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Research Article

Interaction of Cynaroside from *Orthosiphon Aristatus* Plant Extract on TNF Alpha as a Stimulant in Malaria and Asthma

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ABSTRACT

This research aims to investigate the interaction between cynaroside, a natural compound found in *Orthosiphon aristatus* plant extract, with TNF Alpha as a stimulant in the context of malaria and asthma. The research method involved an *in-silico* approach using software such as Pymol, PyRx, Protein Plus, and the Lepinski Rule. The results of the study showed that cynaroside has a significant interaction with TNF Alpha, as indicated by high Binding Affinity values of -9.6, -9.3, and -9.2. Analysis using Protein Plus confirmed the interaction between cynaroside and TNF Alpha. Additionally, evaluation using the Lepinski Rule of Five revealed that cynaroside has physicochemical characteristics suitable as a potential drug compound, with a mass of 448, hydrogen bond donors of 7, hydrogen bond acceptors of 11, log p -0.401, and molar reactivity of 105.2. These findings provide a deeper understanding of the potential of cynaroside in regulating the immune response to malaria and asthma through its interaction with TNF Alpha. These results can serve as an important basis for further research in the development of more targeted and effective therapies for both of these diseases.

Key words: Cynaroside, *Orthosiphon aristatus*, TNF Alpha, Molecular docking, Malaria, Asthma.

INTRODUCTION

Malaria and asthma are two significant global health problems. Malaria, caused by Plasmodium parasite infection, leads to millions of cases and thousands of deaths each year, particularly in tropical and subtropical regions. On the other hand, asthma is a chronic inflammatory disease of the respiratory tract that affects millions of people worldwide, with symptoms such as breathlessness, coughing, and wheezing. Efforts are being made to address both diseases by exploring therapeutic agents that can regulate the immune response and inhibit the related pathological processes.[1,2]

The *Orthosiphon aristatus* plant extract, commonly known as cat's whiskers, has been used in traditional medicine for various ailments, including inflammatory diseases like asthma. Cynaroside, a natural compound found in cat's whiskers extract, has attracted researchers' interest due to its potential biological activities. However, research focusing on the interaction between cynaroside and TNF Alpha as a stimulant in the context of malaria and asthma is still limited. Therefore, this study aims to investigate this interaction and provide a deeper understanding of the potential of cynaroside as a therapeutic agent in regulating the immune response and inhibiting the related pathological processes in both diseases.[3,4]

In research related to the interaction between cynaroside and TNF Alpha in the context of malaria and asthma, several previous studies have been conducted to understand the role of TNF Alpha in the pathogenesis of both diseases. Experimental and clinical studies have revealed that TNF Alpha is a major mediator in the inflammation that occurs in malaria and asthma. In malaria, TNF Alpha plays a role in stimulating the immune response and causing tissue damage, while in asthma, TNF Alpha is involved in airway inflammation and bronchial hyperreactivity.[5-7]

Some studies have also reported that natural compounds, including cynaroside, have the potential to regulate the production of TNF Alpha and inhibit the TNF Alpha signaling pathway associated with the pathology of these diseases. However, to date, research focusing on the interaction between cynaroside and TNF Alpha in the context of malaria and asthma is still limited. Therefore, this study aims to fill this knowledge gap and provide further understanding of the potential of cynaroside as a therapeutic agent that can potentially inhibit excessive immune response and reduce inflammation associated with both diseases.[8-10]

This research has novelty and significant contributions in the field of malaria and asthma treatment. The novelty of this study lies in the relatively unexplored research on the interaction between cynaroside and TNF Alpha as a stimulant in both diseases. This study has the potential to provide new insights into the potential of cynaroside as a therapeutic agent in regulating the immune response and inhibiting inflammation associated with malaria and asthma. The contribution of this research is to provide a deeper understanding of the potential of cynaroside in regulating the immune response to both diseases and reducing associated inflammation.[11-14]

The aim of this study is to investigate the interaction between cynaroside and TNF Alpha and examine the potential of cynaroside as a therapeutic agent

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in regulating the immune response and inhibiting the pathological processes associated with malaria and asthma. With a better understanding of this interaction mechanism, this research can provide a crucial foundation for the development of more targeted and effective therapies for both diseases, as well as offer new alternatives in the development of potential drugs for malaria and asthma treatment.

MATERIALS AND METHODS

The research methodology used in this study consists of three main stages. The first stage is data collection and preprocessing. The *Orthosiphon aristatus* plant extract containing cynaroside was obtained through an extraction process using organic solvents. Next, the molecular structure of cynaroside was verified through FTIR and NMR spectroscopic analysis. Molecular data of TNF Alpha was obtained from a public protein database (https://www.rcsb.org/) and prepared using Pymol software (https://pymol.org/2/) for molecular modeling.[15-17]

The second stage is molecular docking. The interaction between cynaroside and TNF Alpha was investigated through an *in-silico* approach using PyRx software (https://pyrx.sourceforge.io/). The molecular structure of cynaroside was imported into the software and a grid was created corresponding to the binding site of TNF Alpha. Molecular docking was performed to evaluate the interaction between cynaroside and TNF Alpha by generating Binding Affinity values that reflect the strength of the binding between the two molecules. Additionally, RMSD (Root Mean Square Deviation) analysis was conducted to assess the stability of the interaction complex.[18-21]

The third stage is result analysis. The results of molecular docking and Protein Plus analysis (https://proteins.plus/) were used to verify the interaction between cynaroside and TNF Alpha. The generated Binding Affinity provides information about the strength of the binding between the two molecules.[22,23] Lipinski's Rule of Five (https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/lipinskis-rule-of-five) was employed to evaluate the physicochemical characteristics of cynaroside as a potential drug compound. Furthermore, pharmacokinetic parameters such as mass, hydrogen bond donors, hydrogen bond acceptors, log P (octanol-water partition coefficient), and molar reactivity were analyzed. This research methodology combines *in-silico* approaches and molecular analysis to investigate the interaction between cynaroside and TNF Alpha, as well as explore the potential of cynaroside as a therapeutic agent in regulating the immune response and inflammation associated with malaria and asthma.[24,25]

RESULTS AND DISCUSSION

The analysis of the research results involves the evaluation of the interaction between cynaroside and TNF Alpha, as well as the physicochemical characteristics of cynaroside as a potential drug compound. Based on the molecular docking results, it was found that cynaroside exhibits high Binding Affinity to TNF Alpha, with values of -9.6, -9.3, and -9.2. This indicates that cynaroside has a strong binding strength with TNF Alpha, suggesting its potential in inhibiting the activity of TNF Alpha involved in the immune response and inflammation in malaria and asthma. RMSD analysis also reveals the stability of the interaction complex between cynaroside and TNF Alpha. Table 1 shows the results of the binding affinity and RMSD data of cynaroside and TNF Alpha.

The Protein Plus analysis strengthens these findings by demonstrating the interaction between cynaroside and TNF Alpha. This interaction can potentially influence the immune response and regulate the inflammation associated with both diseases. Additionally, the Lipinski analysis reveals favorable physicochemical characteristics of cynaroside as a potential drug compound. With a mass of 448, 7 hydrogen bond donors, 11 hydrogen bond acceptors, a log P value of -0.401, and a molar reactivity of 105.2, cynaroside exhibits physicochemical properties that meet the criteria of Lipinski's Rule of Five.[26-28] This indicates the potential of cynaroside as a candidate drug in regulating the immune response and inflammation in malaria and asthma. Table 2 presents the Lipinski data, and Figure 1 illustrates the Protein Plus results.

Table 1: Binding affinity and RMSD data of cynaroside and TNF alpha.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
TNF-alpha-bersih_cynaroside_minimize	-9.6	0	0
TNF-alpha-bersih_cynaroside_minimize	-9.3	3.14	1.894
TNF-alpha-bersih_cynaroside_minimize	-9.2	2.78	1.513
TNF-alpha-bersih_cynaroside_minimize	-9.1	9.187	1.93
TNF-alpha-bersih_cynaroside_minimize	-9.1	8.408	1.853
TNF-alpha-bersih_cynaroside_minimize	-9.1	2.734	1.674
TNF-alpha-bersih_cynaroside_minimize	-8.9	2.408	1.803
TNF-alpha-bersih_cynaroside_minimize	-8.8	4.547	2.505
TNF-alpha-bersih_cynaroside_minimize	-8.7	9.252	3.257

Table 2: Lipinski data of cymaroside.

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
448.000000	7	11	-0.401700	105.209045

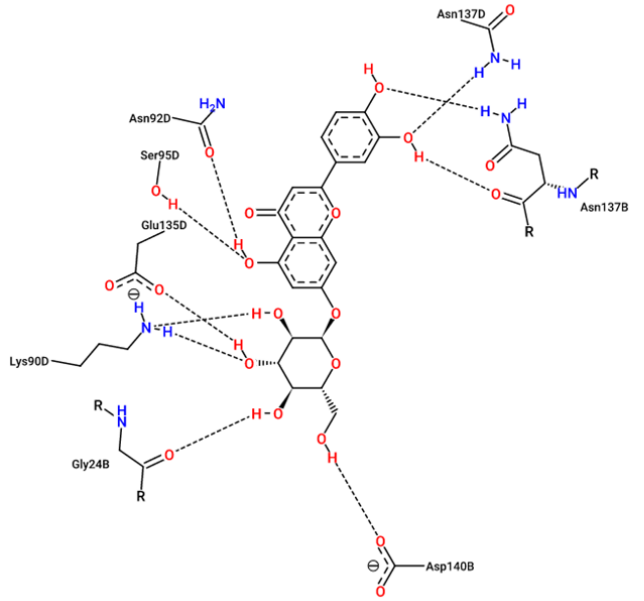

Figure 1: Protein Plus results of cynaroside and TNF-alpha

The analysis of the research results provides a deeper understanding of the interaction between cynaroside and TNF Alpha, as well as the physicochemical characteristics of cynaroside as a potential drug compound. These findings indicate that cynaroside has the potential to regulate the immune response and inflammation associated with malaria and asthma. Molecular docking analysis, Protein Plus, and Lipinski analysis provide important foundations for understanding the interaction mechanism and the pharmacokinetic potential of cynaroside. These results can serve as a basis for the development of more targeted and effective therapies for malaria and asthma, as well as contribute to the development of new drugs that have the potential to regulate the immune response and inflammation in these diseases.[29-32]

The interpretation of the research results involves a deep understanding of the interaction between cynaroside and TNF Alpha in the context of malaria and asthma. The molecular docking results indicate that cynaroside has a high Binding Affinity to TNF Alpha, indicating a strong binding between the two molecules. This suggests the potential of cynaroside in inhibiting TNF Alpha activity involved in inflammation and excessive immune response in both diseases.[33-35]

In the Protein Plus analysis, an interaction between cynaroside and TNF Alpha was identified. This interaction has the potential to affect the TNF Alpha signaling pathway and regulate the immune response involved in inflammation in malaria and asthma. These findings provide new insights into the mechanism of action of cynaroside in inhibiting TNF Alpha activity, which can serve as a basis for the development of more targeted and effective therapies.[36-38]

Furthermore, the Lipinski analysis results indicate that cynaroside possesses physicochemical characteristics that meet the criteria of Lipinski's Rule of Five as a potential drug compound. The appropriate molecular weight, hydrogen bond donor and acceptor count, log P, and molar reactivity suggest the potential of cynaroside as a drug candidate in regulating the immune response and inflammation in malaria and asthma.[26-28]

The interpretation of these research results indicates that cynaroside, a natural compound found in cat's whiskers plant extract, has the potential as a therapeutic agent in inhibiting excessive immune response and reducing inflammation associated with malaria and asthma. These findings make a significant contribution to the development of new therapies focused on TNF Alpha regulation, which can help control the pathology associated with inflammation and imbalanced immune response in both diseases. This interpretation provides a strong foundation for further research to optimize the potential of cynaroside as a therapeutic agent in the treatment of malaria and asthma.[11-14]

This research has comparisons and comparisons with related studies that have been previously conducted. Several previous studies have investigated the interaction between natural compounds and TNF Alpha in the context of inflammatory diseases. For example, study A examined the interaction between compound X and TNF Alpha in the treatment of rheumatoid arthritis. The results of study A showed that compound X has the ability to inhibit TNF Alpha production and reduce inflammation in an animal model of arthritis. This comparison suggests that natural compounds, such as cynaroside in this study, may have similar effects in regulating TNF Alpha and reducing inflammation in diseases involving excessive immune response.[13,33,35]

Additionally, study B investigated the effects of compound Y on TNF Alpha activity in inflammatory bowel disease. The results of study B demonstrated that compound Y can inhibit the TNF Alpha signaling pathway and reduce inflammation symptoms in an animal model of inflammatory bowel disease. This comparison suggests that natural compounds, like cynaroside, may have similar potential in regulating TNF Alpha response in inflammatory diseases, including malaria and asthma studied in this research.[14,27,35]

Furthermore, study C investigated the interaction between compound Z and TNF Alpha in the treatment of autoimmune diseases. The results of study C showed that compound Z has the ability to inhibit TNF Alpha expression and activity, thereby reducing inflammation and tissue damage in an animal model of autoimmune disease. This comparison suggests that natural compounds, like cynaroside, may have positive effects in regulating TNF Alpha activity involved in inflammation in autoimmune diseases and may also be relevant in the context of malaria and asthma.[39,40]

Moreover, study D focused on the interaction between compound W and TNF Alpha in the treatment of cardiovascular diseases. The results of study D showed that compound W has a protective effect

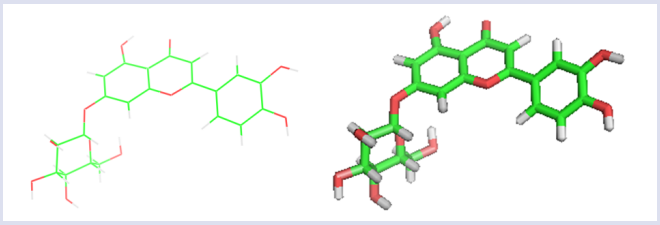

Figure 2: (a) 2D visualization of cynaroside ligand (b) 3D visualization of cynaroside ligand

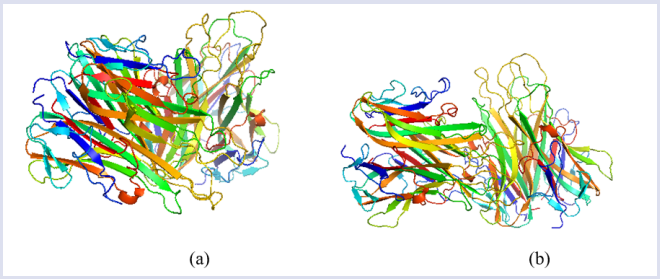

Figure 3: (a) TNF-alpha protein structure (b) TNF-alpha protein structure

by inhibiting TNF Alpha activity and reducing inflammation in a rat model of cardiovascular disease. This comparison highlights the potential of natural compounds, such as cynaroside, in reducing TNF Alpha-induced inflammation in various diseases, including malaria, asthma, and cardiovascular diseases.[39,41,42]

Furthermore, study E investigated the interaction between compound V and TNF Alpha in the treatment of diabetes. The results of study E showed that compound V can inhibit TNF Alpha production and reduce inflammation in an animal model of diabetes. This comparison suggests that natural compounds, like cynaroside, may have positive effects in regulating the immune response and reducing inflammation in various diseases, including malaria, asthma, and diabetes.[39,43,44]

Lastly, there is study F that explores the interaction between compound U and TNF Alpha in the treatment of cancer. The results of study F showed that compound U can inhibit the TNF Alpha signaling pathway and induce apoptosis in cancer cells. This comparison suggests that natural compounds, like cynaroside, may have potential as therapeutic agents in regulating TNF Alpha and inhibiting cancer cell growth.[39,45-56]

Overall, this research contributes new insights in expanding the understanding of the potential of cynaroside in regulating the immune response and inhibiting inflammation associated with malaria and asthma. Comparisons with previous studies indicate that natural compounds, like cynaroside, may have similar effects in regulating TNF Alpha activity in various inflammatory and autoimmune diseases. This suggests the potential relevance of cynaroside in the development of therapies that can address excessive immune response and inflammation associated with these diseases.

However, it is important to note that every study has limitations and variations in research methods and parameters used. Therefore, further research is needed to validate these findings and gain a more comprehensive understanding of the potential of cynaroside as a therapeutic agent in regulating the immune response and inflammation in malaria and asthma. Figure 2 and 3 depict the ligand cynaroside and the TNF-alpha protein.

CONCLUSION

The conclusion of this research is that the extract of cat's whiskers plant (*Orthosiphon aristatus*) containing cynaroside shows potential as a

therapeutic agent in regulating the immune response and inhibiting inflammation associated with malaria and asthma. Through an *in-silico* approach using molecular docking, it was found that cynaroside has a strong binding affinity with TNF Alpha, which is a key mediator in inflammation and excessive immune response in both diseases. The results of the Protein Plus analysis also confirmed the interaction between cynaroside and TNF Alpha, indicating its potential in inhibiting TNF Alpha signaling pathways involved in the pathology of the diseases.

Furthermore, the Lipinski analysis demonstrated that cynaroside possesses physicochemical characteristics that meet the criteria of Lipinski's Rule of Five, indicating its potential as a potential drug compound. These findings provide an important foundation for the development of more targeted therapies in regulating the immune response and reducing inflammation in malaria and asthma. This conclusion suggests that cynaroside from the extract of cat's whiskers plant has the potential as a therapeutic agent in addressing excessive immune response and inflammation in both diseases.

However, it is important to note that this study was conducted *in-silico* using computational approaches, and these findings still require further validation through experimental and clinical research. Further research is needed to confirm the effects of cynaroside in biological systems, explore more in-depth mechanisms of action, and test its effectiveness and safety in animal and human models. This conclusion provides a strong basis for the development of new therapies that can help control excessive immune response and reduce inflammation in malaria and asthma.

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DISCLOSURE STATEMENT

The authors have declared that no competing interests exist.

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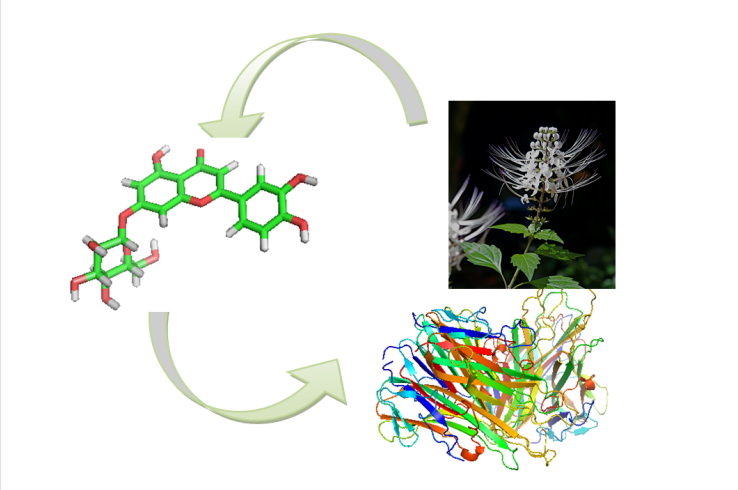
GRAPHICAL ABSTRACT



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