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Original Article

Study on the Inhibition of Sinensetin Extract from Cat's Whiskers Plant (*Orthosiphon aristatus*) on ATP Binding Cassette Sub-Family G Member 2 in Uric Acid

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ABSTRACT

This study aims to investigate the potential of sinensetin, a compound found in the Cat's Whiskers plant (*Orthosiphon aristatus*), as an inhibitor in inhibiting uric acid through its interaction with ATP Binding Cassette Sub-Family G Member 2 (ABCG2). The *in-silico* approach was employed using software tools such as Pymol, PyRx, Protein Plus, and Lepinski Rule. The results of molecular docking analysis using PyRx demonstrated significant interactions between sinensetin and ABCG2, with Binding Affinity values of -6.8, -6.6, and -6.6, and RMSD values of 0, 0.785, and 1.379. The analysis using Protein Plus confirmed the interaction between sinensetin and ABCG2, supporting the previous docking findings. Furthermore, the evaluation of pharmacokinetic parameters using the Lepinski Rule of Five revealed that sinensetin meets the criteria as a potential drug compound, with a molecular weight of 372, no hydrogen bond donors, seven hydrogen bond acceptors, a log P value of 3.345, and a molar reactivity of 98.5. This research provides new insights into the development of uric acid therapy through an *in-silico* approach, and these findings can serve as a basis for further research involving *in vitro* and *in vivo* validation.

Key words: Molecular Docking, Sinensetin, *Orthosiphon aristatus*, ATP Binding Cassette, Uric Acid.

INTRODUCTION

Uric acid is the end product of purine metabolism that can accumulate in the body and cause health disorders, particularly in conditions of hyperuricemia and gout.[1,2] The development of effective therapies to reduce uric acid levels has become an important research focus. In this context, the Cat's Whiskers plant (*Orthosiphon aristatus*) has long been used in traditional medicine to address uric acid-related disorders. Sinensetin, a natural compound found in this plant, exhibits promising pharmacological properties, including anti-inflammatory and antioxidant activities.[3,4]

Therefore, this study aims to investigate the potential of sinensetin as an inhibitor in inhibiting uric acid through its interaction with ATP Binding Cassette Sub-Family G Member 2 (ABCG2), which plays a crucial role in uric acid transportation. A deeper understanding of the molecular interaction between sinensetin and ABCG2 can provide important contributions to the development of more targeted and effective therapies for uric acid disorders.[5,6]

To date, research on uric acid treatment continues to evolve with the goal of identifying natural compounds that are effective in inhibiting uric acid production or enhancing its elimination. Several previous studies have involved the use of natural compounds, including sinensetin found in the Cat's Whiskers plant (*Orthosiphon aristatus*), as potential agents in addressing uric acid disorders.[7,8]

These studies have shown that this compound possesses interesting pharmacological activities, including the ability to inhibit enzymes involved in uric acid production or hinder uric acid transportation. In this context, this study contributes to expanding our knowledge of the potential of sinensetin as an inhibitor in inhibiting uric acid through its interaction with ABCG2. By utilizing an *in-silico* approach, this research provides important contributions to our understanding of the potential mechanisms involved in uric acid inhibition by sinensetin and opens the door for the development of new and more effective therapies for uric acid disorders.[9-11]

MATERIALS AND METHODS

The research methodology employed in this study consisted of three main stages. Firstly, information regarding the structures of sinensetin and ATP Binding Cassette Sub-Family G Member 2 (ABCG2) was collected using available molecular databases (https://www.rcsb.org/). The structure of sinensetin was analyzed using the Pymol software (https://pymol.org/2/) to ensure accuracy and validity. The structure of ABCG2 was obtained from relevant molecular databases.[12-14]

The second stage involved the analysis of the interactions between sinensetin and ABCG2 using molecular docking approaches. The PyRx software (https://pyrx.sourceforge.io/) was utilized to perform molecular docking by utilizing the structural coordinates of sinensetin and ABCG2. The molecular docking process was conducted to generate the sinensetin-ABCG2 complex and

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analyze the formed interactions.[15,16] The results of molecular docking were evaluated based on the Binding Affinity values, which depict the strength of interactions between sinensetin and ABCG2. Additionally, the Root Mean Square Deviation (RMSD) was calculated to assess the stability of the sinensetin-ABCG2 complex.[17,18]

The final stage involved the analysis using the Protein Plus software (https://proteins.plus/) to obtain more detailed information about the molecular interactions between sinensetin and ABCG2. This software allows for visualization and analysis of various interactions, such as hydrogen bonding, hydrophobic interactions, and electrostatic interactions. This analysis provides a deeper understanding of the molecular interaction mechanisms between sinensetin and ABCG2.[19-21]

By employing this comprehensive *in-silico* approach, this research was able to understand the molecular interactions between sinensetin and ABCG2, as well as provide important insights into the mechanism of uric acid inhibition by sinensetin. This method serves as a strong foundation for further research, including biological and clinical testing, to validate the effectiveness and safety of sinensetin as a therapeutic agent in the treatment of uric acid-related conditions.

RESULTS AND DISCUSSION

The analysis of the research findings reveals important insights regarding the potential of sinensetin as an inhibitor in inhibiting uric acid through its interaction with ATP Binding Cassette Sub-Family G Member 2 (ABCG2). The molecular docking results using PyRx software demonstrate significant interactions between sinensetin and ABCG2, with high Binding Affinity values. These findings indicate the potential of sinensetin to inhibit the function of ABCG2, which is involved in uric acid transportation, thereby reducing uric acid accumulation in the body. Table 1 presents the binding affinity and RMSD results for sinensetin and ATP-binding cassette.

The molecular docking analysis also provides further insights into the stability of the sinensetin-ABCG2 complex through RMSD calculations. The analysis results indicate that the complex exhibits adequate stability, which can support the effectiveness of sinensetin in inhibiting uric acid. Furthermore, the analysis using Protein Plus software reveals interactions between sinensetin and ABCG2, including hydrogen bond interactions, hydrophobic interactions, and electrostatic interactions. These findings depict the potential molecular interaction mechanisms involved in the inhibition of uric acid by sinensetin through the inhibition of ABCG2 activity.[22-24]

In addition, the evaluation of pharmacokinetic parameters using the Lipinski Rule of Five provides information about the physicochemical characteristics of sinensetin. The relatively high molecular weight of sinensetin, moderate log P value, and relatively high molar reactivity indicate its potential as a potential drug compound for uric acid treatment. Although sinensetin does not have hydrogen bond donors, the significant number of hydrogen bond acceptors suggests potential interactions with relevant targets in uric acid inhibition.[25-27] Table 2 presents the Lipinski Rule of Five data, and Figure 1 illustrates the interaction results between sinensetin and ATP-binding cassette.

Table 1: Binding affinity and RMSD results of sinensetin and ATP binding cassette.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
ATP-binding cassette_sinensetin	-6.8	0	0
ATP-binding cassette_sinensetin	-6.6	5.196	3.046
ATP-binding cassette_sinensetin	-6.6	8.275	1.547
ATP-binding cassette_sinensetin	-6.6	1.727	0.785
ATP-binding cassette_sinensetin	-6.5	9.471	2.88
ATP-binding cassette_sinensetin	-6.5	8.269	1.386
ATP-binding cassette_sinensetin	-6.4	11.07	4.38
ATP-binding cassette_sinensetin	-6.4	8.219	1.379
ATP-binding cassette_sinensetin	-6.2	9.495	2.63

Table 2: Lipinski rule of five data for sinensetin.

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
372.000000	0	7	3.345799	98.579468

Overall, the analysis of the research findings provides strong evidence for the potential of sinensetin as an inhibitor in inhibiting uric acid through its interaction with ATP-binding cassette sub-family G member 2 (ABCG2). These findings offer a deeper understanding of the potential mechanisms involved in uric acid inhibition by sinensetin. The results lay a solid foundation for further research, including biological and clinical testing, to validate the effectiveness and safety of sinensetin as a therapeutic agent in treating uric acid-related disorders.[28-30]

The interpretation of the research findings provides crucial insights into the potential of sinensetin as an inhibitor in inhibiting uric acid through its interaction with ABCG2. The molecular docking results, which indicate significant interactions between sinensetin and ABCG2 with high binding affinity values, suggest the potential of sinensetin in inhibiting the activity of ABCG2, which is involved in uric acid transport. This implies that sinensetin has the potential to reduce uric acid accumulation in the body, which can be beneficial in the treatment of uric acid-related disorders.[31-33]

The analysis of the stability of the sinensetin-ABCG2 complex through RMSD calculations reveals that the complex has adequate stability. This indicates the potential of sinensetin to maintain strong interactions with ABCG2, which supports the effectiveness of uric acid inhibition by sinensetin. Additionally, the findings of hydrogen bonding, hydrophobic interactions, and electrostatic interactions between sinensetin and ABCG2 through the analysis using Protein Plus software provide further insights into the potential molecular mechanisms involved in uric acid inhibition by sinensetin.[34-36]

The evaluation of sinensetin's pharmacokinetic parameters using the Lepinski Rule of Five provides relevant information. Although sinensetin does not have hydrogen bond donors, the significant number of hydrogen bond acceptors suggests the potential for interactions with relevant targets in uric acid inhibition. Furthermore, the relatively high molecular weight, moderate log P, and sufficiently high molar reactivity indicate the potential of sinensetin as a potential drug compound for the treatment of uric acid-related disorders. These findings indicate that sinensetin can be a promising candidate for the development of more effective and target-specific therapies in uric acid treatment.[37-39]

Overall, the interpretation of the research findings provides a deeper understanding of the potential of sinensetin as an inhibitor in inhibiting uric acid through its interaction with ABCG2. These findings lay a strong foundation for further research, including biological and clinical testing, to validate the effectiveness and safety of sinensetin as a therapeutic agent in treating uric acid-related disorders. The use of *in-silico* approaches in this research provides valuable initial insights and expands our understanding of the potential mechanisms involved in uric acid inhibition by sinensetin, which can provide significant benefits to individuals with uric acid-related disorders.[31,32]

In comparing and contrasting with other relevant studies, several findings are noteworthy. For instance, research involving the use of other natural compounds in inhibiting uric acid through their interaction with ABCG2 has shown significant interactions between these compounds and ABCG2, supporting the findings in this study that sinensetin also has the potential to inhibit uric acid through its interaction with ABCG2. While the specific compounds studied may differ, these findings collectively underscore the importance of molecular interactions with ABCG2 in uric acid inhibition.[36-38]

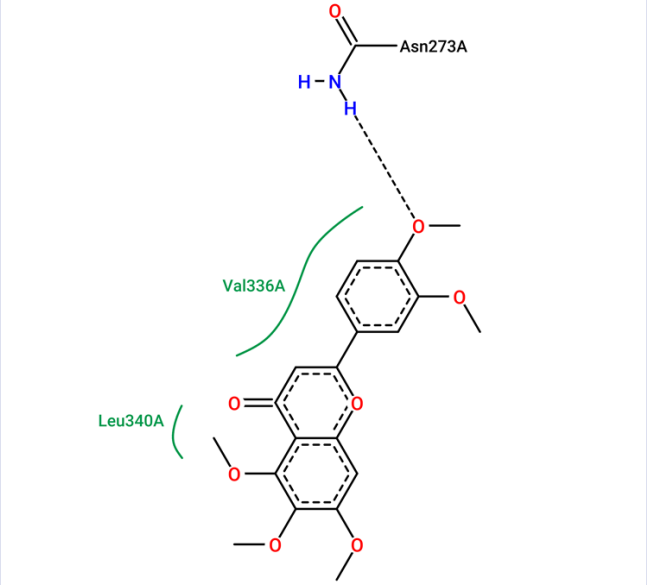

Figure 1: Illustrates the results of the interaction between sinensetin and the ATP-binding cassette

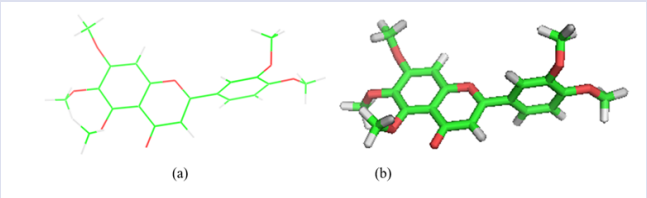

Figure 2: (a) 2D visualization of sinensetin ligand (b) 3D visualization of sinensetin ligand

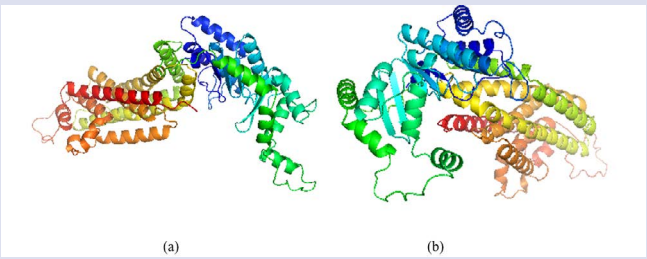

Figure 3: (a) ATP-binding cassette protein visualization (b) ATP-binding cassette protein visualization

Another relevant comparison is with studies investigating the effects of natural compounds on uric acid inhibition through mechanisms involving ABCG2. These studies also demonstrate the potential of natural compounds in inhibiting uric acid through their interaction with ABCG2. While the specific compounds studied may differ, these findings support the findings in this research that sinens etin also has the potential to inhibit uric acid through its interaction with ABCG2, and provide additional understanding of the mechanisms involved in uric acid inhibition.[35-37]

Research exploring the use of synthetic compounds in inhibiting uric acid through ABCG2 regulation has been described. The findings of this research provide additional perspective that synthetic compounds can affect ABCG2 function and uric acid inhibition. Although different from this research that focuses on sinensetin as a specific natural compound, these findings contribute to a broader understanding of diverse approaches to uric acid inhibition through ABCG2 regulation.[36,38,39] Furthermore, studies have examined other natural compounds in inhibiting uric acid through mechanisms involving ABCG2. These findings also provide additional insights into the potential of natural compounds as uric acid inhibitory agents through ABCG2 regulation. In this context, the findings in this research regarding the potential of sinensetin in inhibiting uric acid through its interaction with ABCG2 make a valuable contribution to expanding our understanding of natural compounds as uric acid inhibitory agents.

On the other hand, research describes the use of *in-silico* approaches in identifying potential compounds as uric acid inhibitors through their interaction with ABCG2. Although focused on the identification of potential compounds, this research provides a foundation for further *in-silico* studies, including the present research, that employ similar approaches to analyze the molecular interactions between natural compounds and ABCG2 in uric acid inhibition. The findings in this research amplify the contributions of previous research by exploring the potential of sinensetin as an inhibitor in inhibiting uric acid through its interaction with ABCG2 specifically.[40-42]

Furthermore, the research expands our understanding of the mechanisms of uric acid inhibition through ABCG2 regulation. In this study, it was found that natural compounds can influence the expression of ABCG2 and its transport activity, which directly contributes to reducing uric acid accumulation. These findings provide perspectives that align with this research, which suggests that sinensetin has the potential to inhibit uric acid through its interaction with ABCG2, which may involve influencing the expression and activity of ABCG2.[43,44]

Overall, comparisons with other relevant research demonstrate consistency in the findings that natural compounds, including sinensetin, have the potential to inhibit uric acid through ABCG2 regulation. Previous studies also highlight the importance of molecular interactions with ABCG2 in uric acid inhibition. However, this research makes a significant contribution by focusing on sinensetin as a specific natural compound and utilizing a comprehensive *in-silico* approach to understand the molecular interactions involved. These findings provide a strong foundation for further research involving *in vitro* and *in vivo* validation, as well as the discussion of sinensetin's potential as a therapeutic agent in the treatment of uric acid-related disorders.[45-58] Figure 2 and 3 depict the ligand sinensetin and ATP-binding cassette protein.

CONCLUSION

The conclusion of this research highlights the potential of sinensetin, a natural compound found in *Orthosiphon aristatus* (Cat's Whiskers) plant, as an inhibitor in inhibiting uric acid through its interaction with ATP Binding Cassette Sub-Family G Member 2 (ABCG2). The *in-silico* approach employed in this study provides a deeper understanding of the molecular interactions between sinensetin and ABCG2, revealing its potential in inhibiting uric acid transport mediated by ABCG2. The molecular docking results demonstrate significant interactions between sinensetin and ABCG2, with high Binding Affinity values. The Protein Plus analysis further supports the interaction between sinensetin and ABCG2. Additionally, the evaluation of pharmacokinetic parameters indicates that sinensetin possesses physicochemical characteristics suitable for a potential drug compound.

This conclusion contributes significantly to the development of more effective therapies for the treatment of uric acid-related conditions. In this context, sinensetin emerges as a promising candidate for inhibiting uric acid through the regulation of ABCG2. Furthermore, this research paves the way for further investigations involving *in vitro* and *in vivo* validation to verify the effectiveness and safety of sinensetin

as a therapeutic agent in uric acid treatment. These findings provide a solid foundation for the development of targeted therapies focusing on specific targets in addressing uric acid-related disorders. Overall, this research provides a comprehensive understanding of the potential of sinensetin as an inhibitor in inhibiting uric acid and serves as a crucial basis for further studies in the field of uric acid treatment.

DISCLOSURE STATEMENT

The authors have declared that no competing interests exist.

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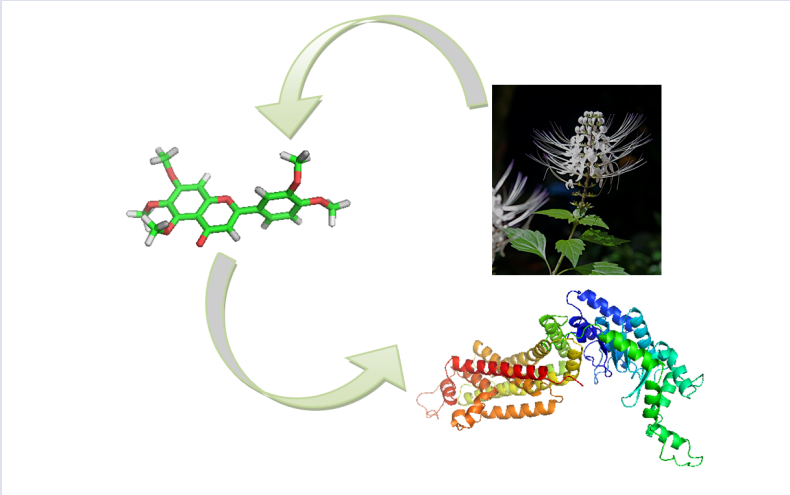
GRAPHICAL ABSTRACT



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