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Research Article



Molecular docking and dynamic study with polyphenolic constituents as inhibitors of human tyrosinase enzyme for hyperpigmentation therapy and skin complexion management

Diptendu Sarkar¹  and Gopal Dev Mandal² 

¹Department of Microbiology, Ramakrishna Mission Vidyamandira, Belur Math, Howrah, Pin-711202, West Bengal, India

²Department of Botany, Ramsaday College, College Road, Amta, Howrah, Pin- 711401, West Bengal, India.

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(✉) Corresponding Author: diptendu81@gmail.com

Abstract

This research has revealed the molecular docking and dynamics study with few phytomolecules against the human tyrosinase enzyme protein in order to control hyperpigmentation and skin tone in the future. This study set out to find certain phytomolecules that have the capacity to attach to the protein model for the tyrosinase enzyme and block the enzyme's ability to function. We took into account all nine molecules in total, coupled with a protein model of the tyrosinase enzyme, for docking, with energy ranges between -5.3 and -7.4 Kcal/mol. The greatest lowest binding energy for quercetin was -7.4 Kcal/mol. With a model protein, this molecule displayed a variety of interactions, including Van der Waals, conventional hydrogen bonds, covalent bonds, and carbon hydrogen bonds. In this interaction, 3 hydrogen bonds were discovered. The other compounds, such as kaempferol and chlorogenic acid, also demonstrated correct binding with the model tyrosinase and had -7.2 Kcal/mol energy with 3 and 5 hydrogen bonds, respectively. Quercetin, Kaempferol, and Chlorogenic acid are therefore thought to be far more potent than Benzotropine and may be used in further clinical research.

Keywords: Molecular Docking, Molecular Dynamics, Hyperpigmentation, Skin Tone, Binding Energy.

Introduction

Melanin, the main pigment responsible for skin tone. Melanogenesis is the name of the melanin biosynthesized cascaded. Tyrosine, an amino acid, is oxidised to start melanin biosynthesis in human body. Sun exposure, pregnancy, hormonal contraception, and family history are the most common causes of skin hyperpigmentation among Asians (Anders et al., 1993). Human complexion is mostly dictated by melanin. It can be detected in the stria vascularis of the ear drum, hair, and the pigmented tissue underlying the iris of the eye. Elements in the brain that contain melanin include the medulla as well as neurons that contain pigmentation, such as the locus coeruleus, in some regions of the cerebellum. It can also be found in the adrenal gland's zona reticularis. Melanin levels are double that as in normal skin, contributing to darker skin phenotypes in which the pigment is expressed in

melanocytes in the epidermal layer's basal layer. Several natural skin whitening treatments with phenolic moiety are accessible as tyrosinase inhibitors (Antal et al., 1993; Arooj et al., 2013). Phenolics are secondary metabolites produced by plants for regular cellular physiological processes such as hormone control, cell division, including photosynthetic activity, as well as in response to major climatic circumstances or environmental stressors (Azam et al., 2013). Hydroxy cinnamates, such as caffeic acid and ferulic acid, have been reported for their melanin suppression by Balimane et al and Beaulieu et al., (Balimane et al., 2013; Beaulieu et al., 2019). p-coumaric acids (Beeching et al., 2014) and their esters, such as chlorogenic acid (Bissantz, et al., 2000; Braga et al., 2016), are found in common plant-based foods such as fruits, grains, vegetables, and seeds. These are widely used in cosmetic preparation as antimelanogenic agents. Quercetin and kaempferol are flavonoids that are plentiful in foods such as

apples, berries, onions, beans, tomato, tea, and other fruits and vegetables. Tyrosinase is an enzyme that is involved in both animal melanogenesis and neuromelanin production in the human brain, primarily in the substantia nigra (Brehm et al., 2016). Melanoma-specific anticarcinogenic action is also connected to tyrosinase activity. Melanin biosynthesis and storage are seen in keratosis nigricans, melasma (pregnancy mask), poikiloderma of Civatte, periorbital hyperpigmentation, post-inflammatory melanoderma, ephelides, and ageing spots, among other skin conditions (Castillo et al., 2008). Tyrosinase is a brain enzyme that produces neuromelanin and can induce neurodegenerative diseases like Parkinson's disease by oxidising excessive dopamine to make dopaquinone, resulting triggers Parkinson's disease, Huntington's disease (brain cell death), as well as neuronal injury (Dezani et al., 2016).

Natural compounds such as epigallo catechin gallate, aloesin, hydroxystilbene derivatives, and liquorice extracts have been described as tyrosinase inhibitors in a number of scientific

study studies. Molecular docking investigations on compounds produced from the phenyl propanoid cascade, notably phenolic acid and flavonols as tyrosinase inhibitors, as well as a thorough explanation of the ADME parameters, were carried out in this study.

Materials and methods

Modelling and refinement of protein structure

The amino acid sequence of human tyrosinase enzyme protein has been obtained from Uniport Accession No P14679 (Fig 1). This protein model has been created by using SWISS MODEL program (<https://swissmodel.expasy.org/>) (Gasteiger et al., 2016; Sarkar et al., 2022). It is a fully automated service for homology modelling of protein structures that may be accessed using the Expasy web server or the software DeepView. Best selected model was refined by using Galaxy web server (<http://galaxy.seoklab.org>) (Irvine et al., 2016).

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>sp|P14679|TYRO_HUMAN Tyrosinase OS=Homo sapiens OX=9606 GN=TYR PE=1 SV=3
MLLAVLYCLLWSFQTSAGHFPRACVSSKNLMEKECCPPWSGDRSPCGQLSGRGSCQNILL
SNAPLGPQFPFTGVDDRESWPSVFYNRTCQCSGNFMGFNCGNCKFGFWGPNCTERRLLVR
RNIFDLSAPEKDKFFAYLTLAKHTISSDYVIPIGTYGQMKNGSTPMFNDINIYDLFVVMH
YYVSM DALLGGSEIWRDIDFAHEAPAFLPWHRLFLLRWEQEQKLTGDEFNFTIPYWDWRD
AEKCDICTDEYMGQHPNPNLLSPASFFSSWQIVCSRLEEYNSHQSLCNGTPEGPLRRN
PGNHDKSRTPLRPSSADVEFCLSLTQYESGSM DKAANFSFRNTLEGFASPLTGIADASQS
SMHNALHIYMGNTMSQVQGSANDPIFLHHAFFVDSIFEQWLRRHRPLQEVYPEANAPIGH
NRESYMPFPIPLYRNGDFFISSKDLGYDYSYLQSDPDSFQDYIKSYLEQASRIWSWLLG
AAMVGAULTALLAGLVSLLCRHKRQKLPKQPLLEKEDYHSLYQSHL
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Fig. 1 Sequence of human tyrosinase enzymatic protein (Uniport Accession No P14679).

Ligand selection and preparation for docking

Form the extensive review of literatures related to tyrosinase inhibiting phytomolecules, a list has prepared (Table 1). 3D structure of all antiviral drugs was downloaded from PubChem database. The ligands have been put through an automated preparation procedure using PyRx software (Khabbaz et al., 2015). There was total 10 molecules used in this study (Table 1). The 'Ligand' option was used to rectify

the torsional tree, non-polar hydrogens, charges, and atom variety once all ligands were uploaded into the AutoDockTools (Koes, 2018). Using SWISS ADME (<http://www.swissadme.ch>) to screen all biologically active compounds relying on the Lipinski rule of five, further adsorption, distribution, metabolism, and excretion prediction were carried out with all the structure (Morris et al., 1998; Nimlos et al., 2006).

Table 1. List of phytochemicals used for study the interaction with modelled human tyrosinase protein. Name of the phytomolecules, their PubChem ID as well as their Molecular formula are also presented in the table.

SI No	Name	PubChem ID	Molecular formula
1	Arbutin (reference compound)	440936	C ₁₂ H ₁₆ O ₇
2	Kojic acid	3840	C ₆ H ₆ O ₄
3	Tropolone	10789	C ₇ H ₆ O ₂
4	Hydroquinone	785	C ₆ H ₆ O ₂
5	Quercetin	5280343	C ₁₅ H ₁₀ O ₇
6	Kaempferol	5280863	C ₁₅ H ₁₀ O ₆
7	Chlorogenic acid	1794427	C ₁₆ H ₁₈ O ₉
8	Ferulic acid	445858	C ₁₀ H ₁₀ O ₄
9	Caffeic acid	689043	C ₉ H ₈ O ₄
10	4-Hydroxycinnamic acid	637542	C ₉ H ₈ O ₃

Molecular docking study and simulation analysis

Molecular docking analysis was performed with target like membrane-associated best modelled protein VP24 by using PyRx virtual screening tool (Morris et al., 2009). This tool used Auto Dock 4.00 for docking purpose. Here, we first loaded a model of a protein structure as a protein, and then we added each chosen bioactive component (ligand) one at a time. The ligand energy was first reduced by software, and then it was transformed into the Auto Dock ligand format (pdbqt). Finally started docking after covering entire protein structure under grid box to screen best fitted bioactive compounds based on energy value. Approximately ten simulations were performed for each simulation, producing ten docked structures. This led to the conclusion that the binding affinities with the lowest energy were those with the most binding. Intra-molecular associations including hydrogen bonds, van der Waals contacts,

plus hydrophobic correlations with such an individual ligand molecule have really been clearly examined using Discovery Studio software (Mukund et al., 2019). Further by using WEBGRO -protein with ligand simulation server got the MD simulation result of best docking molecule.

Results and Discussion

Molecular docking on human tyrosinase enzymatic protein has been elucidated here. In silico molecular analysis was performed on a variety of bioactive compounds. Various physicochemical parameters such as donors or acceptors of hydrogen bond, number of flexible bonds, molecular mass, and others were often used anticipate and grade drug compliance (Oso et al., 2020). The “Lipinski rule of five” was checked for all of these compounds. The results are summarized in Table 2.

Table 2. ADME predictions analysis of all used phytomolecules based on Lipinski rule of five.

Name	Molecular Weight (g/mol)	No of H bond donor	No of H bond acceptor	No of rotatable bond	Log P _{o/w}	Log S	Lipinski violation
Arbutin	272.25	5	7	3	-0.77	-0.71	0
Kojic acid	142.11	2	4	1	-0.16	-0.70	0
Tropolone	122.12	1	2	0	0.91	-1.51	0
Hydroquinone	110.11	2	2	0	0.87	-1.45	0
Quercetin	302.24	5	7	1	1.23	-3.16	0
Kaempferol	286.24	4	6	1	1.58	-3.31	0
Chlorogenic acid	354.31	9	6	5	-0.39	-1.62	1
Ferulic acid	194.18	2	4	3	1.36	-2.11	0
Caffeic acid	180.16	3	4	2	0.93	-1.89	0
4-Hydroxycinnamic acid	164.16	2	3	2	0.95	-2.02	0

A database of 3D protein structural models produced by the SWISS-MODEL homology modelling workflow is known as the SWISS-MODEL Repository (SMR). It gives users access to a current library of 3D protein models annotated by automated homology modelling for pertinent model species as well as experimental structural data for all UniProtKB sequences (Ostroff et al., 2005; Ramalingam et al., 2011). Regular updates guarantee comprehensive target coverage, use of the most recent sequence and template structure databases, and full utilisation of modelling pipeline enhancements. Additionally, it enables users to evaluate the models' quality using the most recent QMEAN outcomes. If a sequence has not yet been modelled, the user may do it using the SWISS-MODEL workspace to develop models interactively (Roe et al., 2013; Sarkar, 2022). The navigation between resources for protein sequence and structure is made easier by annotating models with functional data and creating cross-links with other databases, such UniProtKB.

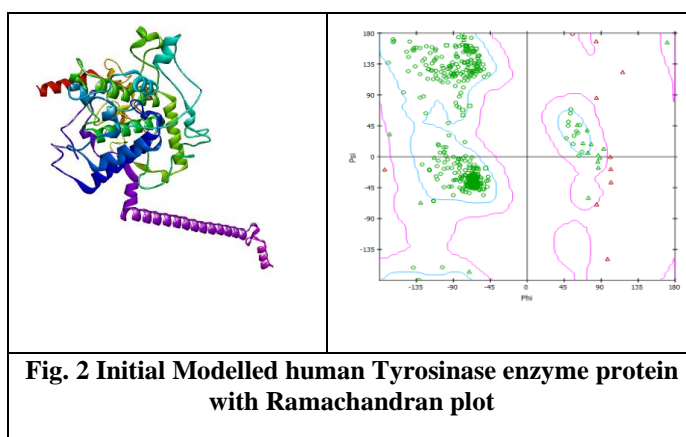


Fig. 2 Initial Modelled human Tyrosinase enzyme protein with Ramachandran plot

The refinement of expect 3D protein models would be critical for getting them closest to practical precision in preparation for future computational investigations. The sampling and scoring steps seem to be the two basic phases of refinement methodologies. Through changing secondary structure components and retaping sidechains, refining 3D models can help bringing them closer to natural structures (Rothman et al.,

2008). Refinement procedures, on the other hand, might, inadvertently, reduce the quality of models. For researchers of 3D model refinement approaches, determining whether such a model has indeed been upgraded or made poorer continues to be a major difficulty (Rougeron et al., 2015; Sarkar, 2021). Galaxy Refine exploits computer simulations modelling to achieve recurrent structure modification and required architectural. Model 1 merely applies structure modification to clusters of side chains, whereas model 2-5 applies more severe alterations to secondary structural system and loops. To eliminate model structure breakdowns induced by turbulence,

the triaxial loop completion algorithm has been applied. Structure refinement information related to the first modelled ACRBP from GalaxyRefine provided below in the Table 3. Higher is the Rama favoured indicates better was the quality of the structure (Sarkar et al., 2023). Before and after refinement of the first modelled ACRBP, it's structure and related Ramachandran Plot information depicted in the Fig. 3, 4, 5 and 6. For Ramachandran plot analysis, we used PROCHECK server for the first model here, produced more quality structure for further use.

Table 3. Structure refinement information related to the first modelled ACRBP from GalaxyRefine. Higher is the Rama favoured indicates better us the quality of the structure.

Model	GDT-HA	RMSD	MolProbity	Clash score	Poor rotamers	Rama favoured
Initial	1.0000	0.000	2.959	6.1	14.0	78.4
MODEL 1	0.9438	0.466	2.355	19.8	0.2	90.2
MODEL 2	0.9300	0.500	2.229	15.8	0.6	90.8
MODEL 3	0.9346	0.484	2.271	17.6	0.8	90.8
MODEL 4	0.9342	0.496	2.231	17.7	0.8	92.1
MODEL 5	0.9291	0.487	2.260	17.4	0.8	90.9

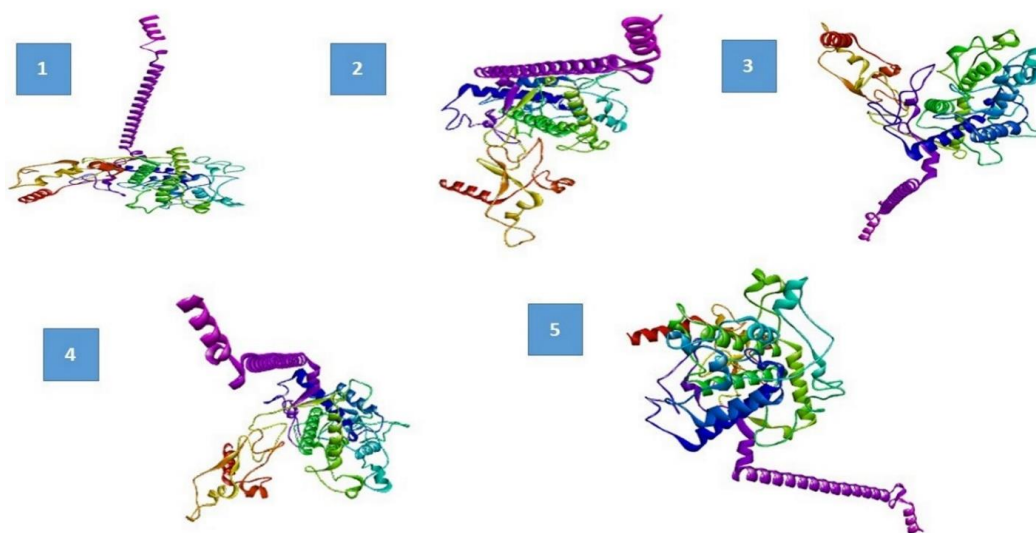


Fig. 3 All five refined model from GalaxyRefine.

Modelling the intermolecular interactions in a ligand-protein molecule has proven difficult due to the wide range of possible variations and the lack of knowledge on the impact of the environment on the binding relationship. Molecular docking tries to arrange molecules into appropriate topologies in addition to connecting complementary characteristics (Sarkar et al., 2022; Wadapurkar et al., 2018). For docking research, the 3-D structure of the protein is required, and this structure is normally available and simple to obtain for any protein from the PDB database. On the other hand, the 3-D structure of the human tyrosinase enzyme protein is unknown. As a

consequence, we examined small compounds by docking them against the modelled protein structure using computational methods to model the protein. As is well known, proteins seem to be the basic building blocks of all living cells and are essential for a variety of biological functions. Every protein in our bodies has a specific function, and that function is dictated by the protein's structure (Wenthur et al., 2018). According to molecular modelling, conformational changes between low and high affinity states induce protein-ligand couplings (Sarkar et al., 2022). Lipid binding interactions would affect both protein structure and functioning. Characterization of couplings in

protein-ligand complexes appears to be crucial for structural bioinformatics, drug development, and biological research projects (Sarkar et al., 2023). Based on the Lipinski rule of five, or mol, ADME predictions study was performed on all drug

molecules used (Table 3). 500 Daltons (g/mol) in mass, 5 H-bond donors, 10 H-bond acceptors, 5 high lipophilicity, and 40–130 molar refractive index.

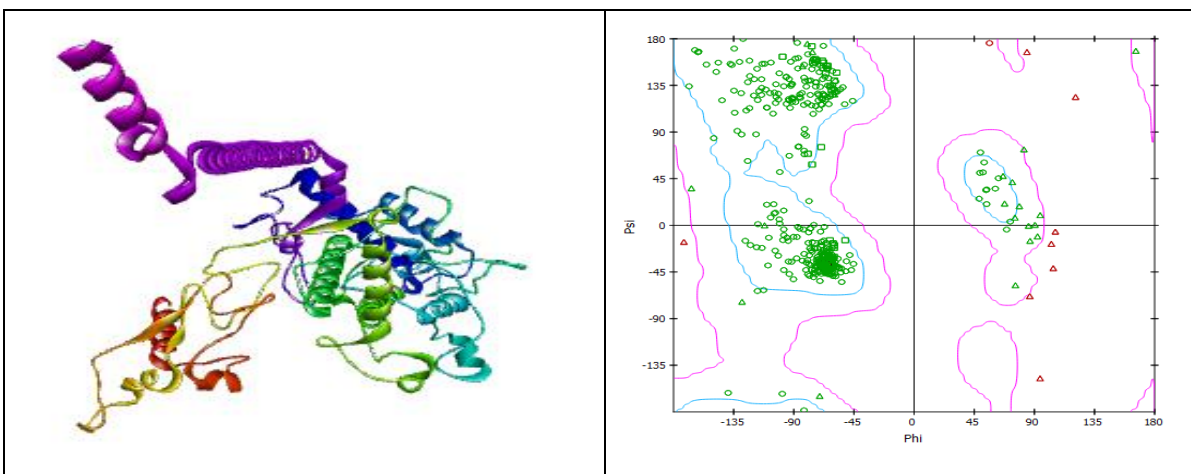


Fig. 4 Best refined model of Human Tyrosinase enzyme with Ramachandran plot. This is used for further docking study.

This study set out to identify specific phytomolecules from neem that have the ability to block the tyrosinase enzyme and bind to the protein model for the tyrosinase enzyme in order to regulate hyperpigmentation and skin tone in the future. We considered all total 9 molecules for docking along with modelled tyrosinase enzyme protein with energy ranges from -5.3 to -7.4 Kcal/mol (Table 4, Fig. 5-14). Quercetin, showed maximum lowest binding energy i.e., -7.4 Kcal/mol. This molecule showed various interaction with modelled protein like Van der Waals, conventional hydrogen bond, covalent bond and carbon hydrogen bond. The number of hydrogen bond found was 3 in this interaction (Table 4; Fig. 9). A polyphenolic flavonoid with possible chemopreventive properties is quercetin. Quercetin, which is widely found in plant-based food sources and is a significant bioflavonoid in the human diet, may

have antiproliferative effects by altering the signal transduction pathways mediated by either EGFR or oestrogen receptors. Arbutin which is a common inhibitor for tyrosinase enzyme, was used as a reference molecule in this study. It showed during the interaction with modelled Human Tyrosinase enzyme protein with no hydrogen bond along with -7.0 Kcal/mol energy (Fig. 5). The other molecules like Kaempferol and Chlorogenic acid also showed proper binding with modelled tyrosinase and found to have -7.2 Kcal/mol energy with 3 and 5 hydrogen bonds respectively. Therefore, it can be assumed that Quercetin, Kaempferol and Chlorogenic acid has much more potency than Benztropine and that can be used further for clinical study. All other molecule's docking related information presented in Table 4 and Fig. 5-14.

Table 4. Overview of results model of Human Tyrosinase enzyme and respective ligand binding with the Binding affinity and Number of residues in interaction as well as Number of hydrogen bond involved in the interaction.

Name	Interaction energy Kcal/mol	Interaction residue	No of H bonds	Figure No.
Arbutin	-7.0	Tyr 235, Leu 126, Ile 233, Phe 134, Thr 232, Tyr 251, Arg 121, Ile 123, Ala 391, Leu 388	0	5
Kojic acid	-5.5	Ser 50, Lys 104, Arg 52, Gly 51, Cys 112, Gln 48, Gly 47, Cys 100, Gly 101, Cys 103, Asn 102	2	6
Tropolone	-6.4	Gly 227, Asp 42, Arg 116, Phe 105, Asn 230, Leu 118, Phe 231, Glu 229, Gln 220, Glu 221, Glu 219, Lys 222, Asp 228, Leu 225, Thr 226	7	7
Hydroquinone	-5.3	Tyr 463, Gln 453, Asp 462, Gln 461, Asp 458, Phe 460, Pro 457	3	8
Quercetin	-7.4	Tyr 137, Leu 140, Phe 231, Leu 225, Asp 228, Gly 227, Gln 223, Lys 224, Ile 222	3	9

Kaempferol	-7.2	Tyr 137, Leu 140, Phe 231, Leu 225, Asp 228, Gly 227, Gln 223, Lys 224, Ile 222	3	10
Chlorogenic acid	-7.2	Asp 42, Unl1, Asn 102, Tyr 149, Asp 148, Glu 221, Gln 220, Gln 223, Ile 222, Leu 225, Arg 43, Gly 227, Thr 226	5	11
Ferulic acid	-5.9	Ala 141, Thr 144, Gly 227, Lys 224, Glu 221, Thr 226, Gln 223, Ile 222, Leu 140, Ile 172	1	12
Caffeic acid	-6.0	Ala 141, Thr 144, Gly 227, Lys 224, Glu 221, Gln 223, Ile 222, Thr 226, Leu 140, Ile 172	1	13
4-Hydroxycinnamic acid	-5.8	Ala 141, Thr 144, Gly 227, Lys 224, Glu 221, Gln 223, Ile 222, Thr 226, Leu 140, Ile 172	1	14



Fig. 5 3D and 2D interaction between refined model of human tyrosinase enzyme with Arbutin

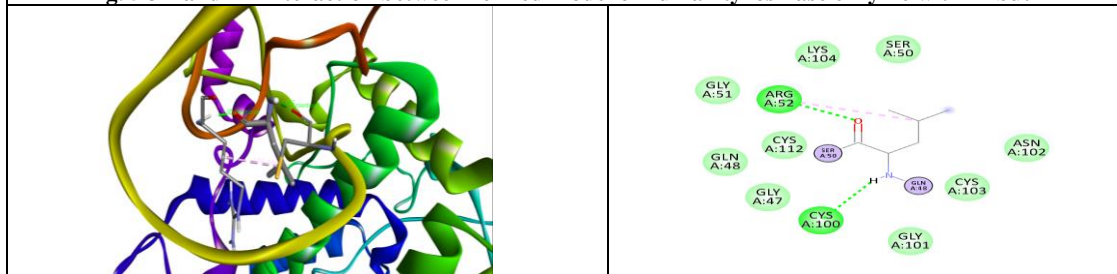


Fig. 6 3D and 2D interaction between refined model of human tyrosinase enzyme with Kojic acid

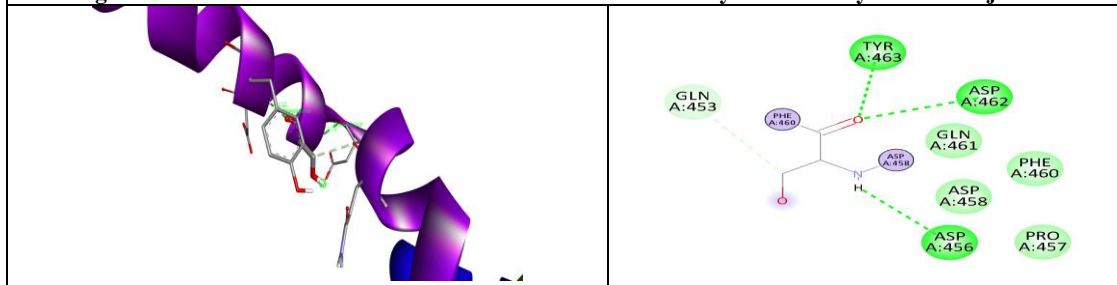


Fig. 7 3D and 2D interaction between refined model of human tyrosinase enzyme with Tropolone

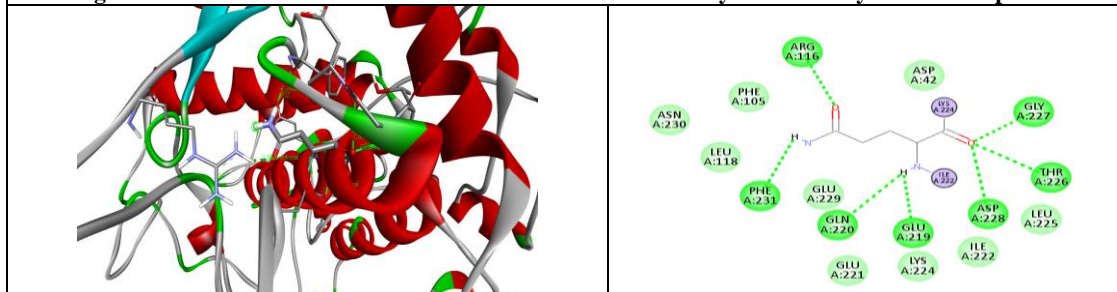


Fig. 8 3D and 2D interaction between refined model of human tyrosinase enzyme with Hydroquinone

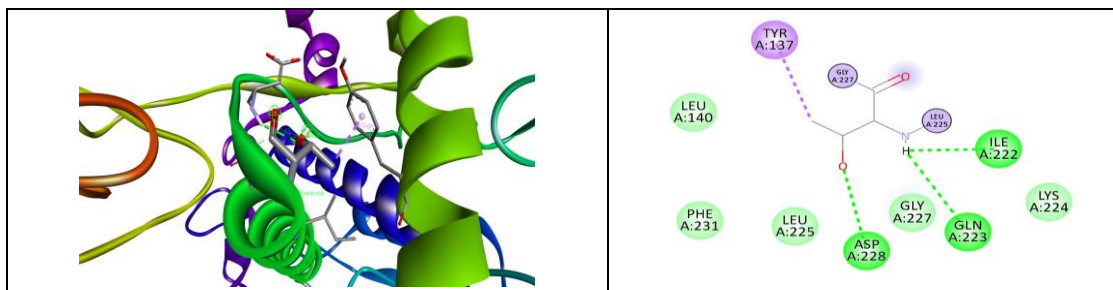


Fig. 9 3D and 2D interaction between refined model of human tyrosinase enzyme with Quercetin

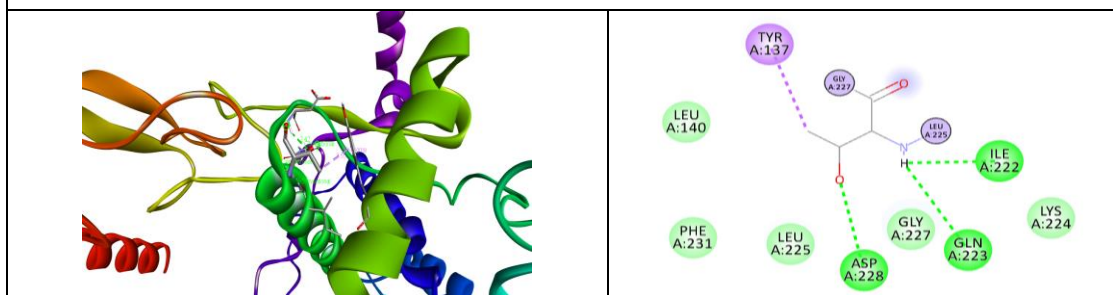


Fig. 10 3D and 2D interaction between refined model of human tyrosinase enzyme with Kaempferol

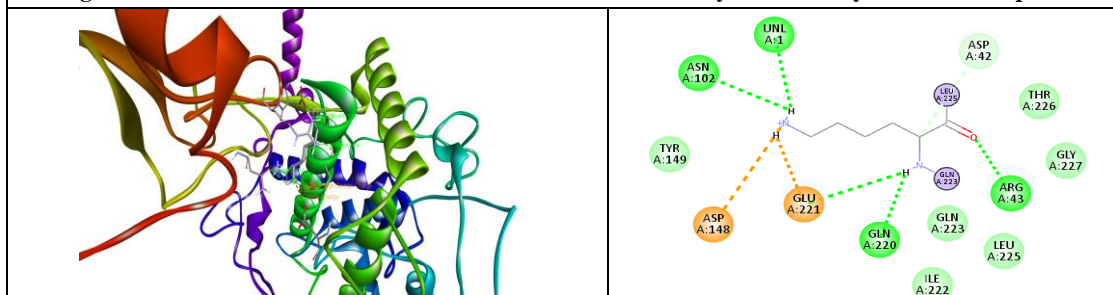


Fig. 11 3D and 2D interaction between refined model of human tyrosinase enzyme with Chlorogenic acid

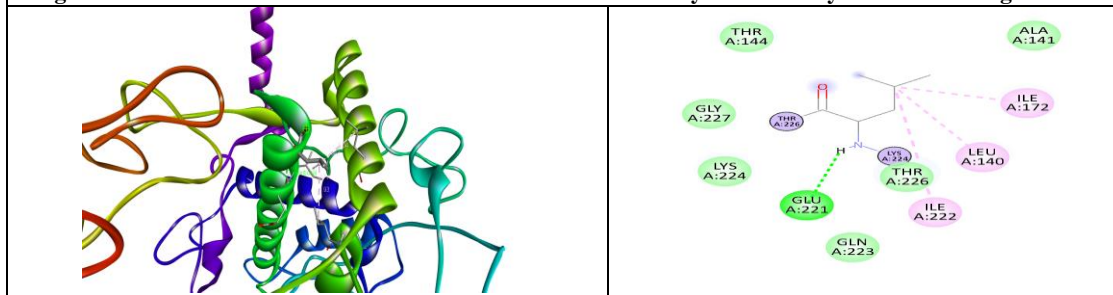


Fig. 12 3D and 2D interaction between refined model of human tyrosinase enzyme with Ferulic acid

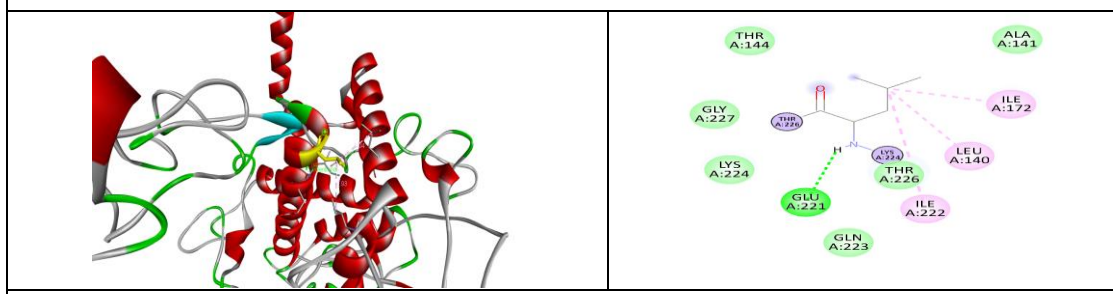
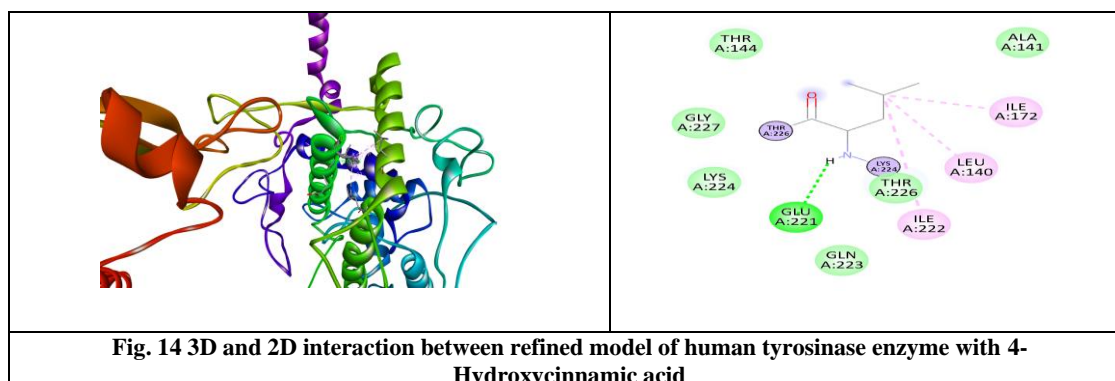
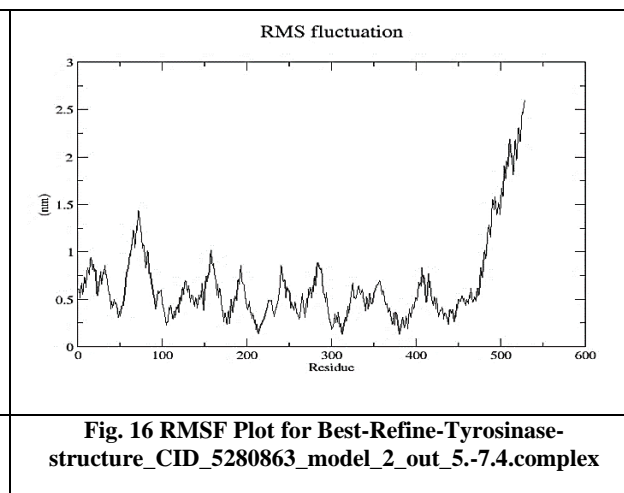
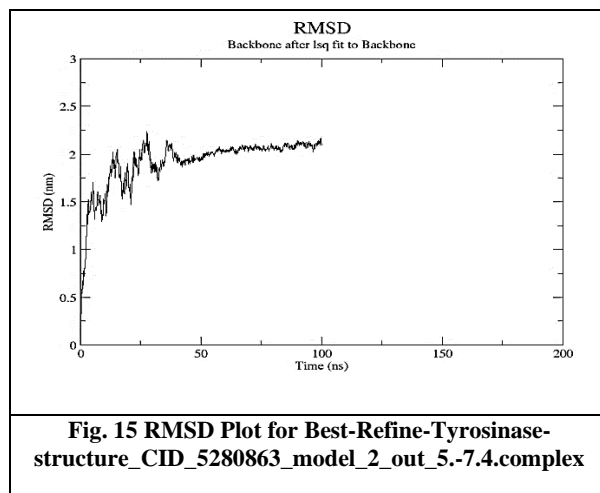


Fig. 13 3D and 2D interaction between refined model of human tyrosinase enzyme with Caffeic acid



Further MD simulation study was performed by using WebGro tools. Fully solvated molecular dynamics simulations are carried out by WebGro using the GROMACS simulation software (Fig. 15-22). Users only need to input their protein file, which should end in.pdb, and WebGro will handle simulation and trajectory analysis. In light of existing research pertaining to GROMACS simulation, default values have been specified for the parameters in the submission page. The real motions of atoms and molecules are examined using a computer simulation method known as molecular dynamics (MD) (Sarkar et al., 2023; Sarkar et al., 2022). The atoms and molecules are allowed to interact for a defined period of time, revealing information on the dynamic "evolution" of the system. The features of such complex systems cannot be determined analytically since molecular systems often contain a large number of particles; MD simulation gets around this issue by employing numerical techniques. Long MD simulations, on

the other hand, are theoretically unsound, leading to cumulative mistakes in numerical integration that can be reduced but not totally avoided with the right choice of techniques and settings. It is possible to compare the outcomes of MD simulations to experiments that quantify molecular dynamics, one of which being NMR spectroscopy (Sarkar et al., 2022). Despite the method's erratic past performance in this sector, community-wide research in Critical Assessment of Protein Structural Prediction (CASP) can confirm MD-derived structure predictions (Sarkar et al., 2022; Sarkar 2022). The RMSD, RMSF, and Rg values from the 50 ns molecular dynamics simulation results demonstrated that the suggested molecule was well equilibrated and, consequently, stable in the protein-ligand complex. This compound's (CID 3851453) significant binding affinities to the receptor cavity were consistent with the findings of the docking studies.



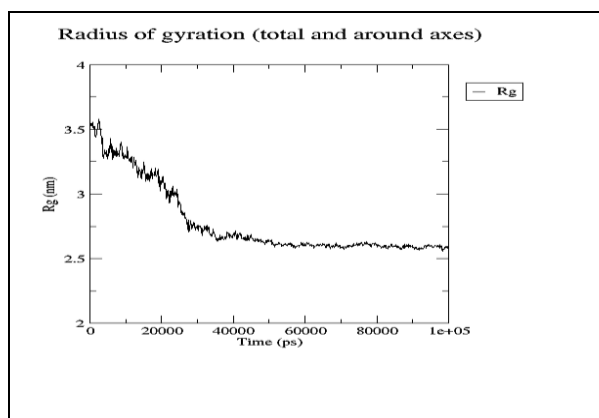


Fig. 17 Rg Plot for Best-Refine-Tyrosinase-structure_CID_5280863_model_2_out_5.-7.4.complex

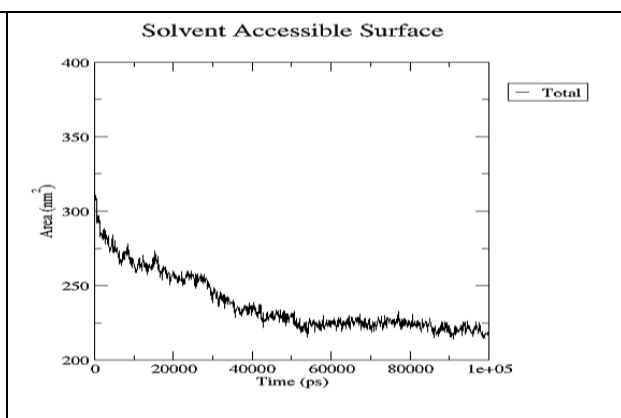


Fig. 18 SASA (total) Plot for Best-Refine-Tyrosinase-structure_CID_5280863_model_2_out_5.-7.4.complex

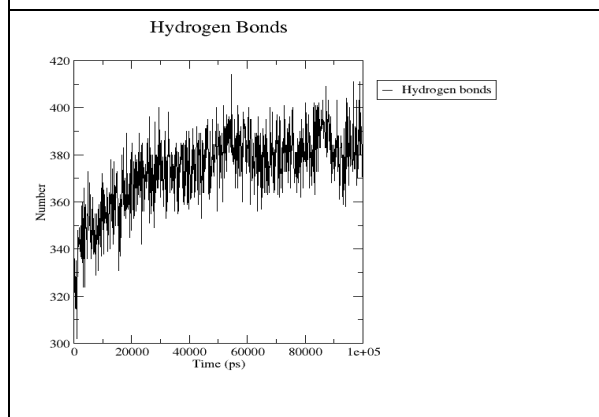


Fig. 19 HBONDS for Best-Refine-Tyrosinase-structure_CID_5280863_model_2_out_5.-7.4.complex

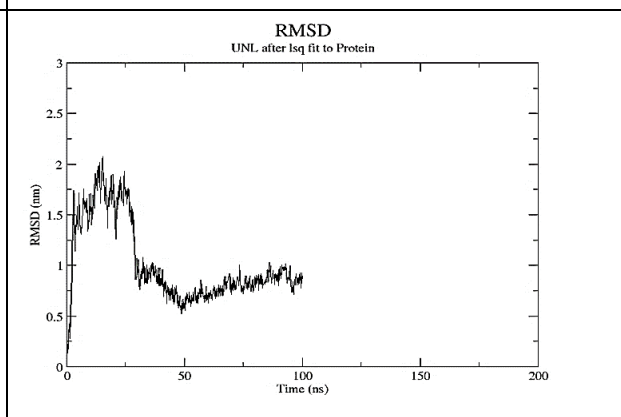


Fig. 20 Ligand RMSD Plot for Best-Refine-Tyrosinase-structure_CID_5280863_model_2_out_5.-7.4.complex

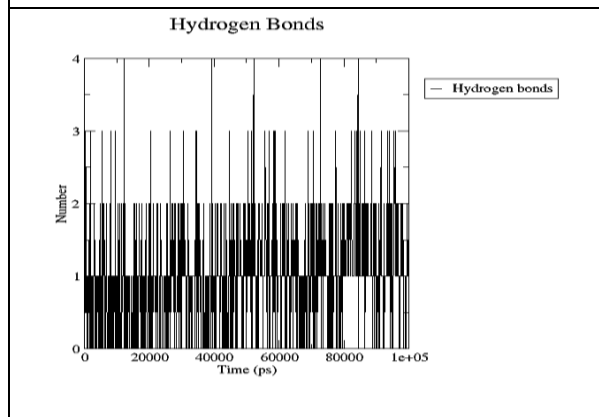


Fig. 21 Protein-Ligand HBONDS Plot for Best-Refine-Tyrosinase structure_CID_5280863_model_2_out_5.-7.4.complex

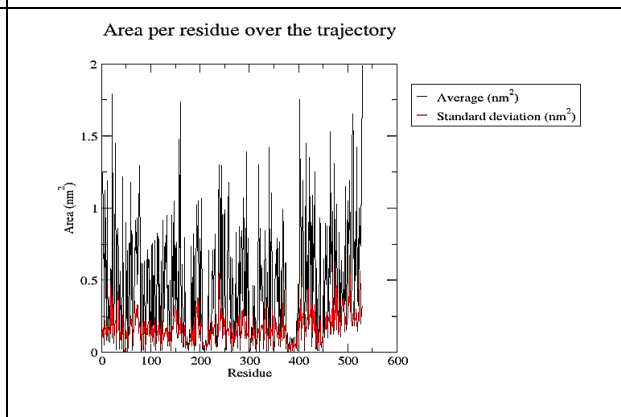


Fig. 22 SAS_area per residue over the trajectory

Conclusion

The molecular docking on the enzyme protein known as human tyrosinase has been clarified in this research. A range of bioactive substances were subjected to *in silico* molecular analysis. This study set out to identify specific phytomolecules

that have the ability to block the tyrosinase enzyme and bind to the protein model for the tyrosinase enzyme in order to regulate hyperpigmentation and skin tone in the future. We considered all total 9 molecules for docking along with modelled tyrosinase enzyme protein with energy ranges from -5.3 to -7.4 Kcal/mol. Quercetin, showed maximum lowest binding energy

i.e., -7.4 Kcal/mol. This molecule showed various interaction with modelled protein like Van der Waals, conventional hydrogen bond, covalent bond and carbon hydrogen bond. The number of hydrogen bond found was 3 in this interaction. The other molecules like Kaempferol and Chlorogenic acid also showed proper binding with modelled tyrosinase and found to have -7.2 Kcal/mol energy with 3 and 5 hydrogen bonds respectively. Therefore, it can be assumed that Quercetin, Kaempferol and Chlorogenic acid has much more potency than Benztrapine and that can be used further for clinical study.

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

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