

# Molecular docking and its application in search of antisickling agent from *Carica papaya*

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## ABSTRACT

Understanding the protein–ligand interaction is a fundamental step for drug discovery in numerous pharmaceutical enterprises. The integration of computational and experimental process can reduce the time and cost for the advancement of novel medications. Molecular docking is one of the modern drug designing strategies, which explore the competence of a ligand by computing the minimum binding energy. Docking is utilized in virtual screening of enormous databases of compounds for hit identification and assessing the impact of chemical modifications during lead optimization. Sickle cell disease is a serious issue that affects people worldwide. Leaf extracts and ripe fruits of *Carica papaya* have been identified for curing sickle cell disease. Molecular docking approach using ArgusLab 4.0.1 was used to study the interaction between 24 different phytochemicals of *C. papaya* and sickle cell protein [2 Deoxyhemoglobin S (2HBS)] to identify the best phytochemicals for curing sickle cell disease. Three phytochemicals, Xanthoangelol D, N-[(4R)-4-(3-fluorophenyl)-6-oxo-4,5-dihydro-H-pyrimidin-2-yl]-3-methoxybenzamide, and Carpaine showed the highest inhibitory activity against the 2HBS protein which may become potent anti-protein drugs for the treatment of sickle cell disease with the support of further studies.

## 1. INTRODUCTION

The structures of protein complexes are basics for understanding the sub-atomic systems of protein–protein interaction, analyzing genetic disorders, and controlling binding affinity. The difficulties with respect to time and cost for X ray-crystallography and nuclear magnetic resonance methodologies create a gap between the experimentally determined complex structures and sequences accessible for protein buildings [1]. The inadequacy of complex structures can be mitigated by molecular docking, which gives a quick and proficient alternative in the field of bioinformatics.

Molecular Docking is a tool to predict the energetically favored conversion of one molecule to the next molecule when bound to form a relatively stable complex with the overall least energy. Docking expects to accomplish an optimized conformation and

relative direction between protein–ligand. It helps us to see how small ligands bind to different proteins, for example, transport protein, signal receptors, catalysts, viral proteins, and so forth so as to suppress or actuate their function. For molecular docking, it is basic to recognize the ligands that can bind protein at an explicit dynamic site.

Docking is utilized in *in-silico* screening of huge databases of compounds for hit ID and assessing the impacts of chemical alterations during lead optimization [2,3]. Hit identification is the significant objective of high throughput screening (HTS) that intends to recognize dynamic compounds (hits) by screening enormous quantities of various chemical compounds against chosen targets [4]. For most of the disease-related proteins, experimental structures are not accessible thus; ligand docking can be performed on hypothetical models [5]. The inaccuracies in a homology modeling can be overcome by utilizing computational docking techniques which decide the gross basic highlights of a complex, but find it exceedingly difficult to effectively anticipate high-goals structures of such protein–protein complex, indicating

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the need to form new docking calculations which include the essential degrees of freedom to make up for the errors.

Thus, the present study intends to portray the leading edge of protein–ligand docking and its application looking for appropriate antisickling agents from *Carica papaya*.

## 2. DOCKING PROCEDURE

Whole docking procedure can be described in following simple steps:

### 2.1. Search for Protein and Ligand Structure

The search for convenient target protein and ligands is essential for performing docking. So, one has to search whether the target protein is deposited in the Protein Data Bank (PDB) database (<http://pdb.org>) or Swiss UniProt knowledge base (<http://expasy.org/sprot>). If the target protein is not present in the database but similar sequences are there, then homology modeling can be done by using the Swiss model repository (<http://swissmodel.expasy.org/repository/>), modeller tools—I-TASSER, etc. Next, the ligand can be found from the PubChem database (<http://pubchem.org>) or Zinc (<http://blaster.docking.org/zinc/>).

### 2.2. Search for Protein–Ligand Binding Site

The search for potential protein–ligand binding site can be achieved by using two approaches, i.e., (a) first, identify the protein–ligand binding site and then dock the ligand (b) dock ligand directly onto the complete receptor structure; blind docking [6].

### 2.3. Development of Docking Program

Molecular docking has turned into an essential part in many drug discovery programs, particularly for virtual screening of phytochemicals as potential drug molecules. The first docking software was developed in the mid-1980s by Irwin Kuntz, University of California and attempts are still in the process to improve the docking calculations. Ongoing advancements in docking tools predict the capacity of an enzyme by distinguishing

its natural substrates [7]. Table 1 gives the characteristic features of some important docking programs.

The successful predictions of protein complexes were done by identifying the protein of interest belonging to a specific super family so that the search for potential substrates and types of reactions are restricted to a specific area. However, various methodologies were utilized to precisely rank the docked molecules by using different programs such as:

- **DOCK 3.5.x**—This program used the idea that enzymes catalyze reactions by restricting the transition state superior to the substrate, docking transition state-like molecules ought to give a superior signal than docking substrates by using the knowledge of amidohydrolase super family performed hydrolysis reactions. The protein was kept rigid [8].
- **Glide**—The program distinguishes the enzymes having a place with a specific subgroup of enolase super family permitted tapering the arrangement of potential substrates, and precision in the positioning was improved by refining and rescoring the docked complex with an increasingly confounded material science-based scoring capacity and permitting receptor side chains to move [9].

## 2.4. Mechanism of Docking

### 2.4.1. Search algorithms

The principle target of the search algorithm is to locate every single imaginable direction and conformation of the protein combined with the ligand. It is classified into two types-

- **Systematic methods or Direct methods**—There are three subtypes of systematic methods as follows:
  - **Conformational search**—Here, the structural parameter of ligand, i.e., torsional (dihedral) translational and rotational degrees of freedom are altered gradually [10].
  - **Fragmentation**—Multiple fragments are either dock and tried to interface them with bonds, or anchor fragments is

**Table 1:** Key attributes of some chosen protein–ligand docking programs.

Program	Current version	Needs ligand set up	Needs protein set up	Input format	Method for conformational search of the ligand	Scoring function	Can deal with receptor flexibility	Allows to dock several ligands with a single set up	Free for academic research
AutoDock	V4.2.6	Yes	Yes	Pdbqt, pdbq mol2, pdb	Stochastic (GA), Stochastic (MC)	AMBER derived (FF)	Yes	No	Yes
GOLD™	V5.2 Suite	Yes	Yes	sd (lig), mol (lig) mol2 (lig/prot) PDB (lig/prot)	Stochastic (GA)	GOLD score (FF) Chem score (EM) User defined score	Upto 10 user defined residues	Yes	No
eHITS	V6.2	No	No	mol sd/sdf, pdb mol2, tma tmb	Systematic (F)	eHITS score hybrid KB-EM user trained score	No	Yes	Yes
MVD™	V5.5	No	No	Pdb, mol2 Mol, sd/sdf Mdl, omvdm1	Stochastic (TS), Stochastic (GA)	Mol dock score (EM) Mol dock score grid (EM)	Yes (only with the mol dock score (grid))	Yes	No
Argus lab	V 4.0.1	Yes	Yes	Pdb,mol,xml,agl,mol2,log	Stochastic (GA)	A score (FF)	Yes	Yes	Yes
Glide™	V4.5	Yes	Yes	Sd, pdb Maestro (mae) mol2	Systematic pose generation with stochastic optimization	Sp 4.5 Glide score (EM) Xp 4.5 glide score (EM)	Yes through prime™	Yes	No

Abbreviations: EM = empirical, F= fragmentation method, FF = force field, GA = genetic algorithm, KB = knowledge-based, MC = Monte Carlo, TS: tabu search.

dock first and manufacture outward in ventures from that bound position. Tools—Flex X™, LUDI, DOCK, etc.

- **Database search**—Various sensible conformations of each and every small molecule that is already stored in the database can be generated by this method and then dock them as firm bodies. Tools—FLOG
- **Stochastic methods or Random methods**—There are three subtypes of stochastic methods.
  - **Monte Carlo (MC)**—In this method, ligands are haphazardly set in the receptor binding site, it is then scored, and the new configuration is created by haphazard changes. Tools—ICM, MCDOCK, etc.
  - **Genetic algorithm (GA)**—It begins with a populace of postures, where descriptors of configuration and position in respect to the receptor are the “gene” and the score is the “fitness”; perform transformations, hybrids, etc., of the fittest to make the next generation and rehash to concurrence [11]. Tools—AutoDock, GOLD, etc.
  - **Tabu search (TS)**—It works by striking restrictions that prevent the previously exposed territories of the ligands conformational space from being checked again and, therefore, support the study of a novel configuration. Tools—PRO\_LEADS, Molegro Virtual Docker (MVD)™.

#### 2.4.2. Scoring functions

Scoring functions helps in the evaluation of which ligand configuration and rotation is most favorable with respect to the receptor (protein) and by using virtual screening ranked them (ligand) according to their binding affinity [12]. The scoring function is categorized into four major groups:

- **Force field-based**—It measures the binding affinity by adding the contribution of bond-like angle bonding, and torsional deviation and non-bonded interaction like van der Waal forces, hydrogen holding, or Columbic electrostatics in an ace capacity [13]. Tools—GoldScore, AutoDock, DOCK, etc.
- **Empirical function**—It depends on multiple linear relapse investigation of a preparation set of complex structures by utilizing protein–ligand complex with known binding affinities, containing functional groups and sort of interaction. For example, N-O hydrogen bond, O-O hydrogen bond, salt scaffold, aromatic ring stacking, etc. [14]. Tools—LUDI score, ChemScore, AutoDock scoring, etc.
- **Knowledge-based**—It gives separation ward pair potential to particles, functional groups by statistical analyzing of a set of complex structures [15]. Tools—PMF, DrugScore, etc.
- **Consensus**—It basically consolidates the scores or rankings got from various scoring capacities in different ways.

## 2.5. Software’s for Docking

There are various softwares used for docking and some of the important ones are mentioned as follows:

### 2.5.1. Dock (<http://dock.compbio.ucsf.edu/>)

The Dock is a structure-based design developed in the 1980s by Irwin Kuntz and co-worker, University of California. Firstly Dock version 1 (Dock 1) calculated the quality of ligand and receptor complex on steric overlap [16]. Later on, Dock 2 provides more sophisticated control on the sampling algorithm, which provides better timing and accuracy [17].

Dock 3 includes an extremely thorough and careful parameter for an input of ligand and receptors. The first virtual screening of enzyme thymidylate synthase was performed by using Dock 3 [18]. Dock 4 was developed with an improved graph matching algorithm for ligand orientation [19]. Dock 6 (version 6.0–6.8) is being used for performing a docking with improved sampling, scoring, optimization, and numerous bug fixes [20]. Latest version Dock 6.9 provides new ligand searching method DOCK\_DN, i.e., De Novo design using program based assembly [21].

### 2.5.2. Autodock (<http://autodock.scripps.edu>)

AutoDock is a broadly utilized non-business docking program. It was the first docking programming that ties ligand with full compliance adaptability. The Autodock was created by Prof. Arthur J. Olson at the Department of molecular biology of The Scripps Research Institute in La Jolla (CA, USA). The software comprises two consecutively connected programs, i.e., AutoDock and AutoGrid [22].

AutoGrid is utilized to compute the non-covalent vitality of interaction between the firm piece of the receptor and a probe atom that is available in the ligands that will be docked for the receptor. The principle job of AutoDock is to control the docking procedure of the chosen ligand through the cross section volume.

There are several versions of AutoDock like AutoDockFR that re-enacts fractional receptor adaptability by permitting countless unequivocally indicated receptor side-chains to investigate their conformational space while scanning for vivaciously positive restricting postures for a given ligand. Researcher made higher docking progress rates by utilizing receptor adaptability in the binding site of receptor adaptations that are tentatively decided without the ligand present, for example, Apo conformations [23].

AutoDock Vina can achieve two orders of magnitude speedup in comparison to AutoDock 4. With the help of AutoDock Vina, accuracy level increases twice as compared to previously published software and naturally ascertains the framework maps and bunches the outcomes in a manner straightforward to the client [24].

### 2.5.3. Argus lab 4.0.1 (<http://www.arguslab.com>)

Argus lab is a molecular modeling software developed by Mark Thomson, Department of Energy at Pacific Northwest National Laboratory, USA. Argus lab is based on algorithms for modeling solvent effects by combining quantum mechanics with classical mechanics. This program can be used for drug designing, generating graphics, and molecular modeling.

#### 2.5.4. Genetic optimization for ligand docking (GOLD™) ([http://www.ccdc.cam.ac.uk/products/life\\_sciences/gold](http://www.ccdc.cam.ac.uk/products/life_sciences/gold))

GOLD's principle qualities are that: (i) spine and side chain adaptability can be incorporated into the computations, (ii) the program utilizes client characterized scoring capacities and can adjust likewise, (iii) the vitality capacities depend on both conformational and non-reinforced contact data. (iv) an assortment of imperative alternatives can be characterized for the docking, (v) crystallographic water particles in the ligand binding site can be well-out during the docking, (vi) it can handles metal atoms consequently on the off chance that they are set up effectively in the protein information record, and (vii) virtual screening high throughput screening results can be broke down and post-prepared effectively with the sidekick programs SILVER™ or GoldMine™.

Latest version of GOLD Suite 5.2 is a combination of three components, i.e., Gold 5.2 to carry out protein–ligand docking, Hermes 1.6 for comprehensive protein visualisation, and Gold Mine 1.5 for analysis of docking grades.

#### 2.5.5. MVD (Molecule & allegro virtual docker)

MVD™ (MolDock) is developed by Molegro Aps [25]. MVD's special qualities are: (i) it automatically allocates charges, bond orders, hybridization, and add hydrogen to the given structures, (ii) it naturally foresees potential binding destinations in the receptor, (iii) it manages receptor side chain adaptability by considering incited fit interaction, (iv) it docks in predetermined vitality lattices (which accelerates the figuring's), (v) it manages client characterized imperatives during docking, (vi) it can profit by the utilization of layouts (for example, pharmacophores) during docking, and (vii) it can convey the computations on various PCs.

### 2.6. Applications of Molecular Docking

- Modeling the structure of a protein–ligand complex is significant for understanding the coupling interaction between a potential restorative compound (the ligand) and its remedial objective (the protein).
- The motion space of the protein–ligand complex can be explored by using computer-aided docking so as to compute a vigorously steady configuration that models the structure of the complex [26].

- The investigation of the movement space is finished by an inspecting calculation and the steadiness of confirmation of the complex is assessed by utilizing a scoring or vitality work that measures the binding affinity of the complex.
- Drug configuration dependent on the peptides or peptidomimetics is quickly picking up footing in the pharmaceutical business. These compounds are getting to be prominent as a result of their low lethality and high explicitness. Enthusiasm for these compounds has likewise expanded with the advancement of refined assembling methods. The quantity of peptides approved by the United States Food and Drug Administration is expanding at a yearly pace of 8% and it is anticipated that the market for peptide-based medications will be tremendous.
- In expansion to pharmacodynamics information, e.g., strength, proclivity, viability, selectivity, pharmacokinetic properties, ADMET: absorption, distribution, metabolism, excretion, and toxicity have likewise been concentrated through the use of these techniques.
- Covalent medications have exhibited to be lucky options in a few remedial zones, for example, malignant growth, diabetes, and contagious, cardiovascular, gastrointestinal and neurologic ailments. Recent studies suggest that around 33% of enzyme modulators present in the market are covalent inhibitors. Covalent ligands irreversibly inactivate their target due to which recuperation of the biological functions requires the re-synthesis of the target molecule [27].

### 3. MOLECULAR DOCKING AS A TOOL FOR IDENTIFYING POTENTIAL DRUGS TO PREVENT SICKLE CELL ANEMIA

Sickle cell anemia is an autosomal recessive hereditary disease caused due to alteration in hemoglobin gene due to which the red blood cells (RBCs) become sickle/bow-shaped rather than round-shaped (Fig. 1) [28]. Sickle cell disease is known to affect the population living mostly in Africa, India, the Mediterranean, and Middle Eastern [29,30]. Blood of sickle cell patients contains a surprisingly enormous number of juvenile cells and many long, lean, bow-shaped erythrocytes that look like the sharp edge of a sickle. At the point when hemoglobin from sickle cells (Hbs) is deoxygenated, it brings about polymerization and misshapes the RBCs into a sickle shape [31].

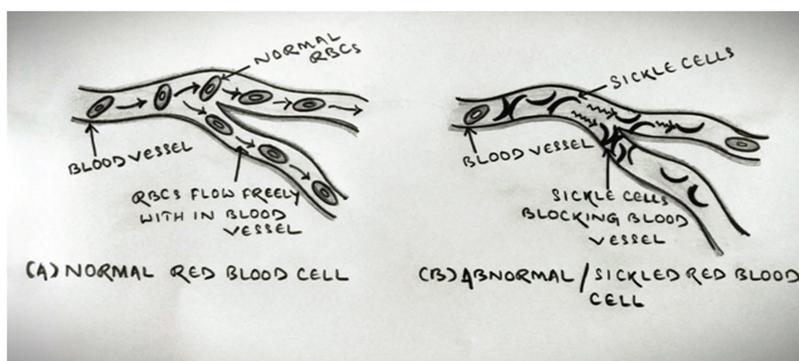


Figure 1: Difference between normal and sickle red blood cells.

Nucleotide sequencing of  $\beta$ -globin mRNA from the sickle  $\beta$ -globin gene uncovered that the typical codon GAG at position  $\beta 6$  has been replaced by GUG [32]. This change decides the addition of valine at this position rather than glutamic acid as in the case of normal HbA [33]. The sickness and characteristic appear in individuals of African lineage, Mediterranean nations, India, and the Middle-East however once in a while in individuals of European and white lineage also. People suffer from many health problems such as anemia, bacterial infection, brain damage, thrombosis, liver damage, strokes, etc. [34].

### 3.1. Antisickling Property in Plants

Various plant species show antioxidant treatment vital for the counteractive action of thick cell arrangement and free radicals preventing oxidative cell damage leading to prolongation of red blood cell life [35]. Table 2 enlists some of the important plants used in cure and prevention of sickle cell disease.

### 3.2 *Carica papaya* Linn.

*Carica papaya* is a long herbaceous plant, with plentiful smooth latex coming to 16–20 ft. in stature, the stem up to 30 cm thick, evergreen, erect, a perennial plant in habitat (Fig. 2). *Carica papaya* Linn. belongs to family Caricaceae which is known for its medicinal property like antimicrobial, antibacterial, antiulcer, anticancer, antioxidant, and antifungal. Papaya is being used since the past time for treating jaundice and sickle cell disease by the tribes of Nigeria. Many scientists reported that ripe fruit and leaf of *C. papaya* are used for treating sickle cell in humans [42–44].

### 3.3. Sickle Cell Target Protein (2HBS Protein)

A computational approach for drug discovery is done by the protein–ligand docking, in which an active site of a protein is taken as the target and inhibited by a ligand that may be a synthetic or a natural compound as a drug. There are several well-known target sites for drug-resistant treatment/control. Here, the target protein is employed for the evaluation and effectiveness of plant chemical compound obtained from *C. papaya*.

## 4. METHOD FOR DOCKING OF SICKLE CELL PROTEIN WITH AN ANTISICKLING AGENT

The discussed antisickling compounds and target protein were taken for docking study; these were downloaded from PubChem and PDB. Downloaded 3D protein structure and compound's relevant information are listed in Table 3. Furthermore, conversion of the (.sdf) file to the (.pdb) file of phyto-compounds was performed in online SMILE translator and the removal of the

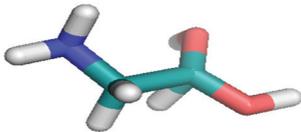
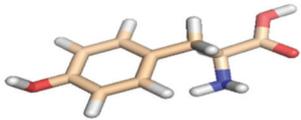
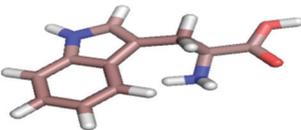
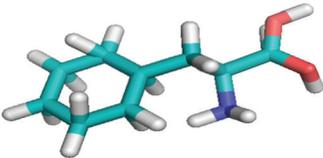
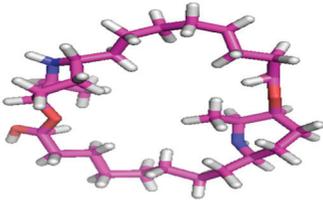
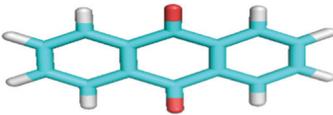
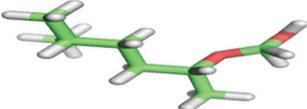


Figure 2: *Carica papaya* plant.

Table 2: Phytocompound used in managing sickle cell disease and its modes of action [36].

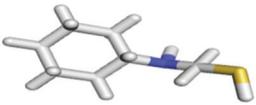
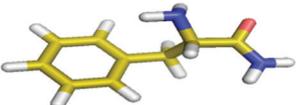
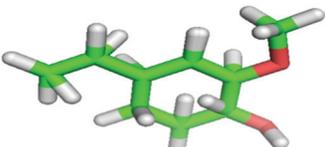
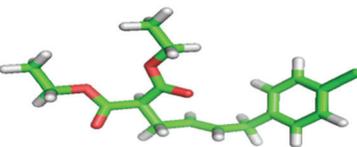
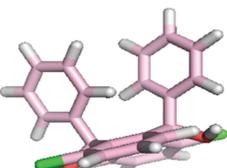
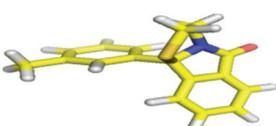
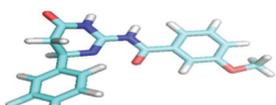
Herbs	Phytocompound and its modes of action
<i>Fagara zanthoxyloides</i> (root)	Three isomeric divanilloylquinic acids (burkinabin B, A, and C) were recognized with possible antisickling properties. Some workers have reported the antisickling properties of vanillic acid, coumarins, paraflurobenzoic acid, and parahydroxybenzoic.
<i>C. papaya</i> (unripe fruit and leaf)	Researchers have discovered that by fermenting unripe fruit of <i>C. papaya</i> at 2.5 mg/ml of water shows antisickling impacts of 87% inhibitory and 74% inversion action. They also found that methanol concentrate had 64% inhibitory and 55% inversion action while the chloroform concentrate was dormant. Phenylalanine, tyrosine, and glycine were believed to be capable of showing antisickling properties [37].
<i>Hymenocardia acidai</i> (leaf)	Scientists have related the anti-sickling action of anthocyanins present in <i>H. acida</i> [38]
<i>Cajanus cajan</i> (seed)	Phenylalanine is an active ingredient of <i>C. cajan</i> seed which is used in the preparation of Ciklavit—an antisickling phytomedicine, developed in Nigeria [39].
<i>Khaya senegalensis</i> (stem bark/leaf)	Some workers ascribed the antisickling impacts of limonoids found in <i>K. Senegalensis</i> [40].
Niprisan:	The drug Niprisan was developed in Nigeria. Its ingredient <i>Sorghum bicolor</i> and <i>Pterocarpus osun</i> are rich source of red/orange flavonoids and possibly act as hematonics. It had been assumed that active component of Niprisan such as <i>Pterocarpus guineense</i> and clove helps in moderate, conceal, or lessen the recurrence of sickle cell anemia [41].
(a) <i>P. guineense</i>	
(b) <i>S. bicolor</i>	
(c) <i>P. osun</i>	
(d) Clove	

**Table 3:** Name of the phytochemicals with their 3D structure and docking scores against sickle cell protein (2HBS).

Sl. no.	Compound name	Ligand structure	Docking score (kcal/Mol) & Information
	Glycine		-5.58397 kcal/mol Compound ID: 750 Molecular Weight: 75.067 g/mol Molecular Formula: C <sub>2</sub> H <sub>5</sub> NO <sub>2</sub> H-Bond Donor: 2 H-Bond Acceptor: 3
	Tyrosine		-6.99467 kcal/mol Compound ID: 6057 Molecular Weight: 181.191 g/mol Molecular Formula: C <sub>9</sub> H <sub>11</sub> NO <sub>3</sub> H-Bond Donor: 3 H-Bond Acceptor: 4
	Tryptophan		-8.06312 kcal/mol Compound ID: 6305 Molecular Weight: 204.229 g/mol Molecular Formula: C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> H-Bond Donor: 3 H-Bond Acceptor: 3
	Phenylalanine		-8.2888 kcal/mol Compound ID: 6140 Molecular Weight: 165.192 g/mol Molecular Formula: C <sub>9</sub> H <sub>11</sub> NO <sub>2</sub> H-Bond Donor: 2 H-Bond Acceptor: 3
	Carpaine		-9.23601 kcal/mol Compound ID: 442630 Molecular Weight: 478.718 g/mol Molecular Formula: C <sub>28</sub> H <sub>50</sub> N <sub>2</sub> O <sub>4</sub> H-Bond Donor: 2 H-Bond Acceptor: 6
	Anthraquinone		-9.07431 kcal/mol Compound ID: 6780 Molecular Weight: 208.216 g/mol Molecular Formula: C <sub>14</sub> H <sub>8</sub> O <sub>2</sub> H-Bond Donor: 0 H-Bond Acceptor: 2
	Formic Acid-2 MethylHex3yl		-5.70657 kcal/mol Compound ID: 54515185 Molecular Weight: 144.214 g/mol Molecular Formula: C <sub>8</sub> H <sub>16</sub> O <sub>2</sub> H-Bond Donor: 0 H-Bond Acceptor: 2
	N-Methyl Asparticacid		-6.43191 kcal/mol Compound ID: 852 Molecular Weight: 147.13 g/mol Molecular Formula: C <sub>5</sub> H <sub>9</sub> NO <sub>4</sub> H-Bond Donor: 3 H-Bond Acceptor: 5

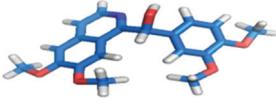
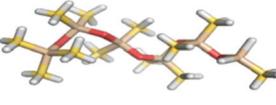
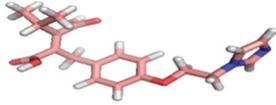
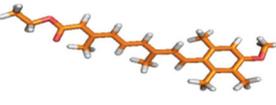
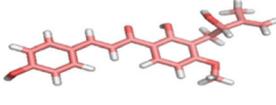
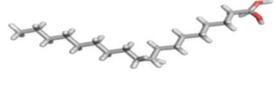
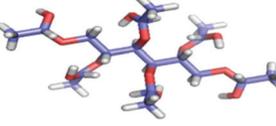
(Continued)

**Table 3:** (Continued)

Sl. no.	Compound name	Ligand structure	Docking score (kcal/Mol) & Information
	Cyclohexyl Isothiocyanate		-6.64558 kcal/mol Compound ID: 14289 Molecular Weight: 141.232 g/mol Molecular Formula: C <sub>7</sub> H <sub>11</sub> NS H-Bond Donor: 0 H-Bond Acceptor: 2
	Phenylalaninamide		-8.36549 kcal/mol Compound ID: 445694 Molecular Weight: 164.208 g/mol Molecular Formula: C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O H-Bond Donor: 2 H-Bond Acceptor: 2
	2-Methoxy-4- Vinylphenol		-6.41212 kcal/mol Compound ID: 332 Molecular Weight: 150.177 g/mol Molecular Formula: C <sub>9</sub> H <sub>10</sub> O <sub>2</sub> H-Bond Donor: 1 H-Bond Acceptor: 2
	2-[(E)-4(4- Chlorophenyl)-2 Butenyl] malonic acid diethyl ester		-8.50388 kcal/mol Compound ID: 4594935 Molecular Weight: 324.801 g/mol Molecular Formula: C <sub>17</sub> H <sub>21</sub> ClO <sub>4</sub> H-Bond Donor: 0 H-Bond Acceptor: 4
	(9R,10R)-1,5- dichloro-9,10- diphenylanthracene- 9,10-diol		-7.4063 kcal/mol Compound ID: 40736904 Molecular Weight: 433.328 g/mol Molecular Formula: C <sub>26</sub> H <sub>18</sub> Cl <sub>2</sub> O <sub>2</sub> H-Bond Donor: 2 H-Bond Acceptor: 2
	9b-(3-methylphenyl)- 2,3-dihydro- [1,3]thiazolo[2,3-a] isindol-5-one		-9.02044 kcal/mol Compound ID: 2413 Molecular Weight: 281.373 g/mol Molecular Formula: C <sub>17</sub> H <sub>15</sub> NOS H-Bond Donor: 0 H-Bond Acceptor: 2
	Heneicosane		-7.24859 kcal/mol Compound ID: 12403 Molecular Weight: 296.583 g/mol Molecular Formula: C <sub>21</sub> H <sub>44</sub> H-Bond Donor: 0 H-Bond Acceptor: 0
	N-[(4R)-4-(3-fluorophenyl)-6- oxo-4,5-dihydro-H-pyrimidin- 2-yl]-3-methoxybenzamide		-9.33596 kcal/mol Compound ID: 92655510 Molecular Weight: 341.342 g/mol Molecular Formula: C <sub>18</sub> H <sub>16</sub> FN <sub>3</sub> O <sub>3</sub> H-Bond Donor: 2 H-Bond Acceptor: 5

(Continued)

**Table 3:** (Continued)

Sl. no.	Compound name	Ligand structure	Docking score (kcal/Mol) & Information
	Papaverinol		-7.42727 kcal/mol Compound ID: 275192 Molecular Weight: 355.39 g/mol Molecular Formula: C <sub>20</sub> H <sub>21</sub> NO <sub>5</sub> H-Bond Donor: 1 H-Bond Acceptor: 6
	Hexasiloxane, Dodecamethyl		-6.40461 kcal/mol Compound ID: 71338303 Molecular Weight: 430.941 g/mol Molecular Formula: C <sub>12</sub> H <sub>38</sub> O <sub>5</sub> Si <sub>6</sub> H-Bond Donor: 0 H-Bond Acceptor: 5
	(E)-2-[[4-(2-imidazol-1- ylethoxy)phenyl] methyl]-3-propan -2-ylbut-2 -enedioic acid		-6.223 kcal/mol Compound ID: 90184972 Molecular Weight: 358.394 g/mol Molecular Formula: C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub> H-Bond Donor: 2 H-Bond Acceptor: 6
	2-[(4R)-6-fluoro- 2,2,4-trimethyl-3 ,4-dihydroquinolin -1-yl]acetohydrazide		-7.67236 kcal/mol Compound ID: 100207507 Molecular Weight: 265.332 g/mol Molecular Formula: C <sub>14</sub> H <sub>20</sub> FN <sub>3</sub> O H-Bond Donor: 2 H-Bond Acceptor: 4
	Etretinate		-8.77276 kcal/mol Compound ID: 5282375 Molecular Weight: 354.49 g/mol Molecular Formula: C <sub>23</sub> H <sub>30</sub> O <sub>3</sub> H-Bond Donor: 0 H-Bond Acceptor: 3
	Xanthoangelol D		-10.5994 kcal/mol Compound ID: 11302670 Molecular Weight: 354.402 g/mol Molecular Formula: C <sub>21</sub> H <sub>22</sub> O <sub>5</sub> H-Bond Donor: 3 H-Bond Acceptor: 5
	Oleic Acid		-8.38791 kcal/mol Compound ID: 445639 Molecular Weight: 282.468 g/mol Molecular Formula: C <sub>18</sub> H <sub>34</sub> O <sub>2</sub> H-Bond Donor: 1 H-Bond Acceptor: 2
	D-Glucitol, Hexaacetate		-7.8862 kcal/mol Compound ID: 23613 Molecular Weight: 434.394 g/mol Molecular Formula: C <sub>18</sub> H <sub>22</sub> O <sub>12</sub> H-Bond Donor: 0 H-Bond Acceptor: 12

water molecule and other ligands from target protein was done by Discovery Studio Visualizer 16.1.0 before docking attempts. Argus lab 4.0 was used for docking attempts, and PyMol v1.6 and Discovery Studio Visualizer 16.1.0 software were used for their interaction study.

#### 4.1. Target Protein Selection for Docking Attempts

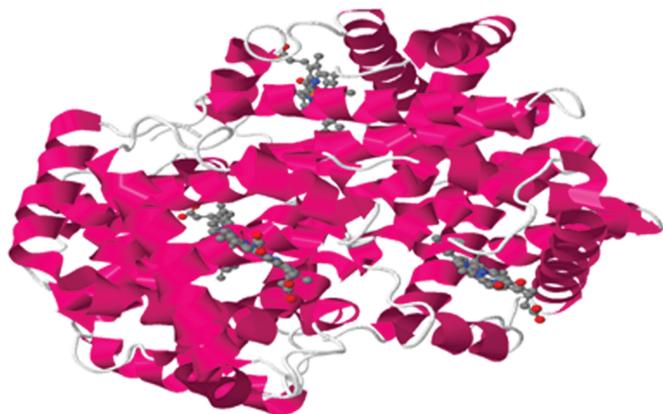
The sickle cell protein, 2 Deoxyhemoglobin S (2HBS) (Fig. 3) was downloaded from Protein Data Bank and phytochemicals were taken from the PubChem database. PyMOL and Discovery studio software is used for analysis and interaction study.

#### 4.2. Phytochemical Selection for Docking Attempts

*Carica* species contains various secondary metabolites including cyanogenic glycosides, amines and alkaloids, gums, fatty acids, terpenes (counting basic oils, phytosterol, triterpene genins, diterpenes, and saponins), nonprotein amino acids, hydrolyzable tannins, consolidated tannins, and flavonoids. The plant is more extravagant in glycine, carpaine, anthraquinone, phenylalanine, tryptophan, and tyrosine. The plant chemical compounds like N-methyl aspartic acid, oleic acid, Hexasiloxane dodecamethyl-, 2-Methoxy-4-vinylphenol, and Cyclohexyl isothiocyanate, D-Glucitol, Hexaacetate, Phenylalanin amide, and Papaverinol, etc., are found in leaf and unripe fruits. Papaya latex contains four cysteine compounds like papain, chymopapain, glycylic endopeptidase, and caracain. Reports are there on the impact of amino acids on gelatine kinetics and solubility of sickle cells [45]. Aromatic amino acids like tyrosine, tryptophan, and phenylalanine were significantly more energetic as anti-sickling [46]. The dense cell formation due to polymerization of the sickle cell can be inhibited by using nutritional antioxidants in combination with Vit. C and E [47]. Many workers have also reported beta carotene, Vit. C, gamma terpinene, citric acid, methionine, lycopene, tartaric acid, alanine, and sucrose have antisickling properties [48].

#### 4.3. Docking with 2HBS

For this study, Argus lab 4.0 was used to dock ligand (phytochemicals from *C. papaya*) into the active site of 2HBS protein. Argus lab has been reported as an effective software having the ability to predict bound configuration and binding energies of the ligand with macromolecular targets rapidly and



**Figure 3:** Sickle cell protein 2HBS (PDB no.-10.2210/pdb2hbs/pdb).

precisely. Polar hydrogen atoms were added to the ligands and its non-polar hydrogen particles were combined. All the adaptable bonds were set to be adaptable. Protein–ligand docking was finished utilizing the GA strategy. The grid box with a dimension of  $20 \times 20 \times 25$  and  $0.400 \text{ \AA}$  frameworks separating was to cover the protein binding site and suit ligands to move unreservedly. Subsequent to docking searches were finished, the best configuration was looked for the most populated bunch with the minimum binding vitality. The connection of docked protein–ligand complex configuration, including hydrogen bond and different interactions were broke down utilizing Discovery Studio Visualizer 16.1.0.

#### 4.4 Steps Involved in Docking of 2HBS

##### 4.4.1. Downloading of protein structures and ligands

- The sickle cell protein (2HBS) was downloaded from protein data bank using protein id and opened in the Argus Lab program. The molecule Tree view tool of 2HBS (positioned on the left part of the monitor) was expanded, plus the residue/misc folder was opened up. The selection of various ligands was taken from previously reviewed articles and then downloaded from Pubchem sites in .sdf format. Ligands were converted to .PDB format using an online smile translator.

##### 4.4.2. Creation of ligand and binding site groups

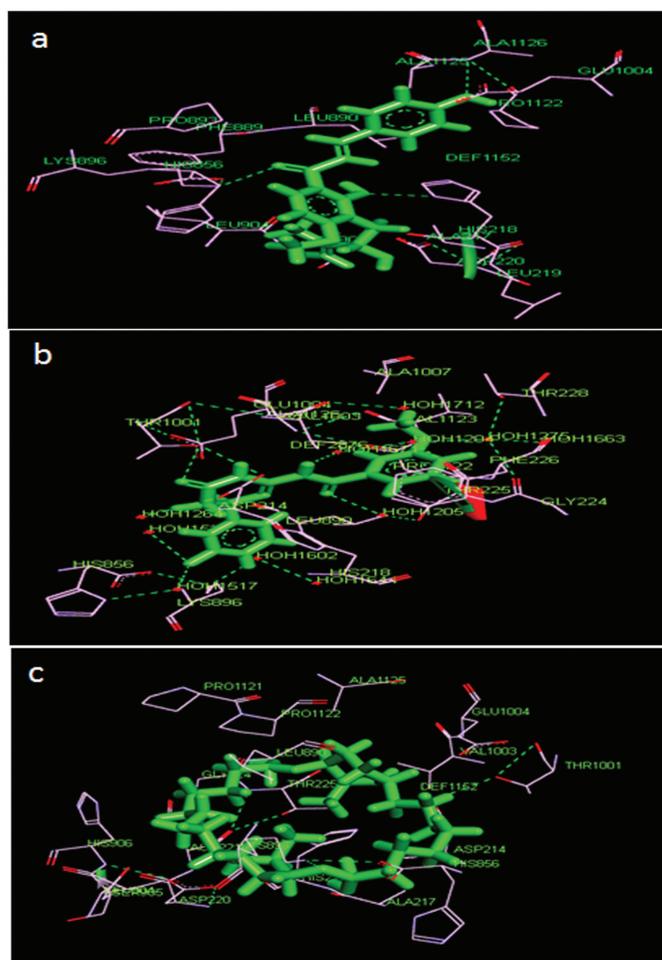
- Sickle cell protein inhibitor was selected from “1440 LK2” in the Tree View, which appeared yellow.
- The Edit/Hide Unselected menu choice was chosen to conceal all molecules that are not chosen. The only atoms appearing on the screen ought to be the sickle cell protein inhibitor.
- Center the sickle cell protein inhibitor in the window by choosing the View/Centre Molecule in the Window menu on the toolbar.
- While the inhibitor is chosen, hydrogen atoms were included by squeezing the H key on the toolbar.
- Right side click on the “1440 LK2” in the Tree View and the “Make a Ligand Group from this Residue” choice was chosen. Argus lab will build a cluster underneath the Groups file with a similar name “1 LK2” that is of sort Ligand.
- Left side clicks on either “1440 LK2” residue in the Residues/Misc organizer. This activity will again choose the atoms of the Ligand on the monitor.
- The selected residue was copied and pasted. In the Residues/Misc organizer in the Tree View tool, a recently featured residue with a name “2480 LK2” will be observed.
- Ligand cluster of this new residue was made in a similar way as done beforehand. Right-tapped on “2480 LK2” and “Make a Ligand Group from this Residue” was selected.
- The binding site for the ligand cluster by right clicking on the ligand cluster in the Groups folder and select the “Make a Binding Site Group for this Group” menu choice. This will create a Binding Site that comprises all residues that have at least one atom within  $3.5 \text{ \AA}$  from any atom in the ligand cluster.

#### 4.4.3. Docking the ligand into the definite binding site

- Dock Setting dialog box was brought up by choosing the Calculation/Dock a Ligand menu choice on the toolbar.
- The ligand to dock in the “Ligand” drop-box was chosen. Make a point to choose the cluster named “ligand” group.
- The “Calculate Size” key was clicked and a docking box custom made to the binding site was made which appeared on the monitor.
- Made sure that “GA Dock” is the chosen docking the Calculation type is “Dock” and the Ligand is Flexible.
- Docking calculation was started by clicking on “Start” button.
- Various docking scores were shown in the screen but the best score was taken into consideration.

## 5. DOCKING RESULT

The results were based on free energy binding and the lowest binding energy. The phytochemicals showing the most negative binding energies were considered to have the strongest binding affinity toward sickle cell protein (2HBS). Twenty-four phytochemicals from *C. papaya* (Table 3) are docked against sickle cell protein, i.e., 2HBS from which three compounds showed the best results. These compounds were Xanthoangelol D; N-[(4R)-4-(3-fluorophenyl)-6-oxo-4,5-dihydro-H-pyrimidin-2-yl]-3-methoxy benzamide, and Carpaine showing minimum energy values in protein–ligand interaction against sickle cell protein (2HBS). The docking of Xanthoangelol D formed a stable complex by the formation of hydrogen bond with ALA1126, GLU1004, ALA1125, PRO1122, PRO893, HIS856, LYS896, ALA217, HIS218, SER905, ASP220, LEU219, LEU904, LEU890, and PHE889 with a binding free energy of  $-10.5994$  kcal/mol, N-[(4R)-4-(3-fluorophenyl)-6-oxo-4,5-dihydro-H-pyrimidin-2-yl]-3-methoxybenzamide formed hydrogen bond with GLY224, PHE226, THR228, THR225, PRO1122, ALA1007, VAL1003, GLU1004, THR1001, ASP214, LYS896, HIS856, LEU890, VAL1123, ALA1126, and HIS218 with an energy of  $-9.33596$  kcal/mol, whereas that of Carpaine to 2HBS showed THR225, ASP214, ALA1126, THR1001, PRO1122, ASP220, ASN221, HIS906, LYS896, HIS856, DEF1152, and ALA217 establishing a hydrogen bond with Carpaine with a binding energy of  $-9.23601$  kcal/mol (Fig. 4). Several workers have used docking methods in search of phytochemicals for possible treatment of diseases or degradation of environmental pollutants. Kurjogi et al. [49] used the docking method in search of possible natural drug for *Staphylococcus aureus* enterotoxins (SEs) like SEA and SEB and based on the minimum binding energy concluded that 28-Norolean-12-en-3-one, a compound present in flowering plants of Lardizabalaceae family acts as a good inhibitor for SEA, while Betulin, a natural triterpene isolated from bark of birch trees will act as good inhibitor for SEB-like enterotoxins. Satapute et al. [50] docked triazole fungicide propiconazole against the superoxide dismutase (SOD) and catalase enzyme of plasmid cured *Pseudomonas aeruginosa* and found that propiconazole binds more efficiently with catalase as compared to SOD and can degrade propiconazole.



**Figure 4:** Interactions of the ligand (a) Xanthoangelol D, (b) N-[(4R)-4-(3-fluorophenyl)-6-oxo-4,5-dihydro-H-pyrimidin-2-yl]-3-methoxybenzamide, and (c) Carpaine with binding site residues of sickle cell protein (PDB ID:2HBS).

## 6. CONCLUSIONS

Docking studies were carried out in order to find the inhibitory activity of the compounds found in leaf extract and ripe fruit of *C. papaya*. Among the 24, three compounds showed the best docking result based on the binding energy. Docking studies and binding free energy calculations of these 24 compounds revealed that Xanthoangelol D has minimum interaction energy ( $-10.5994$  kcal/mol), followed by N-[(4R)-4-(3-fluorophenyl)-6-oxo-4,5-dihydro-H-pyrimidin-2-yl]-3-methoxybenzamide ( $-9.33596$  kcal/mol), and Carpaine ( $-9.23601$  kcal/mol). Hence, the given phytochemicals with minimum binding energy can be further used in a wet lab for the production of drugs to cure or inhibit the action of sickle cell protein.

The current review has highlighted the principle and methods by which molecular docking has been applied in the identification of novel phytochemicals yet challenges still remain, particularly with exactness and scoring capacity governed by quantum mechanics. Most docking program effectively predicts the binding methods of small particles ligands with receptor binding destinations. The present algorithm does not measure the complete energy related with intermolecular interactions with adequate precision.

However, in the present panorama of medication revelation, where high steady loss rates are a noteworthy concern, properly structured virtual screening procedures are efficient, financially savvy, and beneficial options. With the help of molecular docking, we can identify promising phytochemicals that can be used as future medicine for curing diseases.

From the above the experiment, it is concluded that Sick cell anemia has been a major health concern worldwide and has proven to claim the lives of many people yearly [51]. Till now, no cure has been successfully developed for this genetic disease. The current study was focused on an assessment of the inhibitory activity of leaf extract and ripe fruit compounds of *C. papaya* leaves against sickle cell protein. Among the identified 24 compounds, three compounds [Xanthoangelol D,N-[(4R)-4-(3-fluorophenyl)-6-oxo-4, 5-dihydro-H-pyrimidin-2-yl]-3-methoxy benzamide, and Carpaine] showed better binding affinity toward the sickle cell protein (2HBS). Different modes of interaction such as hydrogen bonding and other hydrophobic interactions were observed between the ligands and the 2HBS protein of sickle cell anemia. The information acquired through this study on the binding mode of phytocompounds from *C. papaya* and 2HBS protein will highly facilitate the synthesis and testing of these compounds as drugs for sickle cell disease. The study suggested that compounds from the *C. papaya* will be potent drug candidates against sickle cell anemia.

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#### AUTHOR'S CONTRIBUTION

DK and BPD developed the concept. DRD, DK, and PK wrote the manuscript.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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