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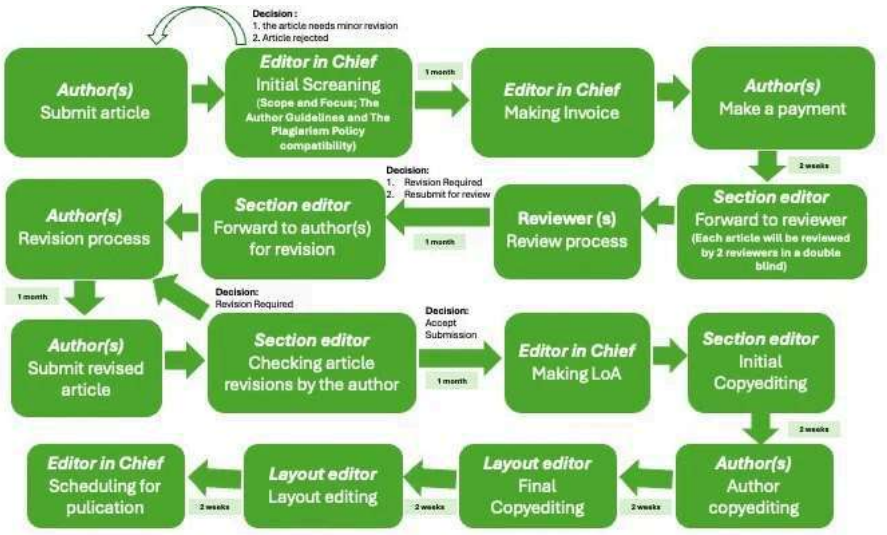


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Research Article

# Integrative Study on the Binding Energy Calculation: Molecular Docking and Molecular Mechanics with Generalized Born Surface Area Targeting *Acetylcholinesterase*

# *Studi Terintegrasi Perhitungan Energi Ikatan: Penambatan Molekul dan Mekanika Molekul Terkombinasi Area Permukaan Generalized Born Menarget Asetilkolinesterase*

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## ABSTRACT

**Alzheimer's disease (AD) imposes a significant global financial burden. Previous studies have reported that acetylcholinesterase (AChE) activity is strongly associated with AD, making it a key target in therapeutic research. Molecular docking and computational techniques are increasingly used to study these associations, yet a surge in publications has led to a departure from strictly designed paradigms. This study evaluates the accuracy of the Gibbs free energy of binding (ΔG) from molecular docking scores, Molecular Mechanics/Generalized Born Surface Area (MM/GBSA), and local Vina scores. The Spearman rank test was applied to compare ΔG predictions and the in vitro results from our previous study. The correlation coefficient for molecular docking was -0.491, the MM/GBSA correlation coefficient calculated at the best molecular docking pose was -0.309, the MM/GBSA correlation coefficient calculated at the last 5**

**nanoseconds (ns) snapshots was 0.164, and the correlation coefficient of the Vina local score calculated at the last 5 ns snapshots was 0.273. Our findings indicate that the ΔG prediction from the Vina local score for the last 5 ns shows the strongest correlation with in vitro results.**

**Keywords: Acetylcholinesterase, Alzheimer, Chalcone, MM/GBSA, YASARA**

***ABSTRAK***

***Penyakit Alzheimer (AD) menimbulkan beban finansial global. Studi sebelumnya melaporkan bahwa aktivitas asetilkolinesterase (AChE) memiliki hubungan yang kuat dengan AD, menjadikannya target utama dalam penelitian terapeutik. Teknik penambatan molekul dan komputasi semakin sering digunakan untuk meneliti hubungan ini, namun lonjakan publikasi telah menyebabkan penyimpangan dari paradigma yang dirancang secara ketat. Studi ini bertujuan untuk mengevaluasi akurasi energi bebas ikatan Gibbs (ΔG) dari skor penambatan molekul, Molecular Mechanics/Generalized Born Surface Area (MM/GBSA), dan skor Vina lokal dalam konteks penelitian ini. Uji Spearman rank dilakukan untuk mengevaluasi perbandingan antara prediksi ΔG dan hasil in vitro dari studi sebelumnya. Ditemukan bahwa koefisien korelasi untuk ΔG pada pose penambatan molekul adalah -0.491, koefisien korelasi MM/GBSA yang dihitung pada pose penambatan molekul terbaik adalah -0.309, koefisien korelasi MM/GBSA yang dihitung pada snapshot 5 nanodetik (ns) terakhir adalah 0.164, dan koefisien korelasi skor Vina lokal yang dihitung pada snapshot 5 ns terakhir adalah 0.273. Temuan kami menunjukkan bahwa prediksi ΔG dari skor Vina lokal menunjukkan korelasi terkuat dengan hasil in vitro.***

***Kata Kunci: Alzheimer, Asetilkolinesterase, Chalcone, GBSA, YASARA***

## I. INTRODUCTION

Alzheimer's disease (AD) begins with neuropathologic changes and leads to the later appearance and progression of clinical symptoms. AD commonly presents as dementia, which involves a continuum of cognitive decline and functional impairment affecting instrumental activities of daily living (Jack et al., 2024). Age, sex, and genetics play a critical role in driving AD risk (Blue et al., 2025; Ramirez et al., 2024). In the past 50 years, the proportion of older adults in Indonesia has increased from 4.5% to 10.7% and it is expected to reach 20% by 2045 (Iwatsubo et al., 2025). Dementia prevalence in Indonesia reached 1.2 million cases in 2015 and is projected to increase to nearly 4 million by 2050 (Turana et al., 2019). Dementia is a rapidly growing public health problem affecting around 50 million people around the world. Nearly 10 million new cases of dementia are reported annually, and this number is projected to triple by 2050. The associated costs of care are estimated to reach US$2 trillion per year by 2030 (WHO, 2019).

Cognitive dysfunction in AD is associated with altered acetylcholine (ACh) levels in the brain. The primary symptomatic treatment of cognitive and behavioral symptoms of mild and moderate stages of AD involves enhancing cholinergic neurotransmission. The acetylcholinesterase (AChE) inhibitors were the currently used drugs' target for AD treatment (Marucci et al., 2021). These regimens are considered cost-effective (Huo et al., 2022).

Drug discovery is complex, time-consuming, costly, and requires labor-intensive techniques. The traditional approach frequently involves large-scale testing and trial-and-error to find suitable compounds (Blanco-González et al., 2023). Computer-Aided Drug Design (CADD) has become essential, allowing for more efficient and cost-effective identification of drug candidates (Brogi et al., 2020). Understanding receptor-drug binding processes and mechanisms is important to rationalize drug design. Advances in molecular modeling and simulation algorithms have made it possible to predict binding free energy and drug kinetics using computational approaches (Adediwura et al., 2024). However, ensuring the accuracy of computational models remains a challenge, as simulation and predictions are based on theoretical frameworks (Niazi & Mariam, 2023).

Since the COVID-19 pandemic, there has been a surge in molecular docking studies that deviate from the strictly designed paradigm and require expertise in the field of drug discovery (Gentile et al., 2023). This phenomenon has produced various scientific dynamics, making understanding Gibbs free energy of binding (ΔG) calculations and their application in the drug discovery pipeline became more important (Cournia et al., 2021).

Hence, there is a challenge to observe the accuracy companion between ΔG values from molecular docking methods, and MM/GBSA method by retrospectively obtaining in vitro data on chalcone derivatives against AChE (Riswanto et al., 2021). This study evaluates the accuracy of these computational methods by comparing the predicted ΔG ranking with the experimentally determined in vitro results ranking, using the Spearman rank test.

## II. METHOD

### A. Material

The main instruments used in this study were the GPU-based Cloud Protein Simulator (CPS), licensed YASARA-Structure version 24.4.10, AutoDock Vina Version 1.1.2 (Trott & Olson, 2010), GROMACS version 2024.5 (Abraham et al., 2015), and Uni-GBSA (https://github.com/dptech-corp/Uni-

GBSA) (Yang et al., 2023). The PC client used to access CPS is an Asus Vivobook X412FL A412FL with Windows 11 operating system, Intel Core i3-8145U CPU 2.30GHz processor, 4GB RAM, and 512GB SSD. The software used on the PC client is YASARA-Structure version 24.4.10 and Avogadro version 1.2.0 (https://avogadro.cc/).

**B. Preparation and Virtual Target Validation**

Structure correction of the AChE-donepezil complex (https://www.rcsb.org/structure/7e3h) was performed using the internet-connected YASARA-Structure version 24.4.10 by adding missing residue models during crystallography and hydrogen atoms at physiological pH (pH 7.4). This procedure was followed by 100 times docking using an in-house prepared protocol (Istyastono, 2023). The protocol that produced the co-crystallized ligand pose with a 95% confidence level will be used for the chalcone derivatives docking protocol.

**C. Chalcone Derivatives Preparation**

Ten structures of the chalcone derivatives in (Riswanto et al., 2021) shown in Table I. were prepared using Avogadro version 1.2.0 and saved as pdb. The preparation was done using YASARA-Structure version 24.4.10 as referred in (Istyastono, 2023). The prepared chalcone derivative files were saved with pdb and sdf extensions.

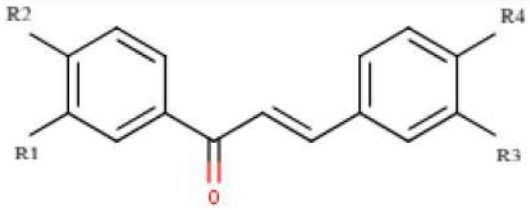
**D. Molecular Docking and Initial Pose Generation**

The prepared structure of the chalcone derivative was docked 100 times with AChE with a validated protocol using YASARA-Structure version 24.4.10 (Istyastono, 2023). Each chalcone derivative docking pose with the best ΔG value will be used as an initial pose for molecular dynamics and ΔG calculation using the MM/GBSA method.

**E. MM/GBSA and Vina Local Score Calculation**

MM/GBSA calculation was performed with Uni-GBSA (Yang et al., 2023). MM/GBSA was measured twice. The first MM/GBSA calculation was performed on the initial pose obtained in the previous step with energy minimization. The second calculation was performed for the last 5 nanoseconds (ns) snapshots after molecular dynamics simulation (Liu et al., 2017) using GROMACS version 2024.5 (Abraham et al., 2015). Vina local score is also calculated for the last 5 ns snapshots using AutoDock Vina Version 1.1.2 (Trott & Olson, 2010).

**Table I.** Chalcone derivative structures evaluated in this study (Riswanto et al., 2021)

| Compounds | |   | | | |
|---|---|---|---|---|---|
| Code | IUPAC | R1 | R2 | R3 | R4 |
| 1a | (E)-3-(4-fluorophenyl)-1-(3-hydroxyphenyl)prop-2 en-1-one | H | OH | H | F |
| 2a | (E)-1-(3-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en 1-one | H | OH | H | $NO_2$ |
| 3a | 4-((E)-3-(3-hydroxyphenyl)-3-oxoprop-1-enyl)benz oic acid | H | OH | H | COOH |
| 1b | (E)-3-(4-fluorophenyl)-1-(3-isopropoxyphenyl)prop 2-en-1-one | H | O-isopropyl | H | F |
| 2b | (E)-1-(3-(cyclopentyloxy)phenyl)-3-(4-fluorophenyl) prop-2-en-1-one | H | O-cylcopentyl | H | F |
| 3b | (E)-1-(3-(benzyloxy)phenyl)-3-(4-fluorophenyl)prop 2-en-1-one | H | O-benzyl | H | F |
| 4b | (E)-1-(3-(cyclopentyloxy)phenyl)-3-(4-nitrophenyl) prop-2-en-1-one | H | O-cyclopentyl | H | $NO_2$ |
| 1c | (E)-3-(4-butoxyphenyl)-1-(4-hydroxy-3-methoxy phenyl)prop-2-en-1-one | $OCH_3$ | OH | H | O-butyl |
| 2c | (E)-3-(4-(benzyloxy)-3-methoxyphenyl)-1-(4-hydro xy-3-ethoxyphenyl)prop-2-en-1-one | $OCH_3$ | OH | $OCH_3$ | O-benzyl |
| 3c | (E)-3-(4-(benzyloxy)-3-methoxyphenyl)-1-(3-hyd roxyphenyl)prop-2-en-1-one | H | OH | $OCH_3$ | O-benzyl |

### F. Data analysis

The ΔG values from molecular docking, MM/GBSA, and Vina local score were ranked in ascending order, whereas the in vitro results (Riswanto et al., 2021) were ranked in descending order. The Spearman's rank correlation was then performed on these rankings to assess the relationship between computational and experimental results. Unstable compound placed in the last rank.

## III. RESULTS AND DISCUSSION

Validated docking protocol produced with a 95% confidence level, which 95% of 100 docking simulations result in Root Mean Square Deviation (RMSD) values ≤ 2 Å (Istyastono, 2023). This protocol was used to dock ten chalcone derivatives. Docking process performed, resulting in one pose for nine chalcone derivatives except for 1b (2 clusters). This cluster implies the finding of two clusters of local minima. The first

cluster (lowest energy -10.247 kcal/mol) and the second cluster (lowest energy -10.178 kcal/mol) consist of 98 and 2 members, respectively. The most frequent pose was used for the MM/GBSA calculation and molecular dynamics simulation initial pose, which represents the AChE-1b complex global minima.

The initial pose was selected from the lowest ΔG of 100 times docking. Ten chalcone derivatives with the lowest ΔG are shown in Table II. The lowest docking score reflected the most stable pose (Hadi et al., 2020). This pose was used for MM/GBSA with energy minimization calculation and the molecular dynamics simulation initial pose.

Molecular dynamics simulation conducted for 10 ns of production time. Stable pose is defined by Liu et al. (2017) as occurring when any simulation among the five parallel MD runs has the RMSD less than 2.0 Å (Liu et al., 2017). RMSD was evaluated from snapshots in the last 5 ns. Nine compounds demonstrated stability according to this criterion, while compound 2a did not. MM/GBSA and Vina local score were calculated for the nine compounds, which were considered stable. Table II represents ΔG obtained from MM/GBSA and Vina local score calculation.

**Table II.** The results of the ΔG evaluation and the inhibition percentage from the previous in vitro study

| Compound | Docking score | | EM + MM/GBSA | | MD + MM/GBSA | | MD + Vina local score | | In vitro | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ΔG | Rank | ΔG | Rank | ΔG | Rank | ΔG | Rank | Inhibition (%) | Rank |
| 1a | -9.879 | 10 | -30.8772 | 10 | -21.006 | 9 | -7.4573 | 7 | 30.1 | 3 |
| 2a | -10.279 | 7 | -42.7184 | 7 | Unstable | 10 | Unstable | 10 | 18 | 6 |
| 3a | -10.465 | 6 | -35.4865 | 9 | -24.6409 | 8 | -8.4587 | 3 | 15 | 7 |
| 1b | -10.247 | 8 | -37.293 | 8 | -24.7833 | 7 | -8.0321 | 5 | 87.6 | 2 |
| 2b | -11.409 | 4 | -47.994 | 4 | -34.6234 | 1 | -9.3555 | 1 | 92.4 | 1 |
| 3b | -11.49 | 2 | -47.9339 | 5 | -27.7862 | 4 | -7.6925 | 6 | 14.7 | 8 |
| 4b | -11.243 | 5 | -52.8336 | 2 | -26.7577 | 6 | -8.5644 | 2 | 14 | 9 |
| 1c | -9.934 | 9 | -46.7292 | 6 | -32.4638 | 2 | -7.1036 | 8 | 22.2 | 5 |
| 2c | -11.414 | 3 | -55.9008 | 1 | -32.3363 | 3 | -8.4153 | 4 | 23.1 | 4 |
| 3c | -11.632 | 1 | -52.7756 | 3 | -27.5501 | 5 | -6.9072 | 9 | 11.3 | 10 |
| r | | -0.491 | | -0.309 | | 0.164 | | 0.273 | | |

Notes: The ΔGs of docking score, energy minimization+MM/GBSA (EM + MM/GBSA), molecular dynamics+MM/GBSA (MD + MM/GBSA), and molecular dynamics+Vina local score (MD+ Vina local score) were presented in the unit of kcal/mol. The Spearman's rank correlation coefficient was coded with r

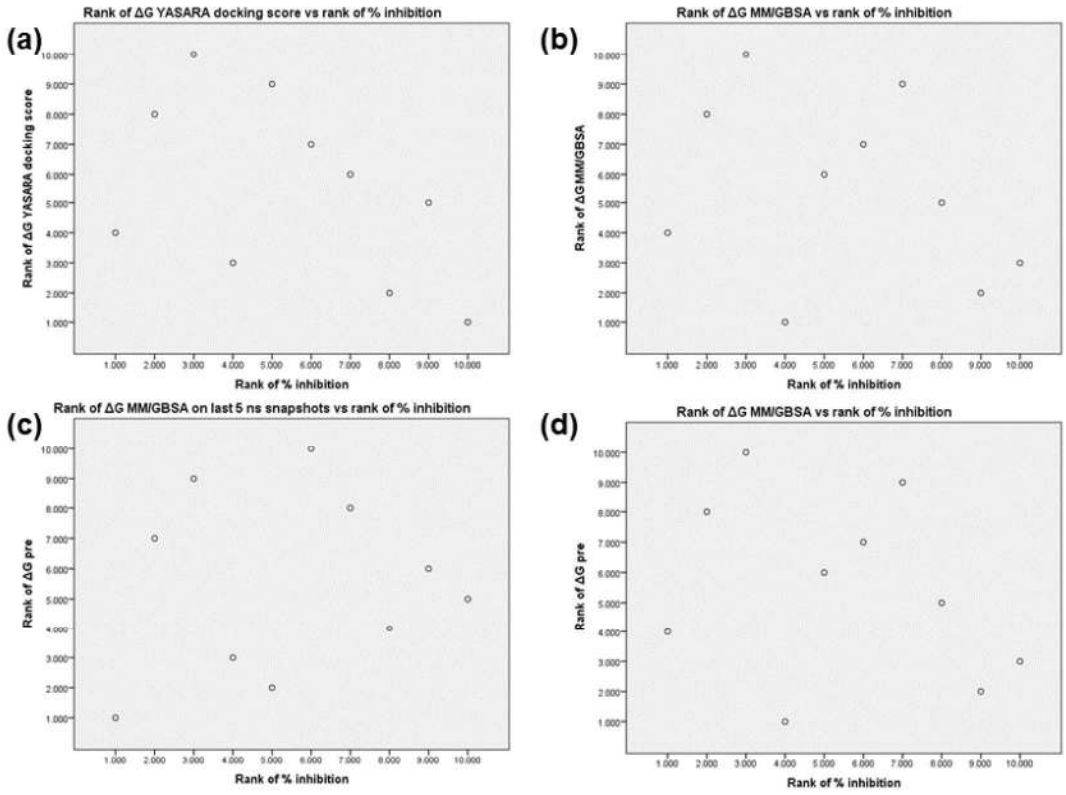



**Figure 1.** Visualization of the scatter plot of ΔG prediction gained from molecular docking using YASARA-Structure and the in vitro results (a), scatter plot of ΔG prediction (MM/GBSA) gained after energy minimization using Uni-GBSA on the initial pose and the in vitro results (b), scatter plot of ΔG prediction (MM/GBSA) gained on the last 5 ns snapshots after molecular dynamics using Uni-GBSA and the in vitro results (c), and scatter plot of ΔG prediction (Vina local score) gained on the last 5 ns snapshots after molecular dynamics using Uni-GBSA and the in vitro results (d)

Spearman's rank was used to describe the monotonic relationship between inhibition percentages from the in vitro evaluation (Riswanto et al., 2021) and ΔG prediction from the docking score, MM/GBSA, and Vina local score calculation. Correlation coefficients describe the direction and strength of two variables (Schober et al., 2018). Spearman's rank correlation coefficient result is shown in Table II. Scatter plots are shown in Figure 1.

The correlation between Vina local score on the last 5 ns and inhibition percentages demonstrates a stronger association (r = 0.273) compared to other methods. A positive correlation coefficient indicates that an increase in one variable corresponds to an increase in the other. In contrast, the correlation for the docking score and MM/GBSA calculated from

molecular docking best pose reveals a negative relationship between ΔG prediction and the in vitro results, indicating that an increase in one variable is associated with a decrease in the other.

## IV.CONCLUSION

The predicted Gibbs free energy of binding (ΔG) from Vina local score on the last 5 ns exhibited the highest correlation with in vitro experimental results.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this research.

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