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"Exploring *Benincasa hispida* Constituents as Inhibitors of Monoamine Oxidase B: Insights from Molecular Docking"

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ABSTRACT
This study investigates the molecular interactions between active chemical constituents derived from *Benincasa hispida* and Monoamine oxidase B (MAO B) using molecular docking techniques. The primary objective was to identify potential inhibitors of MAO B, which plays a crucial role in the pathophysiology of neurodegenerative diseases. Docking studies revealed that quercetin, catechin, hispidulin, and naringenin exhibit significant binding affinities, with quercetin showing the highest docking score of -9.8 kcal/mol. Detailed analysis of the binding poses and interactions indicated that these compounds engage in multiple hydrogen bonds, hydrophobic interactions, and van der Waals forces within the active site of MAO B. These findings suggest that the active constituents of *Benincasa hispida* have substantial potential as MAO B inhibitors, providing a promising foundation for the development of novel neuroprotective agents. Further experimental validation and optimization are necessary to confirm these results and enhance the therapeutic efficacy of these compounds.

Keywords: *Benincasa hispida*, Monoamine oxidase B, MAO B inhibitors, molecular docking, neurodegenerative diseases, quercetin, catechin, hispidulin, naringenin

INTRODUCTION

Monoamine oxidase B (MAO B) [1,2] is a crucial enzyme implicated in the catabolism of monoamine neurotransmitters in the brain, such as dopamine and phenylethylamine.[3,4] The malfunction or overactivity of MAO B is associated with various neurodegenerative disorders, including Parkinson's disease and Alzheimer's disease.[5,6] The enzyme's role in oxidative deamination contributes to the production of hydrogen peroxide, a reactive oxygen species that can lead to neuronal damage.[7]The crystal structure of MAO B (PDB ID: 1S3E) provides a detailed understanding of its active site, enabling the design of inhibitors that can

mitigate its neurotoxic effects.[8] Consequently, identifying potent MAO B inhibitors has become a significant focus in the quest for neuroprotective therapies.

Benincasa hispida, commonly known as winter melon or ash gourd, is a plant renowned for its medicinal properties.[9,10] Traditionally used in various cultures, Benincasa hispida is reported to possess anti-inflammatory, antioxidant, and neuroprotective effects.[11,12,13] The therapeutic potential of plant-derived[14] compounds from Benincasa hispida has garnered considerable interest in recent years, with a growing body of research investigating its bioactive constituents.[15] These compounds have shown promise in modulating key biological pathways, making them attractive candidates for drug development.

Previous studies on Benincasa hispida have identified several active constituents with significant pharmacological activities.[16] These include triterpenoids,[17] flavonoids,[18] and cucurbitacins,[19] which have demonstrated various health benefits, including neuroprotective effects. The anti-neurodegenerative potential of these compounds positions them as potential MAO B inhibitors, warranting further exploration through advanced molecular docking studies.[20]

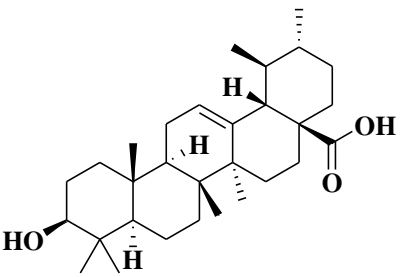
The objective of the current study is to investigate the molecular docking interactions between the active constituents of Benincasa hispida and Monoamine oxidase B (MAO B) with PDB ID: 1S3E. By leveraging computational docking techniques, this study aims to identify promising candidates that exhibit strong binding affinities and favorable interaction profiles with MAO B.[21] These findings will provide a foundation for further experimental validation, potentially leading to the development of novel neuroprotective agents derived from Benincasa hispida.

MATERIALS AND METHODS

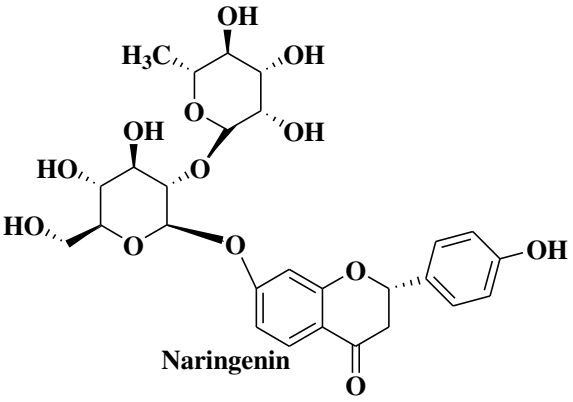
Selection of Plant Constituents:

The selection of active chemical constituents from *Benincasa hispida* was based on an extensive literature review and preliminary phytochemical screening.[22] Published studies and traditional knowledge sources were meticulously analyzed to identify compounds previously reported for their bioactive properties. Special emphasis was given to compounds with potential pharmacological activities, particularly those relevant to neuroprotection and enzyme inhibition.

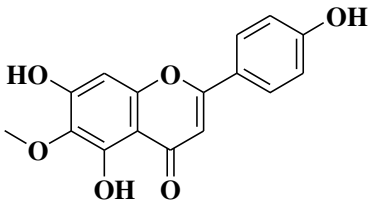
The chemical structures of Benincasa hispida constituents were subjected to molecular docking as detailed in Figure 1.



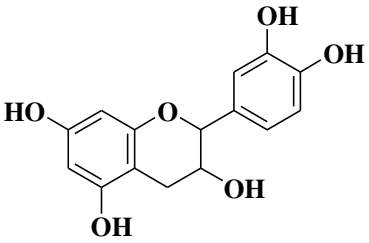
Ursolic Acid



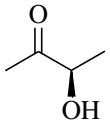
Naringenin



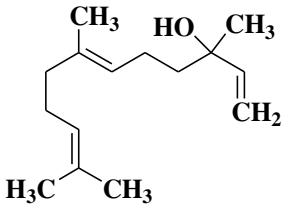
Hispidulin



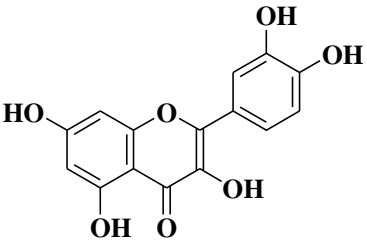
catechin



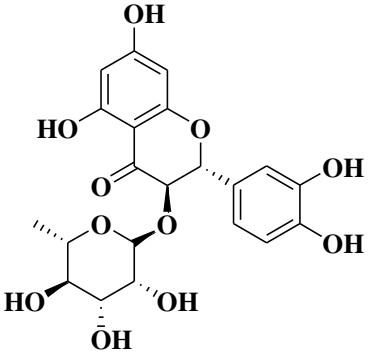
Acetoin



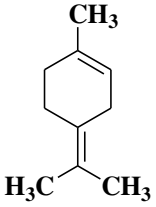
Nerolidol



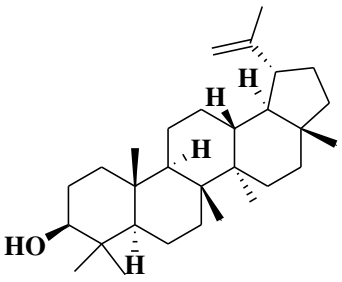
Quercetin



Astilbin



Terpinolene



Lupeol

Fig-1 Chemical structures of *Benincasa hispida* constituents

Protein Preparation:

Monoamine oxidase B (MAO B) was selected as the target protein due to its crucial role in the catabolism of monoamine neurotransmitters and its involvement in neurodegenerative diseases such as Parkinson's and Alzheimer's. Inhibition of MAO B is a validated therapeutic strategy for these conditions, making it a relevant target for screening potential inhibitors from *Benincasa hispida*.

The three-dimensional structure of MAO B (PDB ID: 1S3E) was retrieved from the Protein Data Bank (PDB). The protein structure was prepared by removing all heteroatoms, including water molecules, to avoid non-specific interactions. Hydrogen atoms were added to the protein to ensure proper ionization states of amino acid residues. Energy minimization of the protein structure was performed using the OPLS3e force field to relieve any steric clashes and optimize the geometry for docking.

Molecular Docking Protocol:

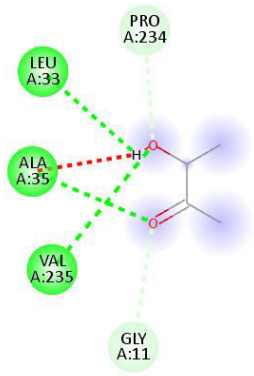
Molecular docking studies were performed using Auto Dock Vina, a widely used and validated tool for predicting the binding affinities and orientations of ligands within the active site of a target protein. The grid box was cantered on the active site of MAO B, with dimensions large enough to accommodate the entire binding pocket and surrounding residues. The exhaustiveness parameter was set to 8 to ensure thorough sampling of the conformational space, and default parameters were used for other docking settings unless specified otherwise. Docking results were evaluated based on the predicted free energy of binding (in kcal/mol), which was used as a primary metric to rank the compounds. Detailed analysis of interactions, including hydrogen bonds, hydrophobic contacts, and π-π stacking interactions, was conducted using visualization tools such as Discovery Studio. The top-ranked poses were further analyzed to identify key residues involved in ligand binding and to understand the potential mechanism of inhibition.

This rigorous approach to the selection, extraction, and docking of *Benincasa hispida* constituents ensures the identification of promising candidates for further experimental validation as MAO B inhibitors.

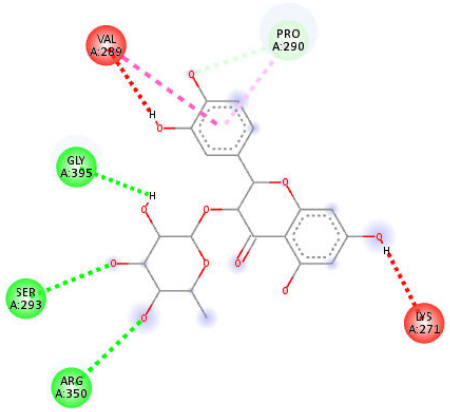
RESULT-

The molecular docking studies conducted on the active chemical constituents from *Benincasa hispida* against Monoamine oxidase B (MAO B) provided significant insights into their binding affinities and interactions. The docking scores, which reflect the binding affinities of the compounds, ranged from -4.2 to -9.8 kcal/mol. Quercetin exhibited the highest binding affinity with a docking score of -9.8 kcal/mol, followed closely by catechin and hispidulin, both with scores of -9.4 kcal/mol, and naringenin with a score of -9.3 kcal/mol. These values suggest a strong potential for these compounds as MAO B inhibitors. (Fig-2 and 3)

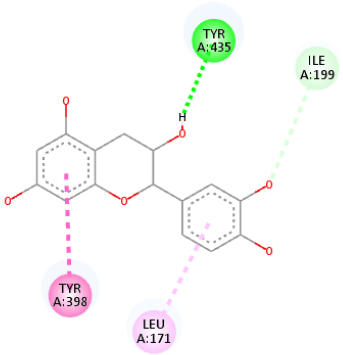
Visualization of the binding poses and interaction diagrams revealed detailed interaction profiles of the compounds within the active site of MAO B. For instance, quercetin formed multiple interactions, including hydrophobic interactions with Tyr398 and van der Waals interactions with several residues such as Arg42, Gly57, Gly58, Ser59, Tyr60, Lys296, Phe343, Cys397, Gly434, Tyr435, and Met436. Similarly, catechin and hispidulin demonstrated significant binding through hydrophobic interactions and hydrogen bonding, with key residues like Arg42, Gly434, and Tyr435 playing crucial roles in stabilizing the ligand within the active site. (Fig-2,3,and 4)



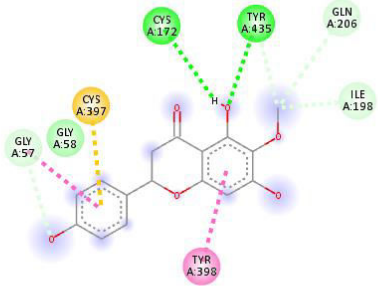
1-Acetoin



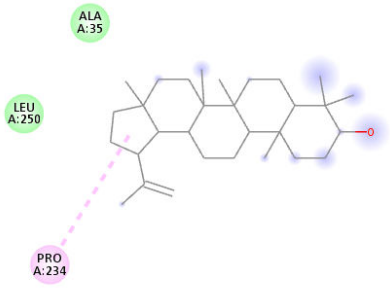
2-Astilbin



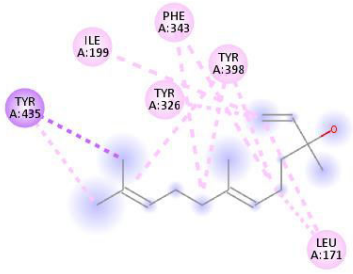
3-Catechin



4-Hispidulin



5-Lupeol



6-Nerolidol

Figure-2 Drug Interactions (Ligand-1,2,3,4,5,6) with Amino acid (**MAO B Protein (PDB ID: 1S3E)**

Table 1Amino Acid Interaction and Bond Type with Docking Score

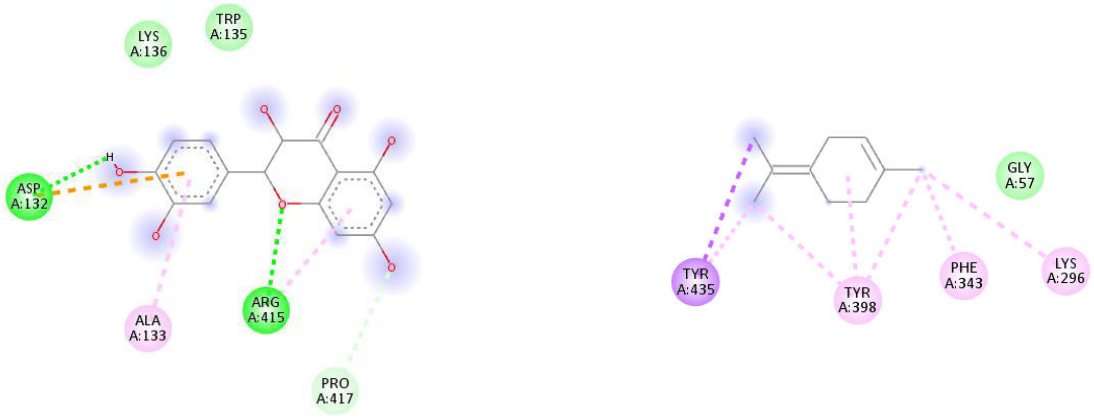
S.NO.	COMPOUND	DOCKING SCORE	Amino Acid INTERACTION	BOND TYPE
1	Ursolic acid	-7.1	Pro 234, Pro 277	Hydrophobic (Alkyl)
			Ala 35, Arg 36, Arg38, Glu232, Try237, Leu250, Glu291, Lys386, Try393	Vanderwaal
2	Naringenin	-9.3	Phe343, Try398	Hydrophobic (pi alkyl)
			Try60, Leu171, GLn206, Tyr326, Leu328	Vanderwaal
3	Hispidulin	-9.4	Cys397	H-bonding (H-accepter)
			Met436	Hydrophobic (Alkyl)
			Arg42, Gly58, Ser59, Tyr66, Gly434,	Vanderwaal
4	Catechin	-9.4	Arg42, Tyr435	Hydrophobic, (Alkyl)
			Gly434, Met436	H-bonding, (H-accepter)
5	Acetoin	-4.2	lle14, Met436, Ala439	Hydrophobic (Alkyl)
			Gly13, Gly40, Arg42, Thr43	Vanderwaal
6	Nerolidol	-7.2	Leu171	Hydrophobic (Alkyl), and pi alkyl
			Cys172, Lys296, Phe343, Tyr398, Tyr435	
7	Quercetin	-9.8	Tyr398	Hydrophobic
			Arg42, Gly57, Gly58 ,Ser59, Tyr60, Lys296, Phe343, Cys397, Gly434, Tyr435,	Vanderwaal (pi alkyl)
8	Astilbin	-7.1	Arg36	H-bonding (H-accepter)
			Tyr44	Hydrophobic (pi alkyl)
			Asp37, Arg38, Glu391, Lys386	Vanderwaal
9	Terpinolene	-6.7	Tyr60, Phe343, Tyr398	Hydrophobic (pi- alkyl)
			Gln 206, Tyr326, Tyr435	Vanderwaal
10	Lupeol	-6.8	Arg36	Hydrophobic
			Asp37, Arg38, Try44, Leu46 ,Pro277, Lys386, Glu390 ,Glu391, Tyr393	Vanderwaal (Alkyl)

The analysis of key interactions indicated that the binding of these plant constituents to MAO B involved a combination of hydrogen bonds, hydrophobic interactions, and van der Waals forces. For example, ursolic acid formed hydrophobic alkyl interactions with Pro234 and Pro277 and van der Waals interactions with residues such as Ala35, Arg36, Arg38, Glu232, Try237, Leu250, Glu291, Lys386, and Try393. Naringenin and nerolidol primarily interacted through hydrophobic and van der Waals forces, while hispidulin and catechin also engaged in hydrogen bonding, highlighting their potential as potent inhibitors.

Comparative analysis of the docking results allowed us to identify the most promising compounds for further investigation. Quercetin emerged as the top candidate due to its highest binding affinity and extensive interaction profile. Catechin, hispidulin, and naringenin also showed strong potential, given their favorable docking scores and interaction patterns. Compounds like acetoin, with a lower docking score of -4.2 kcal/mol, displayed fewer

interactions, indicating a lesser likelihood of effective inhibition compared to the top-ranking compounds.

In conclusion, the molecular docking studies identified quercetin, catechin, hispidulin, and naringenin as the most promising active constituents from *Benincasa hispida* for further experimental validation as MAO B inhibitors. These findings provide a foundation for future research into their therapeutic potential in neurodegenerative diseases.



7-Quercetin 8-Terpinolene

Figure-3 Aminoacid Interaction of Quercetin and Terpinolene with MAO B Protein (PDB ID: 1S3E)

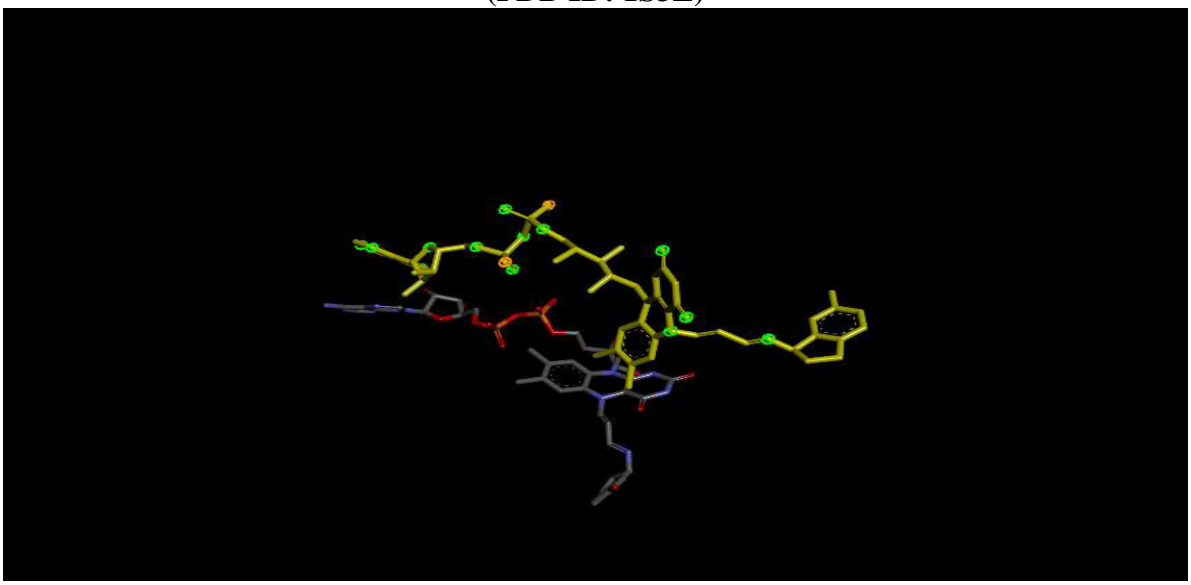


Figure-4 -Reproducing the Pose of co-crystallized ligand into the binding site of MAO B Protein(PDB ID: 1S3E)
(Golden colour Ligand is Co-crystallized)

DISCUSSION-

The docking results revealed significant therapeutic potential for the active constituents of *Benincasa hispida* as inhibitors of Monoamine oxidase B (MAO B). Quercetin, with the highest docking score of -9.8 kcal/mol, demonstrated robust interactions within the active site of MAO B, indicating its strong potential as a neuroprotective agent. The substantial binding affinities observed for catechin, hispidulin, and naringenin further underscore the potential of these compounds to serve as effective MAO B inhibitors, which could be beneficial in the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's.

Comparison with existing literature reveals that compounds like quercetin and catechin have been previously identified for their neuroprotective properties and MAO B inhibitory activities. These findings align well with our results, reinforcing the credibility of our docking studies. Previous research has highlighted the ability of flavonoids to interact with MAO B, suggesting a mechanism of action that includes both competitive inhibition and modulation of enzyme activity through binding at allosteric sites. Our study adds to this body of knowledge by providing detailed interaction profiles and binding affinities, which can aid in the rational design of flavonoid-based MAO B inhibitors.

The implications of these findings for drug development are significant. The identification of potent MAO B inhibitors among the active constituents of *Benincasa hispida* paves the way for the development of novel neuroprotective agents. These compounds can be further optimized through structure-activity relationship (SAR) studies and validated through in vitro and in vivo experiments. The detailed interaction data provided by our docking studies can guide the synthesis of derivatives with improved binding affinities and pharmacokinetic properties, potentially leading to effective therapeutic agents for neurodegenerative diseases.

However, this study has several limitations that should be addressed in future research. The docking studies, while providing valuable insights into the binding interactions, do not account for the dynamic nature of protein-ligand interactions in a biological environment. The absence of solvation effects and the limitations of the docking algorithm in predicting all possible conformations and interactions could affect the accuracy of the binding affinities. Therefore, it is crucial to complement these findings with molecular dynamics simulations and experimental validation to confirm the inhibitory potential of these compounds. Additionally, exploring the bioavailability and toxicity profiles of these constituents will be essential to assess their suitability as drug candidates.

In conclusion, our study has identified promising MAO B inhibitors from *Benincasa hispida*, highlighting their potential in the treatment of neurodegenerative diseases. While the docking results provide a strong foundation, further research involving experimental validation and optimization will be necessary to fully realize their therapeutic potential.

CONCLUSION-

This study has identified key active constituents from *Benincasa hispida* with significant binding affinities towards Monoamine oxidase B (MAO B), highlighting their potential as therapeutic agents for neurodegenerative diseases. Quercetin, catechin, hispidulin, and naringenin emerged as the most promising compounds, with quercetin demonstrating the highest docking score and extensive interaction profile. These findings underscore the potential of *Benincasa hispida*'s active constituents as modulators of MAO B, providing a foundation for the development of novel neuroprotective agents.

The promising results obtained from the molecular docking studies suggest that these plant-derived compounds could serve as effective MAO B inhibitors, contributing to the treatment of conditions such as Parkinson's and Alzheimer's diseases. However, the importance of experimental validation cannot be overstated. Future research should focus on conducting in vitro and in vivo studies to confirm the inhibitory effects and therapeutic potential of these

compounds. Additionally, optimizing the bioavailability and pharmacokinetic properties of these constituents will be essential for their development as viable drug candidates.

In summary, our findings highlight the therapeutic promise of *Benincasa hispida*'s active constituents in modulating MAO B activity. Continued research, including experimental validation and compound optimization, will be critical to fully harness their potential and develop effective treatments for neurodegenerative diseases.

ABBREVIATION:

Benincasa hispida (B. hispida)
Monoamine oxidase B (MAO B)
Protein Data Bank (PDB)
Structure-activity relationship (SAR)

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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