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Original Research Article

Molecular docking analysis of phytochemicals in *Moringa oleifera* leaf extract with aglucocorticoid receptors

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Abstract

Purpose: *To characterize the interactions and binding energies of phytochemicals found in Moringa oleifera leaf extract (MoLE), specifically targeting glucocorticoid receptors (GRs).*
Method: *Gas chromatography-mass spectrometry (GC-MS) was used to determine the phytochemicals in MoLE, and molecular docking was then used to predict aspects of interactions and binding affinities of the bioactive phytocompounds at the GR protein site.*
Results: *The GC-MS analysis identified 41 compounds. Docking results revealed that 1-propanol, 3,3'-oxybis- and dodecanoic acid methyl ester exhibited the strongest binding affinities to GRβ, with scores of -7.7 and -7.5 kcal/mol, respectively. These values are comparable to the reference GR antagonist, mifepristone (-9.1 kcal/mol).*
Conclusion: *The 1-Propanol, 3,3'-oxybis- and Dodecanoic acid methyl ester are potent ligands for GR and can be further investigated through in vitro and in vivo studies to develop novel therapeutics.*

Keywords: *Phytochemical, Anti-inflammation, Receptor, SGRMs, Glucocorticoid receptor*

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INTRODUCTION

Glucocorticoids (GCs) are steroid hormones synthesized and secreted by the adrenal cortex in a circadian rhythm, primarily in response to stress. These hormones mediate diverse biological functions, including metabolism, cardiovascular activity, immune response, skeletal development, reproduction, and cognitive processes [1]. Their secretion is controlled by the hypothalamic-pituitary-adrenal (HPA) axis. The physiological and pharmacological effects of GCs are predominantly mediated through the glucocorticoid receptor (GR, NR3C1), a ligand-dependent transcription factor belonging to the nuclear receptor superfamily [2]. Upon binding its ligand, GR modulates the transcription of a substantial portion (10 to 20 %) of the human genome, either activating or repressing target genes [3]. Ubiquitously expressed and vital for postnatal survival, GR nonetheless elicits highly variable cellular responses that differ in specificity and sensitivity [4].

Synthetic glucocorticoids have been employed for over five decades as first-line therapeutics for numerous inflammatory and autoimmune

disorders, such as asthma, rheumatoid arthritis, and sepsis, owing to their potent anti-inflammatory and immunosuppressive properties [5]. However, long-term clinical utility is significantly limited by a well-documented spectrum of adverse effects, including osteoporosis, diabetes mellitus, hypertension, and skin atrophy [6]. Furthermore, prolonged treatment often leads to tissue-specific glucocorticoid resistance [7].

To address these limitations, selective glucocorticoid receptor modulators (SGRMs) have emerged as a promising therapeutic strategy. SGRMs are designed to retain the beneficial anti-inflammatory effects of traditional GCs while minimizing systemic side effects through selective receptor activation [8]. Natural products, particularly plant-derived compounds with glucocorticoid-mimetic properties, represent a valuable source for the discovery of novel SGRMs [9].

Moringa oleifera is widely consumed in Nigeria for its purported health benefits. Its leaf extract (MoLE) contains a diverse array of polyphenolic phytochemicals with distinct structures and bioactivities [10]. Preliminary investigations suggest several *M. oleifera* constituents may interact with GR [9,10]. Exploring these intricate phytochemical-GR interactions could unlock new avenues for targeted therapy.

Advances in computational molecular docking have become instrumental in early drug discovery. This technique predicts the binding affinity and orientation of small molecules within a protein's active site, providing valuable insights into potential interactions [11]. While *in silico* findings require subsequent experimental validation, docking serves as a powerful and efficient tool to screen natural product libraries and prioritize candidates for further study [12]. Therefore, this study employed molecular docking to systematically evaluate the potential of phytochemicals identified in MoLE to interact with the glucocorticoid receptor.

EXPERIMENTAL

Plant authentication and extraction

Fresh leaves of *Moringa oleifera* were harvested in the early morning from a garden in Abakaliki, Ebonyi State, Nigeria. A taxonomist at the Herbarium unit, Department of Biological Sciences, Alex Ekwueme Federal University Ndufu-Alike (AE-FUNAI), authenticated the plant specimen, assigning voucher number AE-FUNAI UH 504a.

The collected leaves were air-dried in shade at ambient temperature (~25 – 28 °C) for approximately two weeks. The dried material was pulverized into a fine powder. For solvent extraction, 200 g of the powdered leaves was subjected to continuous extraction in a Soxhlet apparatus with 500 mL of methanol for 48 hours. The combined methanol extracts were filtered, concentrated under reduced pressure at 40 °C, and stored at 4 °C until analysis [13].

Phytochemical screening and GC-MS analysis

The methanolic leaf extract was screened for major phytochemical classes, including alkaloids, flavonoids, saponins, tannins, phenols, glycosides, and steroids, following standard qualitative protocols [14].

Chemical profiling was performed using gas chromatography-mass spectrometry (GC-MS) on an Agilent 6890 GC system. Peaks were identified by comparing their retention times and mass spectra with reference data in the NIST11 library [13].

Molecular docking protocol

The three-dimensional crystal structure of the human glucocorticoid receptor beta (GRβ, PDB ID: 3BQD) was obtained from the RCSB Protein Data Bank. The protein structure was prepared for docking by removing water molecules and co-crystallized ligands, followed by the addition of polar hydrogen atoms.

The structures of forty-one phytocompounds identified by GC-MS, along with the reference GR ligand mifepristone, were retrieved from the PubChem database and converted to the required format using Open Babel software [15]. Molecular docking was performed using AutoDock Vina to predict binding affinities (kcal/mol) and interaction poses [16]. A grid box was defined to encompass the known ligand-binding site of GRβ. Protein-ligand interactions were visualized using Discovery Studio Visualizer 2020.

RESULTS

Phytochemical analysis confirmed the presence of multiple bioactive classes in the methanolic leaf extract of *Moringa oleifera* (MoLE). GC-MS profiling led to the identification of forty-one distinct compounds. The predominant compounds belonged to the class of fatty acid methyl esters. The complete list of identified

compounds and their molecular docking results is presented in Table 1.

DISCUSSION

The glucocorticoid receptor (GR) is a member of the steroid hormone receptor family and functions as a ligand-activated transcription factor. Its widespread expression in the body underpins its critical role in regulating essential processes such as development, metabolism, and inflammatory responses [1]. The present investigation employed molecular docking to evaluate the binding affinity (BA) of phytochemicals from *M. oleifera* to GR, where more negative BA values indicate stronger and more stable ligand-protein interactions [11]. The calculated binding energies for the docked compounds ranged from -4.8 to -9.1 kcal/mol.

Among the screened phytochemicals, 1-propanol, 3,3′-oxybis- demonstrated notable potential with a BA of -7.7 kcal/mol. Similarly, dodecanoic acid methyl ester exhibited a strong binding affinity of -7.5 kcal/mol. The stability of the apo-GR complex in the cytoplasm is maintained by a chaperone system including HSP90 [17]. Upon ligand binding, a conformational change triggers nuclear translocation, where GR dimers can modulate gene expression by binding to glucocorticoid response elements (GREs) or via tethering to other transcription factors like NF-κB to exert anti-inflammatory effects [3,18].

Table 1: Binding affinity of identified *Moringa oleifera* compounds to the glucocorticoid receptor (GRβ)

S/no	Name of compound	Binding affinity (kcal/mol)
R	***Mifepristone (Reference)***	***-9.1***
1	1-Propanol, 3,3'-oxybis-	-7.7
2	1-Propanamine, 3-propoxy-	-4.4
3	2-Pentene, 2-methyl-	-4.3
4	Pyridine	-4.0
5	2-Pentanone, 5-hydroxy-	-4.5
6	5-Hexen-2-ol, 5-methyl-	-5.1
7	1,3-Propanediamine, N-(1-methylethyl)-	-4.4
8	1,4-Butanediamine, N, N'-diethyl-	-5.6
9	Hexanoic acid, methyl ester	-6.8
10	Cyclotetrasiloxane, octamethyl-	-
11	1,2,3-Trimethyldiaziridine	-6.8
12	2-Hexyn-1-ol	-4.7
13	Heptanoic acid, methyl ester	-5.4
14	1-Heptene, 3-methyl-	-5.2
15	1-Fluorononane	-4.8
16	Octanoic acid, methyl ester	-5.7
17	Erythritol	-5.0
18	2-Mercaptopropanoic acid	-3.7
19	Triethylene glycol	-5.1
20	Decanoic acid, methyl ester	-6.7
21	Benzene,2-methoxy-1,3,4-trimethyl	-6.1
22	Ethylene, 1,2-dichloro-, (Z)-	-2.7
23	10-Undecenoic acid, methyl ester	-7.1
24	Trisiloxane,1,1,1,5,5,5-hexamethyl-3,3-bis((trimethylsilyl) oxy)-	-
25	7-Hexadecenal, (Z)-	-5.1
26	1-Octanol, 2-butyl-	-6.9
27	3,8-Dioxatricyclo (5.1.0.0(2,4)) octane, 4-ethenyl-	-5.6
28	Dodecanoic acid, methyl ester	-7.5
29	1-Decanol, 2-hexyl-	-6.6
30	Myristyl stearate	-5.1
31	2-Tridecenal, (E)-	-5.7
32	Cyclotetradecane	-6.4
33	Methyl tetradecanoate	-6.2
34	2-Piperidinone, N-(4-bromo-n-butyl)-	-5.9
35	Tetradecanal	-5.7
36	Ethanol, 2-(octadecyloxy)-	-7.2
37	Hexadecanoic acid, methyl ester	-6.6
38	6-Ethoxy-6-methyl-2-cyclohexenone	-5.6
39	n-Dodecyl methacrylate	-6.2
40	9-Octadecenoic acid (Z)-, methyl ester	-6.5
41	Methyl stearate	-4.8

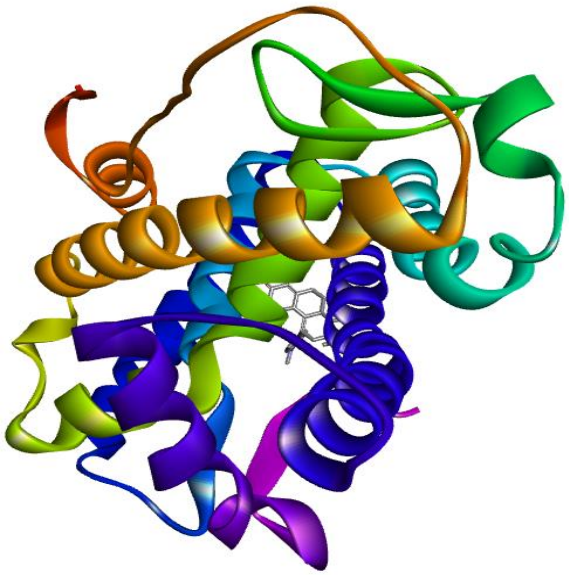

Figure 1: Three-dimensional (3D) view of the interaction between mifepristone and the binding site of glucocorticoid receptor beta (GRβ)

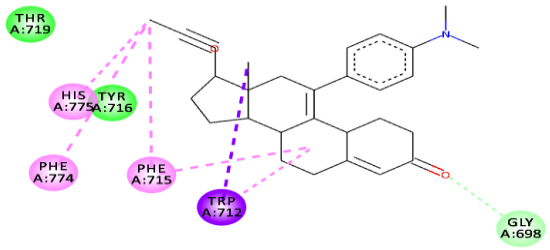

Figure 2: 2D view of the interaction between mifepristone and amino acids in the binding site of glucocorticoid receptor beta (GRβ)

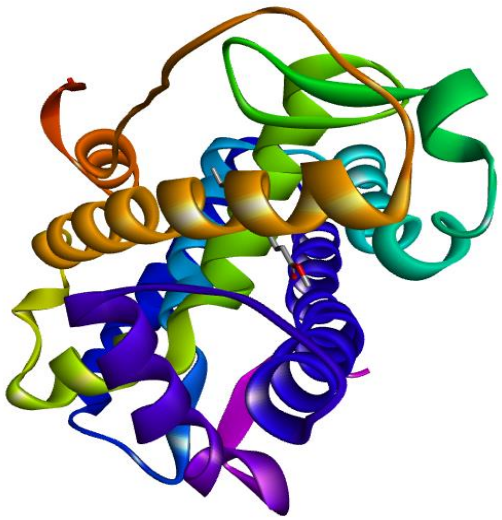

Figure 3: Three-dimensional (3D) view of the interaction between 1-Propanol, 3,3′-oxybis- and the ligand-binding site of the glucocorticoid receptor beta (GRβ)

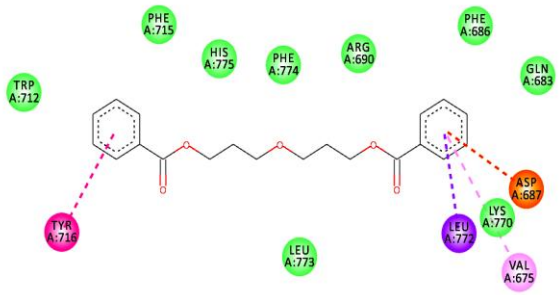

Figure 4: Two-dimensional (2D) schematic of the interaction between 1-Propanol, 3,3′-oxybis- and key amino acid residues in the binding site of the glucocorticoid receptor beta (GRβ)

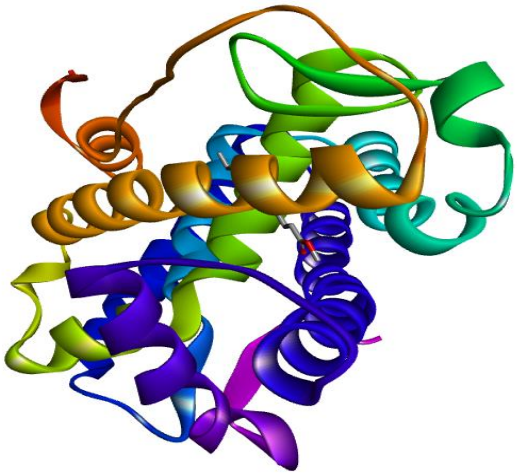

Figure 5: Three-dimensional (3D) view of the interaction between dodecanoic acid methyl ester and the ligand-binding site of the glucocorticoid receptor beta (GRβ)

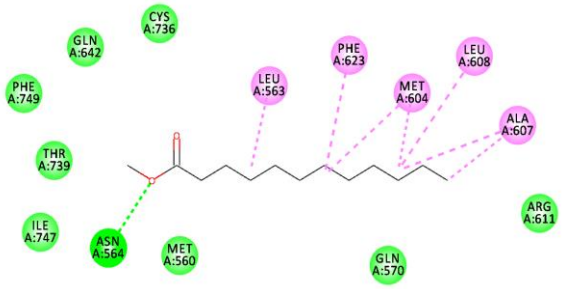

Figure 6: Two-dimensional (2D) schematic of the interaction between dodecanoic acid methyl ester and key amino acid residues in the binding site of the glucocorticoid receptor beta (GRβ)

The cellular response to glucocorticoids is finely tuned by multiple mechanisms, including the expression of regulatory isoforms like GRβ, which exerts dominant-negative effects [7]. This complex regulatory network highlights the importance of identifying selective ligands that can modulate specific GR functions.

CONCLUSION

Molecular docking simulations identified 1-propanol, 3,3′-oxybis- and dodecanoic acid methyl ester as promising lead compounds with strong binding affinities for the glucocorticoid receptor. These *in silico* results suggest their potential as candidates for the development of novel selective GR modulators. Future work should focus on validation through *in vitro* and *in vivo* studies.

DECLARATIONS

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Ethical approval

None provided.

Use of artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article. Odochi O. Chukwu and Anthony C. U. Ezimah conceived and designed the study. Odochi O. Chukwu performed the data collection and analysis. Grace Otthah-Umahi and Odochi O. Chukwu drafted the manuscript. Nnaemeka T. Asogwa and Albert E. Okorocha provided technical expertise, analyzed data, and reviewed the manuscript. All authors approved the final version for publication.

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