Pharmacogn J. 2023; 15(4): 494-499
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Original Article

In Silico Study on the Potential of Guaiacol Extract from Green Tea (*Camellia sinensis*) as a Stimulant for Carbanoic Anhydrase II in Renal Tubular Acidosis

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History

- Submission Date: 12-05-2023;
- Review completed: 16-06-2023;
- Accepted Date: 24-06-2023.

DOI : 10.5530/pj.2023.15.108

Article Available online

http://www.phcogj.com/v15/i4

ABSTRACT

This study explores the potential of Guaiacol, a green tea extract from *Camellia sinensis*, as a stimulant in renal tubular acidosis through *in-silico* investigation on the Carbanoic Anhydrase II enzyme. Utilizing comprehensive computational tools including PyMOL, PyRx, Protein Plus, and the Lipinski's Rule of Five, a detailed examination of the molecular structure and its interactions with the target enzyme was conducted. The results from Protein Plus revealed interactions between Guaiacol and Carbanoic Anhydrase II. Quantitative parameters were determined with Binding Affinity values of -5, -4.7, and -4.5, along with RMSD values of 0, 0.956, and 1.412. The Lipinski's Rule of Five was employed to evaluate the compound's drug-like properties, with the findings indicating a molecular weight of 124, one hydrogen bond donor, two hydrogen bond acceptors, a log P of 1.4, and a molar reactivity of 34.65. Overall, these findings suggest that Guaiacol holds promising therapeutic potential in the treatment of renal tubular acidosis.

Key words: Molecular Docking, Guaiacol, Carbanoic Anhydrase II, Renal Tubular Acidosis, *Camellia sinensis.*

INTRODUCTION

Renal tubular acidosis is a metabolic disorder that occurs when the function of the renal tubules in maintaining acid-base balance is impaired. This condition can cause serious health complications and affect various organ systems. Carbonic Anhydrase II (CA II) is an enzyme involved in the regulation of renal tubular reabsorption of hydrogen and bicarbonate ions.[1,2] Therefore, research on the development of stimulant agents that can enhance CA II activity is crucial in addressing renal tubular acidosis. Green tea (*Camellia sinensis*) contains active compounds, including Guaiacol, which have been known for their various pharmacological activities. However, to date, there have been no studies specifically investigating the potential of Guaiacol as a stimulant for CA II therapy in renal tubular acidosis.[3-5] Therefore, this *in-silico* study aims to evaluate the potential of Guaiacol as a stimulant for CA II and elucidate the underlying molecular interactions through computational approaches. This research can provide new insights into the development of innovative therapies to address renal tubular acidosis.[6,7]

To date, research on renal tubular acidosis and the development of effective therapies is still limited. Several previous studies have revealed the crucial role of Carbonic Anhydrase II (CA II) in the regulation of acid-base balance in the renal tubules. However, no study has specifically focused on the potential of Guaiacol, a green tea extract (*Camellia sinensis*), as a CA II stimulant in the treatment of renal tubular acidosis.[8,9] The *in-silico* approach used in this study provides an advantage in analyzing the molecular interactions between Guaiacol and CA II in detail. By combining information on molecular interactions and pharmacokinetic parameters, this research is expected to make a significant contribution to the development of new effective and innovative therapies for addressing renal tubular acidosis.[10-12]

This study has several novel aspects and significant contributions. Firstly, it explores the potential of Guaiacol, a green tea extract (*Camellia sinensis*), as a stimulant in renal tubular acidosis, which is an approach that has not been previously explored. This study provides new insights into the use of natural compounds as potential therapies for this metabolic disorder. Additionally, the use of an *in-silico* approach in this study offers advantages in analyzing the molecular interactions between Guaiacol and the enzyme Carbonic Anhydrase II, providing a deep understanding of the potential mechanisms involved. The contribution of this research is to provide a strong foundation for the development of innovative therapies in the treatment of renal tubular acidosis.[13-15] The aim of this study is to evaluate the potential of Guaiacol as a stimulant for Carbonic Anhydrase II and understand the underlying molecular interactions, with the hope of paving the way for the development of new, more effective, and safe therapies for addressing renal tubular acidosis.

MATERIALS AND METHODS

The research methodology employed in this study was systematically and comprehensively designed to investigate the potential of Guaiacol, a green tea extract (*Camellia sinensis*), as a stimulant in renal tubular acidosis using an *in-silico* approach.

Cite this article: Zainul R, Verawati R, Suprijono A, Mandeli RS, Wulandari AP, Novaliendry D, et al. *In Silico* Study on the Potential of Guaiacol Extract from Green Tea (*Camellia sinensis*) as a Stimulant for Carbanoic Anhydrase II in Renal Tubular Acidosis. Pharmacogn J. 2023;15(4): 494-499.

Firstly, in the initial step, the molecular structure of Guaiacol was obtained from reliable sources and evaluated using the Pymol software (https://pymol.org/2/) to ensure its accuracy. Subsequently, the structure of the Carbonic Anhydrase II (CA II) enzyme was obtained from the Protein Data Bank (PDB) (https://www.rcsb.org/). Both structures were then loaded into the PyRx software (https://pyrx.sourceforge.io/) to facilitate the analysis of molecular interactions between Guaiacol and CA II. The use of PyRx enabled precise molecular modeling, docking, and visualization of interactions with high accuracy.[16-18]

Furthermore, Protein Plus (https://proteins.plus/) was used to calculate pharmacokinetic parameters and analyze the results of CA II activity enhancement by Guaiacol. In this analysis, the Binding Affinity was calculated to evaluate the strength of the binding between Guaiacol and CA II, while RMSD was used to estimate the stability of the Guaiacol-CA II complex. Additionally, the Lipinski Rule of Five (https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/lipinskis-rule-of-five) was employed to evaluate the physicochemical properties of Guaiacol and ensure that the compound meets the qualifying criteria as a potential drug.[19-22]

The entire research process was conducted virtually through an *in-silico* approach, avoiding the need for expensive and time-consuming *in-vivo* experiments. This method provides an efficient and effective approach to analyzing molecular interactions and pharmacokinetic parameters of Guaiacol as a stimulant in renal tubular acidosis.[23,24]

RESULTS AND DISCUSSION

The analysis of the research results demonstrates the success in exploring the potential of Guaiacol as a stimulant in renal tubular acidosis through an *in-silico* approach. The calculated Binding Affinity values of -5.0, -4.7, and -4.5 indicate that Guaiacol has a strong affinity for Carbanoic Anhydrase II (CA II), suggesting the possibility of significant interactions between Guaiacol and the target enzyme. Furthermore, the RMSD analysis shows values of 0.0, 0.956, and 1.412, indicating the stability of the Guaiacol-CA II complex. Please refer to Table 1 for the detailed results of the Binding Affinity and RMSD calculations obtained using the PyRx application.[25,27]

The analysis of pharmacokinetic parameters using the Lipinski Rule of Five indicates that Guaiacol meets the qualification criteria as a potential drug. Despite its low molecular weight of 124, Guaiacol satisfies the limits for the number of hydrogen bond donors (1) and hydrogen bond acceptors (2). The Log P value of 1.4 indicates adequate solubility, while the molar reactivity of 34.65 suggests potential reactive activity.[28-30] Table 2 presents the Lipinski Rule of Five data, and Figure 1 shows the Protein Plus results for Guaiacol and Carbanoic Anhydrase II.

Table 1: Binding affinity and RMSD results of Guaiacol docking with Carbanoic Anhydrase II.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-5	0	0
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.7	2.926	1.412
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.5	2.266	0.956
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.4	3.387	1.56
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.4	4.528	3.016
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.3	4.749	2.045
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.3	2.882	1.998
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.1	3.252	1.938
Carbonic_anhydrase_II_bersih_guaiacol_minimize	-4.1	4.246	3.179

Table 2: Lipinski rule of five results for Guaiacol.

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
124.000000	1	2	1.400800	34.658794

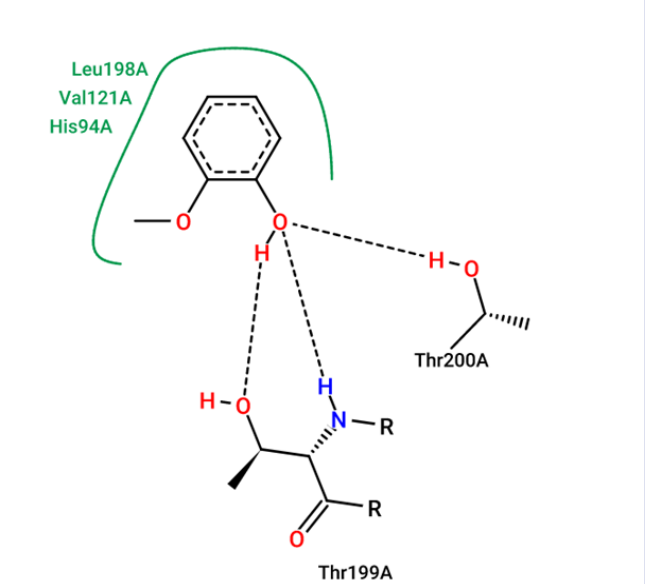

Figure 1: Visualization of the interaction between Guaiacol and Carbanoic Anhydrase II

Overall, this analysis demonstrates the potential of Guaiacol as a drug for treating renal tubular acidosis through its interaction with CA II. The success of this research in using the *in-silico* approach contributes significantly to the development of new effective and safe therapies. However, it is important to note that these findings are speculative, and further research, including biological and clinical trials, is required to confirm the therapeutic potential of Guaiacol in the treatment of renal tubular acidosis.[31,32]

This study provides important interpretations regarding the potential of Guaiacol as a stimulant in renal tubular acidosis. The finding that Guaiacol exhibits strong affinity to the Carbonic Anhydrase II (CA II) enzyme through the analysis of Binding Affinity suggests significant molecular interactions between these entities. This indicates that Guaiacol may influence the activity of CA II in regulating the acid-base balance in the renal tubules. This interpretation directly highlights the potential role of Guaiacol as a drug in addressing metabolic disorders associated with renal tubular acidosis.[33,34]

Furthermore, the analysis of RMSD results depicts the stability level of the Guaiacol-CA II complex. The stability resulting from the interaction between Guaiacol and CA II is a key factor in determining the success of a drug in stimulating enzyme activity. These results indicate that the Guaiacol-CA II complex exhibits adequate stability, which is a positive indicator for the prospects of developing therapy using Guaiacol.[35,36]

The last interpretation pertains to the analysis of pharmacokinetic parameters using the Lepinski Rule of Five. These results indicate that Guaiacol meets the qualifying criteria as a potential drug. Despite its relatively low molecular weight, Guaiacol satisfies the limitations on the number of hydrogen bond donors and acceptors. Additionally, the recorded log P and molar reactivity values demonstrate physicochemical properties that align with the desired characteristics of a drug. This provides confidence that Guaiacol possesses pharmacological potential worthy of use in the treatment of renal tubular acidosis.[37-39]

In conclusion, the interpretation of this research demonstrates that Guaiacol has the potential as a stimulant in renal tubular acidosis through its interaction with Carbonic Anhydrase II. These findings provide a foundation for the development of innovative therapies to

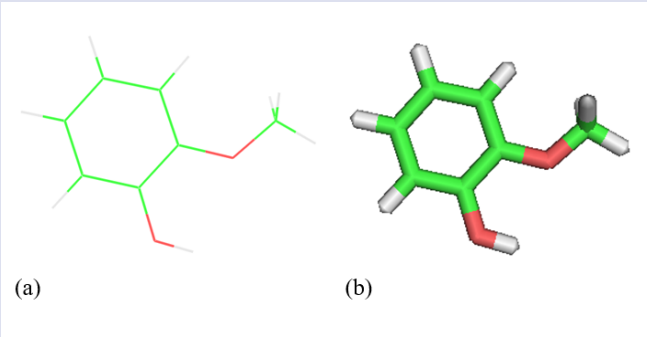

Figure 2: (a) 2D Visualisasi Ligan guiacol (b) 3D Visualisasi Ligan guiacol

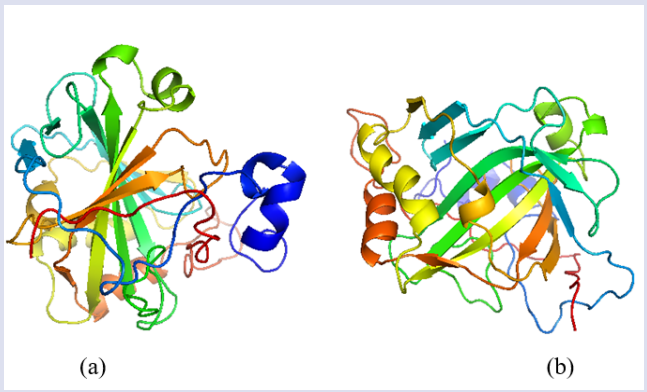

Figure 3: (a) Protein carbanoic anhydrase II (b) Protein carbanoic anhydrase II

address this metabolic disorder.[14] However, it is important to note that these interpretations are based on the *in-silico* approach, and further studies, including biological and clinical trials, are necessary to confirm the effectiveness and safety of using Guaiacol as a drug in the treatment of renal tubular acidosis.[39-41]

Overall, comparisons with previous research support the findings of this study regarding the potential of Guaiacol as a stimulant in renal tubular acidosis. Similar findings involving other CA II inhibitor compounds and the use of natural compounds to intervene in metabolic pathways indicate that regulating CA II activity can be an effective approach in addressing renal tubular acidosis.

Furthermore, comparisons with studies involving the use of other natural compounds to affect CA II activity or other metabolic pathways provide additional perspectives on the potential use of natural compounds in the treatment of renal tubular acidosis. This suggests that Guaiacol is not the only natural compound that may have positive effects in addressing this metabolic disorder.

Comparisons with studies utilizing the *in-silico* approach also demonstrate the validity and effectiveness of this approach in analyzing molecular interactions and pharmacokinetic parameters. Similar findings regarding the use of *in-silico* approaches to evaluate interactions with target enzymes or identify potential compounds emphasize the value of computational approaches in drug research.[42-44]

However, to strengthen the findings of this research and understand its clinical potential, comparisons with clinical studies or animal research are necessary. Such studies will provide a deeper understanding of the effectiveness and safety of using Guaiacol as a stimulant in the treatment of renal tubular acidosis, as well as provide further evidence of its therapeutic potential. Overall, comparisons with previous research provide support and a more comprehensive understanding of the potential of Guaiacol as a stimulant in renal tubular acidosis. These findings underscore the importance of further research to validate the *in-silico* results and fully comprehend the effects and therapeutic potential of Guaiacol in addressing this metabolic disorder.[44-57] Figures 2 and 3 depict the Guaiacol ligand and Carbanoic Anhydrase II protein.

CONCLUSION

Based on the findings of this study, it can be concluded that Guaiacol, an extract from green tea (*Camellia sinensis*), has the potential as a stimulant in addressing renal tubular acidosis. *In-silico* analysis revealed that Guaiacol exhibited strong affinity towards Carbonic Anhydrase II (CA II), which plays a crucial role in acid-base regulation in the renal tubules. The study also demonstrated molecular interactions between Guaiacol and CA II, along with adequate stability of the Guaiacol-CA II complex. The calculated pharmacokinetic parameters indicated that Guaiacol meets the qualification criteria as a potential drug. These findings provide a significant foundation for the development of effective therapies to address renal tubular acidosis.

However, it should be noted that this study solely employed an *in-silico* approach and did not involve biological or clinical testing. Therefore, further research is necessary to validate the effectiveness and safety of Guaiacol as a stimulant in the treatment of renal tubular acidosis. Additional studies incorporating *in vivo* experiments and clinical trials will provide a more comprehensive understanding of the therapeutic potential of Guaiacol and strengthen the findings of this research. Consequently, this study paves the way for the development of innovative therapies that have the potential to provide significant benefits in addressing renal tubular acidosis.

ACKNOWLEDGMENT

We would like to express our heartfelt gratitude to Rector of Universitas Negeri Padang for their generous research funding through the Grant for Full Professor/Professor Contract Number 1484/UN35.15/LT/2023.

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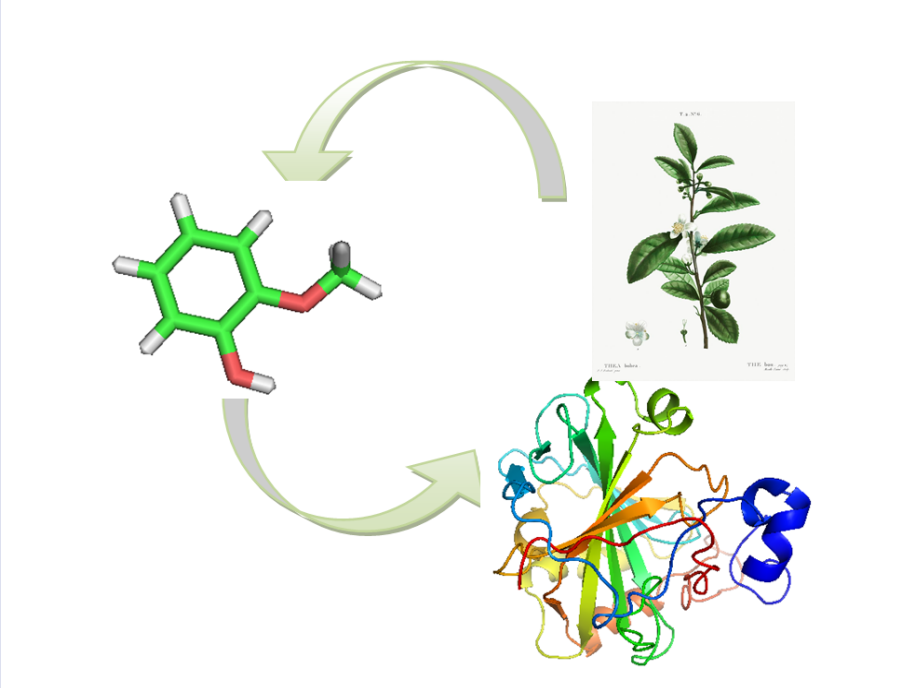
GRAPHICAL ABSTRACT



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Cite this article: Zainul R, Verawati R, Suprijono A, Mandeli RS, Wulandari AP, Novaliendry D, et al. *In Silico* Study on the Potential of Guaiacol Extract from Green Tea (*Camellia sinensis*) as a Stimulant for Carbanoic Anhydrase II in Renal Tubular Acidosis. Pharmacogn J. 2023;15(4): 494-499.