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PHENOLPROPANE AND MEGASTIGMANE FROM *Motandra paniculata* (POIR) I.M. TURNER (APOCYNCEAE) LEAVES: ARTIFICIAL INTELLIGENCE PREDICTIVE ANTIINFLAMMATORY ACTIVITY AND MOLECULAR DOCKING STUDIES

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ABSTRACT

Motandra paniculata, a plant indigenous to Nigeria, is traditionally used in some African communities for the management of pain. This study was undertaken to investigate the anti-inflammatory activity of a phenolpropane (β-hydroxypropiovanillone) and a megastigmane (isololiolide) isolated from the leaves of *M. paniculata*. This research sought to evaluate their potential as anti-inflammatory leads using *in silico* docking studies, alongside predictive assessments from Artificial Intelligence (AI) models, specifically Graph Neural Networks (GNNs) and Chemical Bert Representation Task (ChemBERTa). Targeted and blind *in silico* molecular docking were performed to assess the suitability of the compounds as inhibitors of cyclooxygenase enzymes (COX-1 and COX-2). Separately, a Simplified Molecular Input Line Entry System (SMILES)-based transformer model (ChemBERTa) and a GNN architecture enabled the dual-modal prediction of the compounds' bioactivity. The phenolpropane (β-hydroxypropiovanillone) exhibited stronger affinity and more reliable binding in the docking studies than the megastigmane (Isololiolide). However, both compounds received similar, moderate-to-low AI-predictive anti-inflammatory activity scores (0.398–0.489) from the GNN and ChemBERTa models. This suggests a low likelihood of potent *in vivo* activity in their current scaffolds, despite promising target engagement. The results demonstrate that the phenolpropane (β-hydroxypropiovanillone) and megastigmane (isololiolide) isolated from *M. paniculata* could serve as valuable anti-inflammatory leads. The conflict between their strong target binding (docking) and moderate predicted bioactivity (AI models) highlights the necessity of structural optimisation to improve their overall pharmacological profile for successful drug development.

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INTRODUCTION

The genus Motandra (Apocynaceae) comprises of three known species distributed across parts of Africa including Guinea, Congo, Cameroon, and Nigeria [1-4]. These include *Motandra lujaei* De. Willd., *Motandra poecilophylla* Wernham and *Motandra paniculata* (Poir.) I.M. Turner [1-4]. *Motandra paniculata* [Synonym: *Motandra guineensis* (Thonn) A.DC.)] is a climbing liana typically found in moist forest habitats in the Tropics of West Africa extending to Angola and is the only species of the genus native to Nigeria [5]. The leaves are traditionally prepared as remedies for treating abscesses and inducing sedation [1]. The plant is also used in African traditional medicine for the treatment of pain, fever and malaria [6,7]. Pharmacological investigations have demonstrated that extracts and some compounds from the plant inhibit nitric oxide-mediated inflammatory processes in some cell lines [8,9]. The present study aimed to evaluate the anti-inflammatory activity of a phenylpropane and megastigmane isolated from leaves of *Motandra paniculata* using *in silico* molecular docking studies. Additionally, Artificial Intelligence (AI)-based predictive models, including Graph Neural Networks (GNN) and Chemical Bert Representation Task (ChemBERTa) were employed to assess their suitability as potential anti-inflammatory drug leads.

MATERIALS AND METHODS

Plant material was collected from the wild at Ile-Ife, Osun state, Nigeria, authenticated at Faculty of Pharmacy, Ile-Ife (FPI) Herbarium in the Department of Pharmacognosy, Obafemi Awolowo University, Ile-Ife, Osun state, Nigeria and assigned voucher number FPI 2351. The plant material was processed as stated in our previous studies [8,9].

Computational Assessment of Anti-Inflammatory Potential Using Graph Neural Networks (GNN) and Chemical Bert Representation Task (ChemBERTa)

In this study, deep learning-based cheminformatics techniques were utilised to computationally evaluate the anti-inflammatory potential of the two isolated phytochemical compounds: isololiolide (megastigmane-type) and β-hydroxypropiovanillone (a phenolpropane). The integration of Graph Neural Networks (GNNs) and ChemBERTa, a Simplified Molecular Input Line Entry System(SMILES)-based transformer model, enabled a robust, dual-modal prediction of bioactivity, essential for effective early-stage drug discovery.

Model Training and Architecture

The models were fine-tuned for anti-inflammatory activity prediction using a curated bioactivity dataset comprising over 100,000 compounds annotated with half-maximal inhibitory concentration (IC_{50}) values against cyclooxygenase (COX) enzymes, sourced from the ChEMBL database (version 33). This training was formulated as a binary classification task, where an $IC_{50} \leq 10$ µM defined an active compound, ensuring the predicted score represents the probability (P(Active)] [10].

Graph Neural Network (GNN)

The GNN employed was a three-layer Message Passing Neural Network (MPNN) architecture, as initially described by Gilmer *et al* [10]. This model processes the molecular graph directly, encoding atoms as nodes and bonds as edges to learn feature representations.

Chemical Bert Representation Task (ChemBERTa)

The ChemBERTa model was the ChemBERTa-2-10M-v3 architecture, which was pre-trained on approximately 10 million molecules. It processes the SMILES string sequence to understand long-range chemical relationships, acting as a powerful sequence-based feature extractor [10, 11].

Model Performance and Prediction

The performance of the fine-tuned models was rigorously assessed on an independent external validation set. The final predictive system achieved a mean Area Under the Curve (AUC) of 0.89 and an F1-score of 0.78, confirming its reliable predictive capability for anti-inflammatory classification. Each compound's structure was first converted into a SMILES string, enabling consistent input for both models. Anti-inflammatory activity scores were predicted by both architectures on a normalised scale of 0 (inactive) to 1 (highly active), representing the calculated probability of a compound being active (P(Active)) [10, 11].

Molecular docking

Retrieval and Preparation of Protein

The 3D structures of cyclooxygenase [COX-1] (PDB ID: 3KK6) and cyclooxygenase 2 [COX-1] (PDB ID: 5IKR) were retrieved from the Protein Data Bank (https://www.rcsb.org) . Native ligands and water molecules were removed and missing polar hydrogen atoms and Kollman charges were added using Autodock 4. The prepared proteins were saved in PDBQT format for docking simulations on the command prompt [11].

Ligand Preparation

The 3D structures of two (2) ligands were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) and downloaded in SDF format. The ligands include isololiolide **(1)** and β-hydroxypropiovanillone **(2)**. The structures were converted to Protein DataBank (PDB) format using OpenBabel (version 2.4.1.23) with polar hydrogens added and Gasteiger charges assigned. The ligands were then saved as PDBQT prior to docking simulations [11].

Molecular Docking Studies

Molecular docking was conducted using AutoDock Vina (version 4.2.6) to assess the binding affinity of the bioactive compounds. The docking results were analysed, and the docked complexes were visualised using Discovery Studio Visualiser 2024. Targeted and blind docking was carried out

for the two (two) target proteins. Docking validation was performed by redocking Celecoxib into the active sites of COX-1 and Mefenamic acid to Cox-2 to verify the reliability of the docking procedure. In addition, the ligands were compared with standard drug, Diclofenac.

SWISSADME

The physicochemical properties of the two ligands and Diclofenac were assessed using the SwissADME online server (https://swissadme.ch).

RESULTS

Computational Assessment of Anti-Inflammatory Potential of Selected Phytochemicals Using Graph Neural Networks (GNN) and ChemBERTa

Isololiolide (ligand 1) and β-hydroxypropiovanillone (ligand 2) yielded lower activity scores across both models as seen on Table 1 suggesting these may not be strong candidates for anti-inflammatory pathways in their current forms. Figure 1 shows the structures of both ligands.

Table 1: Predicted Anti-Inflammatory Activity Scores from GNN and ChemBERTa

Compound	GNN Score	ChemBERTa Score
Isololiolide	0.472	0.489
β-hydroxypropiovanillone	0.398	0.417

Anti-inflammatory report of targeted and blind docking of compounds from *M. paniculata*

In silico docking on targeted loci on COX-1 and COX-2 show β-hydroxypropiovanillone showed the stronger and more reliable binding to COX enzymes, making it a promising candidate for anti-inflammatory therapy (Tables 2 and 3).

Table 4 shows the physicochemical properties of both ligands while Figures 2 and 3 shows the protein-ligand interaction between ligand 2 and the two target proteins. Table 5 shows the drug likeness analysis of the 2 ligands and standard.

Table 2: Anti-inflammatory report of Targeted Docking

Targeted docking	Target Enzymes Binding Affinity	
Ligands	**Cox-1**	**Cox-2**
Isololiolide	-5.8	-5.6
β-hydroxypropiovanillone	-6.6	-6.4
Diclofenac	-6.6	-6.6

The more negative (strongest) binding affinity is ligand 2 with -6.6 (Cox-1) and -6.4 (Cox-2).

Table 3: Anti-inflammatory report of Blind Docking

Blind Docking	Target Enzymes Binding Affinity	
Isololiolide	-7.3	-5.9
β-hydroxypropiovanillone	-6.9	-6.2
Diclofenac	-7.7	-6.3

The more negative binding affinity is ligand 1 with **-**7.3 (Cox-1) and -5.9 (Cox-2) but it was observed that ligand 2, -6.9 (Cox-1) and -6.2 (Cox-2). also performed well. Overall, ligand 2 had the better affinity when targeted docking was considered more important.

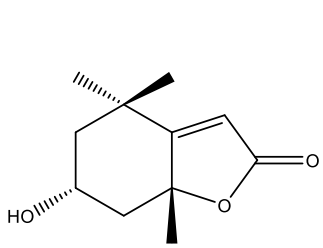
Table 4: Physiochemical properties of the 2 ligands and standard obtained using Swiss ADME

Ligand Name	logP	TPSA	N atoms	MW (g/mol)	nHBA	nHBD	BS	nRotB	MR	SA
Ligand 1	1.61	46.53 Å²	14	213.38	3	1	0.55	0	52.99	3.81
Ligand 2	0.81	66.76 Å²	14	212.33	4	2	0.17	4	51.68	3.50
Diclofenac	3.66	49.33 Å²	19	296.15	2	2	0.85	4	77.55	2.23

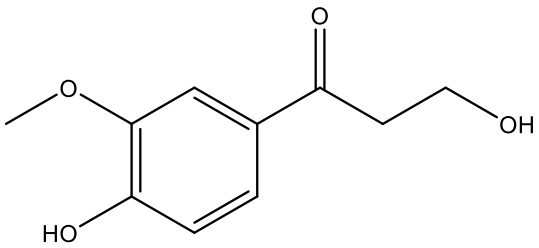
Abbreviations: logP – octanol/water partition coefficient, TPSA – Total polarisable surface Area, Natoms – Number of atoms, MW – Molecular weight, nHBA – Number of hydrogen bond acceptor, nHBD – Number of hydrogen bond donor, BS- Bioavailability Score, Nrotb – Number of rotatable bonds; MR – Molecular Refractivity, SA- Synthetic Accessibility.

Table 5: Drug Likeness Analysis

Ligands	Lipinski	Ghose	Veber	Egan	Muegge	Leadlikeness
1	0, Yes	0, Yes	0, Yes	0, Yes	0, Yes	1, No
2	0, Yes	0, Yes	0, Yes	0, Yes	0, Yes	1, No
Diclofenac	0, Yes	0, Yes	0, Yes	0, Yes	0, Yes	1, No



Isololiolide (**1**)



β-Hydroxypropiovanillone (**2**)

Figure 1: Chemical structures of Ligands 1 and 2 isolated from *M. paniculata*

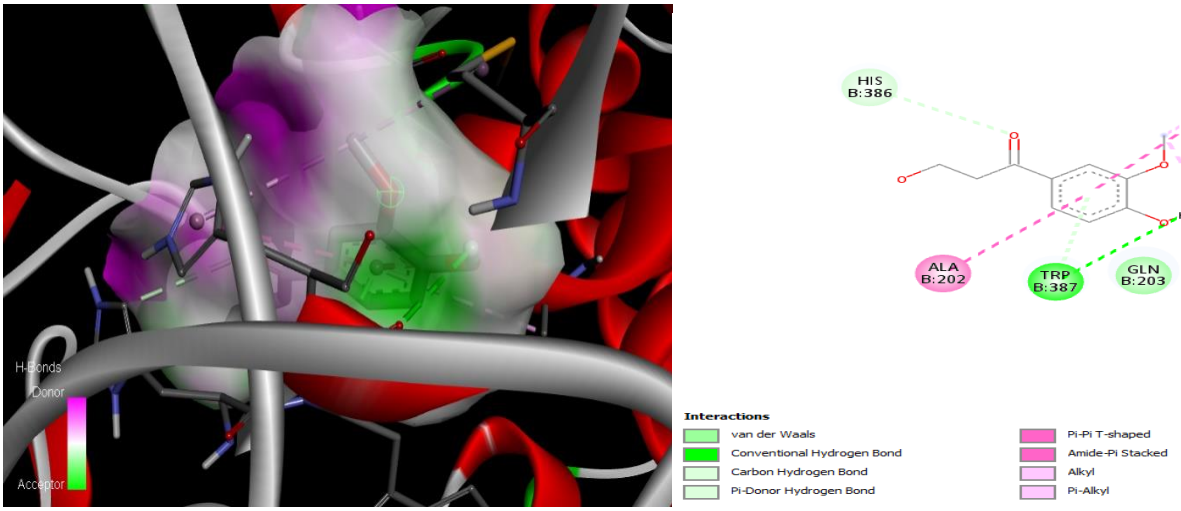


Figure 2: Protein-Ligand Interaction Diagram of Top Hit Phytochemical ligand (ligand 2) with COX-1

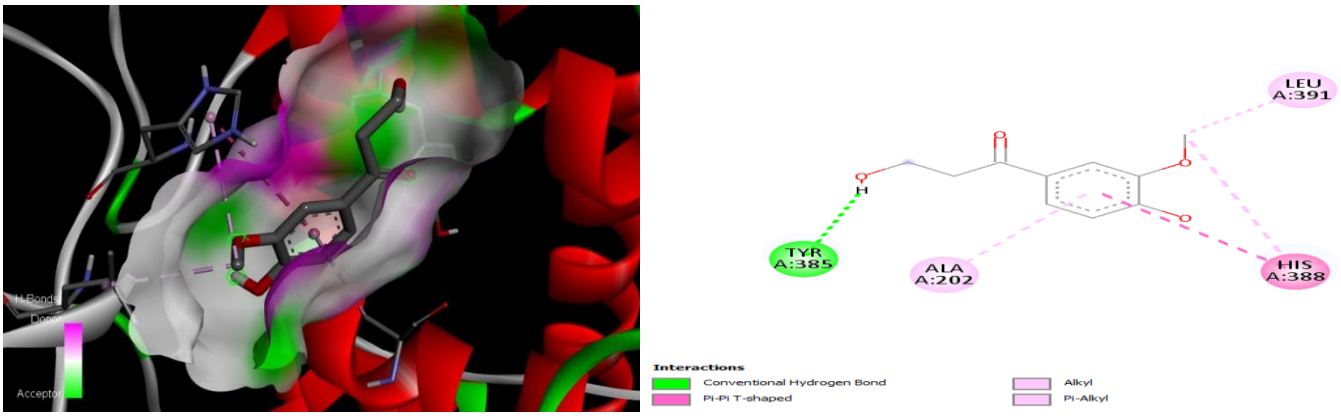


Figure 3: Protein-Ligand Interaction Diagram of Top Hit Phytochemical ligand (ligand 2) with COX-2

DISCUSSION

The *in silico* methodologies employed provided a comprehensive assessment of the anti-inflammatory potential of the isolated compounds, isololiolide (megastigmane-type) and β-hydroxypropiovanillone

(phenolpropane). Model outputs were interpreted in the context of known literature, where available. As both compounds are less well-characterised in this specific anti-inflammatory context, the results warrant further experimental exploration despite their moderate computational scores. The minimal variance between the GNN and ChemBERTa predictions across the board reinforces the validity of these computational techniques as effective, complementary screening tools in natural product drug discovery. While experimental validation remains essential, this dual-model strategy prioritises compounds for *in vitro* and *in vivo* testing, significantly reducing resource expenditure [10,12,13].

The docking results demonstrate that both compounds exhibit affinity for COX enzymes, though with different pharmacological profiles:

Isololiolide **(1):** This monoterpenoid lactone showed moderate binding affinity against COX-1 (-5.8 kcal/mol) and COX-2 (-5.6 kcal/mol) [14]. It has a molecular weight of 213.38 g/mol and a logP of 1.61, reflecting a balanced hydrophilicity. With no rotatable bonds and a synthetic accessibility score of 3.81, the compound is structurally simple and likely easy to prepare. It complies with most major drug-likeness rules (Lipinski, Ghose, Veber, Egan, Muegge) [15]. Its polarity (TPSA: 46.53 Å²) and bioavailability score (0.55) suggest acceptable absorption and oral suitability [15]. However, it does not satisfy lead-likeness criteria.

β-hydroxypropiovanillone **(2):** This compound performs slightly better than isololiolide in docking studies, with stronger affinities of -6.6 kcal/mol (COX-1) and -6.4 kcal/mol (COX-2) [15,16]. Its molecular weight is 212.33 g/mol, and a logP of 1.81 indicates moderate lipophilicity. Its TPSA of 66.76 Å² suggests greater polarity compared to isololiolide. While it complies with major drug-likeness filters, it did not meet lead-likeness thresholds and achieved a low bioavailability score of 0.17 [15].

In comparison with diclofenac with targeted binding, ligand 1 (isololiolide) only attained moderate binding strengths, between -5.4 and -5.6 kcal/mol while ligand 2 was closer to the active binding regions of COX-1 and COX-2 to diclofenac. Although ligand 1 (isololiolide) briefly stood out in the blind search for COX-1, it was ligand 2 (β-hydroxypropiovanillone) that showed the most reliable performance across both enzymes and both docking methods. β-hydroxypropiovanillone (ligand 2) clearly showed the stronger and more reliable binding to COX enzymes, making it a promising candidate for initial anti-inflammatory therapy development.

The most compelling outcome of this study lies in the dichotomy observed between the molecular docking results and the deep learning-based predictive scores. The docking simulations robustly demonstrated that the phenolpropane, β-hydroxypropiovanillone, possessed favourable binding affinities and strong interactions within the active sites of both COX-1 and COX-2, comparable to known inhibitors. This evidence strongly supports its potential for target engagement, that is, its ability to physically interact with the enzyme target. However, the predictive models (GNN and ChemBERTa) offered a more cautious assessment, returning moderate-to-low P(Active) scores (0.398–0.489) for both the phenolpropane and megastigmane. In the context of the deep learning framework, these low scores suggest that while the compounds may bind to the target, their overall molecular profile, which encompasses properties like solubility, permeability, metabolic stability, and general drug-likeness, did not align strongly with the vast landscape of successful anti-inflammatory drugs present in the training data. The AI models are essentially providing a systemic pharmacological filter, whereas docking provides a local target binding filter.

This apparent conflict is not a limitation but rather a critical discovery, providing a clear roadmap for lead optimisation. Specifically, β-hydroxypropiovanillone is established as an excellent scaffold lead because it satisfies the critical first step (high target affinity). The AI models then advise that we must address its sub-optimal physicochemical properties, which are inherently penalised by the predictive network. For instance, its low bioavailability score (0.17), high polarity, and relatively high flexibility indicate possible challenges with oral absorption and systemic availability, despite satisfying the major drug-likeness rules [11].

Therefore, future research should transition into an AI-guided lead optimisation campaign. This would involve using the β-hydroxypropiovanillone scaffold as a starting point for generative AI models (such as deep generative adversarial networks or variational autoencoders). These models can be conditioned to propose structural modifications—for instance, replacing certain hydroxyl groups or adding specific lipophilic substituents—that are predicted to both maintain strong COX binding (verified via subsequent docking) and simultaneously enhance the GNN/ChemBERTa activity score above a high confidence threshold (e.g., P(Active) > 0.85) [15]. This approach efficiently focuses synthetic efforts on analogues with the highest probability of clinical success. Potential strategies include medicinal chemistry modifications to adjust lipophilicity, reduce unnecessary hydrogen-bonding groups, or limit flexibility, as well as formulation approaches like lipid carriers or nanoparticle systems to improve delivery. In summary, β-hydroxypropiovanillone offers strong target interaction and a valuable starting point for development, but structural refinement and formulation improvements will be essential to achieve good oral bioavailability and therapeutic effectiveness.

CONCLUSION

The results of this study provide scientific support for the traditional therapeutic use of the *M. paniculata* in treatment of pain. The phytochemical constituents identified in the plant, particularly β-hydroxypropiovanillone and isololiolide, may underlie its observed anti-inflammatory potential, as demonstrated by the molecular docking and AI-based predictive analyses. Among the compounds evaluated, β-

hydroxypropiovanillone emerged as the stronger candidate due to its favourable binding affinities toward COX enzymes. Overall, these findings reinforce the pharmacological relevance of *M. paniculata* and provide a rationale for its further investigation as a potential source of novel anti-inflammatory agents. Future *in vitro* and *in vivo* studies are recommended to experimentally validate these computational predictions and optimise the compounds for enhanced bioactivity and bioavailability.

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AUTHORS' CONTRIBUTION

JOO developed the research concept and was responsible for data curation and analysis, funding acquisition, methodology, writing the original article draft as well as final approval of the article. AAO was responsible for review and editing the draft and funding acquisition. BOO was responsible for methodology (docking), analysis, resources, software, funding acquisition as well as review and editing the article draft. ADO was responsible for methodology (AI), analysis, resources, software, funding acquisition as well as review, editing and critical revision of the final article draft. PFO was responsible for project administration during isolation of bioactive compounds, funding acquisition as well as review and editing the article draft.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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