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Bioactivity prediction and molecular docking of phytocompounds from *Drynaria quercifolia* against osteoarthritis receptors

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ABSTARCT

Ethnic groups in India have long utilized *Drynaria quercifolia* to treat osteoarthritic disorders. Osteoarthritis is the most prevalent type of arthritis, affecting millions of individuals around the world. Recently, herbs play an important role in modern medicine and are a huge pool for potentially active pharmaceutical drugs all over the globe, and therefore, the hunt for a safe substitute therapy from plant resources has attracted attention. Using computational approaches, we intend to assess the pharmacodynamic and bioactivity properties of molecules from *D. quercifolia*. According to the docking score, 9-octadecanoic acid and ketostearic acid are the most promising compounds with all eight osteoarthritic targets. According to the Lipinski's rule of thumb, the bioactivity prediction of above compounds from *D. quercifolia* showed a good drug likeliness score. The estimated docking score of target and compounds reveals the binding pose and crucial amino acid residues involved in inhibition of osteoarthritic activity. The results presented here will help the biochemists to further test these multi-targeting compounds and develop it as anti-osteoarthritic inhibitors.

1. INTRODUCTION

Drynaria quercifoliais is a healthy epiphytic fern with a long and creeping rhizome that can reach a height of 1 m [1]. It produces two kinds of annual fronds: Short and sterile shoots up to 40 cm long that stay on the plant for so many years and trap organic material for the plant's nutrition, and higher fertile shoots that generate spores [2]. The species' soup has been used as a food supplement and rheumatism remedy [3]. The plant was specifically used by an ethnic community of tribes in India to treat migraine and inflammatory diseases [4]. This medicinal plant's general concern is multifaceted and dynamic, having been applied and studied for anti-fertility, antioxidant, and antimicrobial activity [5]. The root contains numerous medicinal properties, including anti-inflammatory and anti-arthritic activity [6]. Consumption of *D. quercifolia* can aid in the healing and strengthening of broken bones. Sub-Himalayan tribal cultures such as the Mech, Toto, Rabha, and Koch tribes of West Bengal, India, utilize it to encourage the cure of bone fractures [3]. The fronds have been demonstrated to strengthen and mend sinews, muscles, and bones due to their rigorous characteristics [7]. Osteoarthritis is a degenerative joint disease that affects a number of joint tissues and is commonly related with ageing. Although there is no cure for osteoarthritis, there are treatments to reduce pain, be active, maintain a good quality of life, and stay mobility.

D. quercifolia rhizome methanolic extract has been shown to have high pharmacological activity, and the phytochemicals found in the extracts have previously been documented [8]. Furthermore, multiple potential osteoarthritic targets have been discussed in the literature, which is believed to be a useful resource for computer-aided drug discovery [9]. Several compounds from *D. quercifolia* have been shown to have anti-osteoarthritic activity [10]; however, the molecular mechanism of action of these small molecules with a protein has yet to be discovered. The use of an *in silico* approach that includes molecular docking and pharmacokinetic (ADMET) studies that include "drug-likeness" of the compounds using Lipinski's rule of five can help to define their binding affinity and stabilizing interactions at the molecular level, potentially improving our understanding of drug action against specific disorders. Using computational approaches, we intend to assess the pharmacodynamic and bioactivity properties of molecules from *D. quercifolia*. We also want to figure out which compounds in *D. quercifolia* bind to the osteoarthritis targets. Molinspiration tools are used to evaluate the bioactivity of the reported *D. quercifolia* compounds. The major goal of the study is to investigate the anti-osteoarthritic activity of the selected compounds with important targets of osteoarthritis using the molgro software. According to the Lipinski's rule of thumb, the bioactivity predictions of compounds from *D. quercifolia* were computed to assess the drug likeness score.

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The estimated docking score of target and compounds reveals the binding pose and crucial amino acid residues involved in inhibition of osteoarthritic activity. Molecular docking results show that the compounds from *D. quercifolia* have better drug-like properties and inhibit osteoarthritic activity by forming strong stabilizing protein-ligand interactions. The anti-osteoarthritic activity of *D. quercifolia* was investigated in this study using phytochemical profiling, bioactivity prediction of compounds extracted from ethyl acetate and methanol and molecular docking studies.

2. MATERIALS AND METHODS

2.1. Calculation of Molecular Properties and Bioactivity

Phytoconstituents in *D. quercifolia* identified from the GC-MS report were processed to calculate the molecular properties. Phytochemicals, Phytol, 16-Keto stearic acid, 9-Octa decanoic acid, Methyl stearate, Genistein, Flavone, and Dasycarpidan-1-methanol were assigned to calculate octanol-water partition coefficient (LogP), polar surface area (PSA), Number of non-hydrogen atoms, molecular weight, number of hydrogen bond acceptors (O and N atoms), number hydrogen bond donors (OH and NH groups), rule of five (RO5), and rotatable bonds. In addition, the bioactivity of compounds such as Guanine-Protein Coupled Receptors (GPCR) ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor was predicted using molecular inspiration tools, an online webserver [11].

2.2. Ligand Preparation

Phytochemicals, extracted and identified using methanolic and ethyl acetate through GC-MS from *D. quercifolia*, were retrieved from the pubchem database as SDF files [12]. As for docking, phytocompounds such as Phytol, 16-Keto stearic acid, 9-Octa decanoic acid, Methyl stearate, Genistein, Flavone, and Dasycarpidan-1-methanol were prepared using dockprep in UCSF chimera that was adding hydrogen bonds and energy minimization. Besides, ligands were saved in pdb and pdbqt format for docking and modeling studies using molegro virtual docker [13].

2.3. Protein Preparation

The protein targets of osteoarthritis receptors were chosen for docking simulation comprehensive literature review and recent findings. Crystal structures of atomic resolution in the protein data bank, P38 MAKP (p38alpha MAP kinase and PDB ID-1OUY), JAK-1 (Tyrosine-protein kinase JAK1 and PDB ID-4K6Z), JAK-3 (Tyrosine-protein kinase JAK3 and PDB ID: 3ZCB), SYK (Spleen tyrosine kinase and PDB ID:4PUZ), C-JNK (Mitogen-activated protein kinase 10 and PDB ID: 3PTG), MEK1 (MAP kinase 1 and PDB ID: 1S9J), Cathepsin (Cathepsin K and PDB ID: 4DMY), and MAPK14 (Mitogen-activated protein kinase 13 and PDB ID: 4MYG), were downloaded using protein name and identifier (PDB ID) as receptors [14]. Preparation of protein structure was accomplished by adjusting missing residues, side chains, and removing HETATM molecules to complete docking, respectively. Energy minimization of protein structures was fulfilled by assigning charges using AMBERff14SB force field and gasteiger. Receptor structures were saved as molecule files, default.

2.4. Molecular Docking

Protein and ligand files were exported to molegro virtual docker to check the intermolecular forces. Protein structures were set as rigid whereas ligands were set flexibly to rotate into the active site. Rotamers were adjusted to move along the three-dimensional coordinates. Grids were activated and aligned over the ligand-binding domain of proteins. Lamarckian genetic algorithm was preferred for different conformation searches in the pocket. The number of poses and consensus was assigned as default with RMSD calculation. Finally, the complex files generated were saved for molecular modeling and to reveal the binding affinity and major forces using molegro virtual docker [13]. Molegro virtual docker is a platform for predicting protein-ligand interactions that are fully integrated to perform preparation of the compounds, determining the target protein's probable binding positions, and predicting the ligands' binding modes.

3. RESULTS AND DISCUSSION

3.1. Molecular Properties

In quantitative structure-activity relationship studies and drug discovery, a molecule's physicochemical properties and bioactivity play a key role. Predictions of bioactivity in compounds have strong correlation between efficiency and inhibitory properties to target receptors. Following that, using molecular inspiration tools, chosen phytochemicals were tested for bioactivity using the empirical method. When the parameters were compared, the inhibitor, modulator, and activator were discovered to have distinct values. Table 1 presents the bioactivity index of the compounds that present in *D. quercifolia* against six major classes of drug targets such as GPCR, ion channel, kinase, nuclear receptor, protease receptor, and enzyme inhibitor, respectively.

Prediction of bioactivity appears to have a greater significance in computer-aided drug discovery when it identifies lead compounds against a specific class of therapeutic target. Inhibition properties of chemicals were observed by kinase, protease, and enzyme inhibitor scores. In fact, results of bioactivities reveal that the chemicals from *D. quercifolia* seem to have promising agents for osteoarthritis targets. The bioactivity prediction of ligands showed the good drug likeliness score according to the Lipinski's rule of five properties. The G-protein coupled receptor, ion channel modulator, enzyme inhibitors, and nuclear receptors of the identified ligands showed good score by molecular inspiration tools as shown in Table. Chemical descriptors are the building blocks of drug discovery because they encode the physicochemical and structural features of small compounds [15]. The widespread availability of bioactivity data has resulted in enhanced representations of substances that go beyond chemical structures to capture their known biological effects, which have been thoroughly evaluated in the literature [16,17].

3.2. Docking of Osteoarthritis Receptors

Proteins that are osteoarthritis targets have been investigated, and ligand binding sites have been identified for docking studies. To predict binding affinity, protein targets and small molecular compounds were prepared and kept in appropriate format. The phytochemicals of ethyl acetate and methanol extracts of *D. quercifolia* were docked with osteoarthritis receptors. As a result of docking, the docking score is calculated for the different poses and ranked accordingly. The intermolecular forces and biological interaction of active site amino acid residues have been identified. The three dimensional view of the top docking poses of complexes was shown in Figure 1.

Interestingly, among the ligands docked the compound 9-octadecanoic acid prominently inhibit the important targets of osteoarthritis such as MEK1-9-Octa decanoic acid (−125.003), P38 MAKP-9-Octa decanoic acid (−144.568), Cathepsin-9-Octa decanoic acid (−83.1279), MAPK14-9-Octa decanoic acid (−94.2216), respectively, as shown in the Figure 2. According to our findings, the chemical "9-octadecanoic

Table 1: Predictions of biological activities of selected phytochemicals against six major classes of drug targets

Compound name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Phytol	−0.03	−0.01	−0.30	0.23	0.24	0.18
16-Keto stearic acid	0.08	0.02	−0.37	0.30	0.13	0.29
9-Octa decanoic acid	0.12	0.02	−0.24	0.24	0.06	0.22
Methyl stearate	−0.03	−0.04	−0.23	0.00	−0.03	0.05
Genistein	−0.22	−0.54	−0.06	0.23	−0.68	0.13
Flavone	−0.30	−0.21	−0.12	−0.18	−0.52	0.03
Dasycarpidan-1-methanol	0.40	0.28	-0.07	0.01	0.03	0.09

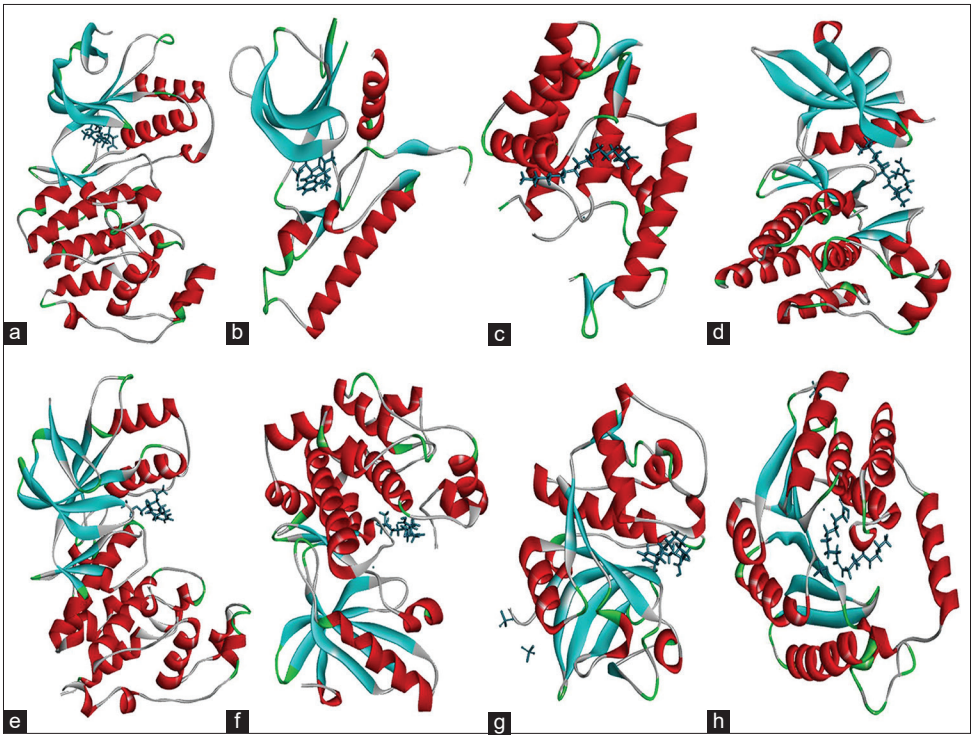

Figure 1: The schematic three-dimensional representation of top protein-ligand complexes for eight targets is shown. The protein-ligand complexes such as P38 MAKP-9-Octa decanoic acid (a), JAK-1- Dasycarpidan-1-methanol (b), JAK-3-16-Keto stearic acid (c), SYK- Phytol (d), C-JNK-Dasycarpidan-1-methanol (e), MEK1-9-Octa decanoic acid (f), Cathepsin-9-Octa decanoic acid (g), and MAPK14-9-Octa decanoic acid (h), respectively, were presented

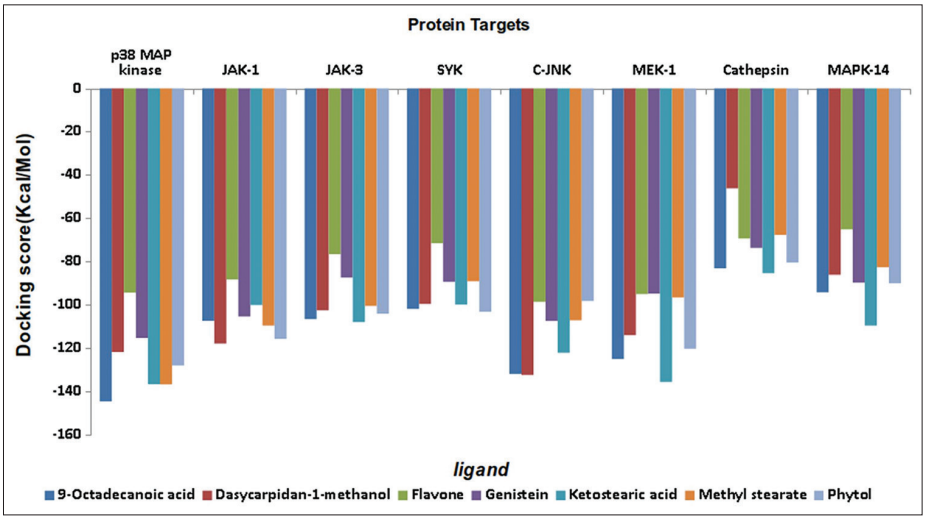

Figure 2: Docking scores for top phytochemicals from *Drynaria quercifolia* against osteoarthritis receptors

acid" acts as a multitarget drug (molecule with the ability to act on different targets at the same time) [18]. Because multitarget drugs have been presented as prospective therapies for the management of complicated disorders, multitarget drug design/discovery is an important topic of research in medicinal chemistry [19]. There is currently no measurement of "multitargeticity," or how multitargeted a ligand is, to the best of our knowledge [20]. Extremely, selective compounds for a single target would seem as multitarget medicines, because the average is a metric sensitive to extreme values. Sophisticated methods for successfully comparing and optimizing the discovered ligands (9-octadecanoic acid) are essential as multitarget drugs are created and tested. Similarly, dasycarpidan-1-methanol actively inhibited C-JNKby docking score (−132.376) and JAK-1 (−117.884). Further, the ligands ketostearic acid actively inhibited the receptors that were confirmed by the docking score JAK-3 (−107.898) and SYK (−103.208).

The interactions between the top compounds and targets, such as hydrogen, hydrophobic, and other non-bonded terms, are shown in Figure 3. The two dimensional chemical interaction figures provide the details about key amino acid residues that contribute to the protein-ligand complex formation. The van der Waals hydrophobic interactions between protein and ligand are dominant, as represented by the light

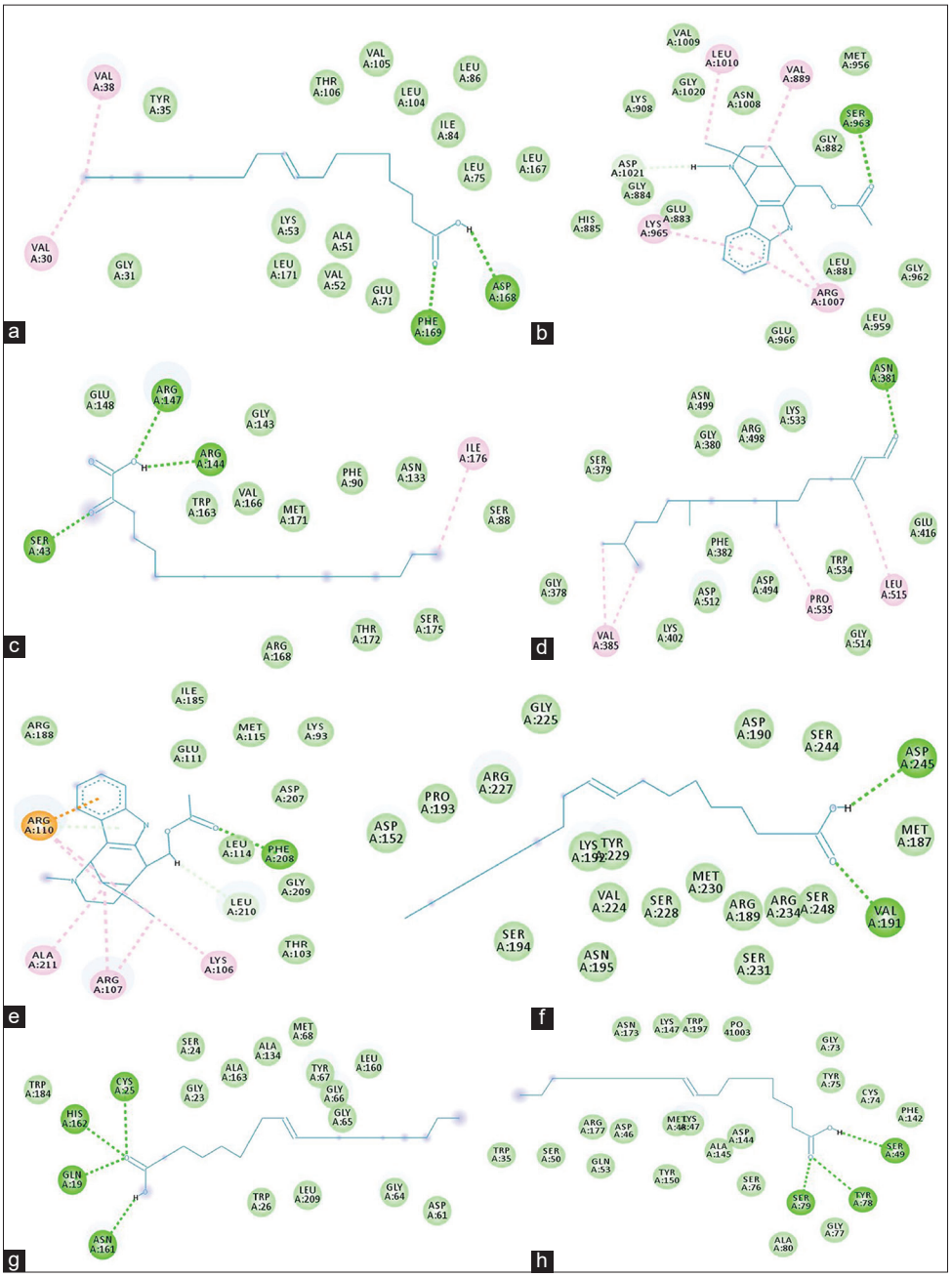

Figure 3: Molecular docking of phytochemicals with protein targets is shown for interacting active site amino acids. The protein-ligand complexes such as P38 MAKP-9-Octa decanoic acid (a), JAK-1- Dasycarpidan-1-methanol (b), JAK-3-16-Keto stearic acid (c), SYK- Phytol (d), C-JNK-Dasycarpidan-1-methanol (e), MEK1-9-Octa decanoic acid (f), Cathepsin-9-Octa decanoic acid (g), and MAPK14-9-Octa decanoic acid (h) respectively were presented. The dark green color in the figure indicates the amino acid residues contributing conventional hydrogen bonds whereas light green color indicates van der Waals interactions. The purple color indicates alkyl interactions whereas yellow color indicates aromatic interactions

green color balls in the figure. The dark green color balls in the figure represent amino acid residues' conventional hydrogen bond contributions. The phytocompounds form the relative number of amino acid residue interactions with the osteoarthritis receptors, as shown in the figure. From our results, we observe that three osteoarthritis targets bind better to 9-Octa decanoic acid, whereas Dasycarpidan-1-methanol binds to two targets. Our docking investigations were preliminary to the best of our knowledge of protein-ligand complex formation that maintains the stable molecular complex. Further, docking computations were conducted in a synthetic (non-water) environment and the proteins have several disordered loops. The present study lays the groundwork for the future effort; the present work is built on foundations.

4. CONCLUSIONS

Docking simulations and bioactivity prediction studies of phytochemicals derived from *D. quercifolia* revealed anti-osteoarthritis activity, as shown by protein-ligand interactions such as hydrogen bonding and other stabilizing interactions. According to the docking score, 9-octadecanoic acid and ketostearic acid are the most stable compounds with all eight osteoarthritic targets. Furthermore, these two compounds have shown good Lipinski's parameters, low aqueous solubility (Log S), and TPSA 140, indicating good permeability in biological membranes. The findings of this study could serve as a foundation for further molecular optimization of phytocompounds identified in *D. quercifolia*, resulting in improved molecular interactions with receptors and more effective osteoarthritic inhibitors.

5. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

8. ETHICAL APPROVALS

Not Applicable.

9. DATA AVAILABILITY

The data is available upon requesting corresponding author.

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