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Exploring The Potential of *Momordica charantia L*. as a Natural Therapeutic Agent for Osteoarthritis: In-Silico Analysis of ADAMTS-5 and Binding Potential Assessment

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Abstract

Osteoarthritis (OA) is a prevalent global health issue, with its incidence increasing steadily due to aging populations and unhealthy lifestyles. This study explored the potential of *Momordica charantia L*, a plant known for its potent antioxidant, anti-inflammatory, and anti-degenerative properties, as a therapeutic agent for osteoarthritis. An *in-silico* analysis was conducted to investigate the phylogeny, antigenicity, and structural insights of a Disintegrin and Metalloproteinase with ThromboSpondin motifs 5 (ADAMTS-5), a key enzyme involved in OA progression and the binding potential of *Momordica charantia L* on ADAMTS-5. Techniques in structural bioinformatics and theoretical chemistry were used to discover novel inhibitors of ADAMTS-5 by utilizing molecular docking and molecular mechanics generalized Born surface area (MM-GBSA). This novel technique facilitated the discovery of new molecules that hold potential as inhibitors of ADAMTS-5, thereby providing an alternative avenue for osteoarthritis treatment. Given the pressing need for safe and effective OA treatments, this study offers a promising therapeutic approach and highlights the importance of further research.

Keyword: Osteoarthritis; Aggrecan; ADAMTS-5; Molecular docking; ADMETox; Disease-modifying Osteoarthritis Drugs (DMOADs)

1. Introduction

Osteoarthritis (OA) is a disabling, progressive, and painful joint disease that ranks prominently among global public health priorities (Chow & Chin, 2020). It is one of the most common diseases that affect millions of people globally, with older people above fifty years being the most affected (Pegreffi *et al.,* 2023). OA is defined as wearing joint cartilage and subchondral bone, causing intense pain, stiffness, and reduced motion and flexibility, significantly affecting daily functioning and quality of life (Grässel *et al.,* 2021). The global rates of OA have been rising steadily due to increased lifespans and a higher prevalence of risky dieting and non-physical activities (Scheuing *et al.,* 2023). Despite negatively impacting millions worldwide, OA is a burden due to treatment costs and lost productivity (Fang & Zhao, 2021; Liu *et al.,* 2024). The pathogenesis of OA involves several biological processes related to the disease that may occur in parallel or sequentially. Since aggrecan is an important cartilage structural protein, degraded aggrecan is likely to impact the stability of joints. Other alterations in the properties of aggrecan are important in understanding OA through the accelerated breakdown of the cartilage matrix (Peng *et al.,* 2021).

One more enzyme, identified as ADAMTS-5 (A disintegrin-like and metalloproteinase with thrombospondin motifs-5), participates in the aggrecan breakdown within the cartilage. This enzyme is recognized as the most potent aggrecanase affecting human cartilage. Notably, ADAMTS-5 is primarily linked with the deterioration of the N-terminal IGD segment of aggrecan, as documented by Santamaria and de Groot in 2020, also Kemberi *et al* in 2023. This cleavage produces aggrecan residuals, which are more susceptible to other proteases, and this enhances the release of aggrecan and the weakening of the extracellular matrix, ultimately contributing to the development of OA (Yamamoto *et al.,* 2021; Li *et al.,* 2022). The breakdown of aggrecan and other extracellular matrix (ECM) proteins has a notable effect on the chondrocyte signaling cascade and various metabolic processes within cartilage. This process alters the production of ECM proteins and diminishes the creation of anabolic signals typically responsible for maintaining healthy cartilage, as evidenced by (Chery *et al.,*2020; Peng *et al.,* 2021). The degradation of aggrecan and other ECM proteins can lead to changes in the signaling cascade of chondrocytes and metabolic

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processes, ultimately affecting the maintenance and repair of cartilage. This has implications for cartilage's overall health and function, particularly in conditions such as osteoarthritis (Peng *et al.,* 2021). These changes also affect the mechanical properties of cartilage and weaken them, thereby making them more vulnerable to mechanical stress and other related factors that contribute to cartilage degeneration. It has been shown that aggrecan degradation is one of the key factors in the pathogenesis of OA, which directly affects joint tissue remodeling and breakdown of the extracellular matrix and contributes to increased production of inflammatory cytokines in chondrocytes of osteoarthritic joints (Liu *et al.,* 2022).

The approach targeting ADAMTS-5 is a potential solution for formulating a new class of DMOADs (Oo *et al.*,2021; Kim *et al.,* 2022; Lin *et al.,* 2023). Currently, no approved DMOADs are available in the market, but few inhibitors specifically targeting ADAMTS-5 have given promising outcomes, reducing aggrecan breakdown and delaying OA progression in different animal models (Brebion *et al.,* 2021; Latourte & Richette, 2022). Hence, the attempt at targeting ADAMTS-5 presents a potential way to treat OA; the design of effective ADAMTS-5 inhibitors appears as a major advancement toward forming DMOADs for this painful disease.

Bitter gourd is a monoecious plant called '*Momordica charantia L*' and falls under the family Cucurbitaceae, which has proven to have enormous nutritive and medicinal importance (Waqas Mazhar *et al.,* 2024). Previous works have also demonstrated that *Momordica charantia L* possesses strong antioxidant activity, anti-inflammatory ability, anticancer propensity, and anti-degenerative effect, suggesting it might be used to cure OA (Shal *et al.,* 2018). Experimental research has also shown promising results on different models of why the compound could slow cartilage degeneration and reduce the inflammation seen in OA.

Momordica charantia contains a diverse array of active ingredients, including alkaloids, flavonoids, terpenoids, and phenolic compounds, which have been identified as potential therapeutic agents (de Oliveira *et al.,* 2018; Gayathry & John, 2022). These compounds exhibit anti-inflammatory and antioxidant properties, suggesting that their mechanisms of action involve the modulation of signaling pathways related to oxidative stress and inflammation. Given the increasing prevalence of OA and its substantial economic burden, identifying novel therapeutic avenues for safe and effective treatments is paramount (Cai *et al.,* 2021).

This study contributes a novel dimension to the existing knowledge of OA biology by providing a comparative analysis of ADAMTS-5. Through in-silico analysis, the phylogeny, antigenicity, and structural insights of ADAMTS-5 were explored, offering valuable insights into the molecular characterization of this enzyme. Furthermore, the binding potential of *Momordica charantia L* on ADAMTS-5 was investigated using a computational approach. This investigation explores the potential of natural products, such as *Momordica charantia L*, in inhibiting ADAMTS-5 activity and reducing inflammation, offering a valuable avenue for treating OA.

2. Materials and Methods

2.1. Computational Investigation

The computational investigation used the Schrödinger Suite software (Maestro 12.8) (https://www.schrodinger.com).

2.2. Target Preparation

The three-dimensional crystal structure of ADAMTS-5 complexed with the inhibitor GLPG1972 (PDB ID: 6YJM) was selected from the RCSB Protein Data Bank. This structure has a resolution below 2.3Å, an R-value free of 0.256, an R-value Work of 0.212, and an R-value observed of 0.215 (https://www.rcsb.org). Maestro's Schrödinger Suite's Protein Preparation Wizard tool (https://www.schrodinger.com) was employed to import and prepare the protein structure (Ruswanto *et al.,* 2024). The preparation process encompassed several steps: assigning bond orders, adding hydrogens, creating zero-order metal bonds, generating disulfide bonds, removing water molecules, and generating het states using Epik at pH levels ranging from 7.0 to 9.0. PROPKA pH 7.0 (https://propka.readthedocs.io) was utilized to refine the protein by optimizing hydrogen bond assignments. After removing water molecules located further than 3.0 Å from het groups, restrained minimization was done using the OPLS4 force field to minimize the protein. The Ramachandran Plot was generated and saved to validate the protein structure.

2.3. Ligand Preparation

118 compounds associated with *Momordica charantia L* were gathered from the PubChem database. To predict their inhibitory potential, these compounds underwent molecular docking with the active site of ADAMTS-5. The structures of these compounds, obtained in SDF format, were imported into the LigPrep tool in the Maestro Schrödinger panel. The OPLS4 force field (https://www.schrodinger.com/platform/products/opls4) was employed to perform energy minimization, ensuring the generation of a maximum of one stereoisomer per ligand.

2.4. Active Site Prediction

The active site of the ADAMTS-5 protein (PDB ID: 6YJM) was predicted for ligand binding using the Receptor Grid Generation tool. This tool created a three-dimensional cubic grid box around the binding site, encompassing all the amino acid residues in the active site region (Ruswanto *et al.,* 2024). The grid was generated by selecting the co-crystallized ligand present at the active site of ADAMTS-5. The calculated three-dimensional coordinates of the generated grid were 77.81 Å, 26.87 Å, and -29.61 Å. Predicting the active site of a protein is a crucial step in structure-based drug design and virtual screening. Grid-based methods are commonly used to represent the binding site and efficiently sample the conformational space of potential ligands. The grid allows for rapid evaluation of different ligand poses and facilitates the identification of favorable interactions between the ligand and receptor (Tung *et al.,* 2023).

2.5. Molecular Docking

Molecular docking was performed using the ligand docking tool in Maestro version 12.8. The process began

with High-Throughput Virtual Screening (HTVS), which rapidly identified potential ligands by treating both the ligand and target as rigid entities. This was followed by Super Precision (SP) docking, which employed increased sampling precision to refine ligand binding evaluation. Extra Precision (XP) docking was conducted with a rigid body, utilizing a more refined scoring function and exhaustive conformational exploration. Finally, XP docking with Flexible Docking was performed to simulate better realistic ligand-target interactions and account for potential conformational changes in target proteins. The binding free energy of all the docked complexes was determined using MM-GBSA, a tool compatible with Prime in Schrödinger Maestro 12. 8. This was done through thermodynamics calculations within the program to establish the extent of interaction between the molecules (Srinivasa *et al*., 2024).

2.6. Drug-likeness, Pharmacokinetic, and Toxicity Prediction

The investigated ligands ' pharmacokinetic aspects and possible toxicity were analyzed using the SwissADME and Pro-Tox II online tools to determine the drug-likeness. This assessment entailed the general evaluation of the ADMET properties, which are significant measures that indicate the nature of a compound and its functionality within the human body. ADMET comprises parameters such as Absorption, Distribution, Metabolism, Excretion, and toxicity that define any compound's suitability for the likely use of a drug (Diningrat *et al.*, 2023). Besides the ADMET evaluation, other significant molecular descriptors such as the molecular weight (MW), the number of HBA (hydrogen bond acceptors), the number of HBD (hydrogen bond donors), and the TPSA (topological polar surface area) were calculated for the considered compounds. These descriptors were measured based on the Lipinski rule of 5.

2.7. Quantitative Structure-Activity Relationship (QSAR) Model.

Data concerning the activity of ADAMTS-5 inhibitors was sourced from the CHEMBL database. To initiate the process of QSAR and search for antagonists, the protein's FASTA sequence extracted from the PDB under the accession code 6YJM (https://www.rcsb.org/structure/6YJM), was employed to query the CHEMBL database (https://www.ebi.ac.uk/chembl/). The list of inhibitors was transformed into an ".SDF" format through the use of DataWarrior software, after which the ligands were prepared and used for QSAR creation with the AutoQSAR module. Among the generated models, the best model was determined based on ranking, leading to the selection of the KPLS_MOLPRINT2D_7 model. This model was utilized to predict the bioactivity of the top compounds highlighted in the research.

3. Results and Discussion

Osteoarthritis is among the most prevalent forms of arthritis, characterizing joint pain in millions of people worldwide and the elderly population. It is now prevalent all over the globe due to aspects like population ageing and others, including obesity and a sedentary lifestyle (Hawker, 2019; Allen *et al.*, 2022). Aggrecan degradation contributes to the emergence of discomfort, rigidity, and limited movement, resulting in disability and reduced economic productivity globally. Aggrecan plays a pivotal role as a primary proteoglycan in cartilage tissue, vital for maintaining joint integrity. The involvement of ADAMTS-5 in aggrecan degradation is associated with the progression of OA. Therefore, discovering compounds capable of inhibiting ADAMTS-5 represents a potential approach to managing OA (Hawker, 2019).

Table 1. Docking and MMGBSA scores of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site.

COMPOUND NAME	DOCKING SCORE (Kcal/mol)	MM/GBSA (ΔGbind)
Isoquercitrin	-11.659	-51.54
Chlorogenic acid	-11.648	-53.77
Quercitrin	-11.172	-68.96
Epicatechin	-10.443	-54.61
Catechin	-10.349	-54.24
Naringenin-7-O-glucoside	-10.188	-59.78
Luteolin-7-O-glucoside	-9.863	-57.61

In this study, a computational method was used to look for possible lead compounds from MC that can antagonise the activity of the ADAMTS-5 enzyme. Schrodinger Maestro 12. 8 was used to perform molecular docking on 118 compounds against the binding pocket of ADAMTS-5 enzyme (PDB ID: 6YJM). Firstly, the compounds were sorted according to the docking score and then further evaluated according to their MMGBSA score and ADMETox features. These findings indicated that the selected hit compounds were well positioned into the active site of the ADAMTS-5.

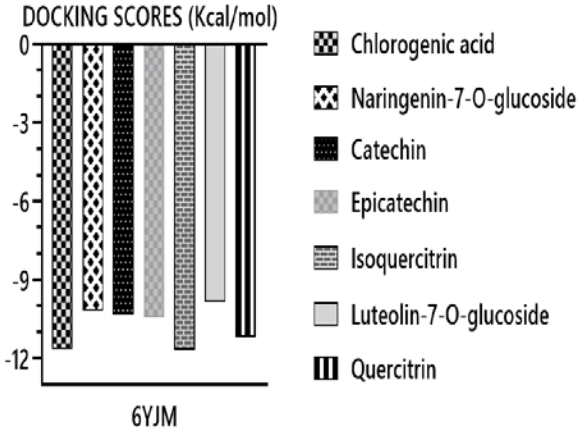


Figure 1: Chart showing the docking scores of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site.

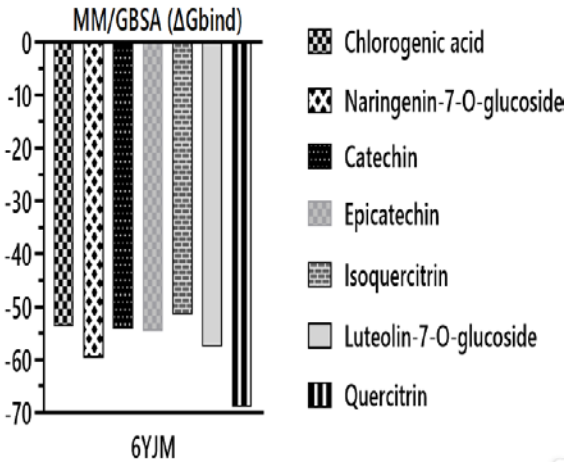


Figure 2: Chart showing the MMGBSA scores of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site.

From Isoquercitrin to Luteolin-7-O-glucoside, the compounds displayed a pronounced binding affinity with the ADAMTS-5 active site, with negative binding energies indicating a high level of affinity. The lead compounds listed in Table 1 exhibited primary amino acid interactions with crucial hydrophobic amino acid residues such as PHE 406, ILE 442, LEU 443, LEU 379, and MET 381(Figure 3), which are essential for ADAMTS-5's binding site and catalytic activity. These docked molecules also form hydrogen bonds with GLH 411, GLY 380, LEU 379, and THR 378 within the ADAMTS-5 binding pocket, thereby effectively saturating its active region. The best bioactive molecule Isoquercitrin, which has a maximum binding energy of -11.659Kcal/mol, forms a hydrogen bond with the residues GLH 411, GLY 380, LEU 379, THR 378 and ASP 377 and interact with the hydrophobic amino residues PHE 406, LEU 438, ILE 442, LEU 443, ILE 446, LEU 379 and MET 381(Figure 3; Table 2).

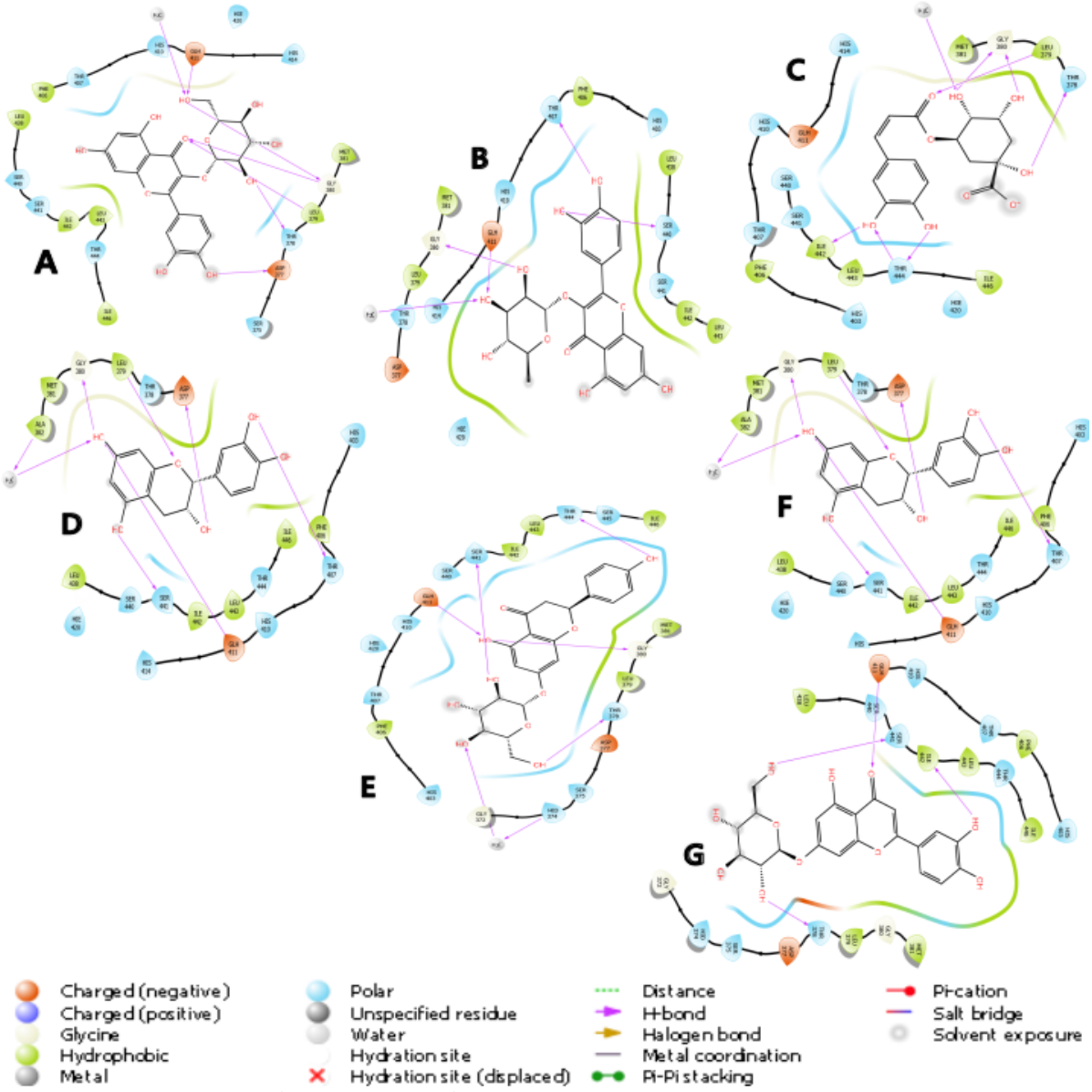


Figure 3: 2D-molecular interaction of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site: **(A)** Isoquercitrin **(B)** Quercitrin **(C)** Chlorogenic acid **(D)** Epicatechin **(E)** Naringenin-7-O-glucoside **(F)** Catechin **(G)** Luteolin-7-O-glucoside

With binding energies of -11.648Kcal/mol, Chlorogenic acid is thought to form hydrogen bonds with the aliphatic amino acids GLY 380, LEU 379, THR 378, ILE 442 and THR 444 and interact with the key amino acids MET 381, LEU 379, PHE 406, ILE 442, LEU 443 and ILE 446. Quercitrin completely occupied the ADAMTS-5 binding site, displaying a binding energy of -11.172Kcal/mol while interacting with the hydrophobic amino acids MET 381, LEU 379, LEU 443, ILE 442, LEU 438, and PHE 406, alongside amino acid residues GLY 380, GLH 411, SER 440, and THR 407 via hydrogen bonds.

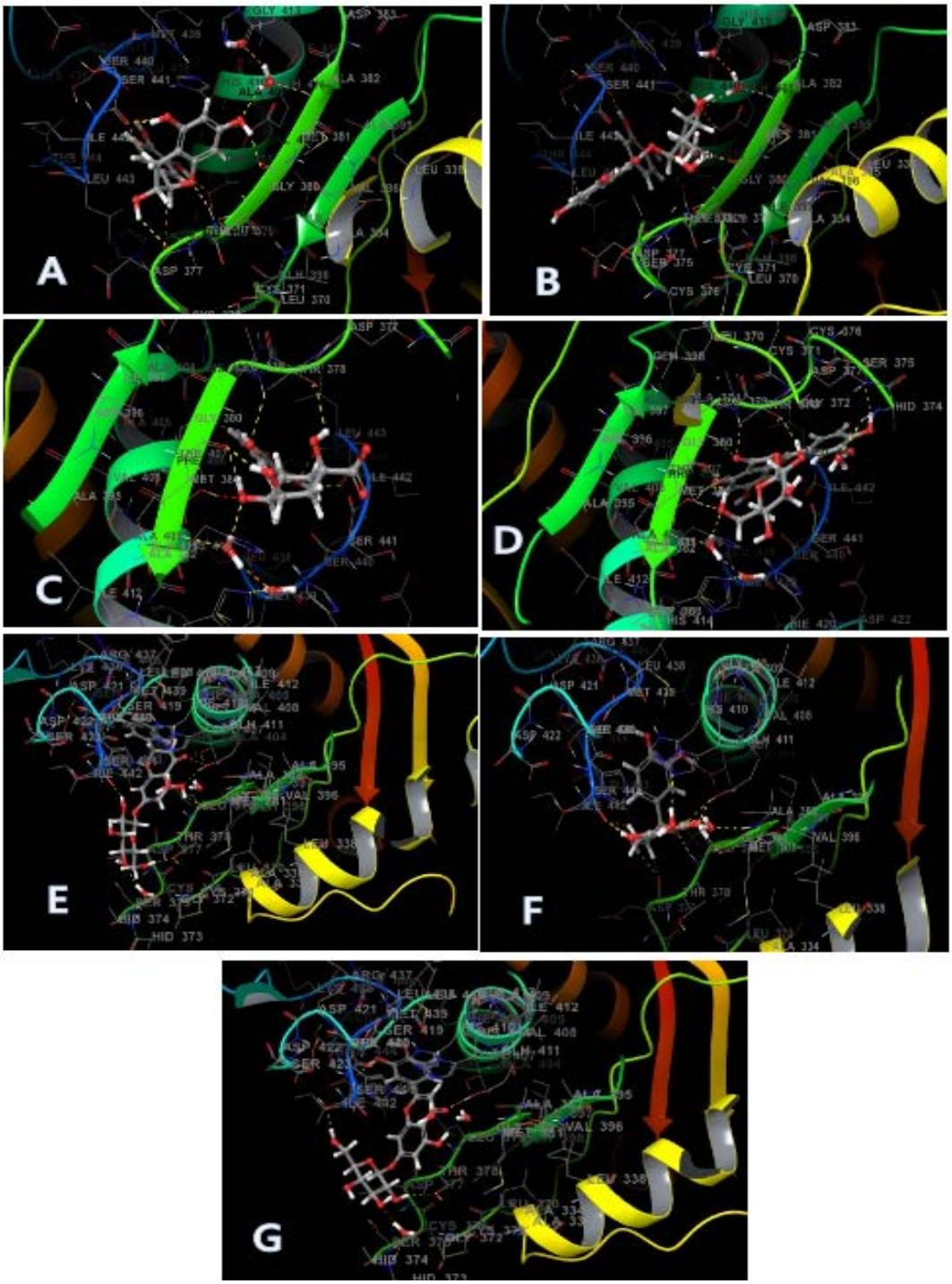


Figure 4: 3D-molecular interaction of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site: **(A)** Isoquercitrin **(B)** Quercitrin **(C)** Chlorogenic acid **(D)** Epicatechin **(E)** Naringenin-7-O-glucoside **(F)** Catechin **(G)** Luteolin-7-O-glucoside

While establishing a hydrogen bonding connection with the amino acid GLY 380, LEU 379, ASP 377, GLH 411 and THR 407, Epicatechin and Catechin had binding energies of -10.443Kcal/mol and -10.349Kcal/mol respectively, with both interacting with the hydrophobic amino acids ALA 382, MET 381, LEU 379, PHE 406, ILE 446, LEU 443, ILE 442 and LEU 438 residues. Naringenin-7-O-glucoside, with binding eniergies of -10.188Kcal/mol interacts with key residues ILE 446, LEU 443, ILE 442, PHE 406, MET 381and LEU 379 through

amino acid interactions, while also forming hydrogen bonds with THR 444, SER 441, GLY 380, THR 378 and HID 374 residues. Luteolin-7-O-glucoside, having binding energies of -9.863Kcal/mol, forms hydrogen bonds with the residues ILE 442, SER 441, GLH 411 and THR 378 and interacts with the hydrophobic amino residues as Isoquercitrin (PHE 406, LEU 438, ILE 442, LEU 443, ILE 446, LEU 379 and MET 381). These findings indicate that these compounds have strong potential to bind the ADAMTS-5 enzyme in the treatment of various arthritis, particularly osteoarthritis.

Table 2: Hydrogen Bonds and Hydrophobic interactions of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site

COMPOUNDS	H-BOND	Hydrophobic interacting amino acids	Other Interactions
Isoquercitrin	GLH 411, GLY 380, LEU 379, THR 378, ASP 377	PHE 406, LEU 438, ILE 442, LEU 443, ILE 446, LEU 379, MET 381	None
Chlorogenic acid	GLY 380, LEU 379, THR 378, ILE 442, THR 444	MET 381, LEU 379, PHE 406, ILE 442, LEU 443, ILE 446	None
Quercitrin	GLY 380, GLH 411, SER 440, THR 407	MET 381, LEU 379, LEU 443, ILE 442, LEU 438, PHE 406	None
Epicatechin	GLY 380, LEU 379, ASP 377, GLH 411, THR 407	ALA 382, MET 381, LEU 379, LEU 438, ILE 442, LEU 443, ILE 446, PHE 406	None
Catechin	GLY 380, LEU 379, ASP 377, THR 407, GLH 411, SER 441	ALA 382, MET 381, LEU 379, PHE 406, ILE 446, LEU 443, ILE 442, LEU 438	None
Naringenin-7-O-glucoside	THR 444, SER 441, GLY 380, THR 378, HID 374	ILE 446, LEU 443, ILE 442, PHE 406, MET 381, LEU 379	None
Luteolin-7-O-glucoside	ILE 442, SER 441, GLH 411, THR 378	ILE 446, PHE 406, LEU 443, ILE 442, LEU 438, MET 381, LEU 379	None

The binding affinities of ADAMTS-5 lead compounds were further evaluated using the MMGBSA and Schrodinger program. This method involves calculating the free energy change of binding for the ligands in their binding pose. Isoquercitrin, Chlorogenic acid, Quercitrin, Epicatechin, Catechin, Naringenin-7-O-glucoside and Luteolin-7-O-glucoside had binding free energies of -51.54ΔGbind, -53.77ΔGbind, -68.96ΔGbind, -54.61ΔGbind, -54.24ΔGbind, -59.78ΔGbind and -57.61ΔGbind respectively (Table 1; Figure 2).

Table 3: Pharmacokinetics profile of lead compounds of *Momordica charantia L* docked against ADAMTS-5 active site

MODEL	QPlogHERG	QPlogBB	QplogKhsa
Isoquercitrin	-5.085	-3.468	-0.885
Chlorogenic acid	-3.298	-3.328	-0.917
Quercitrin	-5.22	-3.29	-0.661
Epicatechin	-4.41	-1.88	-0.442
Catechin	-4.302	-1.853	-0.441
Naringenin-7-O-glucoside	-5.786	-3.239	-0.719
Luteolin-7-O-glucoside	-5.819	-3.952	-0.808

QPlogHERG: IC50 value for blockage Human Ether-a-go-go-Related Gene (hERG) K+ channels (below − 5)

QPlogBB: Brain/blood partition coefficient (− 3.0 to 1.2)

QplogKhsa: Binding to human serum albumin (− 1.5 to + 1.5)

It is imperative to comprehend the pharmacokinetics of phytochemicals for their use as new agents for drug administration (Rai *et al.*, 2023; Rathaur and SR, 2019). To predict the pharmacokinetic properties of the lead compounds, the QikProp activity available in the Maestro software was used. This included the determination of compounds' affinity to human serum albumin (QPlogkhsa), the blood-brain barrier penetration (QPPlogBB), and finally the 50% inhibitory concentration concerning Human Ether-a-go-go-Related Gene (hERG) K+ channels (QPlogHERG). As shown in Table 3, all designed lead compounds targeting the ADAMTS-5 enzyme are within the QPlogKHSA range of 0-0.5, suggesting their promising drug candidacy. This range of values signals that the compounds may have favourable pharmacokinetic characteristics; longer circulation within the body, improved distribution in the tissues, and slower clearance rates which could benefit their therapeutic outcomes. As demonstrated in Table 3, none of the HERG values recorded for all the compounds selected for the study were above 10µM, proving that these are good compounds to work with for drug discovery and development from the perspective of cardiac safety. Indeed, this discovery is very important to note because substances with low degrees of HERG inhibition can help to prioritize promising drug candidates with better cardiovascular characteristics. As seen earlier, all the lead compounds were found to possess reasonable log bb/p values that fall in between the expected range.

Table 4: In-silico drug likeness prediction of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site

COMPOUNDS	MW	HBA	HBD	TPSA	ILOGP	LOGKP	ROV
Isoquercitrin	464.40	12	8	210.51	0.94	-8.88	2
Chlorogenic acid	354.31	9	6	164.75	0.87	-8.76	1
Quercitrin	448.38	11	7	190.28	1.60	-8.42	2
Epicatechin	290.27	5	5	110.38	1.47	-4.594	0
Catechin	290.27	6	5	110.38	1.33	-7.82	0
Naringenin-7-O-glucoside	434.39	10	6	166.14	2.35	-8.49	1
Luteolin-7-O-glucoside	448.38	11	7	190.28	1.76	-8.00	2

Table 5: The bio-availability and pharmacokinetic properties (ADMETox) of the lead compounds from *Momordica charantia L* docked against ADAMTS-5 active site

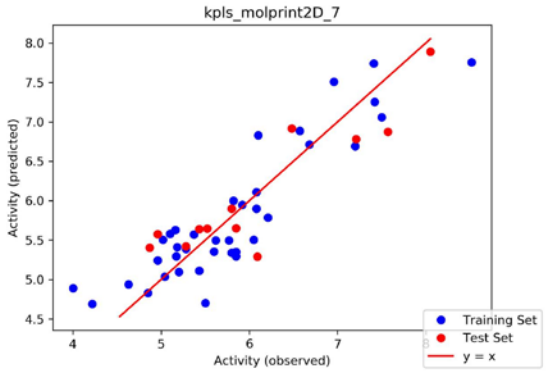
Models	Isoquercitrin	Chlorogenic acid	Quercitrin	Epicatechin	Catechin	Naringenin-7-O-glucoside	Luteolin-7-O-glucoside
BBB	Does not cross	Does not cross	Does not cross	Does not cross	Does not cross	Does not cross	Does not cross
GI absorption	Low	Low	Low	High	High	Low	Low
CYP2C9 Inhibitor	No	No	No	No	No	No	No
CYP2C19 Inhibitor	No	No	No	No	No	No	No
CYP1A2 Inhibitor	No	No	No	No	No	No	No
CYP3A4 Inhibitor	No	No	No	No	No	No	No
CYP2D6 Inhibitor	No	No	No	No	No	No	No
P-gp Substrate	Yes	No	No	Yes	Yes	Yes	Yes
Carcinogenicity	No	No	Yes	No	No	No	No
Hepatotoxicity	No	No	No	No	No	No	No
Mutagenicity	No	No	No	No	No	No	No
Cytotoxicity	No	No	No	No	No	No	No

The drug discovery and development process requires a thorough evaluation of the suitability of potential compounds (Adelusi *et al.*, 2022). One well-established method for assessing this suitability is the Lipinski rule of five (RO5), which takes into account various factors including molecular weight, lipophilicity, hydrogen bond donors, and the number of rotatable bonds (Daoud *et al.*, 2023). As per the Lipinski Rule of Five, a drug is deemed to exhibit favourable oral bioavailability if its molecular weight is under 500, its log P value is less than 5, it possesses fewer than 5 hydrogen bond donors, and has fewer than 10 hydrogen bond acceptors (Chen *et al.*, 2020; Olugbogi *et al.*, 2024). This evaluation is instrumental in determining the potential of a molecule to be developed into an oral drug with minimal adverse effects.

The results of the drug-likeness property analysis are presented in Table 4. All investigated compounds conform to Lipinski's ROV computations. Table 5 shows the result obtained from the ADMETox software, suggesting that none of the ligand molecules selected can pass through the blood-brain barrier. According to the results, the bioavailability level of Epicatechin and Catechin possesses a positive alert of human intestinal absorption in the human body, and all the selected ligand molecules are potential inhibitors of the CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 metabolic enzymes. It can be postulated that Chlorogenic acid and Quercitrin are not effluxed through P-glycoprotein and are therefore not substrates. Moreover, not all the chosen ligand molecules showed any signs of carcinogen, mutagen, hepatotoxic or cytotoxic nature apart from quercetin, which proved to be a carcinogen.

3.1. Auto-QSAR Model

The Quantitative Structure-Activity Relationship (QSAR) methodology is a computational and statistical modelling approach to predict biological activity (or physicochemical properties) of chemical compounds from their molecular structure. It calculates a quantitative correlation between molecular structural features and observed biologic or chemical activities. QSAR has become a popular method in drug discovery, toxicology and environmental chemistry to design new compounds with specific properties or predict a compound's activity for compounds that have not been tested (Samuel *et al.*, 2023).



The developed QSAR model correctly clones the biological activities of the leading compounds and juxtaposes them to the standard ADAMTS-5 inhibition. The AutoQSAR module was used in constructing the QSAR model. The best model (KPLS_MOLPRINT2D_7)

for predicting the pIC50 values of the top compounds has an R-squared value of 0.8097, a Q-squared value of 0.8033 and the root mean square error (RMSE) stands at 0.4391, with a standard deviation (S.D) of 0.4200. Thus, our result is suggestive of the positive therapeutic potential of phytochemical compounds of *Momordica charantia L* on inhibition of ADAMTS-5 when compared to the standard ADAMTS-5 inhibitors.

3.2. LIMITATION

while this study provides a strong foundation for further investigation of *Momordica charantia L.* compounds as potential ADAMTS-5 inhibitors, it should be viewed as a starting point rather than a definitive assessment. The findings warrant experimental validation, cell-based studies, and eventually, animal models of osteoarthritis to elucidate these compounds' therapeutic potential fully.

4. Conclusion

The utilization of *Momordica charantia* leaf in this study has shown great potential as a potential drug for treating osteoarthritis. This plant possesses various beneficial properties, including strong antioxidant, anti-inflammatory, anticancer, and antidegenerative effects. These results have significant implications for the exploration of new therapeutic options for osteoarthritis treatment. Taken together, this study will inspire further research interest among scientists, leading to advancements in developing novel treatments for this debilitating condition.

5. Conflict of interests

The authors declare no conflict of interests.

Author Contribution

Akintoye Olabode Oluwadare, Ajibare Ayodeji Johnson and Olaniyi Kehinde Samuel conceptualised and designed the study.

Akintoye Olabode Oluwadare and Owolabi Blessing Tolulope provided the initial draft.

Akintoye Olabode Oluwadare, Ajibare Ayodeji Johnson, Owolabi Blessing conducted the whole experiment tasks and tests.

Akintoye Olabode Oluwadare, Taylor Olayinka Alfred, Ajibare Ayodeji Johnson, and Owolabi Blessing Tolulope contributed to data collection, formal analysis and statistical analysis.

All authors read and approved the final draft of the manuscript.

References

Adelusi, T. I., Oyedele, A. Q. K., Boyenle, I. D., Ogunlana, A. T., Adeyemi, R. O., Ukachi, C. D., ... & Abdul-Hammed, M. 2022. Molecular modeling in drug discovery. ***Informatics Med. Unlock.***, 29, 100880.

Allen, K. D., Thoma, L. M., & Golightly, Y. M. 2022. Epidemiology of osteoarthritis. ***Osteoarthr. Cartil.,*** 30(2), 184–195.

Brebion, F., Gosmini, R., Deprez, P., Varin, M., Peixoto, C., Alvey, L., ... & Amantini, D. 2021. Discovery of GLPG1972/S201086, a potent, selective, and orally bioavailable ADAMTS-5 inhibitor for the treatment of osteoarthritis. ***J. Med. Chem.,*** 64(6), 2937–2952.

Cai, X., Yuan, S., Zeng, Y., Wang, C., Yu, N., & Ding, C. 2021. New trends in pharmacological treatments for osteoarthritis. ***Front. Pharmacol.,*** 12, 645842.

Chen, X., Li, H., Tian, L., Li, Q., Luo, J., & Zhang, Y. 2020. Analysis of the physicochemical properties of acaricides based on Lipinski's rule of five. ***J. Comput. Biol.,*** 27(9), 1397–1406.

Chery, D. R., Han, B., Li, Q., Zhou, Y., Heo, S. J., Kwok, B., ... & Han, L. 2020. Early changes in cartilage pericellular matrix micromechanobiology portend the onset of post-traumatic osteoarthritis**.** ***Acta Biomater.,*** 111, 267–278.

Chow, Y. Y., & Chin, K. Y. 2020. The role of inflammation in the pathogenesis of osteoarthritis**.** ***Mediators Inflamm.,*** 2020.

Daoud, S., Alabed, S.J., Bardaweel, S.K. Mutasem O.T (2023). Discovery of potent maternal embryonic leucine zipper kinase (MELK) inhibitors of novel chemotypes using structure-based pharmacophores. ***Med. Chem. Res.,*** 32, 2574–2586.https://doi.org/10.1007/s00044-023-03160-5

de Oliveira, M. S., da Costa, W. A., Bezerra, F. W. F., AraÃºjo, M. E., Ferreira, G. C., & de Carvalho Junior, R. N. 2018. Phytochemical profile and biological activities of Momordica charantia L.(Cucurbitaceae): A review. ***Afr. J. Biotechnol.,*** 17(27), 829–846.

Diningrat, D. S., Sari, A. N., & Harahap, N. S. (2023). Potential of Bioactive Compounds from Jamblang (Syzygium Cumini) and Hanjeli (Coix lacryma-jobi L.) Essential Oils as SARS-COV-2 Antivirus Targeting NSP5 and ACE2 Receptors. ***Jordan J. Biol. Sci.,*** 16(4).

Fang, T., Zhou, X., Jin, M., Nie, J., & Li, X. 2021. Molecular mechanisms of mechanical load-induced osteoarthritis. ***Int. Orthop.,*** 45, 1125–1136.

Gayathry, K. S., & John, J. A. 2022. A comprehensive review on bitter gourd (Momordica charantia L.) as a gold mine of functional bioactive components for therapeutic foods. ***Food Prod. Process. Nutr.,*** 4(1), 1–14.

Grässel, S., Zaucke, F., & Madry, H. 2021. Osteoarthritis: novel molecular mechanisms increase our understanding of the disease pathology. ***J. Clin. Med.,*** 10(9), 1938..

Hawker, G. A. 2019. Osteoarthritis is a serious disease. ***Clin. Exp. Rheumatol.,*** 37(Suppl 120), 3–6.

Kemberi, M.; Salmasi, Y.; Santamaria, S. 2023. The Role of ADAMTS Proteoglycanases in Thoracic Aortic Disease. ***Int. J. Mol. Sci.,*** 24, 12135. https://doi.org/10.3390/ ijms241512135

Kim, H., Seo, J., Lee, Y., Park, K., Perry, T. A., Arden, N. K., & Choi, H. 2022. The current state of the osteoarthritis drug development pipeline: a comprehensive narrative review of the present challenges and future opportunities. ***Ther. Adv. Musculoskelet. Dis.,*** 14, 1759720X221085952..

Latourte, A., & Richette, P. 2022. Inhibition of ADAMTS-5: the right target for osteoarthritis?**.** ***Osteoarthr. Cartil.,*** 30(2), 175–177.

Li, T., Peng, J., Li, Q., Shu, Y., Zhu, P., & Hao, L. 2022. The mechanism and role of ADAMTS protein family in osteoarthritis. ***Biomolecules,*** 12(7), 959.

Lin, J., Jia, S., Zhang, W., Nian, M., Liu, P., Yang, L., ... & Zhang, X. 2023. Recent advances in small-molecule inhibitors for the treatment of osteoarthritis. ***J. Clin. Med***., 12(5), 1986.

Liu, S., Deng, Z., Chen, K., Jian, S., Zhou, F., Yang, Y.,& Zhu, W. 2022. Cartilage tissue engineering: From proinflammatory and anti-inflammatory cytokines to osteoarthritis treatments. ***Mol. Med. Rep***., 25(3), 1–15

Liu H, Wu X, Liu R, Wang W, Zhang D, Jiang Q, 2024. Cartilage-on-a-chip with magneto-mechanical transformation for osteoarthritis recruitment**,** ***Bioact. Mater***., 33, 61–68. ISSN 2452-199X,https://doi.org/10.1016/j.bioactmat.2023.10.030.

Muhammad Waqas Mazhar, Muhammad Ishtiaq, Mehwish Maqbool, Eman A. Mahmoud, Fazal Ullah & Hosam O. Elansary (2024) Optimizing bitter gourd (Momordica charantia L.) performance: exploring the impact of varied seed priming durations and zinc oxide nanoparticle concentrations on germination, growth, phytochemical attributes, and agronomic outcomes, ***Coqent Food Agric***., 10(1), 2313052.DOI: 10.1080/23311932.2024.2313052

Olugbogi, E. A., et al. (2024). Unlocking Neurodegeneration: Scaffold-Derived Blockers of MAO-B and AChE inspired by *Bryophyllum pinnatum*: A Structural Exploration**.** Preprint.

Oo, W. M., Little, C., Duong, V., & Hunter, D. J. (2021). The development of disease-modifying therapies for osteoarthritis (DMOADs): the evidence to date. ***Drug Des. Devel. Ther,*** 15, 2921–2945.

Peng, Z., et al. **(**2021). The regulation of cartilage extracellular matrix homeostasis in joint cartilage degeneration and regeneration. ***Biomaterials***, 268**,** 120555.

Pegreffi, F., et al. (2023). Prevalence of Sarcopenia in Knee Osteoarthritis: A Systematic Review and Meta-Analysis. ***J. Clin. Med.***, 12(4), 1532. https://doi.org/10.3390/jcm12041532

Rai, M., et al. (2023). Herbal concoction unveiled a computational analysis of phytochemicals' pharmacokinetic and toxicological profiles using novel approach methodologies (NAMs). **Curr. Res. Toxicol.**, 5, 100118.

Rathaur, P., & SR, K. J. (2019). Metabolism and pharmacokinetics of phytochemicals in the human body. ***Curr. Drug Metab.*** 20(14), 1085–1102.

Ruswanto, R., et al. (2024). Potential Active Compounds of Propolis as Breast Anticancer Candidates: In Silico Study. ***Jordan J. Biol. Sci.***, 17**(**1).

Belfield, S. J., et al. (2023). A review of quantitative structure-activity relationship modelling approaches to predict the toxicity of mixtures. ***Comput. Toxicol.***, 25, 100251. https://doi.org/10.1016/j.comtox.2022.100251

Santamaria, S., & de Groot, R. (2020). ADAMTS proteases in cardiovascular physiology and disease. ***Open Biol.***, 10(12), 200333.

Scheuing, W. J., et al. (2023). The burden of osteoarthritis: Is it a rising problem? ***Best Pract. Res. Clin. Rheumatol.*** 101836.

Shal, B., et al. (2018). Anti-neuroinflammatory potential of natural products in attenuation of Alzheimer's disease. ***Front. Pharmacol.***, 9**,** 548.

Shultz, M. D. (2018). Two decades under the influence of the rule of five and the changing properties of approved oral drugs: miniperspective. ***J. Med. Chem.***, 62(4), 1701–1714.

Srinivasa, M. G., et al. (2024). Novel Thiazolidinedione Linked 1,3,4-Oxadiazole Derivatives as AXL Inhibitors Targeting Breast Cancer: In-Silico Design, ADMET Screening, and MM-GBSA Binding Free Energy. ***Jordan J. Biol. Sci.***, 17(1).

Tung, K. C. C., et al. (2023). Molecular Simulations of *Moringa oleifera* Phytochemicals as Potential Antagonists of the Proinflammatory NF-κB p50 Transcription Factor. ***Jordan J. Biol. Sci.***, 16(3).

Yamamoto, K., et al. (2021). Targeting dysregulation of metalloproteinase activity in osteoarthritis. ***Calcif. Tissue Int.***, 109, 277–290.