In Silico Study on the Inhibition of Sitogluside from Clove Plant (*Syzygium aromaticum*) on Interleukin 2 in B and T Cell Proliferation

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ABSTRACT

This research discusses an in-silico study of sitogluside found in the clove plant (*Syzygium aromaticum*) as a potential inhibitor of B and T cell proliferation through interaction with Interleukin-2. This study utilizes methods such as Swiss Target Prediction, Pymol, Pyrex, Protein Plus, and Lipinski's Rule to predict the biological activity and pharmacokinetic characteristics of sitogluside. From the docking simulation results, sitogluside exhibited strong interactions with interleukin-2 with RMSD values of 0, 1.637, and 2.299, and Binding Affinities of -5.7, -5.5, and -5.5, indicating its potential effectiveness as an inhibitor. In addition, sitogluside fulfills Lipinski's rule with a molecular mass of 520, 4 hydrogen bond donors and acceptors, a log P value of 2.3, and a molar reactivity of 133, indicating a high potential for good bioavailability in biological systems. These results suggest that sitogluside from the clove plant holds potential as a new therapy in inhibiting B and T cell proliferation, however further research is needed to validate these findings and explore its potential in clinical treatments.

Key words: Molecular Docking, Sitogluside, Cell Proliferation, Interleukin-2, Syzygium.

INTRODUCTION

B and T cell proliferation plays a crucial role in the body's immune response, but under certain conditions, such as autoimmune diseases and certain types of cancer, this proliferation can become uncontrolled and harmful. In an effort to find new effective treatments for these conditions, researchers have sought molecules capable of inhibiting B and T cell proliferation.[1-3] One primary target in this search is Interleukin-2 (IL-2), a cytokine that plays a crucial role in the growth and differentiation of B and T cells. Cloves (*Syzygium aromaticum*) are one of the plants long used in traditional medicine and known to contain various bioactive compounds. One compound found in cloves is sitogluside.[4,5]

In recent *in-silico* research, sitogluside, a compound found in the clove plant (*Syzygium aromaticum*), has been identified as a potential IL-2 inhibitor. This study employed various bioinformatics methods like Swiss Target Prediction, Pymol, Pyrex, Protein Plus, and Lipinski's rule to predict the biological activity and pharmacokinetic characteristics of sitogluside.[6,7] Sitogluside demonstrated strong interactions with IL-2 and fulfilled Lipinski's rule, indicating good potential for bioavailability in biological systems. Moreover, sitogluside's potential as an IL-2 inhibitor underscores the importance of further exploration of the therapeutic potential of the clove plant and other plants in the treatment of diseases involving immune system dysfunction.[8,9] Although phytotherapy research has been conducted for thousands of years, there are still many plants and natural compounds yet to be fully explored for their potential in treating human diseases.

The latest *in-silico* research on sitogluside as a potential interleukin-2 inhibitor shows promising results. Nevertheless, there are several crucial gaps that need to be addressed. First, *in-vitro* and *in-vivo* validation has not been performed. So far, research has only predicted the biological activity and pharmacokinetic characteristics of sitogluside, but it has not been verified through laboratory tests or animal models. Second, the precise mechanism of action of sitogluside as an IL-2 inhibitor is not fully understood.[10-12]

While the study identified strong interactions between sitogluside and IL-2, a deeper understanding of how sitogluside functions to inhibit T and B cell proliferation needs to be developed. Furthermore, no clinical trials have been conducted to ensure the effectiveness and safety of sitogluside in patients. All these gaps underline the need for further research to delve deeper into the potential of sitogluside.[13,14] This study showcases the novelty in identifying sitogluside, a compound found in the clove plant, as a potential Interleukin-2 (IL-2) inhibitor. The primary objective of this research is to explore the potential of sitogluside as a new therapy in inhibiting B and T cell proliferation, which could have significant applications in treating diseases involving hyperactivity or dysfunction of these cells, such as in cases of autoimmune diseases and cancer.

MATERIALS AND METHODS

Ligan-Protein preparation

Ligand-Protein Preparation At the initial stage of this research, sitogluside isolated from the clove plant (*Syzygium aromaticum*) was prepared for analysis. The chemical structure of sitogluside was analyzed and translated into a format suitable for

computational analysis using the Swiss Target Prediction software.[16,17] Subsequently, the 3D structure of interleukin-2 (IL-2) was also prepared. This structure data was obtained from the Protein Data Bank (https://www.rcsb.org/) and processed using Pymol and Pyrex to prepare the docking target. On the other hand, masilinic acid, a compound found in the clove plant (*Syzygium aromaticum*), was selected as the ligand based on its antiviral potential. The structural information of the ligand was taken from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/).

Molecular docking

Molecular Docking In the implementation phase, a molecular docking simulation was carried out between sitogluside and IL-2 using Protein Plus (https://proteins.plus/). This involved placing sitogluside into the IL-2 binding site and evaluating the interactions that occurred. The preparation process involved cleaning the structure, adding hydrogen atoms, and optimizing the geometry using the AutoDock Tools software (http://autodock.scripps.edu/). After preparation, molecular docking was performed using AutoDock Vina (http://vina.scripps.edu/), a software that can predict how and how strongly a ligand binds with a protein.[18-20]

Ligan-Protein interaction analysis

Ligand-Protein Interaction Analysis Visualization programs such as PyMOL (https://pymol.org/2/) were used to observe the interactions between sitogluside and the interleukin-2 protein. In the interpretation phase, the results obtained from the molecular docking simulation and pharmacokinetic prediction were interpreted. RMSD and Binding Affinity were used to assess the effectiveness of sitogluside as an IL-2 inhibitor. The lower the RMSD and the higher the Binding Affinity, the more effective sitogluside acts as an inhibitor. The pharmacokinetic profile predicted by Lipinski's rule (https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/lipinskis-rule-of-five) was used to assess whether sitogluside qualifies as a potential drug in terms of bioavailability.[21-25]

RESULTS AND DISCUSSION

PyMol is a molecular visualization tool often utilized in bioinformatics and structural research, including *in-silico* studies such as this one. In the context of this research, PyMol was employed for visualization and 3D structure analysis of Interleukin-2 (IL-2), the molecular target for sitogluside.[26-29] Figure 1a and 1b display the 3D visualization of the sitogluside ligand using the PyMol application.

Before being employed in the molecular docking process, the IL-2 protein required preprocessing to ensure only the relevant segments of the protein were analyzed. For instance, the structures downloaded from the Protein Data Bank (PDB) often contain water molecules, ions, or other molecules that might not contribute to the protein-ligand interaction. In PyMol, these components can be removed to purify the protein.[30-32]

Furthermore, proteins sometimes have more than one conformation or chain. In this scenario, the researcher needs to select which conformation or chain is most relevant to their docking study. This process, called protein purification, is critical for ensuring the molecular docking results accurately reflect the interaction between sitogluside and IL-2, rather than artifacts from irrelevant protein structures or other components that might be present in the PDB file.[33-36] Figures 2a and 2b display the unpurified state of the interleukin-2 protein, while figures 3a and 3b illustrate the interleukin-2 protein after purification in the PyMol application.

Protein Plus is a web-based tool used in this study for performing molecular docking processes between sitogluside (ligand) and Interleukin-2 (protein). The fundamental principle of molecular docking is to find the best position and orientation of the ligand when bound to the protein's active site. Using optimized algorithms, Protein Plus tests various ligand positions and conformations in the protein binding site and then scores them based on binding affinity and other interaction features.[37-40]
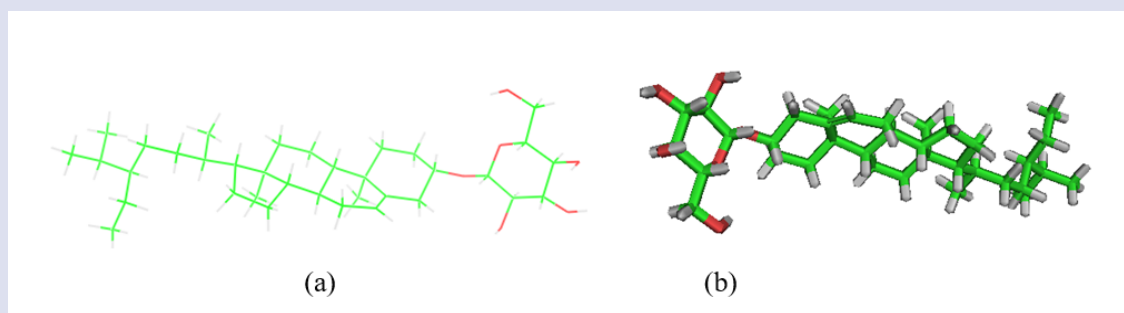

Figure 1: (a) 2D Visualization of Cytogluside Ligand (b) 3D Visualization of Cytogluside Ligand
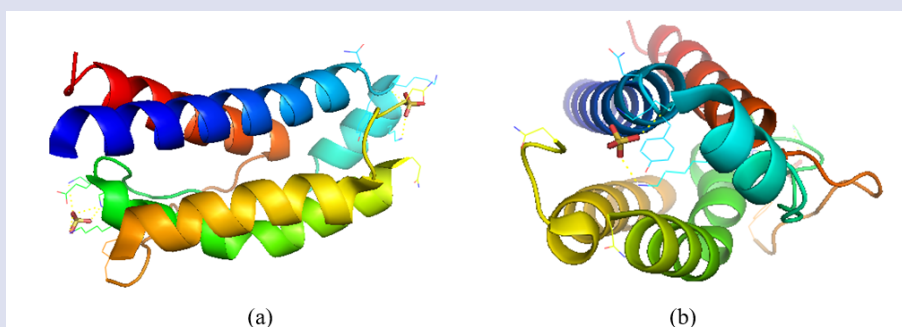

Figure 2: (a) Interleukin-2 Protein is not pure (b) Protein Interleukin-2 is not pure
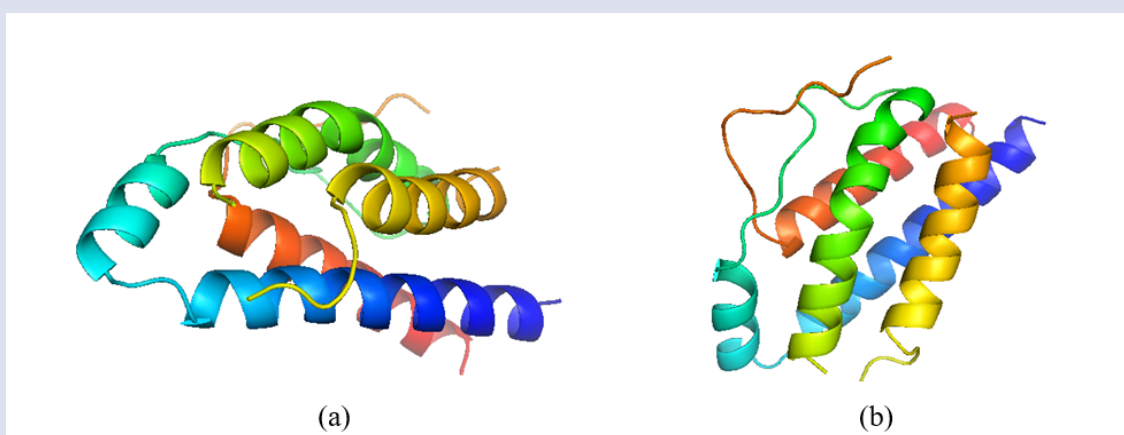
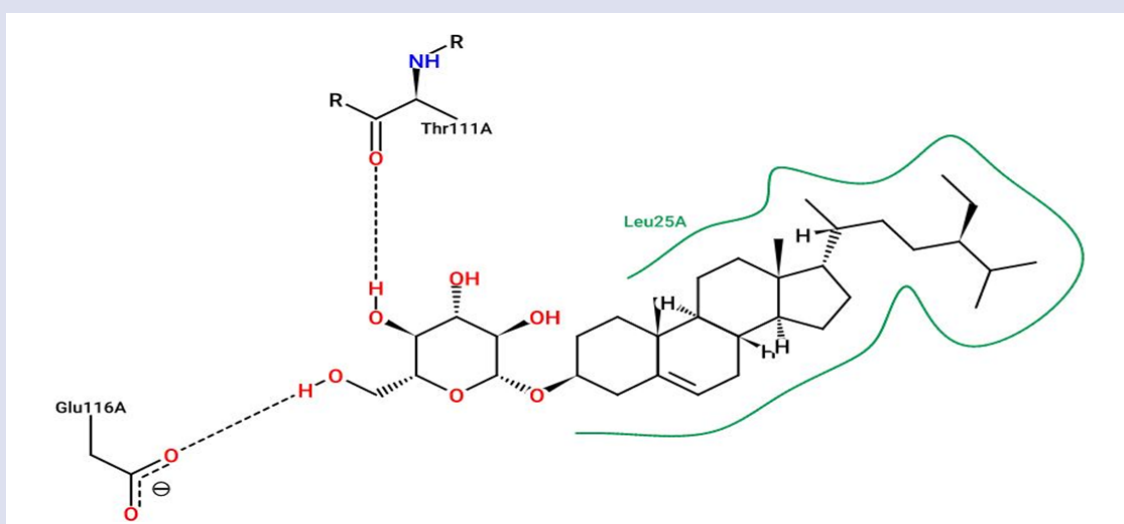**Figure 3:** (a) Interleukin-2 protein after purification (b) Interleukin-2 protein after purification

Figure 4: Visualization of the interaction between cytogluside ligands and interleukin-2 protein

Table 1: Results of binding affinity and rmsd docking of cytogluside and interleukin-2.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Interleukin-2-steril_sitogluside-minimize	-5.7	0	0
Interleukin-2-steril_sitogluside-minimize	-5.5	12.02	5.512
Interleukin-2-steril_sitogluside-minimize	-5.5	12.374	5.549
Interleukin-2-steril_sitogluside-minimize	-5.5	12.592	5.025
Interleukin-2-steril_sitogluside-minimize	-5.2	11.827	5.739
Interleukin-2-steril_sitogluside-minimize	-5.2	2.299	1.637
Interleukin-2-steril_sitogluside-minimize	-5.1	12.183	5.155
Interleukin-2-steril_sitogluside-minimize	-4.9	11.824	5.193
Interleukin-2-steril_sitogluside-minimize	-4.5	12.161	5.024

Table 2: Lipinski data results for Sitogluside.

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
520.000000	4	6	2.320830	133.161133

In this study, the obtained Binding Affinity value of -5.7 indicates that sitogluside binds strongly with IL-2, signalling a robust interaction between the ligand and protein. This suggests that sitogluside has

the potential to inhibit IL-2 activity, ultimately reducing B and T cell proliferation. Table 1 presents the docking results in the form of binding affinity and RMSD obtained in the Pyrex application, and Figure 4 displays the visualization results of the interaction between the sitogluside ligand and interleukin-2 protein on Protein Plus.

The Lipinski rule, or "Rule of Five," is a guideline used in this study to evaluate sitogluside's potential as an effective drug. According to this rule, a compound typically has drug potential if it has a molecular mass of less than 500 Daltons, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and a logP value of no more than 5.[41,42]

In the case of sitogluside, this compound has a molecular mass of 520, 4 hydrogen bond donors, 4 hydrogen bond acceptors, and a logP of 2.3. While the molecular mass is slightly over the limit proposed by Lipinski's rule, the other values fall within the set limits. Thus, according to the Lipinski rule, sitogluside potentially has good bioavailability in biological systems, a key criterion in drug discovery. Table 2 displays the Lipinski data results.[42]

The in-silico experimental results suggest that sitogluside has potential as an inhibitor of B and T cell proliferation due to its strong binding affinity with IL-2. However, *in-vitro* and *in-vivo* studies are required to confirm this hypothesis and fully understand the mechanism of

action of sitogluside. Furthermore, other properties such as ADMET (absorption, distribution, metabolism, excretion, and toxicity) profile need to be assessed to determine the safety and efficacy of sitogluside as a drug. Additionally, it will be crucial to compare sitogluside's efficacy and safety with existing IL-2 inhibitors to determine its potential for clinical use.[43,45-57]

CONCLUSION

This research utilized an *in-silico* approach to study the potential of sitogluside as an inhibitor of Interleukin-2, a cytokine responsible for B and T cell proliferation. Our findings suggest that sitogluside strongly binds to IL-2, indicating a possible inhibitory action. Furthermore, sitogluside largely adheres to Lipinski's Rule of Five, suggesting good bioavailability in biological systems.

However, these findings are preliminary, and the potential of sitogluside as a drug cannot be confirmed through in-silico studies alone. To truly determine its therapeutic potential, further studies are needed. *In-vitro* and *in-vivo* experiments should be conducted to verify the inhibitory action of sitogluside on IL-2 and to further understand its mechanism of action. Additionally, its ADMET profile needs to be examined to ensure the compound's safety and efficacy.

Further, it would be beneficial to compare the performance of sitogluside with existing IL-2 inhibitors to understand how it stands in the current therapeutic landscape. Ultimately, these additional studies can lead to a more comprehensive understanding of sitogluside's potential as a novel therapeutic option in conditions involving excessive B and T cell proliferation, such as autoimmune diseases and certain cancers.

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GRAPHICAL ABSTRACT
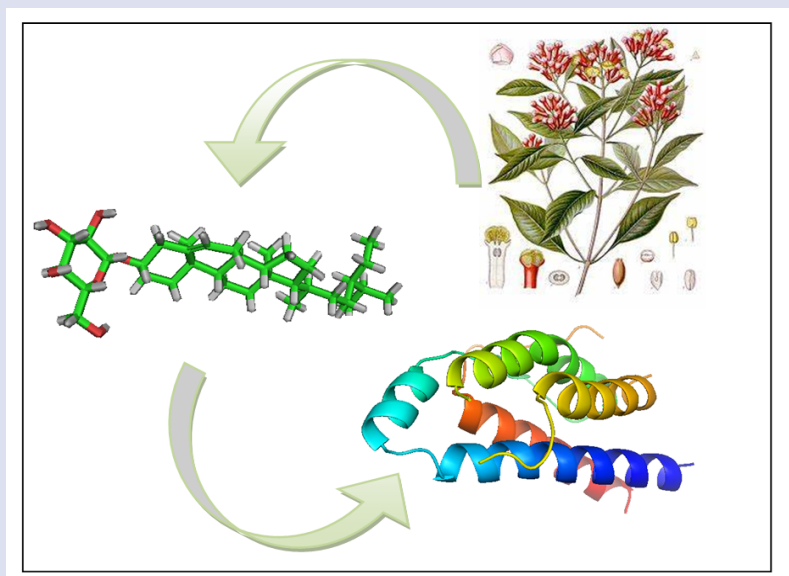
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