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Targeting Homogentisate Dioxygenase Dysfunction in Alkaptonuria: Investigating *Curcuma longa's* Therapeutic Potential

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Abstract

Objectives: *Alkaptonuria is known to have a faulty gene HGO in the metabolic process. In the present research work, the focus is towards investigating the therapeutic capabilities of the Curcuma longa upon the faulty Homogentisate dioxygenase gene using ligand-protein binding, which would assist in the corrective tyrosine metabolism.* ***Methods:*** *This study is based on the computational approach using different phytochemicals for evaluation of the potency against the abnormal Homogentisate dioxygenase gene. The database of protein PDB databank was used for the protein retrieval. The structural evaluation on the secondary aspect was considered and ligand with suitable pursuit was done to visualise their binding on two dimensions by performing molecular docking using Pyrx and visualization through the BIOVIA discovery studio.* ***Results:*** *The Docking results of the Ligand and protein reported that the selected phytochemical compounds of Curcuma longa have a potential binding affinity with the Homogentisate dioxygenase ligand. The resultant docking previewed to have two compounds to have a high binding affinity with (-7.2) both, which proposes to have good efficacy of the drug.* ***Conclusion:*** *The selected compounds in the present research work that is Curcuma longa exhibit to have better efficacy of drug in treating the faulty gene in the tyrosine metabolism in Alakptonuria by revealing high binding affinity.*

Keywords: Alkaptonuria, homogentisate Dioxygenase, *Curcuma longa*, faulty metabolic gene, phytochemical compounds, binding affinity, molecular docking.

INTRODUCTION

Alkaptonuria is an infrequent genetically inherited disorder. It is inherited only if the traits are carried down through the families to the offspring, basically known to be an autosomal recessive disorder [1].

The Mendelian Inheritance was demonstrated in humans by Sir Archibald Garrod featuring Alkaptonuria seven decades ago [2–4]. The elucidation of the origin of Alkaptonuria accounts before that. Alkaptonuria is a disorder that transpires in one in 250,000–1,000,000 individuals [5]. The subject is more inclined to be Onchronosis and Spondyloarthropathy in mummies of Egypt encompassing the Harwa which is convinced to be the first clinical case of Alkaptonuria which is retained at the Museum of Chicago around 1500 BCE. The word Alkaptonuria originates from alkali which was given by Boedeker in 1859 when he observed an unfamiliar decline in the effects of urine. Virchow also noticed HGA pale brownish-yellow coloured (orche-like) pigmentation considered from the microscope [6].

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The Alkaptonuria is a flaw in the metabolous route leading to an excessive assembly of HGA (homogentisic acid). Homogentisate dioxygenase is the gene coding for Tyrosine and Phenylalanine metabolism which when mutated results in Alkaptonuria [2]. Homogentisate Dioxygenase could be mapped on chromosome number 3q13.33, which is a 445 amino-based protein. Alkaptonuria is the misleading assignment of the Homogentisate 1,2-dioxygenase enzyme, which is prominent in hepatocytes of Kidney. Mutation is observed specifically at exons. HGD is a hexamer subunit which is played in two trimers. Many differing mutations could affect the features, construction and solvability of HGD. The hypersynthesis of Homogentisic acid could deposit in the ochronotic pigment in connective tissues, particularly weight-bearing cartilages [3]. Alkaptonuria has major three attributes featuring the Urine being pigmented or Urine turning dark on standing and degeneration or arthritis on prime joints like the spine. Some other extensive demonstrations of the disorder on the body could be the darkening of the skin, sclera pigmentation, mitral valve calcification, emesis and renal calculi [4]. The acuteness of Alkaptonuria differs from person to person even among the offspring of the same mother. The acuteness prevails with ageing due to more and more HGA deposition. No exertion on the spanning of life but the calibre would gradually decrease.

The Homogentisate dioxygenase studied reaction is entirely dissimilar from the other dioxygenases. The ortho-hydroxyl groups substratum includes the cathecholic surface. The estradiol cathecholic dioxygenase which is the uptake of non-haem Fe^{3+} to sunder the ortho-hydroxyl group bond. The estradiol of catholic dioxygenase employs the Fe^{2+} to nick the one bond adjoining one hydroxyl group. The HGO is like the reaction actuated by the bacteria generate 1,2-dioxygenases (GO) 11,12 through which the ortho carbon atoms nick and replaced with the carboxyl and hydroxyl groups which is an aromatic ring.

The Eukaryotic HGO structure was put forward where the β-sandwich between a nine-stranded sideways β-sheet an extreme C terminal for which the β-sandwich is enclosed by the seven stranded β-sheet. The C-terminal whose edge forms β-sheets residue which raised from the N-terminal from either end of the β-strands. The monomer structure is usually impacted by a hexameric coalition. A twist or loop-like structure forms by the Leu 460 and Lys 410 remnants which move along the bend or curve 77–114. The most similar structure to the HGO14 structure is the jelly roll Jack Bean canavalin.

The active sites in HGO are formed from the seven-stranded C-terminal β-sheets. The configuration of active sites is visualized to be excessively reliant on the intersubunit hydrogen bonding a hydrophobic interaction. The proximity with the adjoining subunit of the positioning interface is very critical. The Tyrosine Argenine hydrogen bond has main chain atoms neighbouring three-fold subunit in the middle of the Glutamine and serine to an extra β- strand parallel to the N-terminal which is four-stranded β-sheets, altogether forming a five-strand intersubunit β-sheet. The ligation of the Fe atom domain is contingent on the intersubunit super secondary structure formation which is encompassed by hydrophobic fundamental structures [7, 8].

Curcuma longa is an ancient Indian spice called Turmeric. This belongs to a ginger family called curcuminoid. There are phenols present which exhibit a yellow colour to them. This can be a food colourant for having the brightest yellow colour pigment. Curcuma is proven to be non-toxic and a very medicinal source of plants. It includes antioxidant, anti-inflammatory, anti-viral and anti-fungal properties. Curcuma is an integral herb in Ayurvedic medicines included in food extensively. Curcuma is an extraordinarily potent antioxidant [7]. *Curcuma longa* belongs to the family of Zingiberaceae. It is a perennial plant measuring 1m high, erect with a short stem. It has pointed leaves, and flowers with funnel shaped. Curcuma is a tropical and subtropical place in the world [8]. *Curcuma longa* is accredited to have chemopreventive properties, which could be possible from the neutraceutical efficiency. Curcuminoids have therapeutic value in disease treatment [9]. *Curcuma longa* belonging to Rhizome properties in the family exists with an underground horizontal rhizome, from which the roots and shoots arise. The organoleptic properties of the plant are the yellowish-brown outer layer with a deep orange inner part. It is experienced with aromatic, bitter and hot-tasting abilities [10].

The present project is undertaken on the major aspect that is the expression of the HGO gene during the Tyrosine metabolism for the proper process of the HGA in the body. To evaluate this, the present work has done Docking of the Ligand and Protein whose binding affinity would conclude the objective. The *Curcuma longa* the selected bioactive drug candidate when evaluated reveals a wide scope for the further development of the phytochemical compounds and ligands trials for the best outcomes Figure 1.

Figure 1. *Curcuma longa* plant.

Materials and Method

Selection of Target Protein

The present research work is ideally framed to study receptor-ligand docking. AutoDock is an effective virtual software for Computational Drug Discovery which is essentially used to study the archieved compounds against potential drug compounds. The Homogentisate Dioxygenase (1EY2) which is potentially involved in the metabolism of Tyrosine and Phenylalanine three-dimensional structure was downloaded in PDB format from RCSB Protein Data Bank (https://www.rcsb.org).

The Visualization of protein is performed using The Discovery Studio 2024 (BIOVIA) – (https://discover.3ds.com/discovery-studio-visualizer-download) in which the water molecules, the ions and heteroatoms were detached to purify from the protein which was further retained in PDB format for future Docking process.

Structural Validation

Secondary Structure Prediction

The secondary structure of the protein has primary, secondary, tertiary and quarternary structures. The secondary structures are depicted in two forms alpha-helix and beta sheets. This is an important form of protein which is very important for validation of the fold's identification of protein and an intermediate step in predicting three-dimensional structures [10]. The secondary structure of the protein 1EY2 was abstracted from the PDB sum.

Ramachandran Plot

Ramachandran Plot is the representation of the picturesque and vivid images of protein makeup and torsion angles. Until now the Ramachandran plot is meant to be one of the most widely accepted theories in protein makeup and least inconsistency among the research tasks and simulations. The Ramachandran plot was extracted by PUBsum (https://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPage.pl) and PROcheck was used [11].

Selection of Ligands

The most important component in Docking is the selection of Phytochemical compounds, which in this present study are taken from the plant *Curcuma longa*. The selected Phytochemical compounds were extracted from the IMPPAT webserver(https://cb.imsc.res.in/imppat/) whose three-dimensional

structure is downloaded in (SDF) Structure-data file format and the Canonical smiles necessary for the ADMET analysis process were extracted from the PubChem database(https://pubchem.ncbi.nlm.nih.gov/).

In Silico ADME Analysis

ADME analysis is an interpretation of significant drug-drug interactions. ADME properties are likely to be facilitated by computational filters [12]. ADME analysis mainly exhibits parameters, such as Absorption, Distribution, Metabolism and Extraction parameters which are considered for pharmacokinetics research by ligand assessment using Swiss ADME (http://www.swissadme.ch/). The canonical SMILES of the selected phytochemical compounds were extracted by Pub Chem. The in silico ADME analysis allows the parameters, such as Physicochemical properties, Lipophilicity, Water solubility, Pharmacokinetics, Drug likeliness, and Medicinal Chemistry. One of the very important considerations during the physiochemical analysis is following the LIPINSKIs rule of 5. This rule has certain generalized numbers onto which it should satisfy [13].

The LIPINSKI rule should have a molecular weight less than 500 Dalton, MlogP less than 4.15, Hydrogen Donors less than 5, Hydrogen acceptors less than 10, Molecular refractivity should be 40–130. (https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/lipinskis-rule-of-five)

Molecular Docking

Molecular Docking is a computational approach to examine the structural multiplex of the Protein (1EY2) against the ligands of the Phytochemical compound of *Curcuma longa*. The objective of Molecular Docking is to forecast the binding model of the ligand or multiple ligands with proteins with three-dimensional structures. Docking could be a productive technique to familiarize the three-dimensional structure by high-dimensional spaces search which uses a scoring function that files the nominated dockings [14]. The virtual Molecular Docking was carried out by the AutoDock Vina by using the PyRx – (https://sourceforge.net/projects/pyrx/) virtual screening tool. Before we insert the phytochemicals into the AutoDock tool the phytochemicals should be converted into the PDBQT format of file. The grid centre of purified Homoentisate dioxygenase (1EY2) protein included A chain, Active sites, and Protein Groups. Later the Docking results were collated in the CVS file format, followed by the PDBQT ligand was again changed into PDB file format from Pyrx and was submitted to BIOVIA to observe the structure and interactions in the ligand and the target protein.

Results

Selection of Target Protein

The target protein extraction of Homogentisate dioxygenase protein (1EY2) occurred from the RCBS Protein Data Bank in the PDB format. The removal of undesirable components, such as water molecules was meant to be excluded from the protein using the Discovery Studio (BIOVIA) application. Both unpurified and purified protein extracts are depicted in the following Figures 2 and 3.

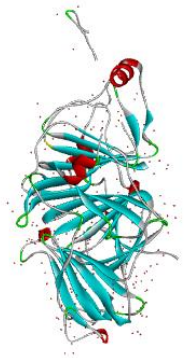

Figure 2. Unpurified protein (1EY2).

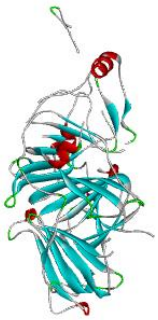

Figure 3. Purified protein (1EY2).

Structural Validation by Ramachandran Plot

The Ramachandran Plot for the Homogentisate Dioxygensae (1EY2) is interpreted in the following Figure 4. The structure of Homogentisate 1,2-dioxygenase contains one chain which is the A chain, usually expressed in Escherichia coli. The resolution was found to be 2.30A with the R-factor 0.193 and R-free to be 0.242. Statistically, the Ramachandran plot explained the Glycine residues are 33 and Proline residues are 32 with the most favoured regions to be A, B, L. The Phi-psi distribution was observed to be -0.41 and the Chi-Chi distribution to be nil. The covalent forces of the main chain bond length is 0.62 and the main chain bond angle is 0.27 which were statistically interpreted.

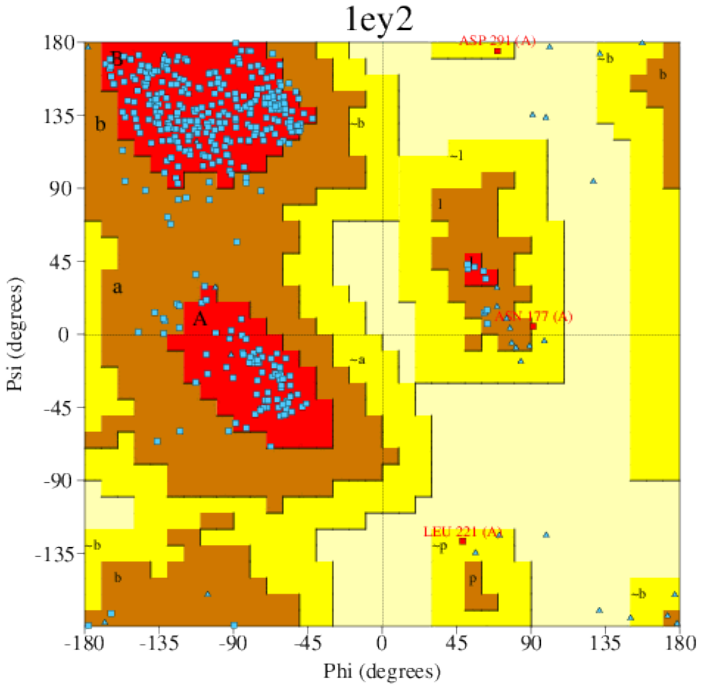

Figure 4. Structural prediction by Ramachandran plot.

Secondary Structure Prediction

The secondary structure of the protein is obtained by PubSum. The protein obtained is with a single (A) chain. The present protein with the A chain has 419 residues. This secondary structure of 1EY2 protein has 6 sheets, 6 beta hairpins, 8 beta bulges, 28 strands, 8 helices, 39 beta turns, and 4 gamma turns. It has an H365-H292 residue. The secondary structure is depicted in the below Figure 5.

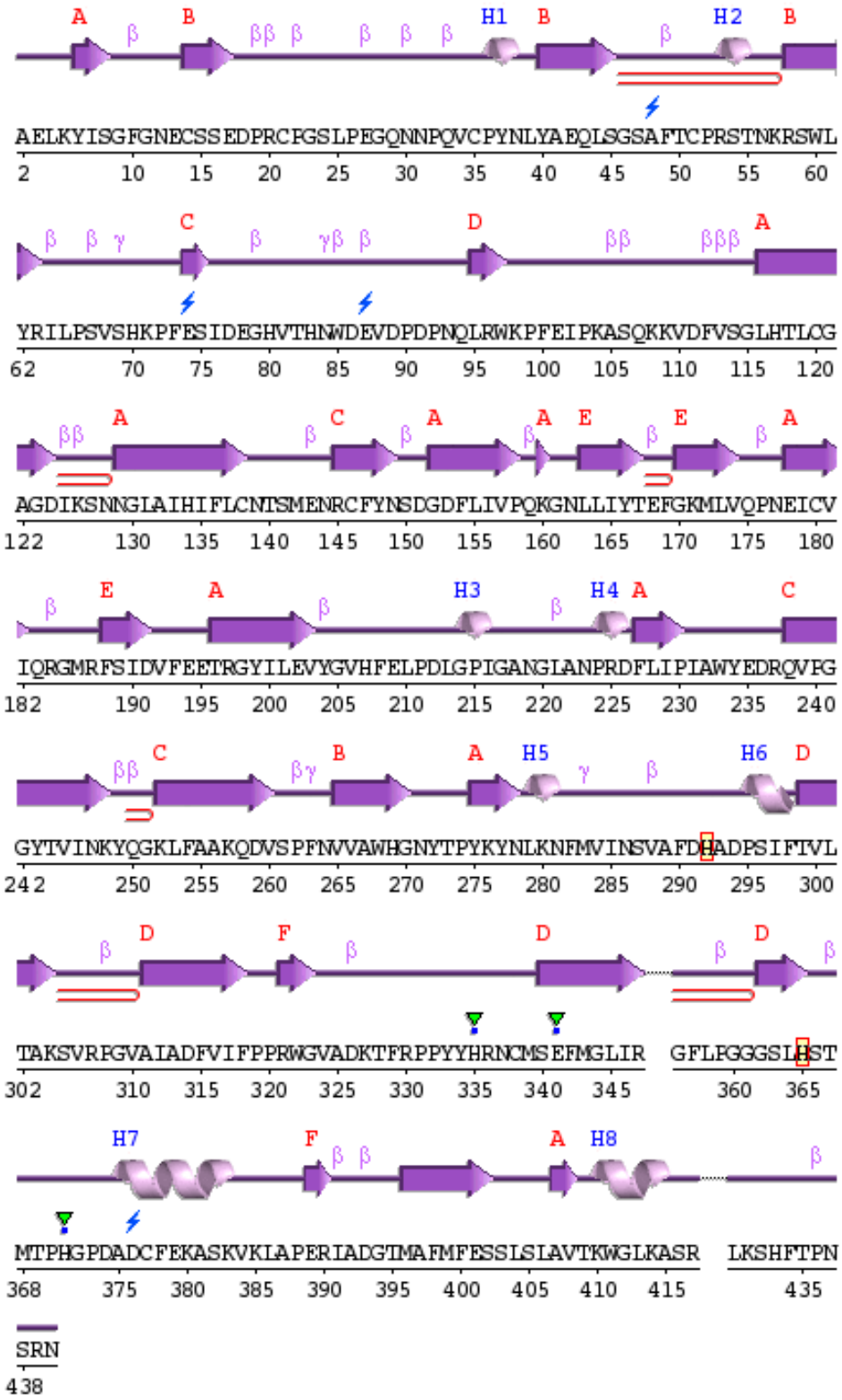

Figure 5. Secondary structure of protein (1EY2).

Selection of Ligands

The below data in the Table 1 gives the list of Phytocompounds screened for the *Curcuma longa*. The best 25 phytocompounds were chosen, in which only 11 of the ligands were upbrought to the Docking process.

Table 1. Selected phytochemical compounds.

Phytochemical Name
beta-Bisabolene
2-(4-Methylphenyl)propan-2-ol
Myrcene
Alpha-Fenchene
Gamma-Terpinene
Bisacumol
Curlone
p-Cymene
Germacrone
Tricyclene
1-Methyl-4-(prop-1-en-2-yl)benzene
Eucalyptol
Curcuphenol
p-Mentha-1,3,8-triene
Alpha-Tumerone
3-Carene
4-Carvomenthenol
2-Undecanone
4-Isopropylbenzyl alcohol
Terpinolene
Alpha -terpinene
Geranyl acetate
Beta-Farnescense
Zinginberene
Humulene

In Silico ADME Analysis

The pharmacological evaluation by ADME analysis was observed and the Table 2 contains all the essential analysis. The following studies reveal the molecular weight, number of heavy atoms, number of hydrogen bond donors and acceptors, the GI absorption as well as the LIPINSKIs rules should be utterly satisfied, this also interprets the violation number.

Molecular Docking

In the following Table 3, interpretation of the 11 ligands was screened from 25 phytochemicals based on the Lipinski rule. The selected 11 ligands were again utilized for the molecular docking analysis. The best ligands are 2-(4-methyl)propane-2-ol, Bisacumol, Curlone, Germacrone, Eucalyptol, Curcuphenol, alpha-Turmorene, 4-Carvomenthenol, 2-Undecanone, 4-Isopropylbenzyl alcohol, Gernamyl acetate.

2D Visualization of Protein with Selected Compounds

The Protein Docking in the Pyrx visualization of ligand interaction using the Discovery Studio 2024(BIOVIA). The two-dimensional structures of the Ligand interaction are depicted.

DISCUSSION

Alkaptonuria is a genetic disorder an autosomal recessive condition. Alkaptonuria is a defect in the Homogentisate Dioxygenase gene which codes for Tyrosine and Phenylanine. Alkaptonuria is a tyrosine pathway disorder which lacks Homogentisate 1,2 dioxygenase potency which lacks the conversion of homogentisic acid (HGA) to Maleylacetoacetic acid. The accumulation of HGA has a

deteriorating effect on health [14]. Alkaptonuria is recognised with darkness in the Urine or pigmented urine or turning dark when standing. The defect in the metabolism leaves an accumulation of Homogentisic acid deposition in the joints causing degeneration or arthritis (Figure 6).

Table 2. ADME analysis for the selected phytochemical compounds and Lipinski analysis.

Molecular Name	Formula	Molecular Weight	Heavy Atoms	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Gi Absorption	Lipinski Violation
beta-Bisabolene	$C_{15}H_{24}$	204.35	15	0	0	LOW	1
2-(4-Methylphenyl) propan-2-ol	$C_{10}H_{140}$	150.22	11	1	1	HIGH	0
Myrcene	$C_{10}H_{16}$	136.23	10	0	0	LOW	0
Alpha-Fenchene	$C_{10}H_{16}$	136.23	10	0	0	LOW	1
Gamma-Terpinene	$C_{10}H_{16}$	136.23	10	0	0	LOW	0
Bisacumol	$C_{15}H_{220}$	218.33	16	1	1	HIGH	0
Curlone	$C_{15}H_{220}$	218.33	16	0	1	HIGH	0
p-Cymene	$C_{10}H_{14}$	134.22	10	0	0	LOW	1
Germacrone	$C_{15}H_{220}$	218.33	16	0	1	HIGH	0
Tricyclene	$C_{10}H_{16}$	136.23	10	0	0	LOW	1
1-Methyl-4-(prop-1-en-2-yl)benzene	$C_{10}H_{12}$	132.2	10	0	0	LOW	1
Eucalyptol	$C_{10}H_{180}$	154.25	11	0	1	HIGH	0
Curcuphenol	$C_{15}H_{220}$	218.33	16	1	1	HIGH	0
p-Mentha-1,3,8-triene	$C_{10}H_{14}$	134.22	10	0	0	LOW	0
Alpha-Tumerone	$C_{15}H_{220}$	218.33	16	0	1	HIGH	0
3-Carene	$C_{10}H_{16}$	136.23	10	0	0	LOW	1
4-Carvomenthenol	$C_{10}H_{180}$	154.25	11	1	1	HIGH	0
2-Undecanone	$C_{11}H_{220}$	170.29	12	0	1	HIGH	0
4-Isopropylbenzyl alcohol	$C_{10}H_{140}$	150.22	11	1	1	HIGH	0
Terpinolene	$C_{10}H_{16}$	136.23	10	0	0	LOW	0
Alpha-terpinene	$C_{10}H_{16}$	136.23	10	0	0	LOW	0
Geranyl acetate	$C_{12}H_{20}O_2$	196.29	14	0	2	HIGH	0
Beta-Farnesense	$C_{15}H2_4$	204.35	15	0	0	LOW	1
Zinginberene	$C_{15}H_{24}$	204.35	15	0	0	LOW	1
Humulene	$C_{15}H_{24}$	204.35	15	0	0	LOW	1

Table 3. The binding affinity of respective ligands.

Ligand	Binding Affinity
2-(4-methyl)propane-2-ol	–6.2
Bisacumol	–5.4
Curlone	–5.2
Germacrone	–5.1
Eucalyptol	–6.7
Curcuphenol	–6.6
Alpha-Turmerone	–6.5
4-Carvomenthenol	–6.3
2-Undecanone	–6.3
4-Isopropylbenzyl alcohol	–6.8
Geranyl acetate	–6.5

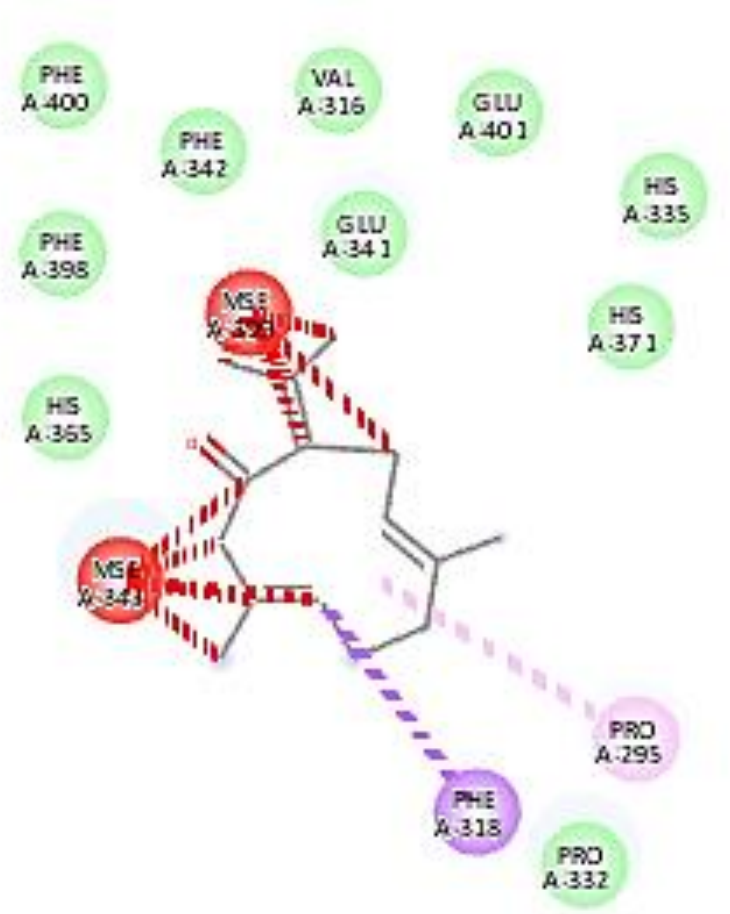

Figure 6. 2D Visualization of the ligand-protein interaction.

The currently selected plant *Curcuma longa* is a medicinal plant traditionally called Turmeric and is extensively considered for treating several disorders, such as anorexia, cough, diabetic dysfunctions and lesions, liver-related disorders, and coryza. *Curcuma longa* is extensively included in almost all the food in India. The traditional use of *Curcuma longa* is done for treating abdominal pain and related disorders, icterus in newborns. The studies of research revealed many therapeutic efficiencies of *Curcuma longa*. The volatile oil of *Curcuma longa* (0.1 ml/kg per day) could repress acute oedema. Pharmacology of *Curcuma longa* India is the highest globally in producing Turmeric which gives about 78% of the yield. The *Curcuma longa* herb is very religiously used as well. *Curcuma longa* is addressed as , also known as Haridra, which is a combination of minerals, protein, fats, carbohydrates and moisture. The yellow colour in *Curcuma longa* precisely includes the presence of curcumin. The curcumin when exposed to acids turns to deep yellow or red. *Curcuma longa* derivatives curcumoides were substantially reviewed over many past centuries. *Curcuma longa* exhibits a wide range of properties, such as chemotherapeutic and cytotoxic effects [15].

The present research is based on the Receptor-Ligand Docking where visualization is done at Discovery Studio (Biovia). The structural validation of the secondary structure is depicted in the form of alpha and beta-helix. The Phytochemical compounds were implemented from the IMPATT webserver. The In-silico ADME analysis where drug-drug interaction is done by computation filters. Lipinski's rule is considered. The Docking was performed to AutoDocking Vina for the Homogentisate dioxygenase (1EY2) protein where the data was extracted in CVS file format followed by PDBQT ligand was converted to PDB file format from Pyrx. The resultant Secondary structure was with 6 sheets, 6 beta hairpins, 8 hairpins, 8 beta bulges, 28 strands, 8 helices, 39 beta turns, and 4 gamma turns. The In-silico ADME analysis occurred where the LIPINSKI's rule was satisfied. Later during the

AutoDocking, 11 best ligands chosen were two dimensional structural and ligand interaction was depicted.

CONCLUSIONS

According to the analysis, result and study, *Curcuma longa* has Curcumin which exhibits cytotoxic, antioxidant, anti-inflammatory, anti-allergic, anti-diabetic and many other properties. In the present study of *Curcuma longa*, there are 25 best phytochemical compounds selected which satisfy the Lipinski rule and from the docking results we could interpret it to have a high binding affinity of -7.2 with the selected receptor protein that is the 1EY which is a potential drug candidate.

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Abbreviations

- HGO: Homogentisate 1,2-dioxygenase
- PDB: Protein Database
- HGA: Homogentisic acid
- Fe^{2+}: Iron divalent metal ion
- Fe^{3+}: Ferric ion
- RCSB: Research Collaboratory for Structural Bioinformatics
- IMPACT: Indian Medicinal Plants, Phytochemistry and Therapeutics
- SDF: Structure Data File
- ADME: Absorption, Distribution, Metabolism, and Excretion
- CSV: Comma-separated values
- GI: Glycemic Index
- 2D: Two-dimensional

REFERENCES

1. Davison AS, Hughes AT, Milan AM, Sireau N, Gallagher JA, Ranganath LR. Alkaptonuria–Many questions answered, further challenges beckon. Ann Clin Biochem. 2020 Mar;57(2):106–20.
2. Zatkova A, Ranganath L, Kadasi L. Alkaptonuria: current perspectives. The application of clinical genetics. 2020 Jan 23:37–47.
3. Davison AS, Norman BP. Alkaptonuria–Past, present and future. Advc Clncl Chem. 2023 Jan 1;114:47–81.
4. Genovese F, Frederiksen P, Bay-Jensen AC, Karsdal MA, Milan AM, Olsson B, et al. Nitisinone treatment affects biomarkers of bone and cartilage remodelling in alkaptonuria patients. Int Molecular Sci. 2023 Jul 1;24(13):10996.
5. Jenkins BD, Fischer CG, Polito CA, Maiese DR, Keehn AS, Lyon M, et al. The 2019 US medical genetics workforce: a focus on clinical genetics. Genet Med. 2021 Aug 1;23(8):1458–64.
6. Titus GP, Mueller HA, Burgner J, Rodríguez de Córdoba S, Peñalva MA, Timm DE. Crystal structure of human homogentisate dioxygenase. Natur Struct Bio. 2000 Jul;7(7):542–6
7. Chanda S, Ramachandra TV. Phytochemical and pharmacological importance of turmeric (Curcuma longa): A review. Research & Reviews: J Pharma. 2019 Feb;9(1):16–23.
8. Vo TS, Vo TT, Vo TT, Lai TN. Turmeric (Curcuma longa L.): Chemical components and their effective clinical applications. J Turkish Chem Society Section A: Chemistry. 2021;8(3):883–98.
9. Ibáñez MD, Blázquez MA. Curcuma longa L. Rhizome essential oil from extraction to its agri-food applications. A review. Plants. 2020 Dec 28;10(1):44.
10. Tam B, Sinha S, Wang SM. Combining Ramachandran plot and molecular dynamics simulation for structural-based variant classification: Using TP53 variants as model. Computl Structl Biotech J. 2020 Jan 1;18:4033–9.

11. Ekins S, Waller CL, Swaan PW, Cruciani G, Wrighton SA, Wikel JH. Progress in predicting human ADME parameters in silico. J Pharmaco Toxicolog Meth. 2000 Jul 1;44(1):251–72.
12. Attar S, Bhor S. A Structure-Based Design Approach to Catharanthus roseus Phytoconstituents as Potential Inhibitors of B-Cell Lymphoma 6 Protein. Int J Bioinf Comput Biol. 2023;1:14–34.
13. Morris GM, Lim-Wilby M. Molecular docking. Molecular modeling of proteins. 2008:365–82.
14. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta medica. 1991 Feb;57(01):1–7.
15. Jyotirmayee B, Mahalik G. A review on selected pharmacological activities of Curcuma longa L. Intl J Food Proper. 2022 Dec 31;25(1):1377–98.

