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IN SILICO MOLECULAR DOCKING ANALYSIS OF MYRICETIN AGAINST MATRIX METALLOPROTEINS

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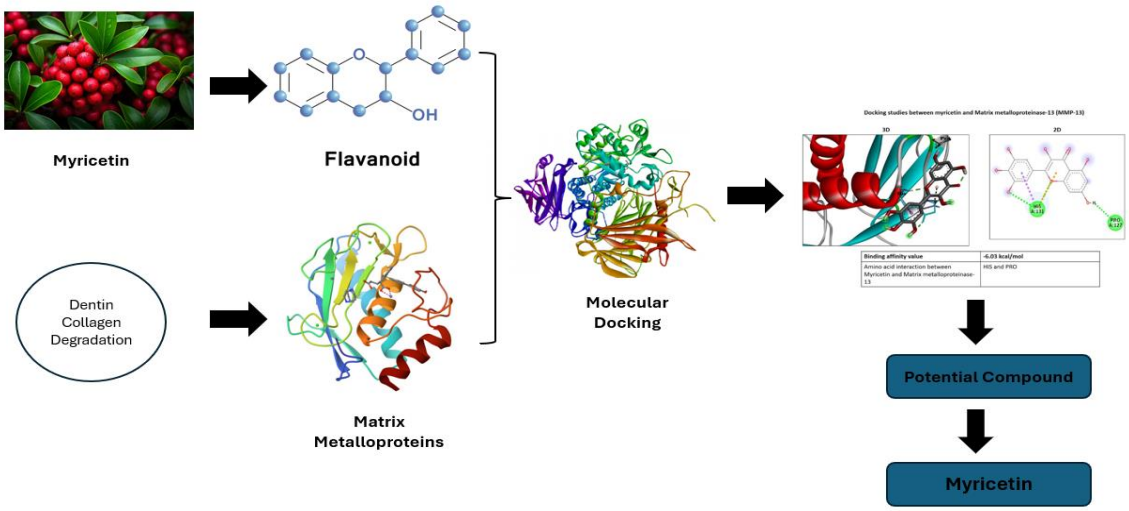
ABSTRACT:

This study delves into the physicochemical and pharmacokinetic properties of myricetin, a natural flavonoid compound, with a particular focus on its interaction with key biomolecules involved in inflammatory and enzymatic processes. The investigation begins by employing in silico methods to predict myricetin's Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties. These computational models reveal that myricetin exhibits a low gastrointestinal absorption rate and is not likely to permeate the blood-brain barrier. Furthermore, it shows interactions with specific cytochrome P450 enzymes, indicating potential metabolic pathways. Moving forward, the study explores myricetin's interactions with two pivotal biomolecules: Tumor Necrosis Factor-alpha (TNF-alpha) and Cyclooxygenase-2 (COX-2). Myricetin's binding to TNF-alpha demonstrates the potential to inhibit inflammatory responses, as evidenced by amino acid interactions involving GLY, LYS, PRO, ALA, and ILE, with a binding affinity of -5.04 Kcal/mol. Additionally, myricetin interacts with COX-2, indicating its ability to modulate prostaglandin production, vital in inflammation, pain, and fever regulation, with amino acid interactions involving ASN, HIS, ARG, LYS, VAL, and GLU and a binding affinity of -5.87 Kcal/mol. Finally, the study investigates myricetin's interaction with Matrix Metalloproteinase-13 (MMP-13) and Matrix Metalloproteinase-9 (MMP-9), crucial enzymes involved in the degradation of extracellular matrix components. Myricetin's interactions with these enzymes suggest its potential role in modulating tissue remodeling processes, with binding affinities of -6.03 Kcal/mol for MMP-13 and -3.64 Kcal/mol for MMP-9. Overall, this research sheds light on myricetin's physicochemical attributes, pharmaco kinetics, and its potential as a bioactive compound in modulating inflammatory and enzymatic processes, making it a promising candidate for further exploration in therapeutic applications.

Keywords: Silico Molecular docking, Myricetin, Matrix metalloproteins, therapeutic applications, pharmacokine tics



1. INTRODUCTION

Myricetin is a natural flavonoid compound found in various fruits, vegetables, and herbs. It has gained attention for its potential health benefits, including its use in dental applications (1). Myricetin possesses anti-inflammatory properties that can help reduce inflammation in the gums and oral tissues(2). This can be beneficial in treating conditions like gingivitis and periodontitis (3). Myricetin exhibits antimicrobial activity against various oral pathogens, including bacteria, fungi, and viruses. It can inhibit the growth of bacteria such as Streptococcus mutans (4), which is associated with dental caries (tooth decay) . Myricetin is a potent antioxidant that can help protect oral tissues from oxidative stress (5,6). This can aid in preventing damage to the gums and teeth caused by free radicals . Myricetin has been investigated for its potential in preventing dental caries. It can inhibit the activity of enzymes involved in the formation of dental plaque and the breakdown of sugars, thus reducing the risk of tooth decay (7) . Periodontal diseases, such as gingivitis and periodontitis, involve inflammation and damage to the gums and supporting structures of the teeth. Myricetin's anti-inflammatory and antimicrobial properties can contribute to the management of these conditions . Myricetin has been studied for its wound-healing properties (8) . In dental applications, it may aid in the healing of oral wounds, such as those resulting from tooth extractions or oral surgeries . Some research suggests that myricetin may have anticancer properties (9) and could potentially play a role in preventing oral cancer. However, further studies are needed to fully understand its effects in this regard .

Matrix metalloproteinases (MMPs) are a family of enzymes that play a crucial role in tissue remodeling and maintenance. MMPs are involved in the degradation of the extracellular matrix (ECM) in dental tissues (10). Excessive MMP activity can contribute to the progression of dental diseases, such as caries and periodontitis. MMPs can play a role in the degradation of the dental hard tissues, such as enamel and dentin, during the progression of dental caries .In dental applications, MMP inhibitors have been studied for their potential to control the destructive effects of matrix metalloproteinases and limit tissue damage in caries and periodontal disease. Inhibiting MMP activity may help to prevent or slow down the demineralization and destruction of tooth structure caused by caries. In dental pulp diseases or injuries, MMPs can contribute to the breakdown of the extracellular matrix within the pulp tissue. MMP inhibition has been explored as a strategy to preserve pulp tissue integrity . In certain dental procedures, such as root surface biomodification for periodontal regeneration,

MMP inhibitors may be applied to the root surface to modulate MMP activity. This helps to promote the attachment of periodontal ligament cells and enhance the regeneration of periodontal tissues. MMPs can contribute to the breakdown of the peri-implant soft and hard tissues, leading to peri-implantitis, a common complication of dental implant placement . MMP inhibitors have been investigated as a potential means to prevent or reduce peri-implant tissue degradation and promote implant stability.

2. MATERIALS AND METHODS

2.1. ADMET prediction

The pkCSM ADMET descriptors algorithm was used to profile drugs' PK characteristics such as absorption, distribution, metabolism, excretion, and toxicity (ADMET). The 2D polar surface area (PSA 2D, a major predictor of fractional absorption) and lipophilicity levels in the form of atom-based LogP are two significant chemical descriptors that correlate well with PK characteristics (AlogP98). Drug absorption is influenced by membrane permeability [as determined by the Caco-2 colon cancer cell line], intestinal absorption, skin permeability levels, and P-glycoprotein substrate or inhibitor . Drug distribution is influenced by variables such as the blood–brain barrier (logBB), CNS permeability, and distribution volume (VDss). The CYP models for substrate or inhibitor are used to predict metabolism (CYP2D6, CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4). The entire clearance model and renal OCT2 substrate are used to predict excretion AMES toxicity, hERG inhibition, hepatotoxicity, and skin sensitivity are used to predict drug toxicity. These parameters were computed and verified to ensure that they were within their normal limits

2.2. Molecular Docking

AutoDock is a popular software program used for molecular docking simulations, which is the process of predicting the binding mode and affinity of a small molecule (ligand) with a target protein (receptor) . AutoDock uses a scoring function to evaluate the interaction energy between the ligand and receptor and performs a search algorithm to explore different binding conformations. Prepare the ligand and receptor structures: Obtain the three-dimensional structures of the ligand and receptor in a suitable file format, such as Protein Data Bank (PDB) or Protein-Ligand (PDBQT) format (11). If needed, perform any necessary preprocessing steps like removing water molecules or adding missing atoms. Prepare the AutoDock input files: Use the AutoDock Tools (ADT) graphical user interface or command-line tools to prepare the input files. This involves assigning atom types, adding charges, and defining rotatable bonds for the ligand. For the receptor, prepare the grid maps that define the search space for docking. Set up the docking parameters: Define the docking parameters, including the search algorithm, number of docking runs, number of evaluations, and scoring function to be used . AutoDock provides various search algorithms and scoring functions to choose from. Run the docking simulation: Execute the AutoDock program using the prepared input files and specified parameters. The program will perform the docking simulation, exploring different ligand conformations and orientations within the defined search space. After the docking simulation completes, analyze the results to identify potential binding modes and evaluate the binding affinity of the ligand . AutoDock provides output files that contain information about the predicted binding energy and the binding poses of the ligand. Visualize and interpret the results: Use molecular visualization software, such as PyMOL or VMD, to visualize the docked complexes and analyze the interactions between the ligand and receptor . This can provide insights into the binding mode and potential binding interactions.

3. RESULT AND DISCUSSION

3.1. Physicochemical and Pharmacokinetics

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) refers to a set of properties that are essential for understanding the pharmacokinetics and potential toxicity of a drug candidate. Predicting ADMET properties can help in the early stages of drug discovery and development to identify potential safety and efficacy issues. In silico methods involve using computational models and algorithms to predict ADMET properties based on the chemical structure of a compound. These methods utilize various approaches, including quantitative structure-activity relationship (QSAR) models, machine learning algorithms, and molecular docking simulations, to predict properties such as absorption, distribution, metabolism, and toxicity. Number of hydrogen acceptors and donors are 8 and 6. TPSA of myricetin is 151.59. Meanwhile the gastrointestinal absorption is low and not capable of blocking the blood brain barrier. The p-gp also indicates no. Myricetin showed no for CYP1A19, CYP2C9, and CYP2D6 inhibitors. Also showed Yes towards the CYP1A2 and CYP3A4 inhibitors. The Log Kp (skin permeation) obtained value of -7.40cm/s

Myricetin

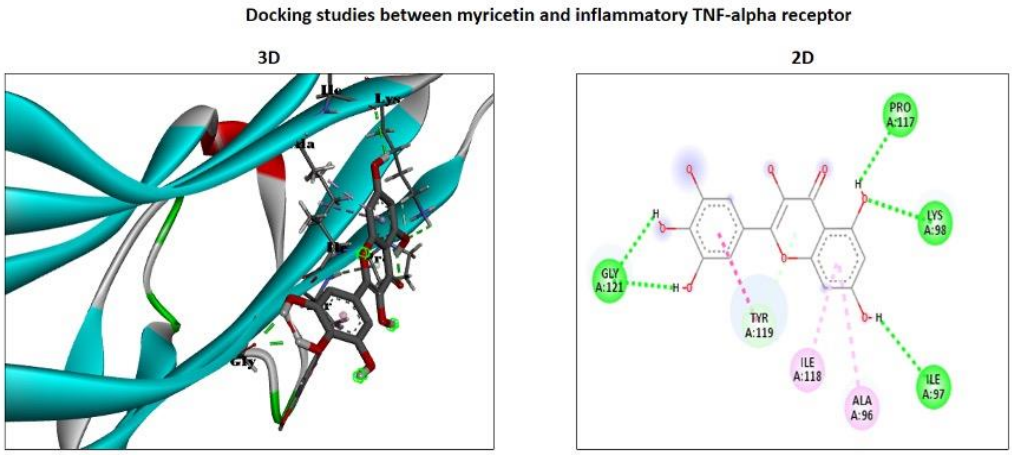
Physicochemical Properties	
Formula	C15H10O8
Molecular weight	318.24 g/mol
Num. heavy atoms	23
Num. arom. heavy atoms	16
Fraction Csp3	0.00
Num. rotatable bonds	1
Num. H-bond acceptors	8
Num. H-bond donors	6
Molar Refractivity	80.06
TPSA	151.59 Å²

Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (skin permeation)	-7.40 cm/s

Fig.1. Physicochemical properties and pharmacokinetics of myricetin

3.2. Myricetin interaction with TNF-alpha

Myricetin interaction with TNF-alpha could inhibit the expression level of inflammatory conditions.Tumor necrosis factor-alpha (TNF-alpha) is a cytokine that plays a crucial role in inflammation and the regulation of the immune response. It is mainly produced during acute inflammation, TNFα triggers various signaling pathways, which can result in cell death via necrosis or apoptosis (12).It plays a critical role in various inflammatory conditions and autoimmune diseases. Inhibiting TNF-alpha can be an effective therapeutic approach to manage these conditions. In the result, 3D and 2D structure shows amino acid interaction between the myricetin and TNF-alpha protein through GLY, LYS, PRO, ALA, and ILE. The binding affinity shows a value of – 5.04 Kcal/mol.

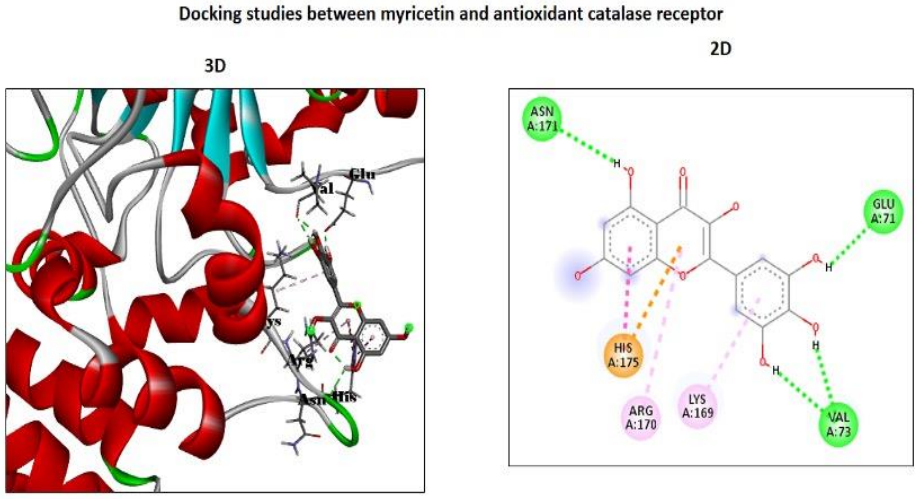


Binding affinity value	-5.04 kcal/mol
Amino acid interaction between Myricetin and TNF-alpha	GLY, TYR, ILE, ALA, ALA, ILE, LYS, PRO

Fig.2. Amino acid interaction and binding affinity value of myricetin and TNF-α

3.3. Myricetin interaction with COX-2

Cyclooxygenase (COX) is an enzyme crucial for converting arachidonic acid into prostaglandins (13).COX-2 (cyclooxygenase-2) inhibition refers to the suppression or blocking of the activity of the enzyme COX-2. COX-2 is an enzyme involved in the production of prostaglandins, which are lipid signaling molecules involved in various physiological processes, including inflammation, pain, and fever. COX-2 inhibitors are medications that selectively target and inhibit COX-2, providing anti-inflammatory and analgesic effects while potentially minimizing adverse effects associated with the inhibition of COX-1, another isoform of the enzyme. In the result, 3D and 2D structure shows amino acid interaction between the MYRICETIN peptide and COX-2 protein through ASN, HIS, ARG, LYS, VAL, and GLU. The binding affinity shows a value of -5.87 Kcal/mol (Figure 1 and 2)

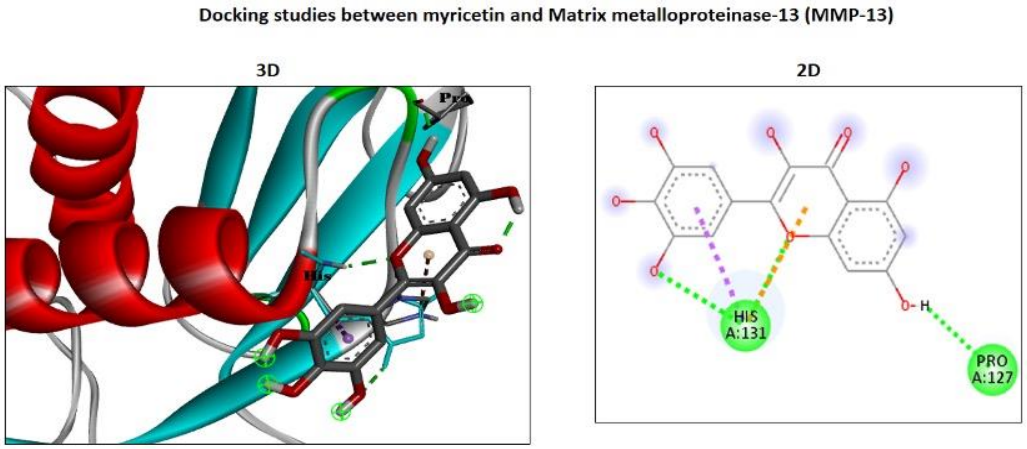


Binding affinity value	-5.87 kcal/mol
Amino acid interaction between Myricetin and catalase	ASN, HIS, ARG, LYS, VAL, and GLU

Fig.3. Amino acid interaction and binding affinity value of myricetin and catalasek

3.4. Myricetin interaction with matrix metalloproteinase-13

Matrix metalloproteinase-13 (MMP-13), also known as collagenase-3, is an enzyme belonging to the matrix metalloproteinase family. It plays a crucial role in the degradation and remodeling of the extracellular matrix (ECM), particularly in the breakdown of collagen, the main component of connective tissues. MMP-13 has a strong preference for cleaving collagen type II, which is the predominant collagen in cartilage. It can also degrade other collagens, including types I, III, and X. The ability of MMP-13 to specifically target collagen type II makes it a critical enzyme in cartilage degradation. In the result, 3D and 2D structure shows amino acid interaction between the myricetin peptide and matrix metalloproteinase-13 protein through HIS and PRO. The binding affinity shows a value of -6.03 Kcal/mol (Figure 3)



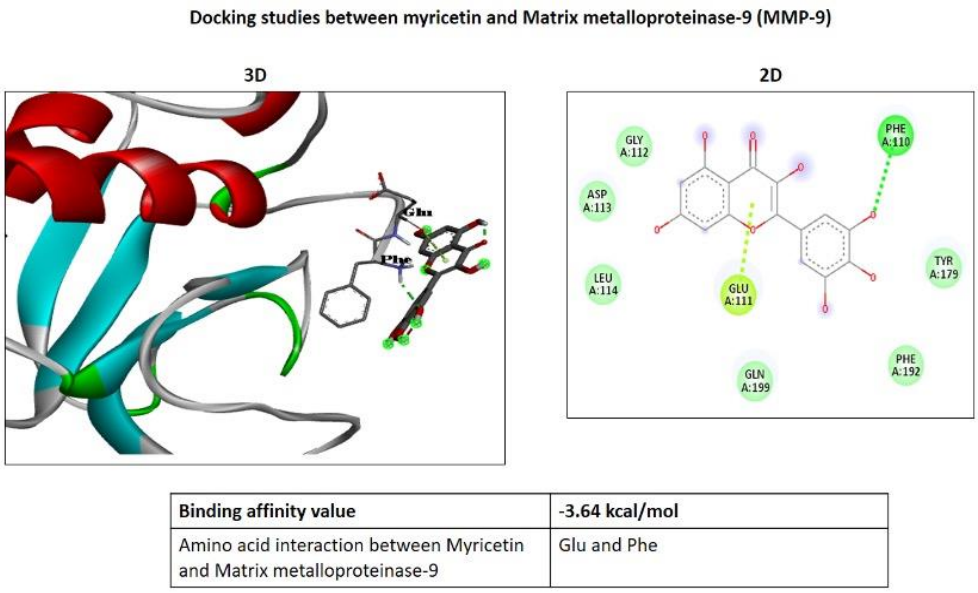
Binding affinity value	-6.03 kcal/mol
Amino acid interaction between Myricetin and Matrix metalloproteinase-13	HIS and PRO

Fig.4. Amino acid interaction and binding affinity value of myricetin and matrix metalloproteinase-13

Figure 4 shows the Amino acid interaction and binding affinity value of myricetin and matrix metalloproteinase-13

3.4. Myricetin interaction with matrix metalloproteinase-9

Matrix metalloproteinase 9 (MMP-9), also known as gelatinase B, is an enzyme belonging to the matrix metalloproteinase family. MMP-9 is involved in the degradation and remodeling of the extracellular matrix (ECM) (14) , which is essential for various physiological and pathological processes. MMP-9 is a zinc-dependent protease that is secreted as an inactive zymogen (proMMP-9). It consists of several domains, including a signal peptide, a propeptide domain, a catalytic domain, a hinge region, and a hemopexin-like domain. Activation of proMMP-9 involves proteolytic cleavage of the propeptide domain to yield the active enzyme. In the result, 3D and 2D structure shows amino acid interaction between the myricetin peptide and matrix metalloproteinase-9 protein through GLU and PHE. The binding affinity shows a value of -3.64 Kcal/mol



Binding affinity value	-3.64 kcal/mol
Amino acid interaction between Myricetin and Matrix metalloproteinase-9	Glu and Phe

Fig.5. Amino acid interaction and binding affinity value of myricetin and matrix metalloproteinase-9

Figure 5 shows the Amino acid interaction and binding affinity value of myricetin and matrix metalloproteinase-9

In recent times, significant focus has been directed towards understanding the MMP-dependent degradation pathway of the extracellular matrix (ECM). Encouraging the use of MMP inhibitors that hinder collagen breakdown during dentinal caries could be a beneficial recommendation for promoting the natural healing of carious dentin matrix, thereby stimulating remineralization.Utilizing MMP inhibitors during dentin bonding procedures could offer several advantages. These inhibitors can effectively impede the degradation of dentin collagen within the hybrid layers, enhance the stability of dentin bonding, and help prevent the occurrence of secondary caries. Future bonding systems should incorporate sustained MMP-inhibitory properties to ensure the longevity of the hybrid layer's integrity and enhance the durability of adhesive restorations on dentin.From this study it is confirmed that myricetin has the ability to interact with the matrix metalloproteinase 9 and 13. During inflammation, MMP-9 generated by PMN cells plays a role in distinguishing between reversible and irreversible pulpitis.

4. CONCLUSION

In conclusion, accumulating data have demonstrated that myricetin has the ability to interact with MMP 9 , MMP 13, COX - 2,TNF alpha.These findings hold significance as they present new possibilities for caries prevention and management. Delaying or halting the irreversible deterioration of the organic matrix could enable natural healing of the lesion through remineralization. Myricetin might offer valuable contributions to halting the advancement of dentin caries.For humans, the optimal method of administering MMP inhibitors like myricetin for dental caries treatment would involve local application. This could be achieved by incorporating them into topical formulations for regular use or directly applying them onto the dentin surface, depending on the specific clinical circumstances.

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