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Investigating Marumoside A as a Bone Sarcoma Anticancer Agent using Computational Insights

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Abstract

Bone sarcoma, a group of aggressive cancers arising from bone or soft tissues, remains challenging to treat effectively. This study investigates the potential of Marumoside A, a phytochemical, as a therapeutic agent against bone sarcoma using computational methods. Molecular docking was performed to explore the

interactions between Marumoside A and key protein targets involved in bone sarcoma progression. Binding affinities and interaction profiles were analyzed to identify its mechanism of action. Drug-likeness and ADMET properties were assessed using SwissADME and StopTox tools, confirming compliance with pharmacokinetic and safety requirements. Marsumoside A exhibited strong binding affinities, favorable pharmacokinetic properties, and a low toxicity profile, highlighting its promise as a candidate for further preclinical evaluation. These findings underscore the therapeutic potential of Marumoside A in bone sarcoma treatment and warrant experimental validation.

Keywords: Bone Sarcoma, Marumoside A, Molecular Docking, Pharmacokinetics, ADMET Analysis

Introduction

Osteosarcoma is a malignant primary bone cancer that typically affects the arm and leg bones. It originates from the bone cells. It is particularly common among young adults and teenagers. Approximately one-third of incidents of bone cancer include osteosarcoma. It is the most frequent type of bone cancer. Every year in the United States, osteosarcoma affects around 1,200 patients. The majority of osteosarcomas are found in adolescents, whereas there is a slight rise in occurrence in those over 60. With a median incidence of 12 years for girls and 16 years for boys, it is the third most prevalent pediatric cancer. It is considered that malignant primitive mesenchymal cells, which develop into osteoblasts, which subsequently generate a malignant osteoid matrix, are the cause of osteosarcoma. Although osteosarcomas may appear in any bone, they generally grow in the long bones' metaphysis. About 60% of those fractures happen in the proximal tibia, proximal humerus, and distal femur. The growth plate, which can be found in a bone's metaphysis, is in the process of developing and lengthening new bone. Lungs are the most frequent site of osteosarcoma systemic metastasis. Metastases often

occur in the bones of another extremity. The scientific research on MAPK/ERK's function in bone sarcomas is partially limited. Diverse opinions regarding the importance of MAPK/ERK show that the exact function of this pathway in sarcoma remains unknown. Increased pMAPK/pERK1/2 expression has been reported in osteosarcomas, Ewing sarcomas, and high-grade chondrosarcomas. Thus, focusing on MAPK/ERK1/2 may lead to the development of an advanced molecular adjuvant treatment for bone sarcomas. Updates to experimental and clinical trial data are required for understanding the therapeutic significance of targeting the RAF-MEK-ERK pathway in bone sarcomas. (Chandhanayingyong et al., 2012).

Naturally occurring bioactive chemicals derived from plants have been acknowledged for their potential therapeutic benefits in the management of several cancer types. These organically sourced products, sometimes called traditional medicines or herbs, have been acknowledged for their efficaciousness as adjuvants in chemotherapy. They accomplish this by working in combination with the medication to increase its effectiveness, leading to greater results than when the medications are taken separately. In order to increase the reactivity of the cancer cells to the medications, these bioactive phytoconstituents are utilized in combination therapies with chemotherapeutic agents. This is achieved by either optimizing the drug's activities or reducingthe dosage needed, which minimizes toxicity. (Iweala et al., 2023). As an essential initial step, the trichloroacetimidate donor was used in this investigation to synthesize Marumoside A, which was isolated from the traditional medicinal herb Moringa oleifera. (Vudhgirl et al., 2016).

This study aimed to explore the therapeutic potential of Marumoside A by evaluating its interactions with key protein targets implicated in bone sarcoma progression using molecular docking, pharmacokinetic profiling, and toxicity predictions.

Materials and Methods

Ligand and Protein Preparation

Protein structures of key targets associated with bone sarcoma were retrieved from the RCSB Protein Data Bank (PDB). The ligand, Marumoside A, was obtained from the PubChem database. All molecules were prepared for docking by adding missing hydrogens, optimizing charges, and converting them into PDBQT format using AutoDock tools.

Molecular Docking Studies

PyRx v0.8 was used to dock the ligands to the target receptor and calculate their binding affinities (Dallakyan et al.,2015). The ligands were kept flexible during this process, whereas the protein remained rigid. With the help of Auto Dock Vina, PyRx was able to perform a number of functions, including creating grid boxes and PDBQT files for ligands and proteins. To construct the grid box, the Vina module from PyRx was utilized. After choosing Vina Wizard from the control window, the ligands and target protein were chosen once the Wizard had started. Next, by choosing "forward," the chosen molecules were sent for grid coverage. The active sites, catalytically significant areas, and applicable structural patterns were all covered by the exact chosen grid dimensions. The centre coordinates were 5.81 £ 60.15 £ 29.97 (for the X, Y, and Z axes, respectively), while the grid box size coordinates were 43.12 £ 35.86 £ 58.03. We used a blind docking technique, which identifies the binding site of a ligand in a target protein with an unknown location, to target the entire length of the E6 Oncoprotein. After docking the complexes, the interactions between the ligands and proteins were

examined by visualizing the complexes with BIOVIA Discovery Studio Visualizer v21.1.0.20298. After receiving a score that was on level with or higher than that of the control medication, phytochemicals underwent ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies for additional screening.

Pharmacokinetics and Toxicity Analysis

Following the first screening procedure, phytochemical, Marumoside A were chosen for ADMET analysis. Given its importance in assessing the pharmacological activity and performance of medications, the SwissADME server was utilized to evaluate a range of pharmacokinetic and pharmacodynamic aspects. PubChem database was used to obtain the canonical SMILES of these phytochemical. To find the ADME features, the server was asked to process these strings. (Daina et al.,2017). When evaluating toxicity, the Stoptox was taken into consideration (Banerjee et al.,2018). SMILES strings of the lead candidates were uploaded with all the parameters validated for prediction in the Stoptox server. (Borba et al.,2022) the Stoptox server assessed the toxicity of compounds for a range of destinations, such as acute inhalation toxicity, acute oral toxicity, ocular irritation, and corrosion, using a collection of quantitative structure-activity relationship (QSAR) models. The largest publicly available datasets have been assembled, organized, and utilized by the Stoptox server before predictions were produced. Although they are useful techniques for initial screening, broad toxicity evaluation in drug development still requires experimental validation.

The compounds were examined using Swiss ADME, a free online program, to determine their drug-like qualities of server that calculates the same's physicochemical attributes using a set of predefined guidelines. The substances were investigated using the drug-likeness guidelines, namely Lipinski, Ghose, Veber, Egan, and Muegge, as well as those who

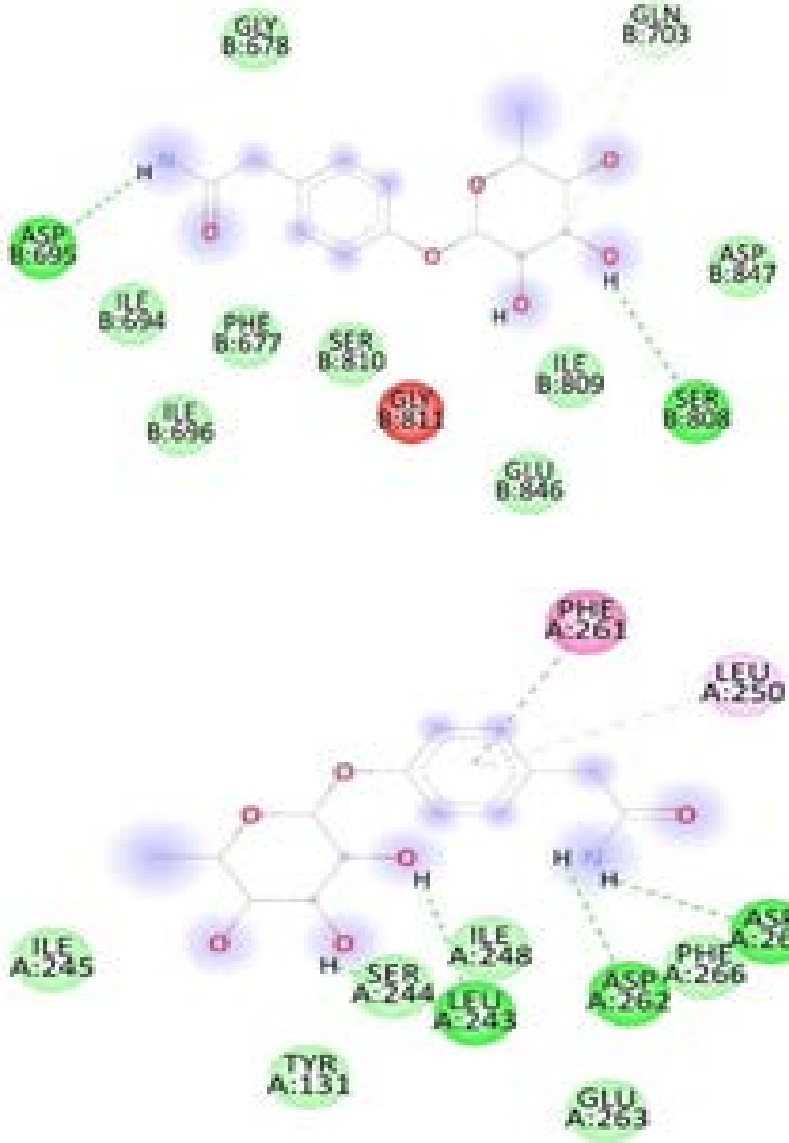
shown no infractions, were exposed to additional simulated in screen-by-silicon. The quick assessment and forecast of numerous pharmacokinetic characteristics connected to the molecular and structural characteristics of the molecules made from phytocompounds were investigated using the free web-based tools prior to ADMET. Stoptox is a quick, dependable, and easy-to-use tool. It was used to predict acute toxicity in humans, including skin irritation and corrosion, eye irritation and corrosion, acute dermal toxicity, acute oral toxicity, and skin sensitization. Stoptox is a substitute method for determining whether a chemical has the potential to cause acute toxicity in humans. The purpose of the acute toxicity testing is to determine the potential hazards that may arise from brief exposure periods.

Results and Discussion

Molecular Docking

Molecular docking is a structure-based virtual screening approach that designs computerized medicines for specific ailments (Mohapatra et al., 2021). It determines the binding orientation of ligands for their target molecules, through which the biological efficacy of phytocompounds can be predicted (Ford et al., 2020). The selected ligands were docked with the protein targets using AutodockVina (Version 4). The docking interactions of compounds Marumoside A with the Kinase suppressor of Ras 2 target molecule exhibited a binding affinity of -6.3 kcal/mol. The docking interaction of Marumoside A. A with the Lymphokine-activated killer T-cell-originated protein kinase target molecule exhibited a binding affinity of -6.7 kcal/mol. The docking interactions of Marumoside A with the target molecule Glutathione S-Transferase revealed a binding affinity of -5.6 kcal/mol. The docking interaction of ligands with the Glutathione S-transferase LANCL1 target molecule revealed a binding affinity of -6.0 kcal/mol. The docking interaction of ligands with the target Cell division protein kinase 2 protein exhibited binding affinity ranging from -6.9

kcal/mol respectively. The top-scoring phytocompounds with receptors were further selected for the docking complex interactions. The results of interactions between amino acid residues at the binding sites and the Marumoside A molecule revealed the participation of hydrogen and an alkyl bond. The interaction of Marumoside A with Kinase suppressor of Ras 2 reveals the different types of interaction, such as Asp:695 and Ser:808, which form two types of interactions, such as conventional hydrogen bonds and Gln:703, which form Vander waals bonds. The interaction of Marumoside A with Lymphokine- activated killer T-cell-originated protein kinase reveals the different types of interactions, such as Asp:262 and Leu:243, Ser:244 and Asp:265 form three interactions, such as a conventional hydrogen bond, and Leu:250 forms a Pi-Pi stacked bond. And Leu:250 forms a Pi alkyl bond. The interaction of Marumoside A with GLUTATHIONE S-TRANSFERASE reveals the different types of interactions, such as Gln:135 forms a conventional hydrogen bond, Leu:132 forms a pi-alkyl bond, and Phe:129 and Gly:95 form two interactions, such as a pi-donor hydrogen bond. The interaction of Marumoside A with Glutathione S-transferase LANCL1 reveals the different types of interactions, such as Ser:232, Leu:399, and Tyr:226, which form two interactions with conventional hydrogen bonds. Pro:231 forms an alkyl bond. The interaction of Marumoside A with Cell division protein kinase 2 reveals the different types of interactions, such as Tyr: 269, Thr: 221, and Val: 226, which form three interactions with conventional hydrogen bonds, and Ala: 244, which forms a carbon hydrogen bond. And Arg:245 forms a Pi- sigma bond. Figure 1 shows the interaction of Marumoside A with the putative targets.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ASP B:847
GLU B:846
PHE A:261
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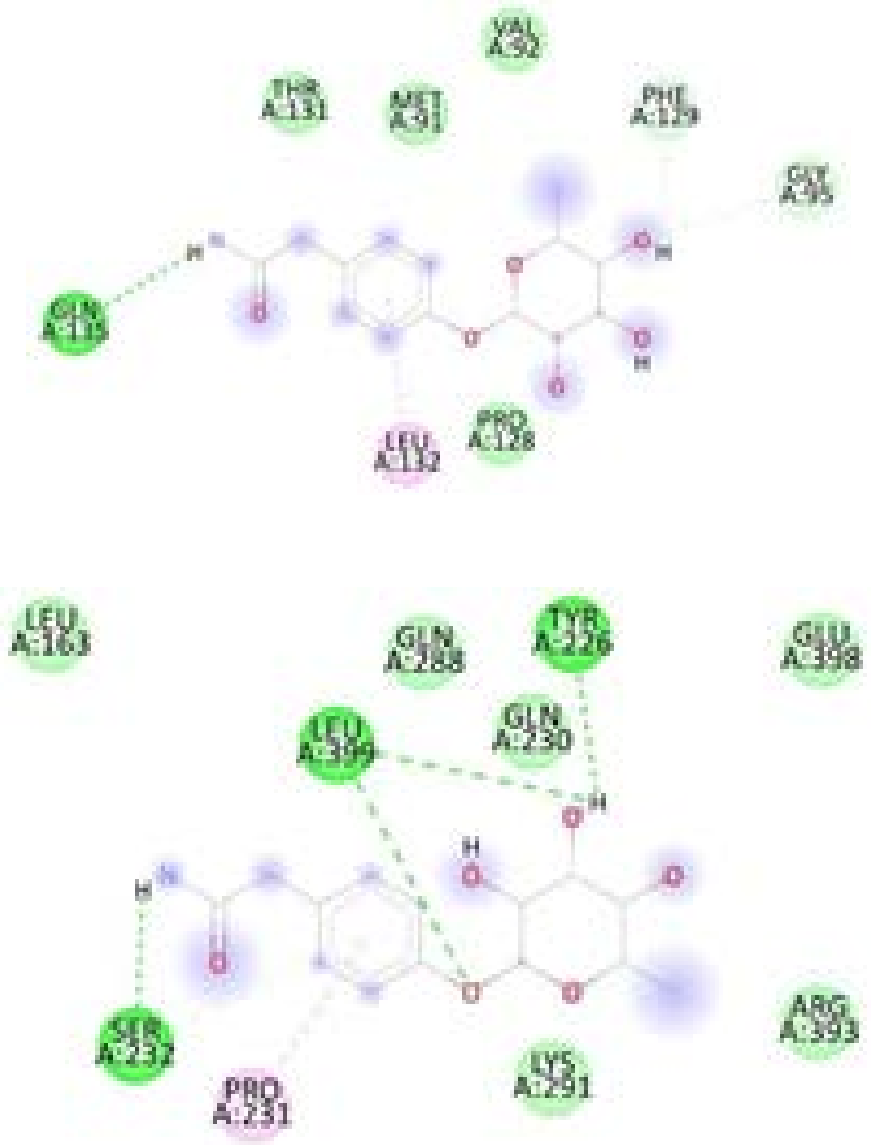
GLU A:263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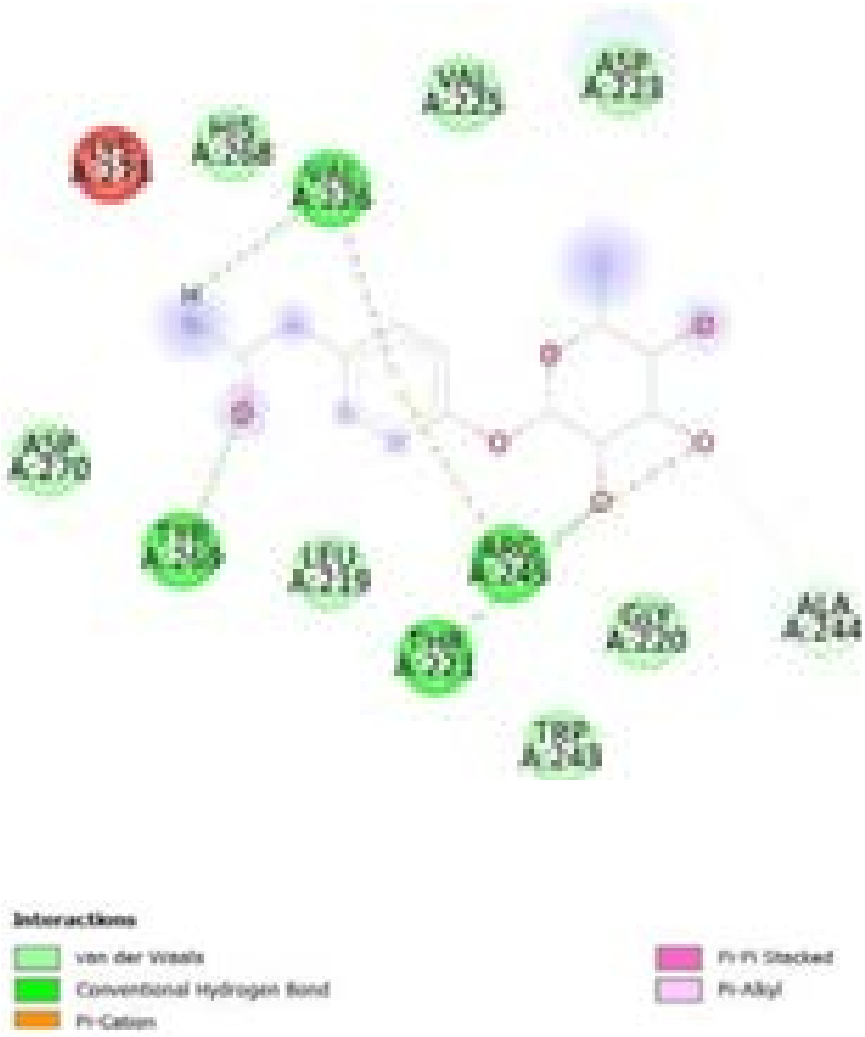

Figure 1 Molecular Docking Analysis of Marumoside A with a- Kinase Suppressor of Ras 2, b- Lymphokine-activated killer T-cell-Originated Protein Kinase, c- Glutathione S- Transferase, d- Glutathione S- Transferase LANCL1, e-Cell Division Protein Kinase 2

Drug Likeness and Pharmacokinetics Analysis

The Swiss ADME tool uses drug-likeness qualities like the Lipinski, Ghose, Veber, Egan, and Muegge rules to forecast a compound's chance of being orally active or not. When a compound's molecular weight was

less than 500 Da, its mLogP was less than 5, its number of rotatable bonds was less than 10, and its number of hydrogen bond donors and acceptors was fewer than 5, the Lipinski rule of five was followed (Lipinski et al., 2004). Ghose rule states that a compound's substructures and functional groups must exist if its molar refractivity falls between 40 and 130, its molecular weight falls between 160 and 480 Da, and its WLogP value falls between −0.4 and +5.6. A chemical must satisfy the following criteria in order to be considered Veber rule-compliant and have acceptable oral bioavailability: total polar surface area (TPSA) <140 Å, rotatable bond count ≤10, and hydrogen bond donors and acceptors ≤ 12. The penetration rate is impacted if the compound exceeds the limits specified for the physic-chemical characteristic (Veber et al., 2002). The Egen rule predicts a compound's absorption based on TPSA≤131.6 Å and WlogP≤5.88(Egan et al., 2000). If a chemical has a molecular weight of 200–600 Da, an XLogP between −2 and +5, a TPSA of 150 Å, 15 or more rotatable bonds, 10 hydrogen bond acceptors, and 5 donors, Muegge identified it as having therapeutic properties (Muegge et al., 2000). The molecular weight and TPSA of a substance determine its oral absorption rate through the biological barrier. A compound's permeability falls when both values rise. According to the above rules, TPSA determines a compound's bioavailability. All of the substances in this study fall within the allowed range, show intestinal absorption, and indicate oral bioavailability (Jia et al., 2020). A compound's absorption rate in the body is determined by its Log P (lipophilicity) value; the lower the lipophilicity, the higher the absorption rate, and vice versa (Sugita et al., 2021). Table 1 shows the predicted drug likeness of Marumoside A. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) are a combination of pharmacokinetic and pharmacological factors that are essential for drug design and discovery in pharmaceutical research. These characteristics are essential because they direct the initial assessment of the drug's safety and efficacy. The interaction of a compound with the

target protein as well as its side effects are significantly influenced by its pharmacokinetic properties. These characteristics also help determine whether a molecule or ligand has favourable qualities, such as being well absorbed and suitable for oral use, which helps prevent problems further on. Thus, ADMET qualities are essential for drug screening, which is done by assessing characteristics that are similar to the compound.

Table 1 Drug Likeness of Marumoside A

S.NO	PHYSICOCHEMICAL PROPERTIES	MARUMOSIDE A
1.	Molecular weight	297.30g/mol
2.	Rotatable bond	4
3.	Hydrogen bond acceptor	6
4.	Hydrogen bond donor	4
5.	Molar refractivity	72.11
6.	Topological polar surface area	122.24A
7.	Fraction Csp3	0.53
8.	Heavy atoms	21
9.	Formula	C14H19NO6
Lipophilicity		
10.	XLogP3	-1.21
11.	WLogP	-1.08
12.	MLogP	-0.090
13.	iLogP	1.45
14.	SILICOS-IT	-0.57

Conclusion

Moringa oleifera, has chemo preventive effects through free radical scavenging, antioxidant pathways, gene expression alteration, and apoptosis, reducing tumour initiation, promotion, and progression. The compound Marumoside A from Moringa shows anticancer activity. Accurately predicting the toxicity

of an effective lead compound promotes further study and improves lead optimization. In molecular dynamic simulations, it was discovered that the targeted protein-ligand complexes had strong hydrogen bond interactions that affected their stability and binding affinity. Thus, the knowledge gained by molecular docking provided insightful direction for subsequent drug development projects. Thus, the study demonstrates the molecule from marumosides potential as a bone cancer treatment alternative. Therefore, the research supports the identification and optimization of natural chemicals as a sustainable and financially viable means of advancing innovative therapeutics.

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