

## IN SILICO MOLECULAR DOCKING AND MOLECULAR DYNAMICS OF BAECKEA FRUTESCENS L. AGAINST TNF- $\alpha$ FOR TREATMENT OF INFLAMMATION-MEDIATED DISEASES

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| ARTICLE INFO                                                                                      | ABSTRACT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| <b>Received:</b> 30/01/2026<br><b>Revised:</b> 16/4/2026<br><b>Published:</b> 20/4/2026           | <p>Tumor Necrosis Factor-alpha (TNF-<math>\alpha</math>) is an essential cytokine in the immune system, but its excessive production is closely linked to the development of chronic inflammatory diseases. In recent years, natural compounds have attracted growing attention because of their potential safety and effectiveness in inhibiting TNF-<math>\alpha</math> activity. In this study, molecular docking was employed to screen and evaluate the phytochemicals found in <i>Baeckea frutescens</i> L., with the goal of identifying promising TNF-<math>\alpha</math> inhibitors. The results revealed ten standout compounds with significantly stronger binding affinities than the reference compound SPD304, namely baeefrutone F, frutescone C, frutescone F, betulinic acid, baeckein A, baeckein B, baeckein F, baeckein G, baeckein I, and BF-6. These TNF-<math>\alpha</math>-ligand complexes were further analyzed through molecular dynamics simulations and binding free energy calculations using the MM-GBSA (Molecular Mechanics Generalized Born Surface Area) method. The findings showed that the TNF-<math>\alpha</math>-baeefrutone F, TNF-<math>\alpha</math>-baeckein F, TNF-<math>\alpha</math>-baeckein G, TNF-<math>\alpha</math>-baeckein I, and TNF-<math>\alpha</math>-BF-6 complexes remained structurally stable throughout the 50 ns simulation and exhibited more favorable estimated binding free energies compared to SPD304. These results highlight the strong potential of natural compounds as sources for developing effective anti-inflammatory drugs and provide a solid foundation for future experimental validation.</p> |
| <b>KEYWORDS</b><br>Docking<br>Molecular dynamics<br><i>Baeckea frutescens</i><br>Baeckein<br>BF-6 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

## NGHIÊN CỨU GẮN KẾT PHÂN TỬ VÀ ĐỘNG LỰC HỌC PHÂN TỬ IN SILICO CỦA CÂY CHỐI SẼ (*BAECKEA FRUTESCENS* L.) ĐỐI VỚI TNF- $\alpha$ TRONG ĐIỀU TRỊ CÁC BỆNH DO VIÊM GÂY RA

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| THÔNG TIN BÀI BÁO                                                                                    | TÓM TẮT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Ngày nhận bài:</b> 30/01/2026<br><b>Ngày hoàn thiện:</b> 16/4/2026<br><b>Ngày đăng:</b> 20/4/2026 | <p>Tumor Necrosis Factor-alpha (TNF-<math>\alpha</math>) là một cytokine quan trọng trong hệ miễn dịch. Tuy nhiên, sự sản sinh quá mức TNF-<math>\alpha</math> có thể dẫn đến sự phát triển các bệnh viêm mạn tính. Những năm gần đây, các hợp chất thiên nhiên có tiềm năng về độ an toàn và hiệu quả trong việc ức chế hoạt tính của TNF-<math>\alpha</math> đang thu hút nhiều sự chú ý. Trong nghiên cứu này, chúng tôi sử dụng phương pháp gắn kết phân tử để sàng lọc và đánh giá các hợp chất hóa thực vật có trong cây Chối sẽ (<i>Baeckea frutescens</i> L.), nhằm xác định các chất ức chế TNF-<math>\alpha</math> tiềm năng. Kết quả cho thấy 10 hợp chất nổi bật có ái lực liên kết mạnh đáng kể so với hợp chất đối chứng SPD304, bao gồm baeefrutone F, frutescone C, frutescone F, betulinic acid, baeckein A, baeckein B, baeckein F, baeckein G, baeckein I và BF-6. Các hệ phức TNF-<math>\alpha</math>-ligand này tiếp tục được phân tích bằng mô phỏng động lực học phân tử và tính toán năng lượng tự do liên kết sử dụng phương pháp MM-GBSA. Kết quả cho thấy, các phức hợp TNF-<math>\alpha</math>-baeefrutone F, TNF-<math>\alpha</math>-baeckein F, TNF-<math>\alpha</math>-baeckein G, TNF-<math>\alpha</math>-baeckein I và TNF-<math>\alpha</math>-BF-6 duy trì được độ ổn định cấu trúc trong suốt quá trình mô phỏng 50 ns và thể hiện năng lượng tự do liên kết ước tính tốt hơn SPD304. Những phát hiện này giúp định hướng các hợp chất thiên nhiên tiềm năng được tìm thấy trong loài Chối sẽ làm nguyên liệu để phát triển thuốc chống viêm hiệu quả, đồng thời cung cấp cơ sở khoa học cho các nghiên cứu thực nghiệm tiếp theo.</p> |
| <b>TỪ KHÓA</b><br>Docking<br>Động lực học phân tử<br><i>Baeckea frutescens</i><br>Baeckein<br>BF-6   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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## 1. Introduction

*Baeckea frutescens* L., a member of the Myrtaceae family, is a traditional medicinal plant used to treat digestive disorders, bleeding, and various infections. The plant is widely distributed across Southeast Asia and Australia [1]. In Vietnam, it is known for its ability to cure rheumatism, body aches, colds, and measles in children, as well as menstrual disorders, boils, abdominal pain, nosebleeds, and stimulating appetite [2]. Additionally, it is beneficial for postpartum women [2]. Phytochemical investigations have shown that *B. frutescens* is rich in diverse bioactive constituents, including sesquiterpenes, flavonoids, flavanones, phloroglucinols, chromones, and chromanones [3]. Previous studies on individual components extracted from this plant have demonstrated a wide range of biological activities, such as cytotoxicity, antibacterial activity, mosquito larvicidal activity, anti-inflammatory activity, antioxidant activity, anti-rheumatoid arthritis activity, and skin-protective properties [4]. Among these, the anti-inflammatory activity is particularly notable, with certain compounds showing strong effects. For instance, frutescone O has demonstrated strong inhibition of nitric oxide (NO) production with an  $IC_{50}$  value of 0.36  $\mu$ M, possibly through modulation of the NF- $\kappa$ B signaling pathway by blocking the nuclear translocation of p65, thereby reducing IL-6 and TNF- $\alpha$  levels [5]. Baeckein I also exhibits NO inhibitory activity ( $IC_{50}$  = 15.2  $\mu$ M), comparable to the positive control indomethacin [6]. Additionally, BF-2 isolated from the leaves can suppress NLRP3 inflammasome activation, while flavones such as baeckeins (from the root), baefrutones (from twigs and leaves), and frutescones (from the root) have been shown to effectively reduce NO production [4]. Despite these findings, studies exploring the mechanisms by which *B. frutescens* compounds regulate complex inflammatory pathways, particularly their role as potential TNF- $\alpha$  inhibitors, remain limited.

Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) is a pivotal inflammatory molecule that plays a critical role in the body's immune system. It is involved in various immune functions, including inflammation, combating infections, and cancer control [7]. In the context of chronic neuroinflammation, TNF- $\alpha$  is closely associated with disease progression, neuronal damage, sustained inflammation, and disruption of the blood-brain barrier [8]. Numerous studies have utilized molecular docking and molecular dynamics simulations to investigate TNF- $\alpha$  inhibitors from natural sources. For instance, curcumin diglucoside and curcumin monoglucoside from *Curcuma longa* have been found to be highly effective in inhibiting TNF- $\alpha$  activity through molecular docking simulations [9]. Similarly, phytochemicals from *Isodon coetsa*, including 2 $\alpha$ ,3 $\alpha$ ,24-trihydroxy-11 $\alpha$ ,12 $\alpha$ -epoxy-urs-20(30)-en-28,13 $\beta$ -olide, xerophilusin B, and 15 $\alpha$ -hydroxy-6,7-seco-1 $\alpha$ ,7:11 $\alpha$ ,6-diolide-ent-kaur-16-en, have been identified as promising candidates with better binding affinities than SPD304 [10].

Building on these insights, the present study employs molecular docking and molecular dynamics simulations to screen compounds isolated from *B. frutescens* for their potential to inhibit TNF- $\alpha$ . The findings are expected to contribute to the discovery of novel lead compounds and provide a scientific basis for the future development of anti-inflammatory drugs derived from natural sources.

## 2. Materials and methods

### 2.1. Molecular docking calculations

The crystal structure of TNF- $\alpha$  (PDB ID: 2AZ5) was obtained from the Protein Data Bank (<https://www.rcsb.org/structure/2AZ5>) and prepared for docking calculations by removing heteroatoms and water molecules [11]. Missing amino acid residues in the protein structure were then added using the PDBFixer program. AutodockTools (ADT) 1.5.6 was employed to merge non-polar hydrogens with carbon atoms, calculate Kollman charges, and save the prepared structure in the \*.pdbqt format. For ligand preparation, 169 compounds collected from previous studies were used [4]. Their structures were drawn using ChemSketch software and converted

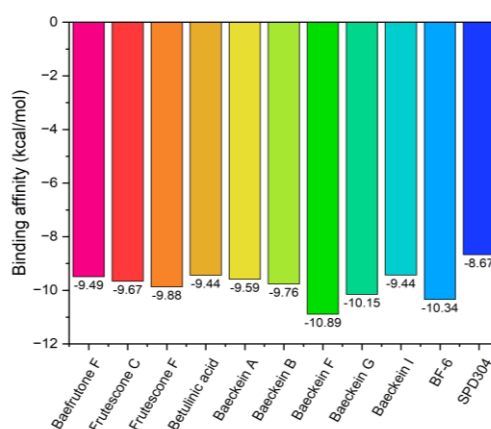
into optimized 3D structures using 3DView software. Subsequently, rotatable bonds and Gasteiger charges were assigned using the prepare\_ligand4.py utility script from ADT for the studied ligands. The AutoDock Vina 1.2.3 program was used for protein-ligand docking with default parameters, except the exhaustiveness value, which was set to 400 [12], [13]. A grid box of  $24 \times 24 \times 24$  points with a spacing of 1 Å was defined, centered on the co-crystallized ligand in the active site. The docking protocol verification was conducted similarly to previous studies [10], [14]. The lowest energy conformation obtained from the AutoDock Vina program was selected as the docking simulation result. Discovery Studio Visualizer software was chosen to illustrate the interactions between TNF- $\alpha$  and the most promising candidates from *B. frutescens*.

## 2.2. Molecular dynamics

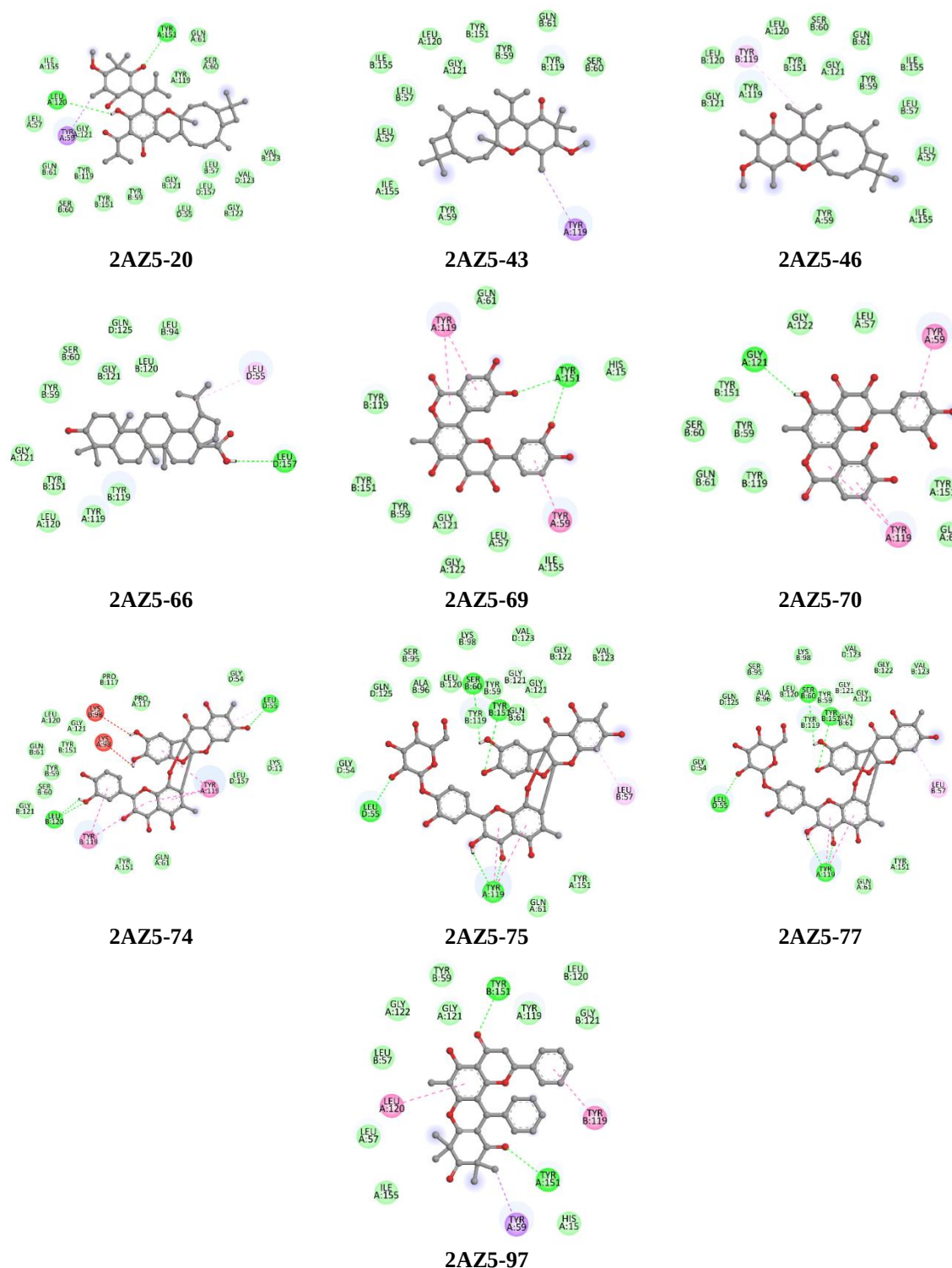
In this section, the GROMACS v2023.2 software package was used to perform molecular dynamics (MD) simulations on TNF- $\alpha$  protein complexes with potential ligands, which were generated through molecular docking simulations [15]. The AMBER99SB-ILDN force field was used to parameterize protein characteristics [16]. The pdb2gmx tool was then utilized to construct the TNF- $\alpha$  protein structure for the GROMACS software. The protein-ligand and unbound protein systems were positioned in the center of a cubic box and solvated using the TIP3P water model. To neutralize the charge of the TNF- $\alpha$ -ligand system, appropriate counterions ( $\text{Na}^+$  or  $\text{Cl}^-$ ) were added. Energy minimization was performed using the steepest descent method over 50000 steps to gradually relax the systems. Following this, the systems were equilibrated for 0.1 ns with position restraints on the protein and ligand systems using NVT and NPT ensembles. Equilibration at 300 K was achieved using the Berendsen thermostat with a coupling time of 0.1 ps, while pressure was maintained at 1 bar with a reference coupling [17]. For short-range interactions during energy minimization, NVT, and NPT relaxation, a smooth switching function with a cutoff of 1.2 nm was applied. Long-range electrostatics were computed with the PME (Particle-Mesh-Ewald) method, and hydrogen bonds were constrained using the LINCS algorithm. Finally, 50 ns of unrestrained MD simulations were carried out with a time step of 2 fs and trajectory snapshots saved every 1 ps. MD trajectories were analyzed with GROMACS modules and plotted using the XMGRACE software, with root mean square deviation (RMSD) parameters calculated for detailed analysis [18]. The gmx\_MMPBSA program was used to calculate the binding free energy from the MD simulation trajectories using the Molecular Mechanics Generalized Born Surface Area (MM-GBSA) approach [19]-[21].

## 3. Results and discussion

### 3.1. Docking results



**Figure 1.** Binding affinities of the top 10 potential compounds obtained from molecular docking simulations



**Figure 2.** 2D interactions of top 10 potential compounds within the active site pocket of TNF- $\alpha$  protein

As is well known, TNF- $\alpha$  plays a critical role in the immune system but is also implicated in chronic inflammatory diseases when produced in excess. Using molecular docking methods, we screened and simulated the interactions between TNF- $\alpha$  and compounds derived from *B. frutescens* to identify the most promising inhibitors. The binding affinity results ( $\Delta G_{\text{dock}}$ ) of these compounds

range from -10.89 to -5.34 kcal/mol, with an average value of -7.32 kcal/mol. These negative values suggest potential interactions between the compounds and TNF- $\alpha$ , and notably, 61 compounds exhibited stronger affinity than the control substance SPD304 ( $\Delta G_{\text{dock}} = -8.71$  kcal/mol). Among these, the compounds with  $\Delta G_{\text{dock}} < -9.43$  kcal/mol (the top 10 potential inhibitors) were further analyzed for their binding modes with TNF- $\alpha$ . As illustrated in Figure 1 and Figure 2, Baeckein F (ID: 74) demonstrated the strongest binding affinity with a  $\Delta G_{\text{dock}}$  of -10.89 kcal/mol. It interacts with LeuB120 and LeuD55 in the active site of TNF- $\alpha$  and also forms alkyl interactions with LeuD55 and  $\pi$ - $\pi$  stacked and  $\pi$ - $\pi$  T-shaped interactions with residues TyrB119 and TyrA119. Baeckein G (ID: 75) has a  $\Delta G_{\text{dock}}$  of -10.15 kcal/mol and establishes similar interactions with residues TyrB119 and TyrA119, along with a  $\pi$ -cation interaction with LysA98. Baeckein F, with a binding affinity of -9.491 kcal/mol, forms hydrogen bonds with TyrA151 and LeuA120 and a  $\pi$ - $\sigma$  interaction with TyrA59. Baeckein I forms hydrogen bonds with SerB60, TyrB151, TyrA119, and LeuD55, along with  $\pi$ -alkyl interactions with LeuB57 and  $\pi$ - $\pi$  stacked and  $\pi$ - $\pi$  T-shaped interactions with TyrA119. BF-6, with a binding affinity of -10.34 kcal/mol, forms hydrogen bonds with TyrB151 and TyrA151, and exhibits  $\pi$ - $\pi$  stacked and amide- $\pi$  stacked interactions with LeuA120 and TyrB119, as well as  $\pi$ - $\sigma$  interactions with TyrA59.

Furthermore, betulinic acid, baeckein A, and baeckein B each form hydrogen bonds with one amino acid residue, specifically interacting with LeuD157, TyrA151, and GlyA121, respectively. Notably, except for betulinic acid, the compounds mentioned above interact with key amino acids such as TyrA151, LeuA120, TyrA119, TyrB119, TyrA151, GlyA121, LeuB120, and LeuA57 of the TNF- $\alpha$  protein [6]. This indicates that the current molecular docking simulation has identified compounds with significant inhibitory potential against TNF- $\alpha$ , paving the way for developing treatments for inflammation-related diseases.

### 3.2. Molecular dynamics results

Next, to examine the stability of the interactions between the TNF- $\alpha$  protein and the potential compounds, molecular dynamics simulations were conducted. For this purpose, 10 complex systems obtained from docking simulations (TNF- $\alpha$ -20, TNF- $\alpha$ -43, TNF- $\alpha$ -46, TNF- $\alpha$ -66, TNF- $\alpha$ -69, TNF- $\alpha$ -70, TNF- $\alpha$ -74, TNF- $\alpha$ -75, TNF- $\alpha$ -77, TNF- $\alpha$ -97) and the control complex TNF- $\alpha$ -SPD304 were subjected to molecular dynamics production runs for a simulation time of 50 ns. The root mean square deviation (RMSD) values of the ligands and proteins were calculated to measure the structural stability of the molecular systems. Lower RMSD values indicate a more stable system, while higher values suggest less stability. From the RMSD plots presented in Figure 3, it is evident that the protein in the TNF- $\alpha$ -46, TNF- $\alpha$ -69, TNF- $\alpha$ -70, and TNF- $\alpha$ -77 systems exhibited structural instability with significant fluctuations. In contrast, the TNF- $\alpha$ -20, TNF- $\alpha$ -43, TNF- $\alpha$ -66, TNF- $\alpha$ -74, TNF- $\alpha$ -75, and TNF- $\alpha$ -97 systems demonstrated stability similar to the unbound protein and the control system TNF- $\alpha$ -SPD304, with average protein backbone RMSD values of 0.2405 nm, 0.3284 nm, 0.2113 nm, 0.2985 nm, 0.2917 nm, and 0.2973 nm, respectively, compared to the control TNF- $\alpha$ -SPD304 value of 0.3156 nm. Regarding ligand structural changes, the RMSD values for most ligands, except compound 77, were lower than the control SPD304. However, compound 77 still showed stability until the end of the simulation, with only minor variations observed between 38-42 ns. The average RMSD values for the ligands TNF- $\alpha$ -20, TNF- $\alpha$ -43, TNF- $\alpha$ -66, TNF- $\alpha$ -74, TNF- $\alpha$ -75, TNF- $\alpha$ -77, and TNF- $\alpha$ -97 were 0.1025 nm, 0.1117 nm, 0.1077 nm, 0.055 nm, 0.071 nm, 0.1017 nm, 0.0702 nm, 0.0647 nm, 0.1902 nm, and 0.0911 nm, respectively. These results clearly indicate that the TNF- $\alpha$ -20, TNF- $\alpha$ -66, TNF- $\alpha$ -74, TNF- $\alpha$ -75, and TNF- $\alpha$ -97 complexes have RMSD values for both protein and ligand that are comparable to the reference inhibitor SPD304, making them the most stable potential inhibitors. Van der Waals energy (vdW), electrostatic energy ( $E_{\text{EL}}$ ), polar solvation energy ( $E_{\text{GB}}$ ), and non-polar solvation energy ( $E_{\text{SURF}}$ ) along with the total binding free energy ( $\Delta G_{\text{binding}}$ ) for both complexes are presented in Figure 4. The  $\Delta G_{\text{MMGBSA}}$  values for the complexes

TNF- $\alpha$ -20, TNF- $\alpha$ -43, TNF- $\alpha$ -46, TNF- $\alpha$ -66, TNF- $\alpha$ -69, TNF- $\alpha$ -70, TNF- $\alpha$ -74, TNF- $\alpha$ -75, TNF- $\alpha$ -77, and TNF- $\alpha$ -97 were -41.73 kcal/mol, -34.38 kcal/mol, -37.32 kcal/mol, -31.66 kcal/mol, -36.64 kcal/mol, -26.84 kcal/mol, -42.33 kcal/mol, -39.11 kcal/mol, -45.89 kcal/mol, and -47.20 kcal/mol, respectively (Figure 4). These values indicate that the binding free energies of TNF- $\alpha$ -20, TNF- $\alpha$ -46, TNF- $\alpha$ -69, TNF- $\alpha$ -74, TNF- $\alpha$ -75, TNF- $\alpha$ -77, and TNF- $\alpha$ -97 are better than the control compound SPD304 ( $\Delta G_{\text{MMGBSA}} = -36.33$  kcal/mol) (Figure 4). These compounds likely interact more favorably in a solvated environment. Biological evidence also shows that compounds 74 (Baeckein F), 75 (Baeckein G), and 77 (Baeckein I) inhibit NO production with  $\text{IC}_{50}$  values of 54.7  $\mu\text{M}$ , 25.4  $\mu\text{M}$ , and 15.2  $\mu\text{M}$ , respectively [4]. Overall, the findings from molecular dynamics simulations suggest that complexes TNF- $\alpha$ -20, TNF- $\alpha$ -74, TNF- $\alpha$ -75, TNF- $\alpha$ -77, and TNF- $\alpha$ -97 form stable complexes with the TNF- $\alpha$  protein and exhibit better binding free energy, thereby providing a basis for further biological testing in the future.

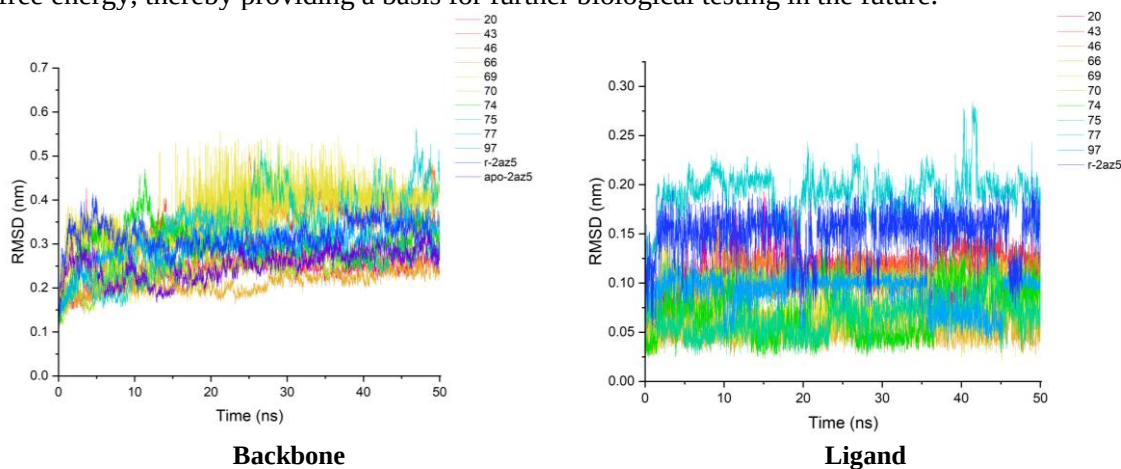


Figure 3. RMSD plot of the ten promising inhibitors and the standard (SPD-304)

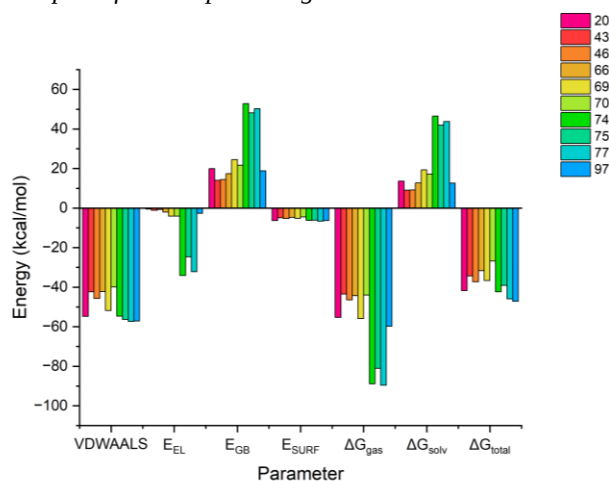


Figure 4. The binding free energy of the selected compounds obtained from the MM-GBSA method calculation

#### 4. Conclusion

This study has uncovered a computational pathway to identifying promising TNF- $\alpha$  inhibitors among compounds derived from *B. frutescens*. Docking scores have highlighted the robust binding interactions of the ten most promising compounds: baefrutone F, frutescone C, frutescone F, betulinic acid, baeckein A, baeckein B, baeckein F, baeckein G, baeckein I, and BF-6 with the TNF- $\alpha$  protein. The binding affinities of these compounds with key amino acid residues of the protein have been indicated. Additionally, the RMSD values for the TNF- $\alpha$ -baefrutone F, TNF- $\alpha$ -

baeckein F, TNF- $\alpha$ -baeckein G, TNF- $\alpha$ -baeckein I, and TNF- $\alpha$ -BF-6 complexes, when compared to the control and unbound TNF $\alpha$  protein, indicated structural stability throughout the 50 ns MD simulations. MM-GBSA calculations further confirmed the stability of protein-ligand interactions within these complexes. In conclusion, baefrutone F, baeckein F, baeckein G, baeckein I, and BF-6 exhibit strong potential as TNF- $\alpha$  protein inhibitors. Nonetheless, these promising findings require validation through subsequent *in vitro* and *in vivo* experiments.

## REFERENCES

- [1] J. Yusuf, "Baeckea frutescens L.," in *Plant resources of South-East Asia No. 12 (2): medicinal and poisonous plants* 2, J. L. C. H. van Valkenburg and N. Bunyaphratharsa, Eds., Backhuys Publisher, 2001, p. 782.
- [2] T. Do, *Vietnamese medicinal plants and remedies*, Hanoi: Medicine Publisher, 2004, p. 151.
- [3] T. Ito *et al.*, "Two new cyclopentenones and a new furanone from Baeckea frutescens and their cytotoxicities," *Fitoterapia*, vol. 112, pp. 132-135, 2016.
- [4] T. L. H. Do, X. D. Dau, and T.S. Ninh, "Baeckea frutescens L.: a review on phytochemistry, biosynthesis, synthesis, and pharmacology," *Natural Product Communications*, vol. 18, no. 7, 2023, doi: 10.1177/1934578X231189143.
- [5] J.-Q. Hou *et al.*, "Anti-inflammatory meroterpenoids from Baeckea frutescens," *Journal of Natural Products*, vol. 80, no. 8, pp. 2204-2214, 2017.
- [6] B.-X. Jia *et al.*, "Baeckeins F–I, four novel C-methylated biflavonoids from the roots of Baeckea frutescens and their anti-inflammatory activities," *Food Chemistry*, vol. 155, pp. 31-37, 2014.
- [7] S. E. Abechi, S. Ejeh, and A. Abduljelil, "In silico screening of potential Tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors through molecular modeling, molecular docking, and pharmacokinetics evaluations," *Scientific African*, vol. 21, 2023, doi: 10.1016/j.sciaf.2023.e01830.
- [8] N. X. Ha *et al.*, "In silico and ADMET study of Morinda longissima phytochemicals against TNF- $\alpha$  for treatment of inflammation-mediated diseases," *Vietnam Journal of Chemistry*, vol. 61, pp. 57-63, 2023.
- [9] S. Xu, H. Peng, N. Wang, and M. Zhao, "Inhibition of TNF- $\alpha$  and IL-1 by compounds from selected plants for rheumatoid arthritis therapy: In vivo and in silico studies," *Tropical Journal of Pharmaceutical Research*, vol. 17, no. 2, pp. 277-285, 2018.
- [10] N. X. Ha and C. H. Le, "In silico molecular docking and ADMET study of Isodon coetsa phytochemicals targeting TNF- $\alpha$  in inflammation-mediated diseases," *Vietnam Journal of Chemistry*, vol. 62, no. 3, pp. 387-393, 2024.
- [11] M. M. He *et al.*, "Small-molecule inhibition of TNF- $\alpha$ ," *Science*, vol. 310, no. 5750, pp. 1022-1025, 2005.
- [12] O. Trott and A. J. Olson, "AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading," *Journal of Computational Chemistry*, vol. 31, no. 2, pp. 455-461, 2010.
- [13] J. Eberhardt, D. Santos-Martins, A. F. Tillack, and S. Forli, "AutoDock Vina 1.2. 0: new docking methods, expanded force field, and python bindings," *Journal of Chemical Information Modeling*, vol. 61, no. 8, pp. 3891-3898, 2021.
- [14] T. V. Pham *et al.*, "Essential Oils of the Leaves of Epaltes australis Less. and Linder myrrha (Lour.) Merr.: Chemical Composition, Antimicrobial, Anti-inflammatory, Tyrosinase Inhibitory, and Molecular Docking Studies," *Chemistry & Biodiversity*, vol. 20, no. 12, 2023, doi: 10.1002/cbdv.202301192.
- [15] D. Van Der Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark, and H. J. C. Berendsen, "GROMACS: Fast, flexible, and free," *Journal of Computational Chemistry*, vol. 26, no. 16, pp. 1701-1718, 2005.
- [16] K. Lindorff-Larsen *et al.*, "Improved side-chain torsion potentials for the Amber ff99SB protein force field," *Proteins: Structure, Function, and Bioinformatics*, vol. 78, no. 8, pp. 1950-1958, 2010.
- [17] A. S. Lemak and N. K. Balabaev, "On The Berendsen Thermostat," *Molecular Simulation*, vol. 13, no. 3, pp. 177-187, 1994.
- [18] P. J. Turner, "XMGRACE," Center for Coastal and Land-Margin Research, Oregon Graduate Institute of Science and Technology, 2005.
- [19] M. S. Valdés-Tresanco, M. E. Valdés-Tresanco, P. A. Valiente, and E. Moreno, "gmx\_MMPBSA: A New Tool to Perform End-State Free Energy Calculations with GROMACS," *Journal of Chemical Theory and Computation*, vol. 17, no. 10, pp. 6281-6291, 2021.
- [20] S. Genheden and U. Ryde, "The MM/PBSA and MM/GBSA methods to estimate ligand-binding affinities," *Expert Opinion on Drug Discovery*, vol. 10, no. 5, pp. 449-461, 2015.
- [21] E. Wang *et al.*, "End-Point Binding Free Energy Calculation with MM/PBSA and MM/GBSA: Strategies and Applications in Drug Design," *Chemical Reviews*, vol. 119, no. 16, pp. 9478-9508, 2019.