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Computational Docking and In Silico Toxicity Prediction of Polydatin as a Potential TNF-α Modulator

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Abstract: This study presents a comprehensive computational evaluation of the interactions of Polydatin (piceid) and Cortisone with members of the TNF superfamily, focusing on TNF-α. Blind docking was performed across multiple TNF proteins, while selective docking targeted TNF-α using the crystallographic binding pocket of its co-crystallized ligand (PDB ID: 7JRA). Both compounds displayed similar binding energies (~ −7 kcal/mol) across several TNF family members. Notably, Polydatin exhibited a significantly higher affinity for TNF-α (−9.7 kcal/mol using AutoDock Vina) compared to Cortisone (−6.6 kcal/mol).Redocking of the crystallographic ligand VGY validated the docking protocol, demonstrating accurate pose superimposition and consistent binding energies. Further docking using AutoDock4 (AMDock) confirmed favorable Polydatin binding (−10.87 kcal/mol), with estimated nanomolar inhibitory constants. In silico toxicity predictions via pkCSM suggest that Polydatin possesses a favorable safety profile, including a high predicted maximum tolerated dose and absence of mutagenicity or hepatotoxicity. Overall, these results indicate that Polydatin is a promising natural compound for TNF-α modulation, warranting further in vitro and in vivo studies.

Keywords: Polydatin, TNF-α, TNF superfamily, molecular docking, SwissDoc

INTRODUCTION

Inflammation is a fundamental biological response to infection, tissue injury, or cellular stress, aiming to restore homeostasis. It can be classified as acute—characterized by rapid mediator release and immune cell recruitment—or chronic, involving persistent immune activation and sustained cytokine production, often associated with pathologies such as rheumatoid arthritis, cardiovascular diseases, and cancer [1–4].

Cytokines are central regulators of inflammatory responses. Among them, Tumor Necrosis Factor-α (TNF-α) is a key pro-inflammatory mediator involved in immune regulation, apoptosis, and cell survival. Dysregulation of TNF signaling contributes to multiple autoimmune and inflammatory disorders, making TNF-α and its receptors important therapeutic targets [9–16].

Glucocorticoids such as Cortisone are widely used anti-inflammatory agents; however, chronic administration can cause systemic adverse effects. Consequently, interest has grown in natural compounds with anti-inflammatory properties and potentially improved safety profiles.

Polydatin, a glycosylated precursor of resveratrol, is a ROS scavenger(6) and has demonstrated antioxidant and anti-inflammatory effects [6–8]; nevertheless, its direct structural interaction with TNF-α is not well understood.

Despite the clinical efficacy of current TNF-α inhibitors, including biologics (such as monoclonal antibodies and receptor fusion proteins) and small-molecule synthetic drugs, several limitations exist. Biologics are costly, require parenteral administration, and can induce immunogenicity, leading to loss of response or adverse effects. Synthetic inhibitors often present off-target activity, systemic toxicity, and limited long-term safety data. These challenges highlight the need for safer, more accessible alternatives. Natural compounds, such as Polydatin, with favorable safety profiles and potential anti-inflammatory activity, offer a promising avenue for TNF-α modulation[11,12]: these theoretical findings provide a computational basis for the development of Polydatin as a safer natural complementary activity to conventional glucocorticoids in inflammatory disorder.

This study aims to:

1. Evaluate the binding affinities of Polydatin and Cortisone across TNF superfamily members using blind docking.
2. Perform selective docking on TNF-α targeting its crystallographic binding pocket.
3. Validate docking reliability via redocking of the co-crystallized ligand.
4. Compare predicted toxicity profiles of Polydatin with several glucocorticoids using in silico tools.

This integrative computational approach aims to provide a structural and toxicological framework supporting future experimental investigations.

MATERIALS AND METHODS

All human TNF ligands and receptors were prepared prior to docking by assigning correct protonation states, removing crystallographic water molecules when necessary, adding missing hydrogens, optimizing bond geometries, and ensuring binding site integrity.

Protein structures used (PDB IDs): TNF-α (7JRA), TNF-β (4MXV), TL1A (2O0O), Fas ligand (4MSV), TWEAK (4HT1), BAFF (4ZCH), RANKL (5BNQ), TRAIL (1D2Q), LIGHT (4EN0), GITR ligand (2Q1M), CD40L (1ALY), OX40L (2HEV), 4-1BB ligand (2X29), LTβR (1RF3), TRAF2 (1D0A), TNFRSF6B (3MHD), DR4 (5CIR), TACI (1XU1). Grid box coordinates were set according to each rotein's binding site (details in the supplementary study).

Docking analyses were conducted using AutoDock Vina via PyRx and validated using AutoDock4 with AMDock. Blind docking explored potential binding regions across protein surfaces, while selective docking targeted TNF-α's crystallographic pocket.

Toxicity predictions were performed using pkCSM, evaluating mutagenicity, hepatotoxicity, maximum tolerated dose, and other pharmacokinetic parameters.

RESULTS AND DISCUSSION

Blind Docking Across the TNF Superfamily

Polydatin generally showed slightly stronger binding to TNF-α (−9.7 kcal/mol) compared to Cortisone (−6.6 kcal/mol), suggesting favorable specificity. (Table 1).

Selective Docking on TNF-α

Selective docking confirmed higher Polydatin affinity for TNF-α, with binding energies of −9.7 kcal/mol (Vina) and −10.87 kcal/mol (AutoDock4; Ki ≈ 10.77 nM), compared to Cortisone (−6.6 kcal/mol, Vina; −9.19 kcal/mol, AutoDock4; Ki ≈ 183.5 nM). Redocking of the crystallographic ligand VGY validated docking accuracy.

Toxicity Prediction

In silico toxicity evaluation indicated that Polydatin is **non-mutagenic, non-hepatotoxic**, and possesses a relatively high maximum tolerated dose (0.569 log mg/kg/day), higher than many glucocorticoids. These results suggest a potentially wider therapeutic window, though experimental confirmation is necessary.

Table 1 displays the comparison of binding energies of Polydatin and Cortisone with Tumor Necrosis Factor superfamily by Blind Docking by Autodock Vina with Pyrx program

TNF superfamily	Binding Energies of Cortisone (kcal/mol)	Binding Energies of Polydatin (kcal/mol)
TNF-alpha *	-6.6	-9.7
TNF-β **	-8.5	-8.3
TL1A **	-7.5	-7.6
Fas ligand **	-6.3	-6.9
TWEAK **	-7.8	-6.5
BAFF **	-7.8	-8.2
RANKL**	-7.6	-6.9
TRAIL**	-6.9	-6.9
LIGHT**	-6.8	-7.3
GITR ligand**	-6.2	-6.3
CD40L**	-6.5	-6.5
OX40L**	-7.8	-7.5
4-1BB ligand**	-6.4	-6.5
LTbetaR**	-7.9	-7.4
TRAF2**	-6.9	-6.6
TNFRSF6B**	-6.5	-6.4
DR4**	-7.2	-6.8
TNFRSF13B	-6.2	-6.2

Selective Docking*; ** Blind Docking

PDB Code 7JRA

HUMAN TNF-ALPHA IN COMPLEX WITH CRYSTAL LIGAND VGY: 2-[5-(3-chloro-4-{[(1R)-1-(2-fluorophenyl)ethyl]amino}quinolin-6-yl)pyrimidin-2-yl]propan-2-ol

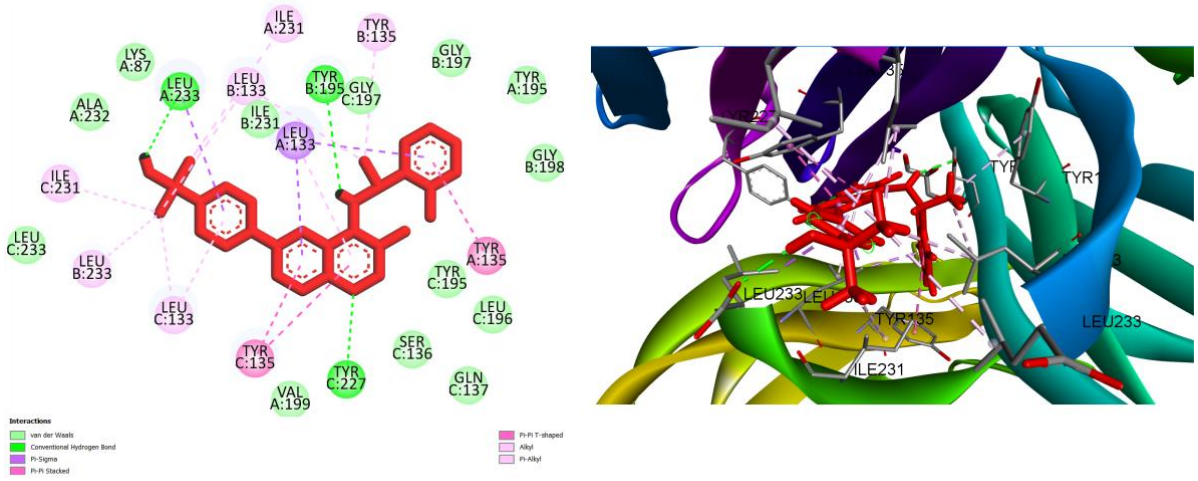

Figure 1 shows the docking of the crystal structure of human TNF-α with ligand VGY within the binding site. The left panel illustrates residue interactions (2D), while the right panel highlights the ligand's location within the binding pocket.

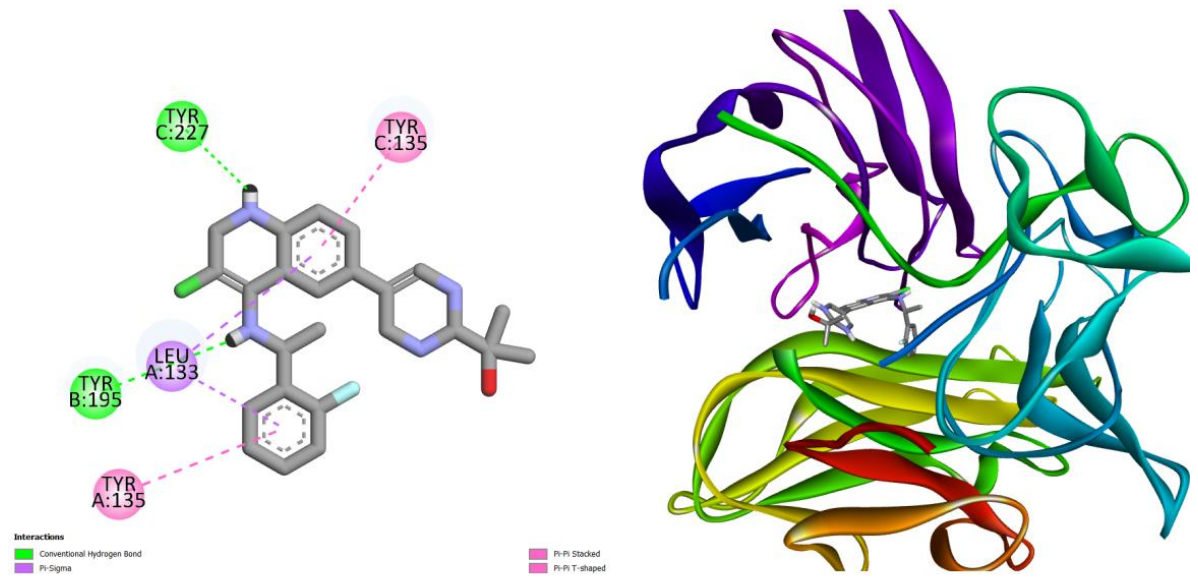

Figure 2 shows the docking of the crystal structure of human TNF-α with docked ligand VGY -13 kcal/mol within the binding site. The left panel illustrates residue interactions (2D), while the right panel highlights the ligand's location within the binding pocket

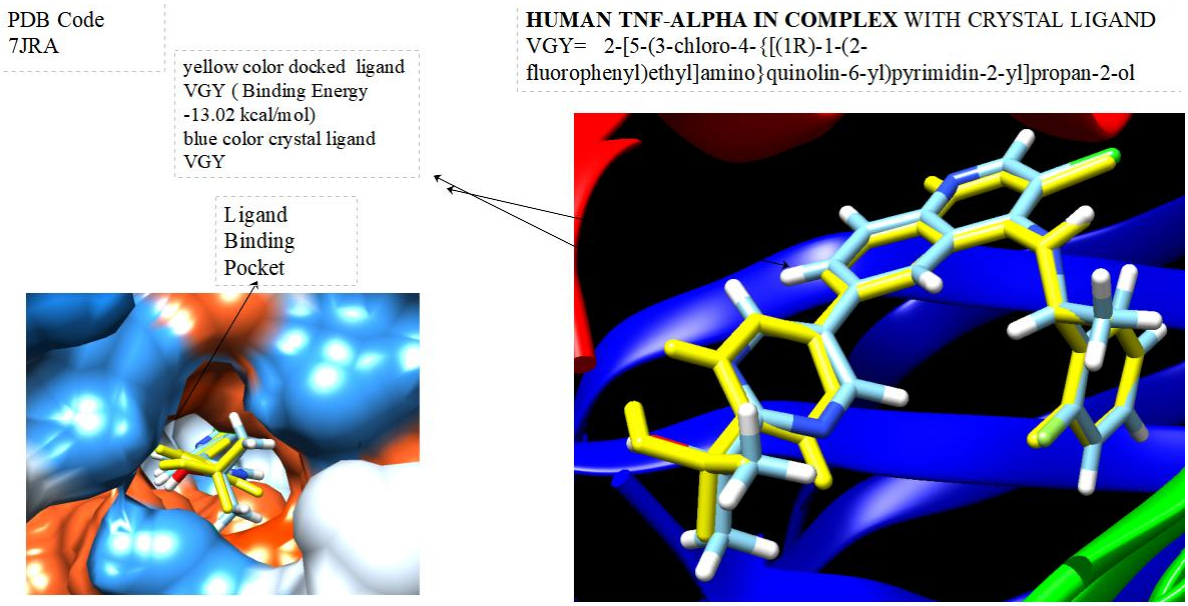

Figure 3 displays the overlapping comparison of the Crystal Structure of Human TNF-alpha in conjunction with docked ligand VGY -13 kcal/mol with crystal ligand VGY within the Ligand Binding Site.

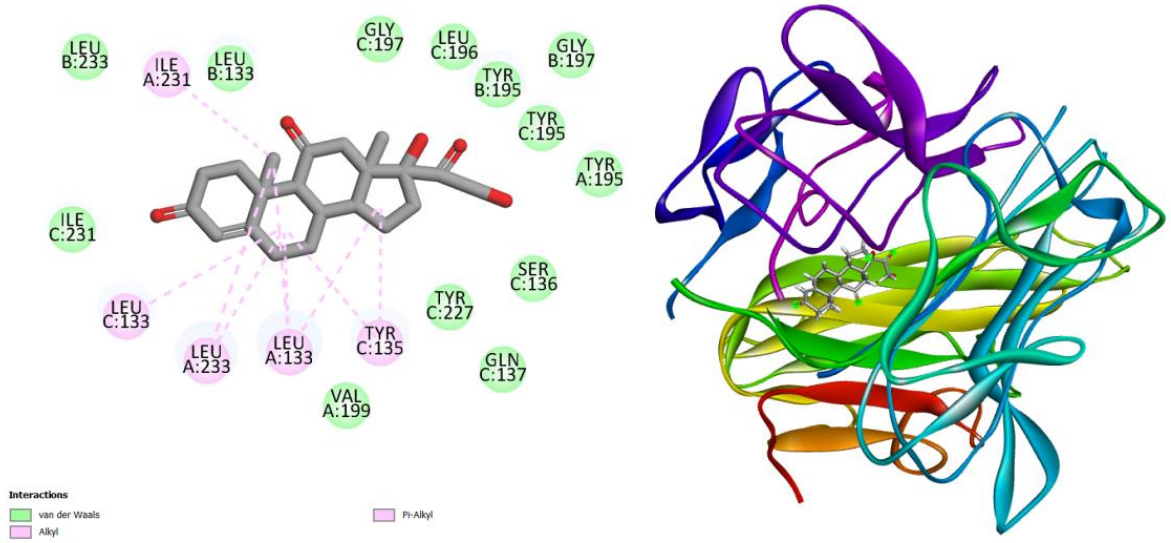

Figure 4 shows the docking of the crystal structure of human TNF-α with docked Cortisone -6.6 kcal/mol within the binding site. The left panel illustrates residue interactions (2D), while the right panel highlights the ligand's location within the binding pocket.

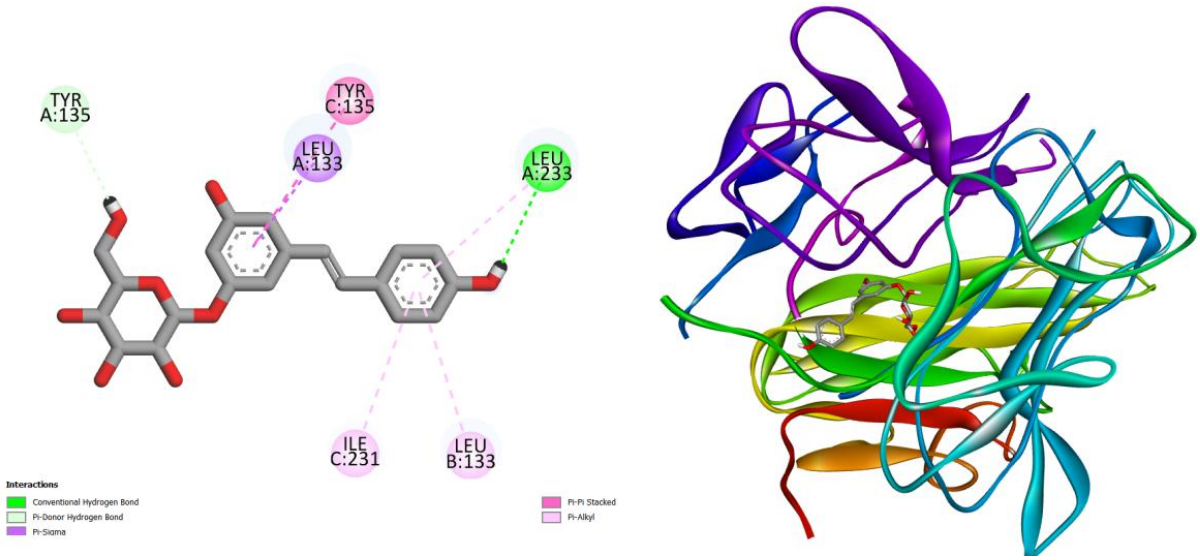

Figure 5 shows the docking of the crystal structure of human TNF-α with docked Polydatin -9.7 kcal/mol within the binding site. The left panel illustrates residue interactions (2D), while the right panel highlights the ligand's location within the binding pocket.

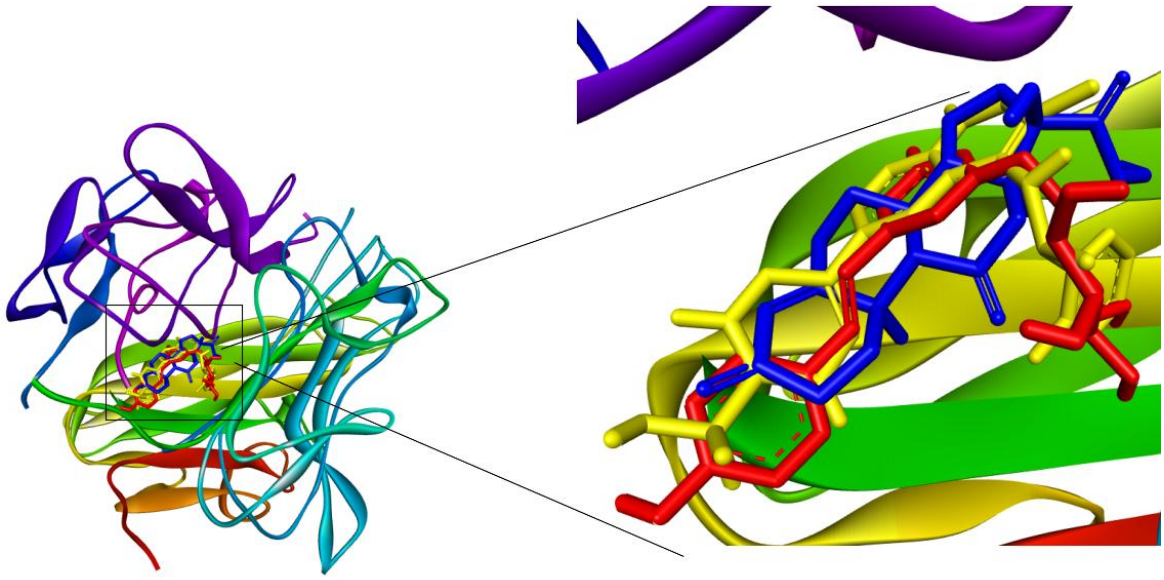

Figure 6 displays the comparison of the Crystal Structure of Human TNF-alpha in conjunction with docked Polydatin -9.7 kcal/mol (red color), with Cortisone -6.6 kcal/mol (blue color) and docked crystalline ligand VGY -13 kcal/mol (yellow color) within the Ligand Binding Site, as analyzed by Autodock Vina through the Pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and docked Polydatin . Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of docked Polydatin

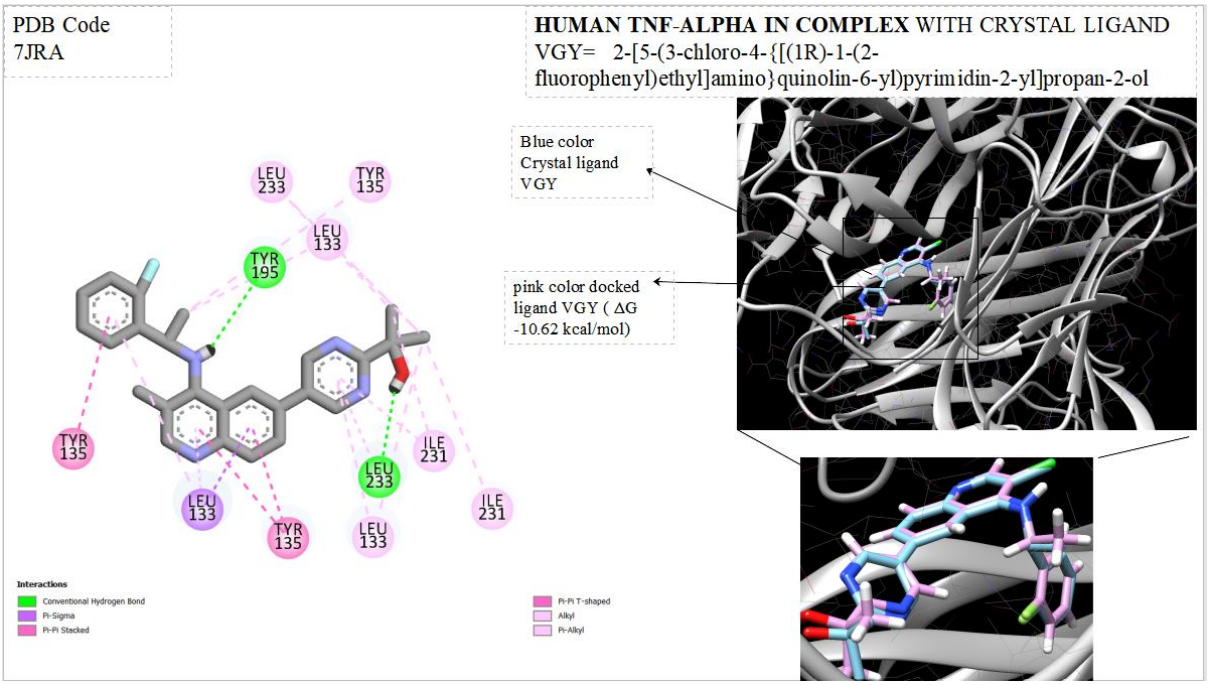

Figure 7 displays the comparison of the crystal structure of Human TNF-alpha in conjunction with crystal ligand VGY (blue color) and docked crystal ligand VGY (pink color) with ΔG -10.6 kcal/mol within the Ligand Binding Site, as analyzed by Autodock Vina through the Pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and docked Polydatin. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of docked Polydatin

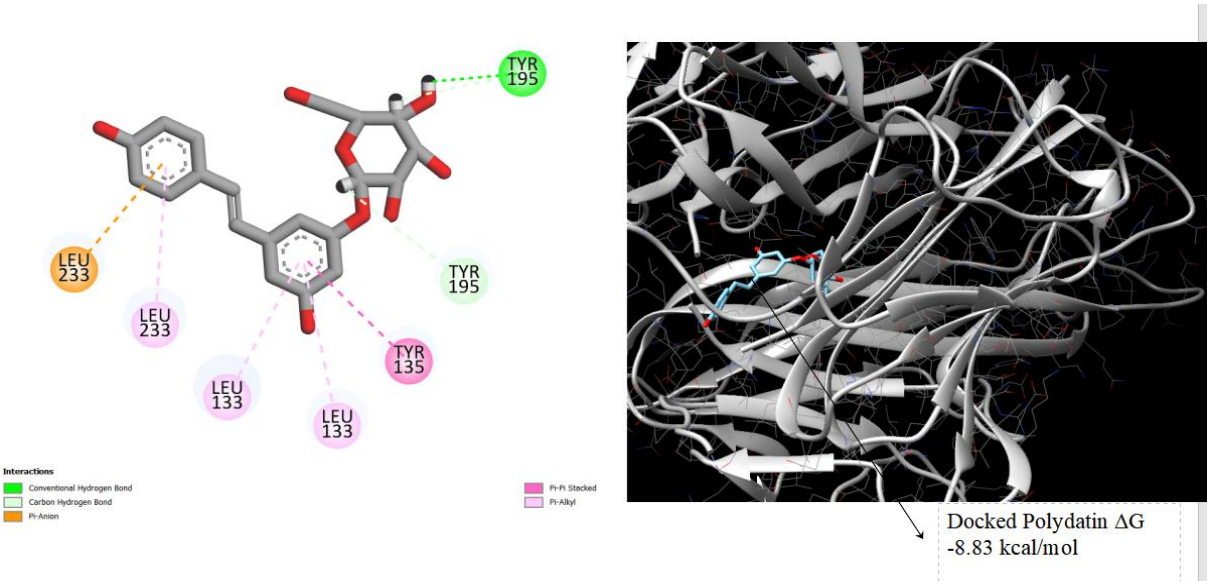

Figure 8 displays the crystal Structure of Human TNF-alpha in conjunction with docked polydatin (blue color) with ΔG -8.8 kcal/mol within the Ligand Binding Site, as analyzed by Autodock Vina through the Pyrx program. On the left side, 2D diagrams illustrate the residue interactions between the protein and docked Polydatin . Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of docked Polydatin.

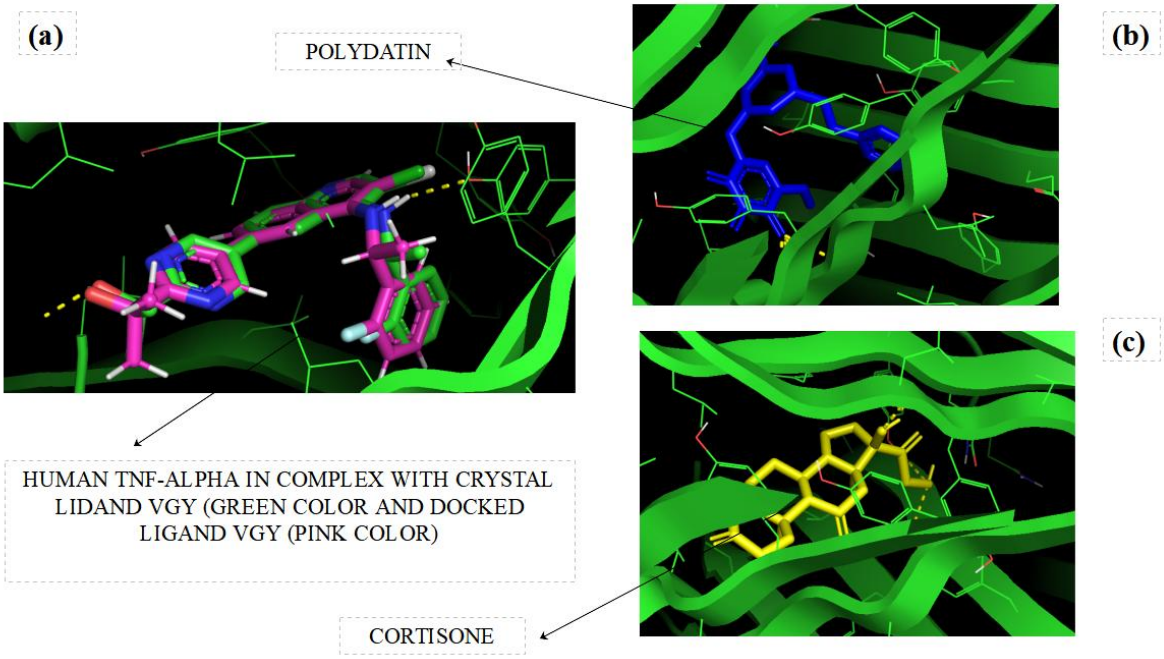

Figure 9 displays a comparison of the crystal structure of Human TNF-alpha in conjunction with docked polydatin (blue color), docked cortisone (yellow color), and docked crystal ligand VGY within the Ligand Binding Site, as analyzed by Autodock 4 through the AMDOCK program

Table 2 shows the investigation of the toxicity profiles of various glucocorticoids, utilizing predictions from the pKCSM Server.

Compounds	AMES toxicity	Max. tolerated dose (human) (log mg/kg/day)	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity	Skin Sensitisation	T. Pyriformis toxicity (log ug/L)	Minnow toxicity (log mM)
18-Hydroxycorticosterone	No	-0.427	1.975	2.592	no	no	0.338	1.827
Corticosterone	No	-0.694	1.937	1.545	no	no	0.624	1.237
Desoxycortone	No	-1.105	2.439	1.78	no	no	0.83	0.412
Fluocortolone	No	-0.576	2.073	1.95	no	no	0.515	1.851
Hydrocortisone Acetate	No	-0.6	2.218	1.757	no	no	0.382	1.385
Medrysone	No	-0.996	1.889	1.724	no	no	0.978	0.695
Prednisolone	No	-0.076	2.538	0.747	no	no	0.338	2.439
18-Oxocortisol	No	-0.265	2.119	2.626	no	no	0.292	2.364
Cortisol	No	-0.183	2.088	2.504	no	no	0.312	1.944
Dexamethasone	**No**	**0.097**	**2.504**	**2.541**	**No**	**No**	**0.299**	**2.535**
Fluorometholone	No	-0.413	2.329	1.698	No	No	0.473	2.179
Hydrocortisone Butyrate	No	-0.748	2.197	1.964	No	No	0.376	1.513
Methylprednisolone	No	-0.183	2.143	0.654	No	No	0.345	1.934
Triamcinolone	**No**	**0.347**	**2.612**	**2.475**	**No**	**No**	**0.286**	**4.181**
Aldosterone	No	-0.616	1.928	2.263	No	No	0.433	1.558
Cortisone	No	-0.35	2.146	2.197	No	No	0.337	1.759
Fludrocortisone Acetate	yes	-0.32	2.588	1.836	No	No	0.305	2.726
Fluoxymesterone	No	-0.073	2.005	1.427	No	No	0.537	2.012
Hydrocortisone hemisuccinate	**No**	**0.398**	**2.516**	**2.425**	**No**	**No**	**0.285**	**2.681**
Paramethasone	**No**	**0.022**	**2.367**	**2.504**	**No**	**No**	**0.302**	**2.471**
Betamethasone	No	-0.632	2.732	2.742	No	No	0.29	2.675
Cortodoxone	No	-0.212	1.938	1.457	No	No	0.417	0.951
Fludrocortisone	No	-0.059	2.544	2.519	No	No	0.296	2.621
Fluprednisolone	**No**	0.024	2.603	1.98	**No**	**No**	0.313	3.111
Hydrocortisone phosphate	yes	-0.687	2.559	2.871	No	No	0.285	2.169
Budesonide	No	-0.589	1.922	2.131	No	No	0.29	0.956
Desoximetasone	No	-0.504	2.172	1.937	No	No	0.479	1.927
Flumethasone	**No**	0.07	2.684	2.596	**No**	**No**	0.294	3.192
Halometasone	No	-0.199	2.309	2.503	No	No	0.289	2.446

Hydrocortisone Valerate	No	-0.794	2.133	1.971	No	No	0.374	1.319
Prednisolone Acetate	yes	-0.591	2.18	1.772	No	No	0.381	1.464
Polydatin	**No**	**0.569**	**2.516**	**4.473**	**No**	**No**	**0.285**	**4.39**

Table 3 displays Docking results of the Crystal Structure of Human TNF-alpha in conjunction with docked ligand VGY, (PDB Code 7jRA), Docked Cortisone, and Docked Polydatin in the Ligand Binding Site pocket, evaluated by Autodock 4 and Autodock Vina with AMDock program

Compounds	**Binding Energy by Autodock Vina (kcal/mol)**	**Binding Energy by Autodock 4 (kcal/mol)**	**Estimated Ki (nM)**	**Ligand Efficiency (kcal/mol)**
Cortisone	-5.3	-9.19	/	-0.35
Polydatin	**-11.0**	**-10.87**	**10.77**	**-0.39**
Crystal Ligand VGY*	-13.1	-11.58	3.25	-0.37

*2-[5-(3-chloro-4-{[(1R)-1-(2-fluorophenyl)ethyl]amino}quinolin-6-yl)pyrimidin-2-yl]propan-2-ol

CONCLUSION

This computational investigation provides structural insights into the potential interaction of Polydatin with members of the TNF superfamily, particularly TNF-α. Docking analyses indicate that Polydatin exhibits stronger predicted binding affinity toward TNF-α compared to Cortisone within the crystallographic binding pocket.

Complementary in silico toxicity predictions suggest a favorable safety profile for Polydatin relative to several glucocorticoids.

However, it is important to emphasize that molecular docking and toxicity prediction studies represent theoretical models Experimental validation through biochemical binding assays, cellular studies, and in vivo investigations will be essential and is currently underway to determine the actual inhibitory potential and pharmacological relevance of polydatin in TNF-α-mediated inflammation. Furthermore, its potential use in complementary therapeutic protocols—particularly when corticosteroid treatments are discontinued due to long-term adverse effects—warrants investigation.

These findings lay the computational groundwork for the experimental validation of Polydatin as a novel TNF-α modulator with potential therapeutic applications in inflammatory diseases. Given its favorable predicted binding affinity and safety profile, polydatin—a well-characterized natural compound - emerges as a promising candidate for further preclinical evaluation as a TNF-α modulator. It may also represent a potential alternative to corticosteroids in mitigating systemic and/or chronic dermatological inflammation.

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