Communication

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Exploring Natural Compounds for Cardiovascular Research: Myeloperoxidase Inhibition and Toxicity Prediction Studies

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Abstract: This study focused on the investigation of myeloperoxidase through a Molecular Docking approach with various natural compounds to identify potential substances for cardiovascular research. Recent research has linked elevated myeloperoxidase levels to the severity of coronary artery disease. The results of the docking analysis revealed Polydatin, Daidzin, Astringin, Ginkgetin, and Amentoflavone as promising compounds with excellent binding capacity. To complement this, toxicity prediction studies were conducted using pkCSM. Overall, all four investigated molecules (Amentoflavone, Daidzin, Ginkgetin, and Astringin) were found to be non-toxic, exhibiting high maximum tolerated doses (human) and favorable values for Oral Rat Acute Toxicity and Oral Rat Chronic Toxicity. Moreover, they showed non-AMES toxicity and non-hepatotoxicity. Astringin, in particular, stood out with the highest positive effects, including a high maximum tolerated dose (human) and favorable values for Oral Rat Chronic Toxicity, along with dual inhibition of hERG II and hERG I. These findings suggest the potential utility of these compounds in cardiovascular research with minimized unwanted effects.

Keywords: cardiovascular research,myeloperoxidase,Astringin,pkCSM,Molecular Docking

1. Introduction

Gaining insights into Myeloperoxidase (MPO) function contributes to our understanding of innate immune processes and their relevance to both health and disease [1,2].The myeloperoxidase gene, located on chromosome 17 in humans, encodes the MPO enzyme expressed primarily in neutrophils, a subtype of white blood cell. Neutrophils use MPO to generate hypohalogen acids, such as hypochlorous acid (HOCl), as part of their antimicrobial activity.

This process involves the catalysis of hydrogen peroxide (H_2O_2) and chloride ions (Cl^-), leading to the formation of potent reactive oxygen species (ROS)[3,4]. Neutrophils utilize hypochlorous acid and tyrosyl radicals for their cytotoxic properties, employing them to eliminate bacteria and various pathogens[2].

Recent studies have reported an association between elevated levels of myeloperoxidase and the severity of coronary artery disease[5,6]. It has also been suggested that myeloperoxidase plays a significant role in the development of atherosclerotic lesions and in rendering plaques unstable[7,8].

The current study concentrates on exploring Myeloperoxidase through a Molecular Docking approach [9] several various natural compounds.

The objective is to discern which natural compounds exhibit potential binding with this enzyme, with implications for potential utilization in cardiovascular research.

Nowadays, there are several computational studies that can serve as valuable tools in the fields of medicine and biology, aiding scientific research. These computational approaches have the capability to identify potential useful substances more efficiently, bypassing costly methods and saving years of analysis.

2. Material and Methods

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- Structure of CRYSTAL STRUCTURE OF HUMAN MYELOPEROXIDASE ISOFORM C was taken from Protein Data Bank (PDB Code:1CXP). Docking investigation was performed by Autodock Vina with Pyrx program[10], using : Grid box Coordinates of binding Center X (26.0016), Y(-12.2539), Z(-5.7823); size_x = 76.5024498844; size_y = 65.1342304993; size_z = 65.4337480927

3. Results and Discussion

The objective is to discern which natural compounds exhibit potential binding with human myeloperoxidase isoform C (MPO)., with implications for potential utilization in cardiovascular research.

For the fist time,this short docking study aims to investigate several natural compounds with crystal structure of human myeloperoxidase isoform C (MPO).According to the Docking results, Daidzin (-11 kcal/mol), Astringin (-10 kcal/mol), Ginkgetin (-11.3 kcal/mol), Amentoflavone (-11.2 kcal/mol) exhibited excellent potential binding capacity with this enzyme.(See below Table 1).
Furthermore, beyond identifying which compounds exhibit excellent binding capacity with this enzyme, toxicity prediction studies were conducted to ascertain which among them, if utilized, would result in fewer undesirable effects. For this specific purpose, the pkCSM tool was employed [11] .

In the toxicity prediction investigations using pkCSM, it was observed that, in general, the four molecules under scrutiny (amentoflavone, daidzin, ginkgetin, and astringin) are non-toxic, exhibiting a high maximum tolerated dose (human) with a value around 0.4-0.5 log mg/kg/day. These molecules also demonstrated excellent values for Oral Rat Acute Toxicity and Oral Rat Chronic Toxicity, and they were found to be non-AMES toxic and non-hepatotoxic.

Upon closer examination, Astringin stood out with the most favorable outcomes. It displayed a high maximum tolerated dose (human) of 0.554 log mg/kg/day and an Oral Rat Chronic Toxicity (LOAEL) of 4.371 log mg/kg_bw/day. Additionally, Astringin not potential considered as both an hERG II inhibitor and an hERG I inhibitor.

Table 1. Comparison of best binding energies scores (kcal/mol) of natural compounds in complex with human myeloperoxidase isoform C (MPO), evaluated by Blind Docking method with Pyrx program.

Ligand	Binding Energy (kcal/mol)
(-)-Epicatechin	-9
Capsaicin	-7.4
Kaemferol	-9.3
Amentoflavone	**-11.2**
NIGERONE	-9.5
Artemetin	-9.1
Daidzin	**-11**
(-)-Epigallocatechin	-9.1
Cianidanol	-9.2
Ginkgetin	**-11.3**
Morusin	-9
Pinosylvin	-8.1
Astringin	**-10**

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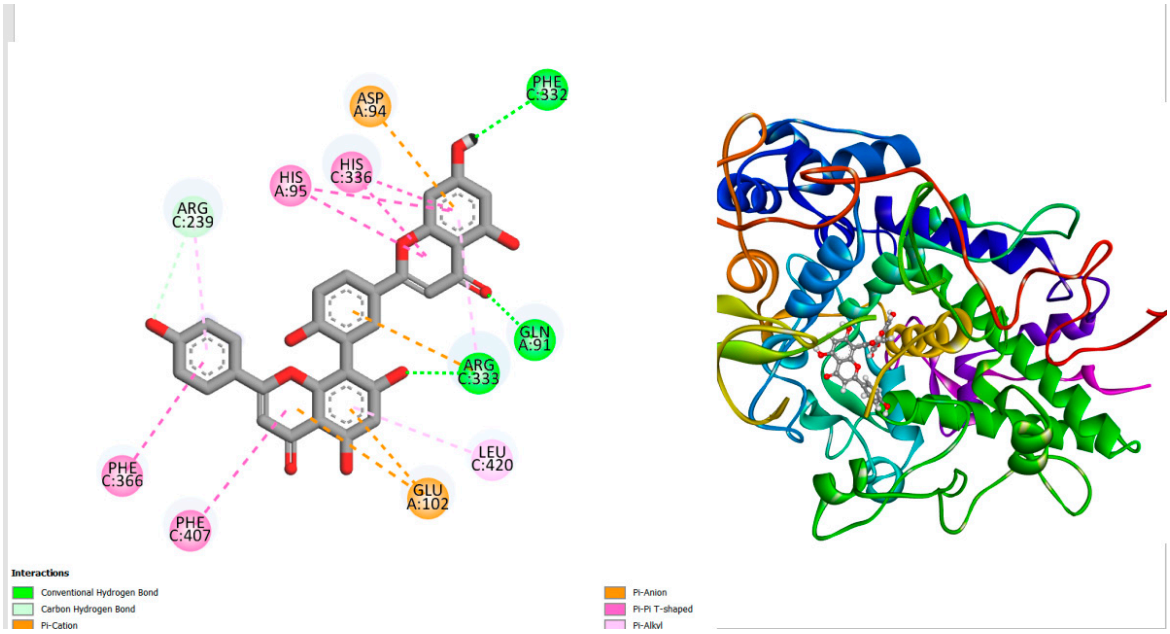

Figure 1. displays the docking outcomes of Structure of Crystal Human human myeloperoxidase isoform C (MPO) in conjunction with docked amentoflavone -11.2 kcal mol , within the Ligand Binding Site, as analyzed by Autodock Vina with pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and amentoflavone. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of amentoflavone.

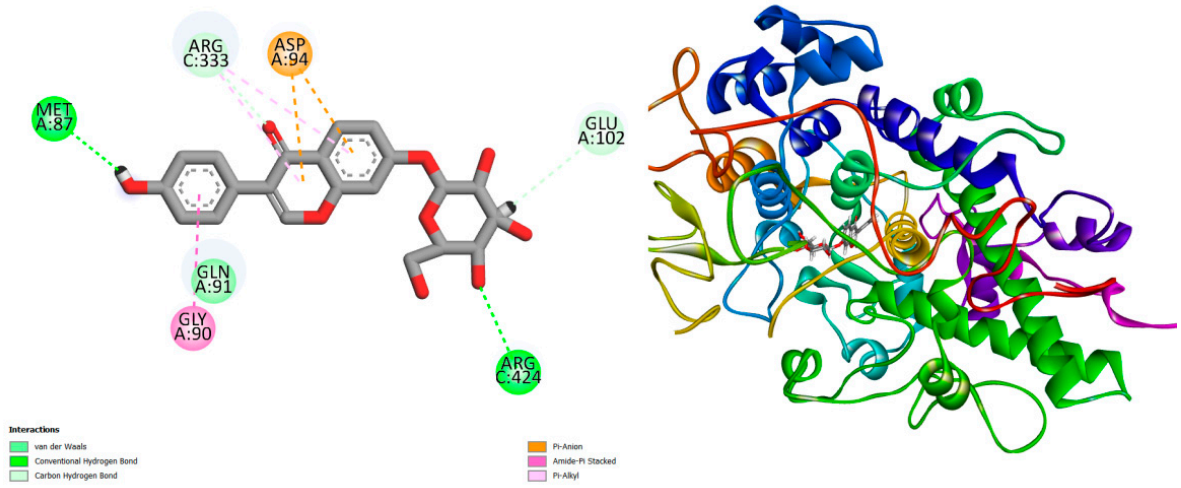

Figure 2. displays the docking outcomes of Structure of Crystal Human human myeloperoxidase isoform C (MPO) in conjunction with docked Daidzin-11 kcal mol , within the Ligand Binding Site, as analyzed by Autodock Vina with pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and Daidzin. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Daidzin.

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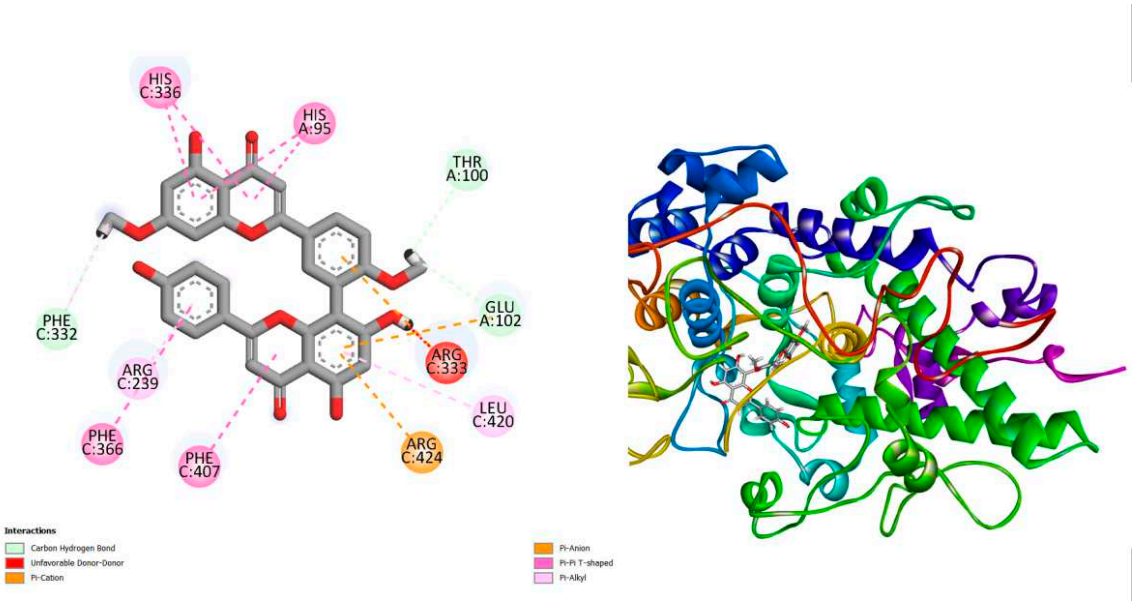

Figure 3. dsplays the docking outcomes of Structure of Crystal Human human myeloperoxidase isoform C (MPO) in conjunction with docked Ginkgetin -11.3 kcal mol , within the Ligand Binding Site, as analyzed by Autodock Vina with pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and Ginkgetin. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Ginkgetin.

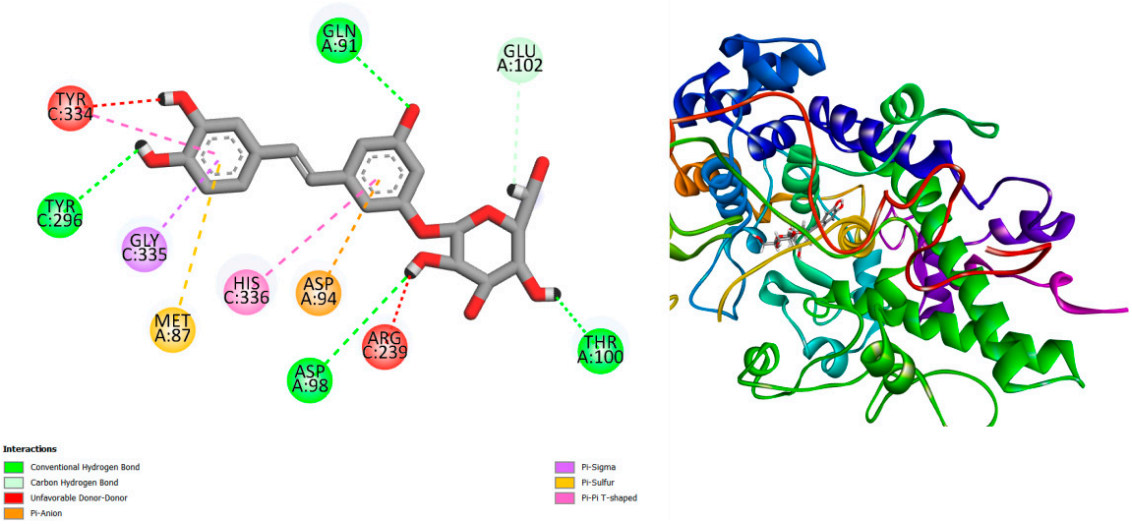

Figure 4. dsplays the docking outcomes of Structure of Crystal Human human myeloperoxidase isoform C (MPO) in conjunction with docked Astringin -10 kcal mol, within the Ligand Binding Site, as analyzed by Autodock Vina with pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and Astringin. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Astringin.

Table 1. shows the comparison of predicted toxicity parameters estimated by PkCSM Server of best docking compounds evaluatred by pyrx program.

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Compounds	AMES toxicity	Max. tolerated dose(human) (logmg/kg/day)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity
Amentoflavone	no	0.438	no	Yes	2.527	3.572	no
Daidzin	no	0.488	no	Yes	2.738	4.717	no
Ginkgetin	no	0.427	no	Yes	2.733	2.475	No
Astringin	**no**	**0.554**	**no**	**no**	**2.495**	**4.371**	**No**

4. Conclusion

In conclusion, our investigation into myeloperoxidase using a Molecular Docking approach with natural compounds revealed promising candidates, including Polydatin, Daidzin, Astringin, Ginkgetin, and Amentoflavone, showcasing excellent binding capacity. Additionally, toxicity prediction studies employing pkCSM indicated that these compounds are generally non-toxic, with Astringin standing out as particularly favorable due to its high maximum tolerated dose (human) and positive effects on Oral Rat Chronic Toxicity, as well as dual hERG II and hERG I inhibition. These findings suggest the potential applicability of these compounds in cardiovascular research, offering insights into their safety and efficacy profiles.

Conflicts of Interest: The authors declare no conflicts of interest.

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