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RESEARCH ARTICLE

An in silico study of the effects of chemical compounds in *Petiveria alliacea* leaf extract on inflammatory mediators

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Abstract

Background: *Petiveria alliacea (P. alliacea)* is a botanical species renowned for its bioactive compounds and is utilised for medicinal purposes worldwide. In Southwestern Nigeria, *P. alliacea* finds common application in herbal medicine to address diverse ailments, including diabetes due to chronic inflammation. **Objective:** This study investigates the drug-like molecular properties of chemical compounds in *P. alliacea*, targeting the interleukin one receptor (IL1R) and Tumor Necrosis Factor-alpha receptor (TNFAR). **Method:** The target binding of the *P. alliacea* chemical compounds was evaluated through drug-likeness tests on the SCFBIO server. All compounds found in *P. alliacea* adhere to Lipinski's Rule of Five, classifying them as drug-like molecules. Employing molecular docking simulations on PyRx v9.9.0, the interaction dynamics between *P. alliacea* ligands and IL1R and TNFAR were simulated. **Result:** Among the compounds found in *P. alliacea*, namely astilbin and isoarborinol, emerge as potential candidates for IL1R and TNFAR protein inhibitors due to their notably elevated negative binding affinity values and involve Van der Waals, hydrogen and alkyl bond interactions. Then, a response was elicited that was marked by diminished oxidative stress and anti-inflammatory activity. **Conclusion:** *P. alliacea* has the potential to inhibit proinflammatory proteins, such as IL1R and TNFAR, due to its content, namely astilbin and isoarborinol.

Introduction

Diabetic patients face an elevated risk, two to three times higher, of developing cardiovascular diseases and are more susceptible to myocardial infarction, stroke, and heart failure, as evidenced by studies (Ogurtsova *et al*., 2017; Tate *et al*.,2019). Notably, the prognosis for diabetic patients afflicted with cardiovascular diseases is considerably worse than that for their non-diabetic counterparts. Among the complications stemming from diabetes mellitus in the cardiovascular system, diabetic cardiomyopathy stands out. This disease, which has the potential to culminate in a fatality, stems from diabetes mellitus and leads to heart failure (Kobayashi & Liang, 2015).

Central to myocardial alterations triggered by diabetes mellitus is oxidative stress, a primary component that triggers these changes. Prolonged exposure to oxidative stress in diabetes mellitus fosters chronic inflammation and fibrosis (Muthmainah *et al*., 2019; De Geest & Mishra, 2022). Characterised by excessive secretion of proinflammatory cytokines, diabetes mellitus represents a chronic inflammatory condition. Emerging evidence underlines the pivotal role of interleukin-1β (IL-1β), a central player in numerous

inflammatory diseases, as a significant instigator of systemic tissue inflammation in diabetes mellitus (Sumpter *et al*., 2011). The expression of IL-1β is apparent under high glucose conditions in human monocytes and macrophages, pancreas, and myocardium (Niu *et al*., 2014). Proinflammatory cytokines, including IL-1β, play a significant role in the genesis of cardiovascular complications associated with diabetes mellitus (Raines & Ferri, 2005). Importantly, IL-1β is implicated in both diabetes pathogenesis and the induction of cardiomyocyte apoptosis (Shen *et al*., 2015).

Petiveria alliacea (P. *alliacea*), commonly known as Guinea Hen Weed, boasts a plethora of bioactive compounds that render it a staple in traditional medicine across diverse regions (Cseke *et al*., 2016). In Southwestern Nigeria, it goes by the monikers "Awogba" or "Ojusaju" in the Yoruba language, "Kanunfari" in Hausa in the Northern region, and "Akwa-Ose" in Igbo in the South-East region. In this locale, *P. alliacea* finds application in herbal medicine to combat various ailments such as diabetes, arthritis, toothache, and skin infections. Notably, essential oils from this plant are chiefly constituted by phytol (Oluwa *et al*., 2017). Moreover, the extract of *P. alliacea* can lower blood glucose levels in rat models of diabetes mellitus through the activation of AMPK-α (Mustika, Indrawati, & Sari, 2017). The self-nanoemulsifying drug delivery system (SNEDDS) derived from the plant's leaf extract has demonstrated efficacy in reducing homeostatic model assessment-insulin resistance (HOMA-IR) values, along with suppressing TNF-α and IL-6 levels in the streptozotocin-induced diabetic rat model (Olomieja *et al*., 2021). Apart from these attributes, the plant's flavonoids hold significance due to their multifaceted functionalities. These compounds encompass antimalarial, antioxidant, anti-inflammatory, and antithrombotic properties. Furthermore, they are potentially anti-cancer and anti-inflammatory agents, inhibiting inducible nitric oxide synthetase (iNOS) expression and, subsequently, NFκB activation (Mustika, & Sari, 2021).

This study aims to evaluate the activity of diverse compounds within Guinea Hen Weed (*P. alliacea*) and conduct an in-silico analysis of these compounds concerning their interaction with target proinflammatory cytokine proteins, including IL-1β and TNFα.

Methods

Ligand preparation

The chemical compounds analysed in this study were ligands extracted from the SDF file. These compounds included myricetin, myricitrin, nonadecanoic acid, pinitol, quercetin, quinone, senfol, (2-hydroxyethyl) cysteine sulfoxides, allantoin, astilbin, barbinervic acid, benzaldehyde, benzoic acid, coumarin, daucosterol, dibenzyl disulfide, dibenzyl trisulfide, engeletin, isoarborinol acetate, isoarborinol, leridol, and lignoceric acid. The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) served as the source for these compounds, along with additional details such as CID and citation references. Converting the SDF file to the PDB format for the ligands was facilitated using OpenBabel v2.3.1 software to enhance molecular flexibility (Onyango *et al*., 2022).

Target retrieval

This study's focus involved the binding targets of the compounds within *P. alliacea*, namely the Interleukin 1 receptor (IL1R) and Tumor Necrosis Factor-alpha receptor (TNFAR). The 3D structures of these targets were procured from the RCSB PDB database (https://www.rcsb.org/). To optimise and prepare these targets for molecular docking, PyMol v2.5 uses the edu version, free software was employed to eliminate water molecules and contaminant ligands (Rigsby and Parker, 2016).

Drug-likeness identification

To determine the drug-like nature of the chemical compounds in Guinea Hen Weed (*P. alliacea*), a drug-likeness test was conducted using the SCFBIO server (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp).

This evaluation leveraged Lipinski's Rule of Five, a criteria involving molecular mass, LogP (lipophilicity), hydrogen bond donors, hydrogen bond acceptors, and molar refractivity (Lipinski, 2004). The drug-likeness test aimed to ascertain the similarity between the properties of the query compounds and established drug-like molecules by referencing the five parameters stipulated by Lipinski's Rule of Five (Lipinski, 2004).

Molecular docking

The interaction simulation involving the ligands from Guinea Hen Weed (*P. alliacea*) with IL1R and TNFAR was executed via molecular docking simulations using PyRx 9.9.0 $Id: LICENSE.txt 112 2012-02-13 22:33:36Z sarkiss $ Copyright (c) [2008-Forever], Sargis Dallakyan and individual contributors, all rights reserved

software. The primary objective of these docking simulations was to ascertain the binding activity of the ligands and their specific interaction patterns with the respective targets. This affinity, quantified as negative energy, signifies the stability of the molecular complexes formed upon the interaction between the ligand and the target (Lipinski, 2004; Wijaya *et al*., 2021).

Chemical interaction

Detection and classification of chemical interactions within the ligand-protein complexes constituted another facet of this study. Employing Discovery Studio 2016 software, various chemical bond interactions were identified, including van der Waals, hydrogen, hydrophobic, and electrostatic bonds (Lipinski, 2004). Characterised by their weak bond nature, these interactions can trigger distinct biological responses, influencing aspects such as molecular complex stability and inhibition degree (Lipinski, 2004).

Structural visualisation

The visualisation of ligand-target complexes in 3D structures was accomplished using PyMol v2.5 software, employing colour-coding and structure selection methodologies. The colour scheme employed was contingent on the atomic composition of the ligand and the singular protein structure. This study opted for a combination of structural representations such as cartoons, sticks, and transparent surfaces, adhering to established publication standards (Onyango *et al*., 2022).

Results

Structural visualisation of the ligands and targets from the docking simulation of astilbin IL1R (B) isoarborinol TNFAR can be seen in Figure 1. Figure 2 shows the molecular interaction of astilbin IL1R and isoarborinol TNFAR. Table I shows Docking results for guinea hen weed *P. alliacea* compound-target interactions and the drug-likeness analysis.

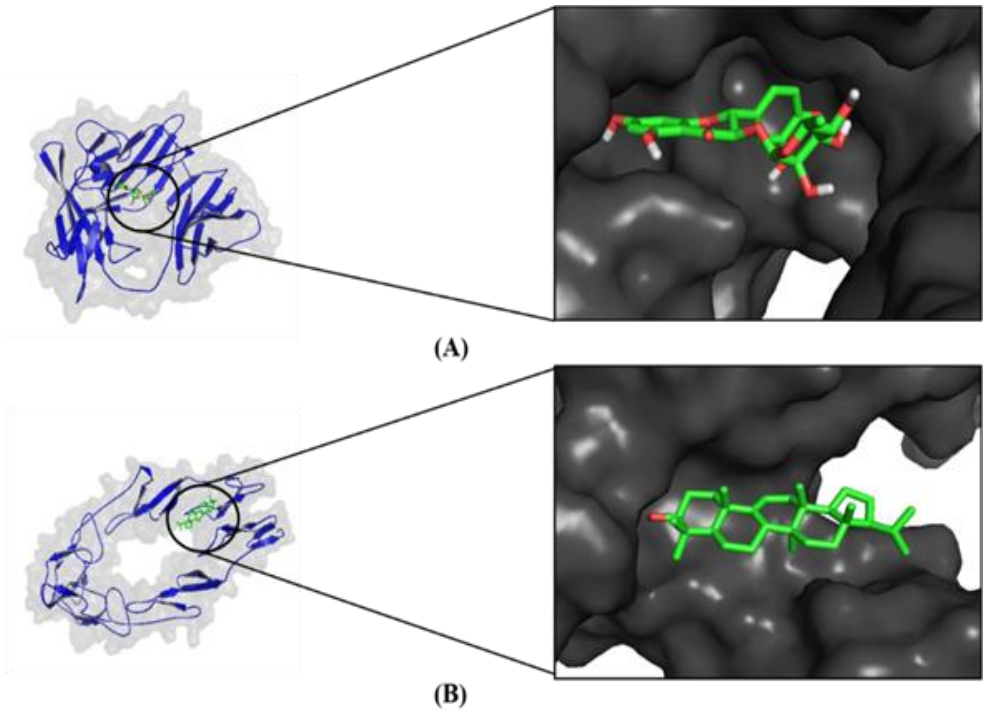
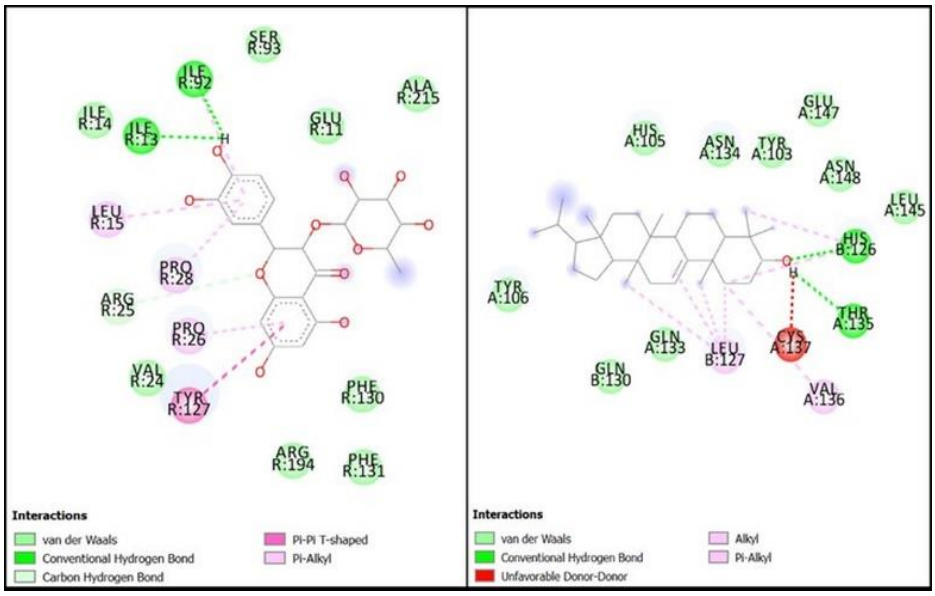


Figure 1: Structural visualisation of the ligands and targets from the docking simulation (A) Astilbin_IL1R (B) Isoarborinol_TNFAR



(A) **(B)**

Figure 2: Visualisation of molecular interaction (A) Astilbin_IL1R (B) Isoarborinol_TNFAR

Table I: Docking results for guinea hen weed (*P. alliacea*) compound-target interactions and the drug-likeness analysis

Compounds	Binding affinity (kcal/mol)		Molecular mass (≥500D)	High lipophilicity (≥5)	Hydrogen bond donor (≥5)	Hydrogen bond acceptor (≥10)	Molar refractivity (40-100)	Probable
	IL1R	TNFAR						
Myricetin	-7.9	-6.7	318,000	1.716	6	8	75.715	Drug-like molecule
Myricitrin	-7.4	-7.2	464,000	0.002	8	12	106.526	Drug-like molecule
Nonadecanoic acid	-5.8	-4.3	298,000	5.243	1	2	104.661	Drug-like molecule
Pinitol	-5.2	-4.8	194,000	-3.180	5	6	40.830	Drug-like molecule
Quercetin	-7.9	-6.7	302,000	2.010	5	7	74.050	Drug-like molecule
Quinone	-5.0	-3.9	108,000	0.250	0	2	28.293	Drug-like molecule
Senfol	-4.3	-3.6	144,000	1.192	0	2	39.785	Drug-like molecule
(2-hydroxyethyl) cysteine sulfoxides	-4.9	-4.0	206,000	2.953	1	2	58.473	Drug-like molecule
Allantoin	-5.3	-3.9	158,000	-2.179	5	7	33.181	Drug-like molecule
Astilbin	-8.2	-7.5	450,000	0.038	7	11	104.471	Drug-like molecule
Barbinervic acid	-7.2	-6.5	488,000	5.176	4	5	135.483	Drug-like molecule
Benzaldehyde	-5.4	-5.3	106,000	1.499	0	1	31.829	Drug-like molecule
Benzoic acid	-6.3	-4.5	122,000	1.384	1	2	33.401	Drug-like molecule
Coumarin	-6.2	-5.3	146,000	1.618	0	2	41.110	Drug-like molecule
Daucosterol	-4.5	-7.4	312,000	-0.053	5	6	77.145	Drug-like molecule
Dibenzil disulfida	-7.0	-4.2	246,000	4.768	0	0	75.473	Drug-like molecule
Dibenzyl trisulfide	-7.0	-4.2	278,000	5.416	0	0	83.064	Drug-like molecule
Engeletin	-8.0	-7.0	434,000	0.332	6	10	102806	Drug-like molecule
Isoarborinol acetate	-3.6	-6.8	468,000	8.595	0	2	140.197	Drug-like molecule
Isoarborinol	-6.0	-7.6	426,000	8.024	1	1	130.649	Drug-like molecule
Leridol	-6.8	-6.6	314,000	2.908	2	5	84.077	Drug-like molecule
Lignoceric acid	-5.9	-3.9	368,000	6.775	1	2	131.996	Drug-like molecule

Discussion

The target protein IL1R (RCSB ID: 1G0Y) possesses a sequence length of 162 amino acids, a resolution of 3.00 Å, and a structural weight of 38.32 kDa. It is characterised by the chain R. Similarly, the target protein TNFAR (RCSB ID: 1NCF) boasts a resolution of 2.25 Å, a structural weight of 36.67 kDa, and is constituted by chains A and B.

The process of drug-likeness identification entailed assessing the resemblance of the query compounds' properties to those of established drug molecules based on specific physicochemical parameters such as molecular mass, high lipophilicity (LogP), hydrogen bond donors, hydrogen bond acceptors, and molar refractivity. This assessment adhered to Lipinski's Rule of Five, which stipulates that a query compound should adhere to at least two specific rules to exhibit similarity to a drug molecule (De Geest & Mishra, 2022). Notably, all the compounds found in Guinea Hen Weed (*P. alliacea*) demonstrate drug-like attributes as they meet the criteria of at least two rules outlined by Lipinski's Rule of Five (Table I).

Ligand activity, in this context, corresponds to the magnitude of the binding energy score. The binding affinity, a negative energy metric, materialises when the ligand connects with the target (Ogurtsova *et al*., 2017). The ligand's activity level hinges on the binding affinity value it forms upon interaction with the target. Within this framework, negative binding affinity values denote the bond's strength, with higher negative values indicating more robust ligand bonds (Lipinski, 2004). The results of the docking simulations unveiled that among the various compounds within Guinea Hen Weed (*P. alliacea*), Astilbin and Isoarborinol displayed notably superior negative binding affinity values compared to their counterparts (refer to Table I). Moreover, both Astilbin and Isoarborinol exhibited the potential to elicit the inhibition of IL1R and TNFAR activity. The ligand-protein complexes that garnered the highest negative binding affinity values from the docking simulations are showcased through a combination of stick structures, transparent surfaces, and cartoons embellished with a single stain (see Figure 1).

Chemical interactions between the ligands and their targets emerge from specific weak bonds encompassing van der Waals, hydrogen, hydrophobic, and electrostatic bonds (see Figure 2). These weak bond categories contribute to initiating distinct biological responses, serving, for instance, as inhibitory agents. To maintain stability, the count of unfavourable bond interactions within molecular complexes must remain below three (Widyananda *et al*., 2021).

Conclusion

In conclusion, this study highlights the significance of certain chemical compounds found within Guinea Hen Weed (*P. alliacea*), with Astilbin and Isoarborinol emerging as notable contenders. These compounds stand out due to their elevated negative binding affinity values and propensity to foster weak bond interactions, including van der Waals, hydrogen, and alkyl bonds. The influence of these weak bonds may trigger ligand activity and affect the inhibition of both IL1R and TNFAR, subsequently eliciting a response marked by diminished oxidative stress and anti-inflammatory activity.

Author contributions

N.F and A.M conceived and designed the experiments; N.F and S.A.S performed the experiments; N.F and A.M analysed the data; A.C.F and L. A wrote the paper.

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