inamura, N., & Hisatsune, T. (2021). Consumption of oleic acid on the preservation of cognitive functions in Japanese elderly individuals. *Nutrients*, *13*(2), 1–10. https://doi.org/10.3390/nu13020284

Salvatore, S. R., Vitturi, D. A., Fazzari, M., Jorkasky, D. K., & Schopfer, F. J. (2017). Evaluation of 10-nitro oleic acid bio-elimination in rats and humans. *Scientific Reports*, *7*. https://doi.org/10.1038/srep39900

Shannon, M. W., Borron, S. W., & Burns, M. J. (2007). *Haddad and Winchester's clinical management of poisoning and drug overdose*. Saunders.

Song, J., Kim, Y.-S., Lee, D. H., Lee, S. H., Park, H. J., Lee, D., & Kim, H. (2019). Neuroprotective effects of oleic acid in rodent models of cerebral ischaemia. *Scientific Reports*, *9*(1), 10732. https://doi.org/10.1038/s41598-019-47057-z

Wang, D., Zheng, J., Sun, X., Xie, L., & Yang, Y. (2024). Study on the pharmacological mechanism of icariin for the treatment of Alzheimer's disease based on network pharmacology and molecular docking techniques. *Metabolites*, *14*(1). https://doi.org/10.3390/metabo14010001

Zhao, M., Ma, J., Li, M., Zhang, Y., Jiang, B., Zhao, X., Huai, C., Shen, L., Zhang, N., He, L., & Qin, S. (2021). Cytochrome P450 enzymes and drug metabolism in humans. *International Journal of Molecular Sciences*, *22*(23). https://doi.org/10.3390/ijms222312808