VIRTUAL SCREENING OF PHYTOCHEMICALS TO HIGHLIGHT THE HIT MOLECULES FOR SKIN LIGHTENING FORMULATIONS

A thesis submitted toward partial fulfillment of the requirements for the degree of

Master of Engineering in Biomedical Engineering

Course affiliated to the Faculty of Engineering & Technology

Jadavpur University

Submitted by

Meghant Prasad Chowdhary

CLASS ROLL NO: 002130201004
EXAMINATION ROLL NO: M2BMD22007

Under the guidance of

Dr. Piyali Basak

Associate Professor
School of Bioscience and Engineering
Jadavpur University
Kolkata-700032

School of Bioscience and Engineering

Faculty of Engineering and Technology

Jadavpur University

Kolkata-700032

India

2023

M.E. (Biomedical Engineering) course affiliated to

Faculty of Engineering and Technology

Jadavpur University

Kolkata-700032

CERTIFICATE OF RECOMMENDATION

We hereby recommend that the thesis entitled "VIRTUAL SCREENING OF PHYTOCHEMICALS TO HIGHLIGHT THE HIT MOLECULES FOR SKIN LIGHTENING FORMULATIONS" carried out under my supervision by ***Meghant Prasad Chowdhary*** may be accepted in partial fulfilment of the requirement for awarding the Degree of Master in Biomedical Engineering of Jadavpur University. The project, in our opinion, is worthy for its acceptance.

Dr. Piyali Basak

(Thesis Advisor)
Associate Professor
School of Bioscience and Engineering
Kolkata-700032

DIRECTOR

School of Bioscience and Engineering
Jadavpur University
Kolkata-700032

Dean

Faculty Council of Interdisciplinary Studies, Law and Management
Jadavpur University, Kolkata – 700032

M.E. (Biomedical Engineering) course affiliated to
Faculty of Engineering and Technology
Jadavpur University
Kolkata-700032

Certificate of Approval

The forgoing thesis is hereby approved as a creditable study of an engineering subject carried out and presented in a manner satisfactory to warrant its acceptance as a prerequisite to the degree for which it has been submitted. It is understood that by this approval the undersigned do not necessarily endorse or approve any statement made, opinion expressed or conclusion drawn therein but approve the thesis only for the purpose for which it is submitted.

_____

Dr. Piyali Basak
(Thesis Advisor)
Associate Professor
School of Bioscience and Engineering
Jadavpur University
Kolkata-700032

_____

Signature of External Examiner

Declaration of Originality

I, ***Meghant Prasad Chowdhary,*** Roll Number: 002130201004, Examination roll Number M2BMD22007, hereby declare that this M.Tech thesis entitled **'**VIRTUAL SCREENING OF PHYTOCHEMICALS TO HIGHLIGHT THE HIT MOLECULES FOR SKIN LIGHTENING FORMULATIONS**'** presents my original work in , Jadavpur university, Kolkata as a postgraduate student of Jadavpur University, Kolkata, and to the best of my knowledge contains no material previously published or writtenby another person, nor any material presented by me for the award of any degree or diploma of Jadavpur University, Kolkata, or any other institution. Any contribution made to this research by others, with whom I have worked at Jadavpur University, or elsewhere, is explicitly acknowledged in the thesis. Works of other authors cited in this dissertation have been duly acknowledged under the section "References". I am fully aware that in case of any non-compliance detected in future, the Senate of JadavpurUniversity, Kolkata may withdraw the degree awarded to me on the basis of the present thesis.

Meghant pd Chowdhary

School of Bioscience and Engineering
Jadavpur University
Kolkata-700032

Acknowledgment

At the very onset, I would like to thank Jadavpur University for giving me the opportunity to be part of its rich heritage, culture, and academic setup. When a student progresses ahead in his/her life, his/her ambition is to enter premier institutes of the likes of Jadavpur University. I would like to thank all my faculty members, who made sure that we could adjust ourselves in the tough period post-pandemic. I would like to thank especially Prof. Dr. Piyali Basak and Prof. Dr. Monisha Chakraborty, whose able guidance propelled us further in our academic pursuit. without their support, guidance, and critical feedback, this thesis work would not have been possible. I would like to thank my peers, Sudipta, Shreeparna, Sanjoy, Keshav, Lina, Debolina, Souradip and Avik, who have shaped me as an individual and whose friendship and support I would look forward to, in the years to come.

A single parchment of paper is not enough to show gratitude to scores of other people in my life, who have been influential and encouraging to me and who have chiselled me to become the person I am today. And for that reason, I believe God must be thanked, in every way and sense possible.

Meghant Pd Chowdhary

INDEX

ABSTRACT

In molecular biology and drug discovery, the capacity to anticipate the binding conformation of ligands within receptors is of utmost relevance. The computational method known as molecular docking is essential to this procedure since it is capable of making precise predictions about ligand-receptor interactions. The objective of this thesis is to enhance molecular docking algorithms, and explore their possible applications. For lighter skin appearance, skin whitening products are available commercially - Melasma and Post-inflammatory hyperpigmentation are the major disorder of this. These all are treated by whitening agents which acts as various levels of melanin production in the skin. The enzyme tyrosinase plays a major role in this known as competitive inhibitors of tyrosinase (the key enzyme in melanogenesis). In this study we elucidated how natural whitening products may decrease the pigmentation in skin and evaluate the potential tyrosinase, collagenase and elastase inhibitory activities of phytochemicals.

1: INTRODUCTION

Skin is a soft, flexible layer of tissue that covers vertebrate and human bodies. This layer is classified as an organ and is responsible for functions such as protection, regulation, and sensation (1). The human skin has three primary layers (epidermis, dermis, and hypodermis) (2). The epidermis contains a nonviable layer known as the stratum corneum, which acts as a barrier for the body, protecting it from external agents and maintaining cutaneous hydration, whereas the dermis is primarily composed of connective tissue (collagen and elastin), sweat glands, and nerves. Its main function is to protect the epidermis (3). Collagen fibres give the skin strength, whereas elastin fibres give the skin elasticity and resistance. Melanocytes are found on the basal layer of the skin, which separates the dermis and the epidermis (4). A single melanocyte is surrounded by 36 keratinocytes (5). They combine to form the epidermal melanin unit. Dendrites transport melanin produced and stored within the melanocyte in the melanosomal compartment to the overlying keratinocytes (6).

This thesis intends to identify and assess phytochemicals with skin-lightening characteristics using computational methods, particularly molecular docking. The main goal is to find the possible ligands who can alter target proteins involved in melanogenesis, the process of melanin formation. The study also aims to evaluate the therapeutic potential of the identified phytochemicals and clarify the molecular mechanisms underlying their skin-lightening effects.

1.1 Research Objectives

This thesis intends to identify and assess phytochemicals with skin-lightening characteristics using computational methods, particularly molecular docking. Finding possible candidates who can alter target proteins involved in melanogenesis, the process of melanin formation, is the main goal. The research also seeks to assess how the discovered plant compounds could be used for therapeutic purposes and elucidate the molecular processes responsible for their ability to lighten the skin.

The following research questions are addressed in the thesis:

- Can molecular docking accurately anticipate the interactions and binding affinities between phytochemicals and target proteins involved in controlling skin pigmentation?
- Which phytochemicals have the most binding affinity and have the greatest potential as skin lightening treatments?
- What are the main molecular interactions and processes through which these phytochemicals influence the pathways leading to melanogenesis?

Some research articles were taken from google scholar, crossref, and pubmed. Finally some articles were selected from it in order plan this research. There is a discussion on how and which type of enzymes/proteins has to be selected in order to carry out this research. Some medicinal plants has been chosen which are reported for the treatment of skin. Lastly three enzymes have been selected and further on we will study that how the protein-ligand interaction occurs via Autodock software.

2. LITERATURE REVIEW

2.1 Mechanisms of Skin Pigmentation

Melanin, the pigment that determines skin colour, is produced, transported, and distributed as part of the intricate biological process known as skin pigmentation (7). Several proteins and enzymes, such as tyrosinase, the melanocortin-1 receptor (MC1R), and the microphthalmia-associated transcription factor (MITF), control melanogenesis, or the formation of melanin (8). To find possible targets for skin-lightening therapies, it is essential to understand the molecular processes that underlie skin pigmentation. The selection of elastase, tyrosinase, and collagenase as the three targets for a study that can be motivated by their relevance to skin health and appearance. Elastase is an enzyme responsible for breaking down elastin, a protein in the skin that helps to maintain skin's elasticity and firmness. Excessive elastase activity can lead to skin aging and the formation of wrinkles (9). Researchers may choose elastase as a target because they are interested in finding compounds that can inhibit or modulate its activity, potentially promoting skin elasticity and reducing the signs of aging.

Tyrosinase is a key enzyme involved in melanin production. Melanin is responsible for skin pigmentation, and overactivity of tyrosinase can lead to hyperpigmentation issues such as melasma or age spots (10). Researchers may select tyrosinase as a target to identify substances that can regulate melanin production and potentially lead to skin-lightening or evening of skin tone. Collagenase is an enzyme that breaks down collagen, a crucial protein for maintaining skin structure and reducing the appearance of wrinkles and sagging (11). Excessive collagenase activity can contribute to skin aging (12). By targeting collagenase, researchers aim to identify compounds that can inhibit its action, potentially preserving collagen levels and promoting youthful skin appearance.

2.2 Skin-lightening Phytochemicals

Natural substances called phytochemicals, which are produced from plants, have drawn attention for their capacity to lighten skin (13). Numerous phytochemicals have been investigated for their capacity to prevent melanogenesis, including flavonoids, polyphenols, and terpenoids (14). By specifically targeting important enzymes involved in the melanogenesis pathway, such as tyrosinase and tyrosinase-related proteins, these substances can influence the formation of melanin (15).

The literature offers details on the structure-activity connections, modes of action, and prospective uses of phytochemicals in skin-lightening remedies.

2.3 Techniques for Molecular Docking

A popular computer method for analysing and predicting the interactions between ligands (phytochemicals) and target proteins is molecular docking (16). To calculate the binding affinity and locate advantageous binding conformations, docking methods use scoring functions. A scoring function is a mathematical model that calculates a score or energy value for each ligand pose generated during the docking process. This score represents the predicted binding affinity or energy of the interaction. Scoring functions typically consist of several components: Van der Waals Interactions that account for the attractive and repulsive forces between atoms and molecules (17). Electrostatic Interactions that consider the charges and distribution of charges within the molecules. Hydrogen Bonding in which scoring functions assess the potential for hydrogen bonding between the ligand and the protein (18). Solvation Energy is the component accounts for the change in energy when the ligand enters the solvent (water) environment. Entropy in which some scoring functions include terms related to entropy or conformational changes upon binding (19). The scoring function computes a score or energy value for each ligand pose based on the components mentioned above. The poses are ranked based on their computed scores. Lower scores generally indicate better binding affinity or stronger interactions. The top-ranked ligand poses are often selected as potential binding modes, and these poses can then be further analyzed or refined. Scoring functions are developed through the parameterization of their components. These parameters are often optimized using experimental data to improve the accuracy of the scoring function (20).

Recent advancements include the use of machine learning algorithms to develop scoring functions that can better predict binding affinities based on training data (21). AutoDock,

GOLD, and Vina are frequently used molecular docking software that provide a variety of search methods and score options. These methods have been useful in lead optimisation and virtual screening, offering insightful information on ligand-receptor interactions (22).

2.4 Benefits of Molecular Docking in Research on Skin Lightening

Molecular docking has various benefits for skin-lightening studies, including:
It makes it possible to search through enormous chemical databases to find prospective skin-lightening chemicals.
The computational method helps with both the rational design of skin lightening agents and the study of structure-activity correlations (23).

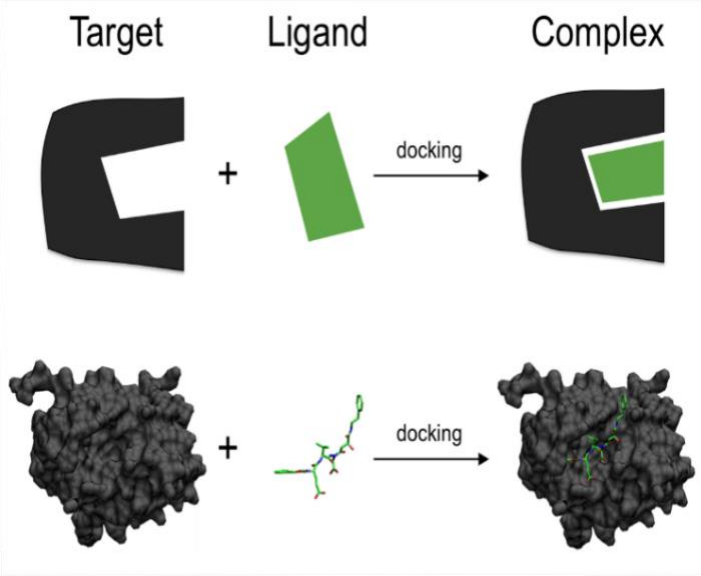


Figure 1: Schematic diagram showing the theory behind molecular docking

2.5 Molecular Docking

Molecular docking predicts the orientation of each molecule within a complex. While one molecule is docked per second, others form stable, permanent connections. This explains that molecular docking predicts the orientation of individual molecules within a complex (24). Information can be mounted in any direction of rotation expect a strong commitment or bond. Two molecules bind with each other by affinity, Molecules such as proteins, peptides and nucleic acids, carbohydrates and lipids play a central role in signal transduction (25). Besides Relative orientation of two interacting partners It can affect the type of signal formed (e.g., Agonist vs. antagonist). Agonists and antagonists are two types of molecules or compounds

that interact with receptors in the body, particularly in the context of cell signaling. They have opposite effects on these receptors and play critical roles in various physiological processes and drug actions. Agonists are molecules or compounds that bind to specific receptors and activate them. When an agonist binds to its target receptor, it triggers a cellular response or signaling cascade. Agonists mimic the natural ligand (substance) that typically binds to the receptor, leading to the same biological response. They promote receptor activation and the downstream physiological or pharmacological effect (26). Antagonists are molecules or compounds that bind to specific receptors but do not activate them. Instead, they block or inhibit the receptor's activation by preventing other molecules, including agonists, from binding.

Antagonists essentially "compete" with agonists for receptor binding sites. When an antagonist occupies the receptor, it prevents the natural ligand or agonist from binding, thereby inhibiting the receptor's signaling pathway (27). Therefore, docking helps to predict both potency and type of interaction between a molecule (typically a ligand) and its target receptor. Molecular docking calculates a score or energy value for each potential binding pose or conformation of a ligand within the receptor's binding site. This score reflects the predicted binding affinity or binding energy. Molecular docking also provides insights into the type of interaction between a ligand and its target receptor. This includes information about the binding mode, such as the orientation of the ligand within the binding site (28).

Basics steps of docking:

- STEP1: Getting the complex PDB.
- STEP2: Cleaning the complex.
- STEP3: Adding the missing hydrogels/side chain atoms and minimize the complex.
- STEP4: Preparing the docking suitable files.
- STEP5: Cleaning of the minimized complex.
- STEP6: Preparing all the required files for docking.
- STEP7: Run the docking.
- STEP8: Analyze the results of docking.

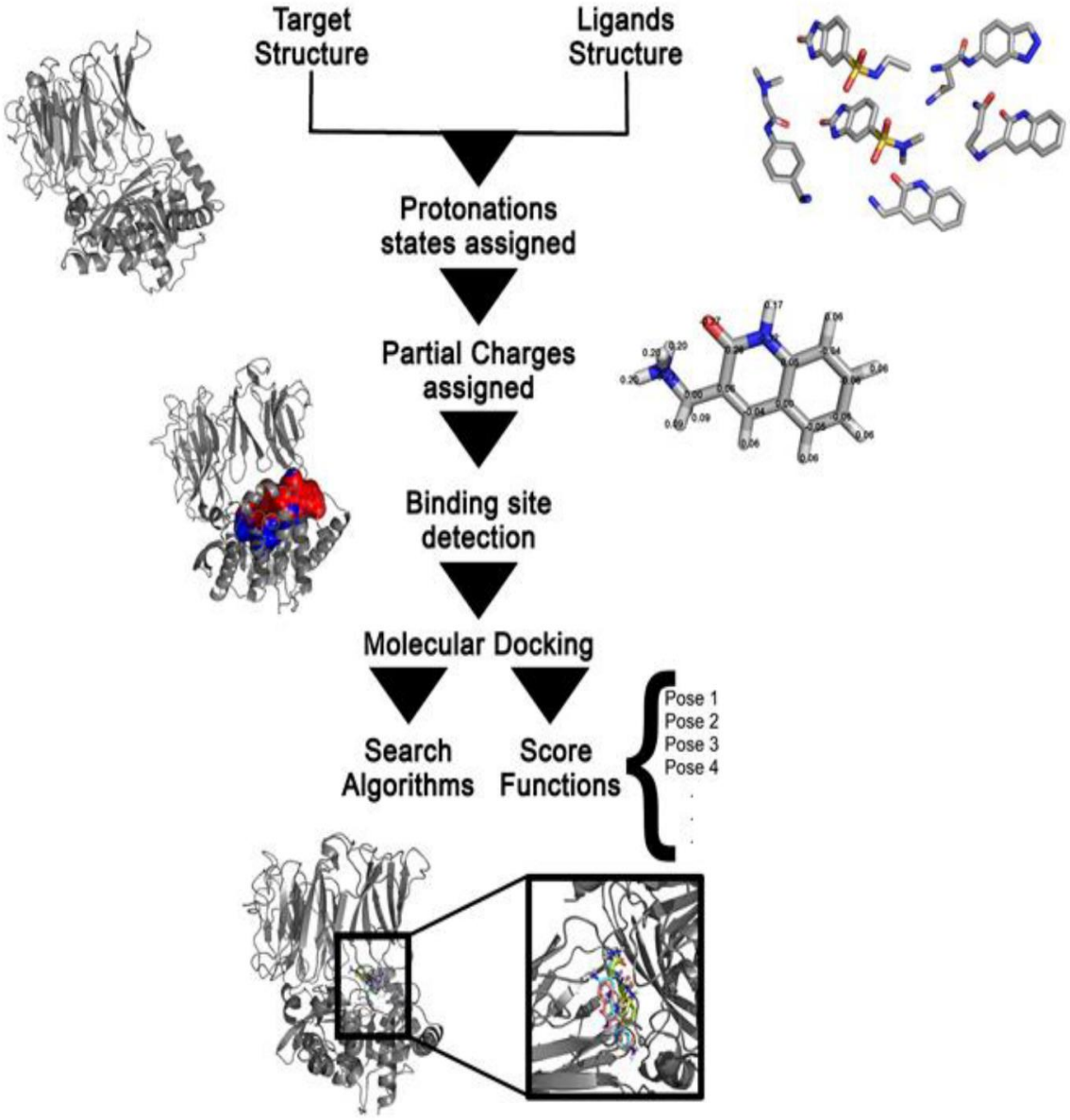


Figure 2: Steps involved in molecular docking

2.6 Mechanism of docking with its importance

The atomic level interactions between tiny chemicals and proteins may be modelled using molecular binding techniques. Small molecule behavior at the binding site can be explained by this. Two fundamental phases make up the joining procedure: i) determination of binding affinity as well as the shape of the ligand, its orientation inside these sites (often referred to as postpositions). Utilizing these two actions scoring should be performed. The effectiveness of docking is considerably increased by knowing the binding site's position prior to docking (29). Comparing the target protein to a protein that crystallizes with a protein family or another ligand with a related function can also reveal information about the location. Blind docking

and targeted docking are two approaches in molecular docking studies, and they differ in their methods and objectives. Here's an elaboration of the key differences between blind and targeted docking. Blind docking is an approach where molecular docking simulations are performed without prior knowledge of the ligand's binding site on the target receptor. The goal is to explore potential binding sites and orientations across the entire receptor surface. Blind docking is typically used in cases where the binding site is unknown or poorly characterized, or when researchers want to investigate the possibility of alternative binding sites on the receptor (30). Targeted docking, on the other hand, involves performing docking simulations with prior knowledge of the binding site on the target receptor. The goal is to predict the binding mode and affinity of a ligand within a specific, predefined binding site. Targeted docking is employed when the binding site is well-defined or when researchers want to explore the interaction of a ligand with a known binding site on the receptor. Blind docking is particularly useful when the binding site is unknown or when researchers want to explore potential off-target interactions. Whereas, targeted docking is applied when the binding site is well-characterized and researchers are interested in studying ligand-receptor interactions within a specific site (31).

Theory of docking: Utilizing computational methods molecular docking aims to anticipate the structure of the ligand receptor complex. Docking can be accomplished by two linked stages. Then use a score system to order these conformations. The scoring function used in molecular docking should assign the highest score or lowest energy to the ligand conformation that closely matches the experimentally observed binding mode. This indicates that the docking method has successfully reproduced the known or expected binding geometry. Placing the experimental binding mode first among all produced conformations is crucial as it indicates the accuracy and reliability of the docking results (32).

Importance of molecular docking are as follows:

1. Predicting the binding affinity (scoring function)
2. Identifying the ligands in binding sites.
3. Designing of drugs rationally

2.7 Types of Docking

RIGID DOCKING: The internal geometry of both the ligands and receptors are treated as rigid. These are also known as lock and key.

FLEXIBLE DOCKING: An enumeration is performed on rotation of smaller molecules generally and after every rotation, energy is calculated and finally the optimum pose is selected. Docking can be between protein-ligand, protein-protein, protein-nucleotide. There are different types of forces which acts at the time of docking such as electrostatics,electrodynamics,steric forces etc (33).

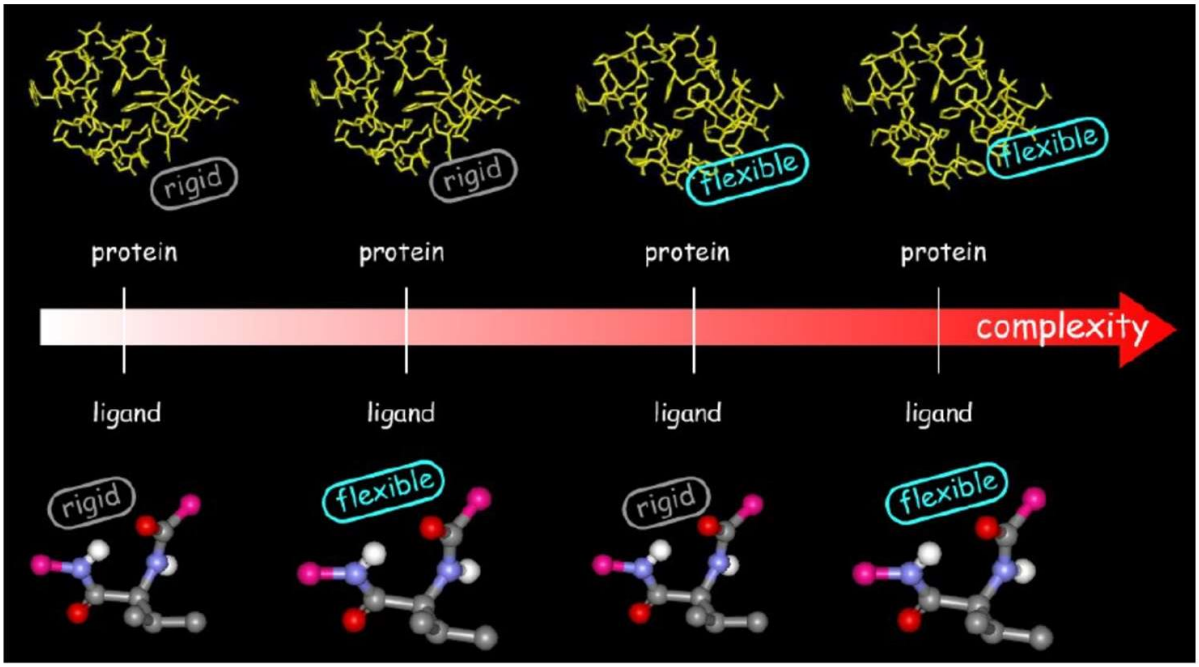


Figure 3: Comparison between rigid and flexible docking

RECEPTOR SELECTION AND PREPRATIONS:

BULIDING THE RECEPTORS: The 3-D structures of the receptors should be taken which can be downloaded from RCSB official site in .pdb file format. the available structures should be processed. The receptors should be biologically active and stable (34).

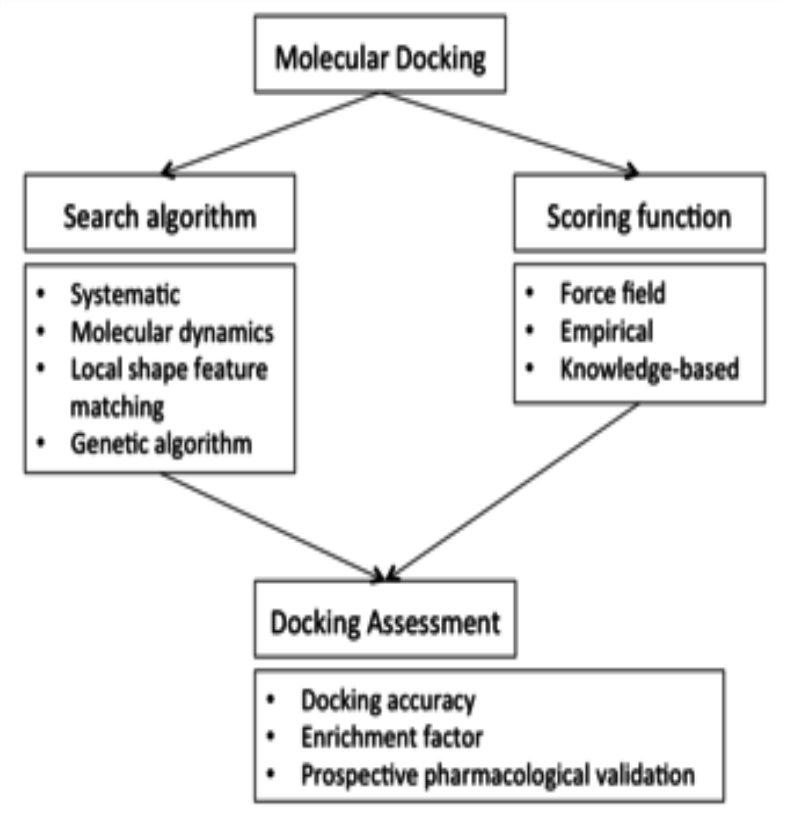
SELECTION OF LIGAND: It can be taken from various databases like zinc, pubchem etc. the ligands are docked onto a receptors are the interactions are checked. After that the scoring function generates the scores depending upon the best fit ligand is selected (35).

THE USE OF AUTODOCK: AutoDock Vina is a computer-assisted docking program based on a simple scoring function and a fast gradient-optimized conformational tool. The docking of drug-like ligands to proteins is very simple and efficient. This is a free open source molecular docking program. It was originally designed and implemented at the Molecular Graphics Lab. The main reasons for its popularity include:

1. Accuracy: AutoDock Vina significantly improves the typical accuracy of the result predictions.

2. Easy to use: All that's needed is that the structures of the molecules being docked and the specification of the search area including the bindingsite (36).

Figure 4: Components of molecular docking



3: METHODOLOGY

3.1 Phytochemical Database Selection

A broad and varied database of phytochemicals is necessary to undertake the screening of skin-lightening phytochemicals. Compounds with proven skin-lightening effects and the availability of structural data are among the selection criteria for the phytochemical database. For gathering the required molecules, well-known databases like PubChem, ChemSpider, or specialised phytochemical databases might be an invaluable resource.

3.2 ADMET properties:

Swiss ADME (www.swissadme.ch) Swiss ADME software of Swiss institute of bioinformatics (http://www.sib.swiss) was accessed in a web server that displays the Submission page of Swiss ADME in Google was used to estimate individual ADME behaviors of the phytoconstituents. The list is made to contain one input per molecule, defined by a simplified molecular-input line-entry system (SMILES) and the results are presented for each molecule in tables and excel spreadsheet.

Water Solubility: The solubility of a compound radically confides on the solvent used, ambient temperature and pressure. The solubility indicate the saturation concentration whereupon adding more solute does not increase its concentration in the solution. A drug is considered highly soluble when the highest dose strength will be soluble in 250 mL over the pH range of 1 to 7.5 less of aqueous media. Two topological approaches included in Swiss ADME to predict water solubility, the first one is the application of ESOL model (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2 very<0<highly) and the second one is adapted from Ali et al., 2012 [27] (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<- 2very<0<highly). Both differ from the fundamental general solubility equation since they avoid the melting point parameter but the linear correlation between predicted and experimental values were strong (R2=0.69 and 0.81 respectively). The third predictor of Swiss ADME was developed by SILICOS-IT (Solubility class: Log S Scale: Insoluble<-10 poorly<-6, moderately<-4 soluble<-2 very<0<highly) where the linear coefficient is corrected by molecular weight (R2=0.75). All predicted values are the decimal logarithm of the molar solubility in water (log S). Swiss ADME also provides solubility in mol/l and mg/ml along with qualitative solubility classes.

Drug likeness: Swiss ADME performs filtering of chemical libraries to exclude molecules with incompatible pharmacokinetic profile and check the drug-likeliness of hit molecules. The Lipinski filter (Pfizer) is the prime pioneer rule of five that characterize small molecules based on their physicochemical property profiles which include Molecular Weight (MW) less than 500, N or O ≤ 10, MLOGP ≤ 4.15, NH or OH ≤ 5. Lipinski considers stringently that all nitrogen and oxygen as H-bond acceptors and all nitrogen and oxygen with at least one hydrogen as H-bond donors. Besides, aliphatic fluorines are acceptors and alinine nitrogen is neither donor nor acceptor. The Ghose filter (Amgen) describes small molecules stationed on the physicochemical property, existence of functional groups and substructures. The qualifying range includes of molecular weight is between 160 and 480 Da, WlogP is between -0.4 to 5.6, molar refractivity (MR) is between 40 to 130 for a total number of atom; the qualifying range is between 20 and 70 atoms in a small molecule. Veber filter (GSK filter) model symbolizes molecules as a drug like if they have ≤ 10 rotatable bonds and a topological polar surface area (TPSA) equal to or less than 140 Å2 with 12 or fewer H-bond donors and acceptors. Compounds with these properties will have good oral bioavailability, reduced TPSA correlates increased permeation rate, increased rotatable bonds counts has a negative effect on the permeation rate. Egan filter (Pharmacia filter) anticipates that drug absorption depends on processes involved in the membrane permeability of the small molecule. These models symbolize molecules as a drug like if they have WLOGP ≤ 5.88 and TPSA ≤ 131.6 respectively. The Egan computational model for human passive intestinal absorption (HIA) of small molecules accounted for active transport and efflux mechanisms and will be therefore robust in predicting absorption of drugs. Muegge filter (Bayer filter) is a self-reliant Pharmacophore point filter that segregates drug-like and non-drug-like molecules. These models symbolize molecules as a drug like if they have a molecular weight between 200 to 600 Da, TPSA ≤ 150, Number of rings ≤ 7, XLOGP between -2 and 5, Number of carbon atoms > 4, number of heteroatoms > 1, number of rotatable bonds ≤ 15, H-bond acceptor ≤ 10, H- bond donor ≤ 5 respectively. Abbott bioavailability score seeks to predicts the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability which predicts the probability of a compound to have F>10% based on the predominant charge at biological pH in a rat model. It focuses on fast screening of chemical libraries to select the best molecules to be synthesized.

3.3 Selection of Protein Targets

For the screening procedure, it is essential to identify relevant protein targets implicated in melanogenesis.

Target proteins should include important enzymes that are involved in regulating the production of melanin. Hence in this research we have taken 3 different proteins that play a pivotal role in skin pigmentation and health:

1.Tyrosinase (PDB CID: 2Y9X)

2. Collagenase (PDB CID: 1CGL)

3. Elastase (PDB CID: 1BRU)

These proteins are potential locations for the control of skin pigmentation and play crucial functions in the melanogenesis process.

3.4 Protocol for Molecular Docking

STEP1: Getting the complex PDB.

STEP2: Cleaning the complex.

STEP3: Adding the missing hydrogels/side chain atoms and minimize the complex.

STEP4: Preparing the docking suitable files.

STEP5: Cleaning of the minimized complex.

STEP6: Preparing all the required files for docking.

STEP7: Run the docking.

STEP8: Analyze the results of docking.

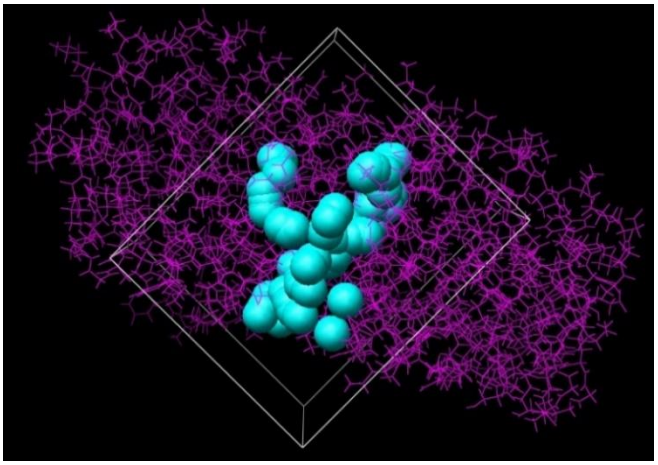
3.5 Preparation of Ligand

The phytochemicals from the chosen database need to be prepared as ligands prior to docking simulations. In order to make a ligand, hydrogen atoms must be added, molecule geometry must be optimised, and the proper charges must be applied. For ligand preparation chores, software tools like Open Babel or DISCOVERY STUDIO can be employed.

3.6 Preparation of Protein

Prior to running docking simulations, the chosen protein structures must be ready (for example, from the Protein Data Bank). In order to prepare proteins, water molecules must be removed, hydrogen atoms must be added, partial charges must be assigned, and the protein structure must be optimised. For the preparation of proteins, one can utilize programmes like AutoDock Tools,

3.7 Grid Generation



To specify the area where ligand binding should take place, a docking grid is created around the target protein.The active site or pertinent binding pockets, where ligands are anticipated to interact with the protein, are covered by the grid.To guarantee thorough sampling while retaining computational efficiency, the grid size and spacing parameters should be properly specified.

Figure 5: Grid box preparation for AutoDock Vina

3.8 Scoring and Docking Simulation

By putting the ready-made ligands inside the created docking grid, docking simulations are carried out. While looking for the ideal binding pose, the docking programme investigates various ligand conformations and orientations. Ranking algorithms assess the ligands' anticipated binding energies and rank them according to their binding affinities. To improve sampling and capture ligand flexibility, we used several docking runs (run number set to 9).

3.9 Evaluation and Analysis

The results of the docking simulations are examined to find top-ranked ligands that may have skin-lightening potential. Focusing on important residues and binding motifs, the molecular interactions between the ligands and target proteins are investigated.

4: RESULTS AND ANALYSIS

4.1 Analysis of ADMET properties

The ADMET properties of all the phytochemicals that are present in the parent database of 112 compounds are presented in Table S2. Initial screening revealed that 37 phytoconstituents do not pass the Lipinski's filter for drug-likeliness of molecules. Hence those compounds are not considered in our subsequent molecular docking. The phytochemicals that do not violate the Lipinski's rule of five are selected as our potential target ligands and the screening of hit molecules is done using the subset of parent database (i.e. containing 175 compounds).

4.2 Analysis of binding affinity and molecular interactions

A set of docking findings is produced by screening the phytochemical database against the chosen protein targets using molecular docking. The entire table of binding affinity of all the chosen ligands with the three receptor molecules is presented in Table S1. The docking outcomes include details on the projected binding mechanisms and binding affinities of the ligands with the target proteins. The intensity of the interaction between the ligand and the protein is indicated by the binding affinities, which are frequently reported as docking scores or binding energies. The outcomes are examined to determine the ligands with the highest binding affinities, which may have skin-lightening potential.

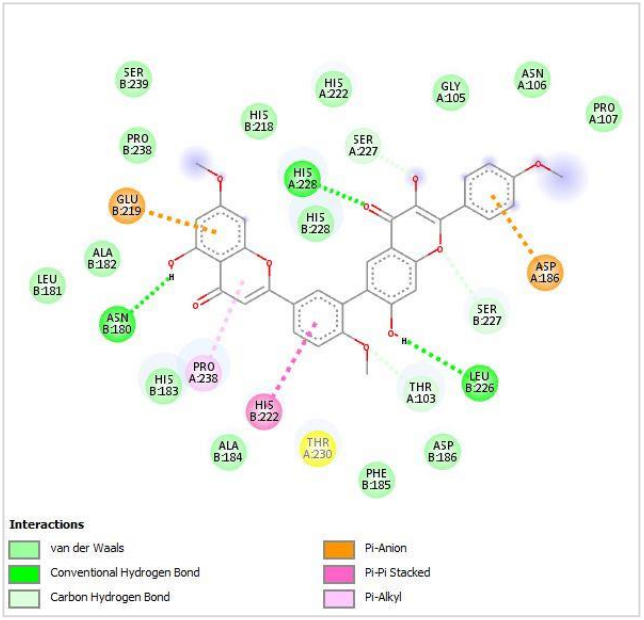
The investigation of the precise molecular interactions between the top-ranked ligands and the target proteins is the main goal of the analysis. Hydrogen bonds, hydrophobic contacts, electrostatic interactions, and - stacking interactions are among the interactions. The binding motifs and potential hotspots are highlighted by the identification of key residues involved in ligand-protein interactions. The molecular processes by which the ligands influence the target proteins and prevent melanogenesis are better understood.

4.3 Prioritisation of Potential Candidates for Skin Lightening

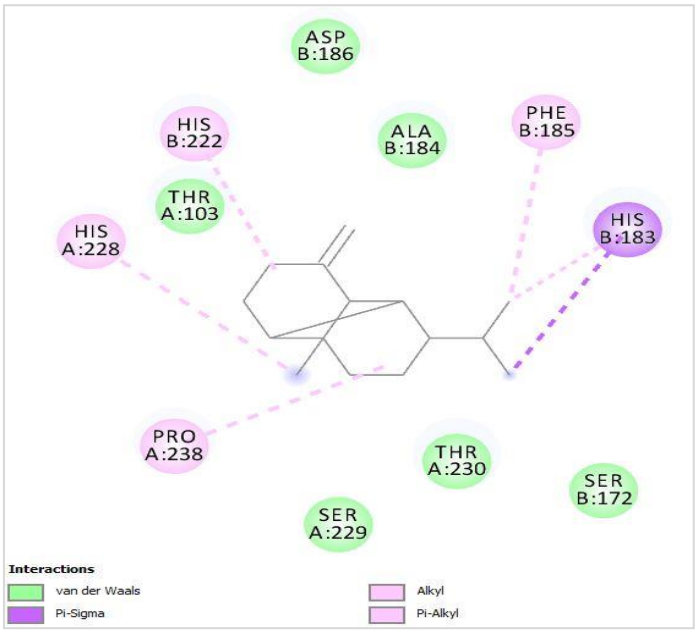
Potential candidates for skin lightening are ranked according to the, binding affinities i.e, molecular interactions. Promising choices are ligands with the highest binding affinities, robust molecular interactions, and advantageous structural characteristics. The potential for skin lightening of the prioritised candidates can be confirmed using further computational techniques or experimental testing.

Table 1: Phytochemicals exhibiting strong interaction with all the chosen 3 receptors

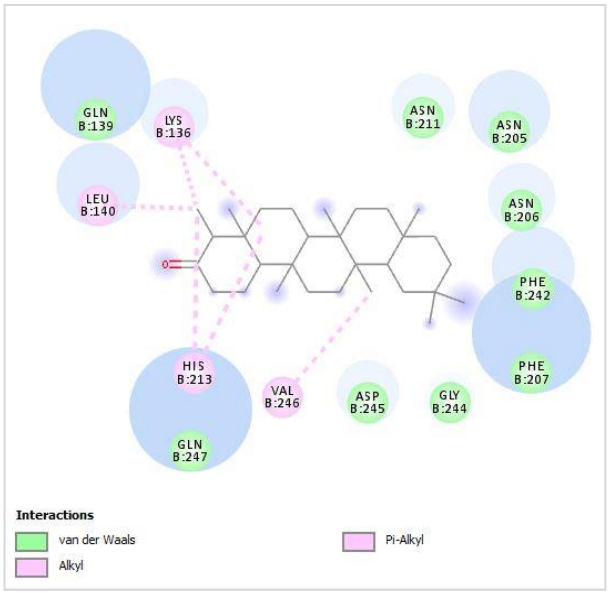
Compound	Binding affinity (in kcal/mol)		
	Tyrosinase	**Elastase**	**Collagenase**
1.beta-Copaene	-10	-9.1	-8.6
2.Kaempferol-7-rhamnoside	-10.1	-8.8	-10.6
3.Abiesin	-10.2	-8.7	-11.5
4.Flavanomarein	-9.2	-8.2	-10.1
5.Quercitrin	-8.5	-8.2	-9.5
6.Taraxerol	-10.9	-8	-10.8
7.Friedelin	-9	-8	-8.6
8.Hesperidin (standard skin-lightening agent)	-9.9	-8.4	-11.2


SER B:239
HIS A:222
GLY A:105
ASN A:106
PRO A:107
HIS B:218
PRO B:238
SER A:227
HIS A:228
GLU B:219
HIS B:228
ALA B:182
ASP A:186
LEU B:181
SER B:227
ASN B:180
PRO A:238
HIS B:183
LEU B:226
THR A:103
HIS B:222
THR A:230
ALA B:184
ASP B:186
PHE B:185
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Pi-Pi Stacked
Pi-Alkyl

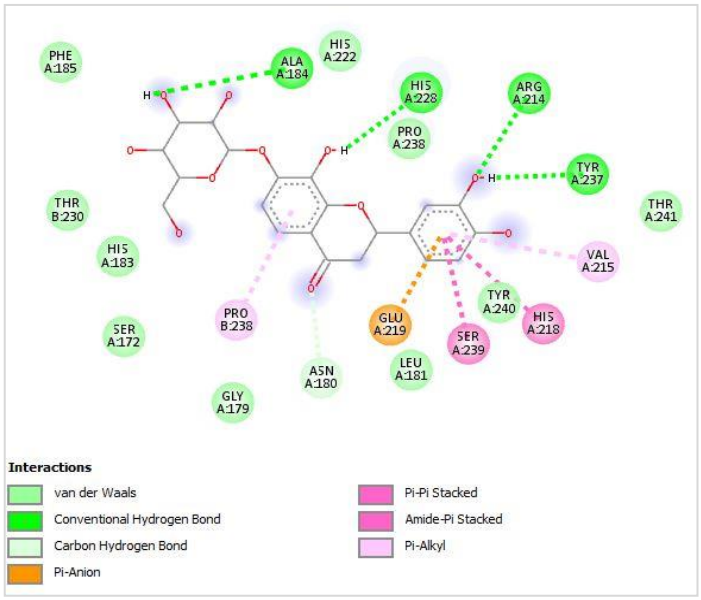
(a)


ASP B:186
HIS B:222
ALA B:184
PHE B:185
THR A:103
HIS A:228
HIS B:183
PRO A:238
THR A:230
SER B:172
SER A:229
Interactions
van der Waals
Pi-Sigma
Alkyl
Pi-Alkyl

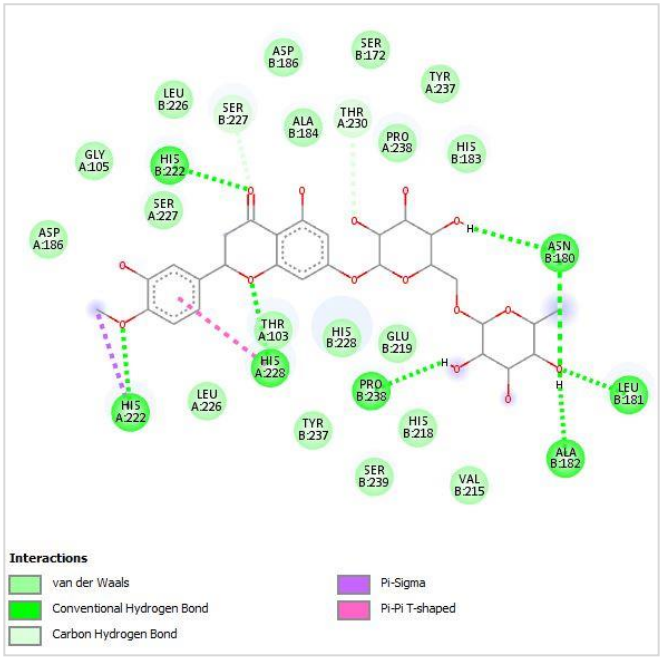
(b)


GLN B:139
LYS B:136
ASN B:211
ASN B:205
LEU B:140
ASN B:206
PHE B:242
HIS B:213
VAL B:246
ASP B:245
GLY B:244
PHE B:207
GLN B:247
Interactions
van der Waals
Alkyl
Pi-Alkyl

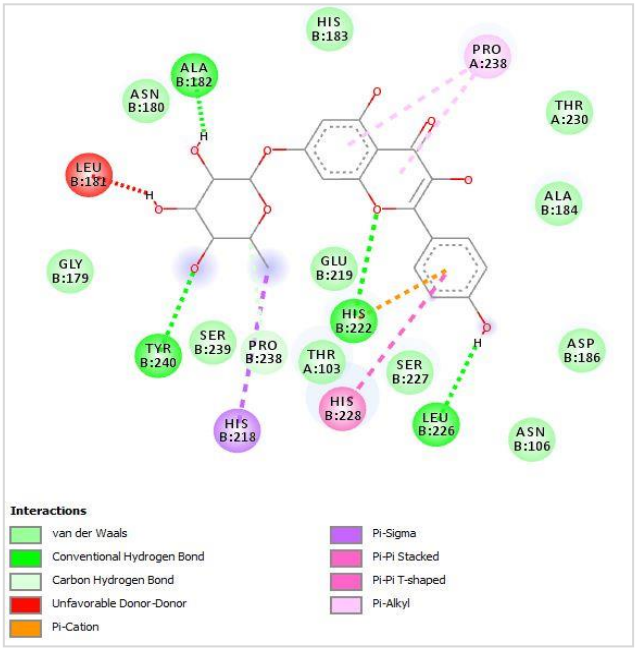
(c)


PHE A:185
ALA A:184
HIS A:222
HIS A:228
ARG A:214
PRO A:238
TYR A:237
THR A:230
THR A:241
HIS A:183
VAL A:215
TYR A:240
PRO B:238
GLU A:219
HIS A:218
SER A:172
SER A:239
LEU A:181
ASN A:180
GLY A:179
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Pi-Pi Stacked
Amide-Pi Stacked
Pi-Alkyl

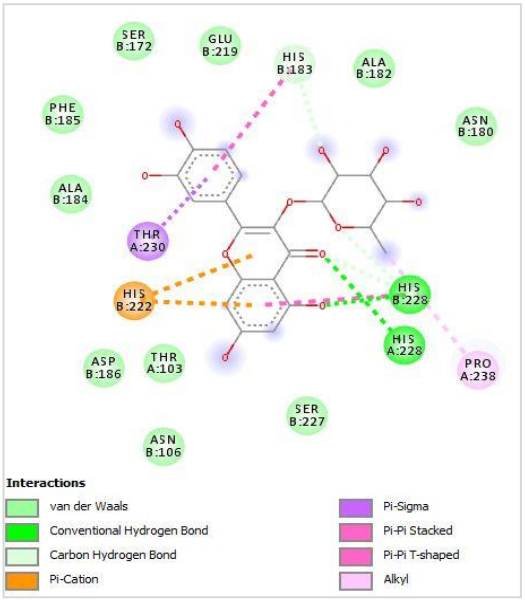
(d)



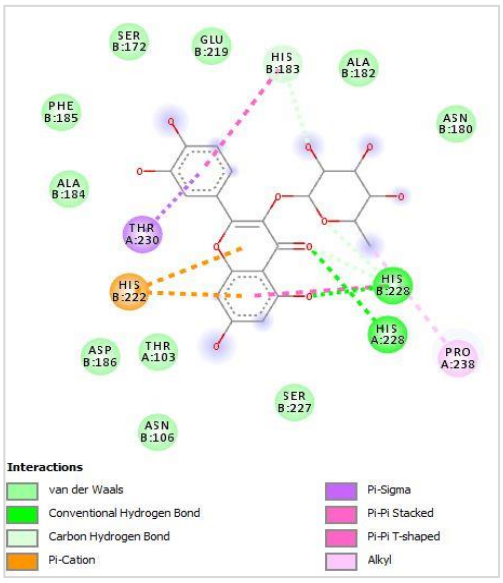
(e)



(f)



(g)



(h)

Figure 6: 2D interaction diagram showing the interacting residues of the hit molecules with the receptor collagenase: (a) abiesin, b) beta-Copaene, (c) friedelin, (d) flavanomarein, (e) Hesperidin, (f) kaempferol-7-rhamnoside, (g) quercitrin, (h) taraxerol

Figure 6 reveals the binding pockets of the hit molecules with the receptor collagenase. It is observed that the phytochemicals abiesin, beta-Copaene, friedelin, flavanomarein, kaempferol-7-rhamnoside, quercitrin, and taraxerol share some identical interacting residues with the standard skin lightening agent hesperidin. This elucidates similar mechanism of action of the highlighted phytochemicals on the three enzymes tyrosinase, elastase and collagenase when compared with the standard compound hesperidin.

4.4 Evaluation in Relation to Common Skin Lightening Agents

The outcomes of molecular docking can be contrasted with those of well-known skin-lightening products, both natural and artificial. By considering the ligands' binding affinities to those of known skin-lightening agents, the comparison of their values aids in determining the effectiveness and potential of the compounds. It sheds information on the uniqueness, superiority, and possibility for use as substitutes for traditional skin lightening agents.

The intrinsic limitations of molecular docking, such as its reliance on structural data and simulation assumptions, may be one source of restrictions. Future efforts might include experimental confirmation of the prioritised ligands, more optimisation using computational methods, or in vivo tests to assess safety and effectiveness.

5. CONCLUSION

In molecular biology and drug discovery, the capacity to anticipate the binding conformation of ligands within receptors is of utmost relevance. The computational method known as molecular docking is essential to this procedure since it is capable of making precise predictions about ligand-receptor interactions. The objective of this thesis is to enhance molecular docking algorithms, and explore their possible applications. For lighter skin appearance, skin whitening products are available commercially - Melasma and Post-inflammatory hyperpigmentation are the major disorder of this. These all are treated by whitening agents which acts as various levels of melanin production in the skin. The enzyme tyrosinase plays a major role in this known as competitive inhibitors of tyrosinase (the key enzyme in melanogenesis). In this study we elucidated how natural skin lightening agents may decrease the pigmentation in skin and highlighted the potential phytochemicals that can act as multi-targeted inhibitors of tyrosinase, collagenase and elastase.

References

1. Chuong, C.M., Nickoloff, B.J., Elias, P.M., Goldsmith, L.A., Macher, E., Maderson, P.A., Sundberg, J.P., Tagami, H., Plonka, P.M., Thestrup-Pederson, K. and Bernard, B.A., 2002.

What is the'true'function of skin?. *Experimental dermatology*, *11*(2), pp.159-187.

2. Feng, X., Li, G.Y., Ramier, A., Eltony, A.M. and Yun, S.H., 2022. In vivo stiffness measurement of epidermis, dermis, and hypodermis using broadband Rayleigh-wave optical coherence elastography. *Acta Biomaterialia*, *146*, pp.295-305.

3. Kanitakis, J., 2002. Anatomy, histology and immunohistochemistry of normal human skin. *European journal of dermatology*, *12*(4), pp.390-401.

4. Yousef, H., Alhajj, M. and Sharma, S., 2017. Anatomy, skin (integument), epidermis.

5. Mahil, S.K., Twelves, S., Farkas, K., Setta-Kaffetzi, N., Burden, A.D., Gach, J.E., Irvine, A.D., Képíró, L., Mockenhaupt, M., Oon, H.H. and Pinner, J., 2016. AP1S3 mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production. *Journal of Investigative Dermatology*, *136*(11), pp.2251-2259.

6. Homma, T., Kageyama, S., Nishikawa, A. and Nagata, K., 2018. Melanosome degradation in epidermal keratinocytes related to lysosomal protease cathepsin V. *Biochemical and biophysical research communications*, *500*(2), pp.339-343.

7. Solano, F., 2020. Photoprotection and skin pigmentation: Melanin-related molecules and some other new agents obtained from natural sources. *Molecules*, *25*(7), p.1537.

8. Kim, H.J., Kim, I.S., Dong, Y., Lee, I.S., Kim, J.S., Kim, J.S., Woo, J.T. and Cha, B.Y., 2015. Melanogenesis-inducing effect of cirsimaritin through increases in microphthalmia-associated transcription factor and tyrosinase expression. *International journal of molecular sciences*, *16*(4), pp.8772-8788.

9. Falcao, B., Vishwakarma, J., Jadav, H. and Vavilala, S.L., 2020. In Vitro Evaluation of The Antioxidant and Anti-Skin Aging Properties of Green Algal Sulfated Polysaccharides. *Archives of Microbiology & Immunology*, *4*(2), pp.75-90.

10. Rathee, P., Kumar, S., Kumar, D., Kumari, B. and Yadav, S.S., 2021. Skin hyperpigmentation and its treatment with herbs: An alternative method. *Future Journal of Pharmaceutical Sciences*, *7*, pp.1-14.

11. Favas, R., Morone, J., Martins, R., Vasconcelos, V. and Lopes, G., 2021. Cyanobacteria and microalgae bioactive compounds in skin-ageing: Potential to restore extracellular matrix filling and overcome hyperpigmentation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *36*(1), pp.1829-1838.

12. Salem, M.A., Radwan, R.A., Mostafa, E.S., Alseekh, S., Fernie, A.R. and Ezzat, S.M., 2020. Using an UPLC/MS-based untargeted metabolomics approach for assessing the antioxidant capacity and anti-aging potential of selected herbs. *RSC advances*, *10*(52), pp.31511-31524.

13. Bharadvaja, N., Gautam, S. and Singh, H., 2023. Natural polyphenols: a promising bioactive compounds for skin care and cosmetics. *Molecular Biology Reports*, *50*(2), pp.1817-1828.

14. Doughari, J.H., 2012. *Phytochemicals: extraction methods, basic structures and mode of action as potential chemotherapeutic agents* (pp. 1-33). Rijeka, Croatia: INTECH Open Access Publisher.

15. D'Mello, S.A., Finlay, G.J., Baguley, B.C. and Askarian-Amiri, M.E., 2016. Signaling pathways in melanogenesis. *International journal of molecular sciences*, *17*(7), p.1144.

16. Hossain, A., Rahman, M.E., Rahman, M.S., Nasirujjaman, K., Matin, M.N., Faruqe, M.O. and Rabbee, M.F., 2023. Identification of medicinal plant-based phytochemicals as a potential inhibitor for SARS-CoV-2 main protease (Mpro) using molecular docking and deep learning methods. *Computers in Biology and Medicine*, *157*, p.106785.

17. Plewczynski, D., Łaźniewski, M., Augustyniak, R. and Ginalski, K., 2011. Can we trust docking results? Evaluation of seven commonly used programs on PDBbind database. *Journal of computational chemistry*, *32*(4), pp.742-755.

18. Khamis, M.A., Gomaa, W. and Ahmed, W.F., 2015. Machine learning in computational docking. *Artificial intelligence in medicine*, *63*(3), pp.135-152.

19. Olsson, T.S., Williams, M.A., Pitt, W.R. and Ladbury, J.E., 2008. The thermodynamics of protein–ligand interaction and solvation: insights for ligand design. *Journal of molecular biology*, *384*(4), pp.1002-1017.

20. Pfeffer P, Gohlke H. DrugScoreRNA Knowledge-Based Scoring Function To Predict RNA− Ligand Interactions. Journal of chemical information and modeling. 2007 Sep 24;47(5):1868-76.

21. Shen, C., Ding, J., Wang, Z., Cao, D., Ding, X. and Hou, T., 2020. From machine learning to deep learning: Advances in scoring functions for protein–ligand docking. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, *10*(1), p.e1429.

22. Wang, Z., Sun, H., Yao, X., Li, D., Xu, L., Li, Y., Tian, S. and Hou, T., 2016.

Comprehensive evaluation of ten docking programs on a diverse set of protein–ligand complexes: the prediction accuracy of sampling power and scoring power. *Physical Chemistry Chemical Physics*, *18*(18), pp.12964-12975.

23. Pillaiyar, T., Manickam, M. and Namasivayam, V., 2017. Skin whitening agents: Medicinal chemistry perspective of tyrosinase inhibitors. *Journal of enzyme inhibition and medicinal chemistry*, *32*(1), pp.403-425.

24. Chen, W.C., Tseng, T.S., Hsiao, N.W., Lin, Y.L., Wen, Z.H., Tsai, C.C., Lee, Y.C., Lin, H.H. and Tsai, K.C., 2015. Discovery of highly potent tyrosinase inhibitor, T1, with significant anti-melanogenesis ability by zebrafish in vivo assay and computational molecular modeling. *Scientific reports*, *5*(1), p.7995.

25. Morris, G.M. and Lim-Wilby, M., 2008. Molecular docking. *Molecular modeling of proteins*, pp.365-382.

26. Fan, J., Fu, A. and Zhang, L., 2019. Progress in molecular docking. *Quantitative Biology*, *7*, pp.83-89.

27. Agarwal, S. and Mehrotra, R.J.J.C., 2016. An overview of molecular docking. *JSM chem*, *4*(2), pp.1024-1028.

28. Gentilucci, L., Tolomelli, A., De Marco, R. and Artali, R., 2012. Molecular docking of opiates and opioid peptides, a tool for the design of selective agonists and antagonists, and for the investigation of atypical ligand-receptor interactions. *Current medicinal chemistry*, *19*(11), pp.1587-1601.

29. Wang, M., Hou, S., Wei, Y., Li, D. and Lin, J., 2021. Discovery of novel dual adenosine A1/A2A receptor antagonists using deep learning, pharmacophore modeling and molecular docking. *PLoS Computational Biology*, *17*(3), p.e1008821.

30. Xi, X., Higgins, D., Zechner, K. and Williamson, D., 2012. A comparison of two scoring methods for an automated speech scoring system. *Language Testing*, *29*(3), pp.371-394.

31. Morris, C.J. and Corte, D.D., 2021. Using molecular docking and molecular dynamics to investigate protein-ligand interactions. *Modern Physics Letters B*, *35*(08), p.2130002.

32. Hussein, A.N., Rasheed, O.A., Mahdi, M.F. and Raauf, A.M.R., 2019. Molecular Docking Studies for Design, Synthesis and Characterization of New Imatinib Analogues. *Pharm Anal Acta*, *10*, p.616.

33. Kumalo, H.M., Bhakat, S. and Soliman, M.E., 2015. Theory and applications of covalent docking in drug discovery: merits and pitfalls. *Molecules*, *20*(2), pp.1984-2000.

34. Bonvin, A.M., 2006. Flexible protein–protein docking. *Current opinion in structural biology*, *16*(2), pp.194-200.

35. Majumder, R. and Mandal, M., 2022. Screening of plant-based natural compounds as a potential COVID-19 main protease inhibitor: an in silico docking and molecular dynamics simulation approach. *Journal of Biomolecular Structure and Dynamics*, *40*(2), pp.696-711.

36. Khamis, M.A., Gomaa, W. and Ahmed, W.F., 2015. Machine learning in computational docking. *Artificial intelligence in medicine*, *63*(3), pp.135-152.

SUPPLEMENTARY MATERIAL

Table S1: Binding affinity of the phytochemicals with the 3 chosen receptors

Compound Name	Tyrosinase	Elastase	Collagenase
Hesperidin (standard skin-lightening agent)	-9.9	-8.4	-11.2
D-Galacturonic Acid	-6.7	-6.1	-6.6
Flavylium	-8.8	-6.8	-8.1
beta-Farnesene	-5	-5.5	-5.5
Famesyl acetate	-6.4	-5.3	-6.9
Ctral	-6	-4.7	-5.4
alpha-Famesene	-6.7	-5.6	-5.8
Nonanoic acid	-5.5	-4.6	-4.7
1-Tetradecene	-5.3	-4.1	-4.6
Ambrettolide	-7.3	-5.7	-7
4-Methyl-2,3-dihydrofuran	-4.2	-4	-4.3
Dihydrofamesol	-5.5	-5.3	-5.5
Tetradecadienyl acetate	-4.6	-4.8	-5.6
Triterpenoids	-9	-7	-9.5
Tetradecenyl acetate	-5.5	-4.7	-5
Hexyl propionate	-5.1	-4.8	-5.3
Pindrolactone	-10	-7.6	-10
Hesperidin	-9.9	-8.4	-11.2
(-)-Bornyl acetate	-5.9	-5	-6.4
(-)-Limonene	-6.1	-5.5	-5.4
Querctrin	-8.5	-8.2	-9.5
Taraxerol	-10.9	-8	-10.8
Friedeln	-9	-8	-8.6
D-Galactose	-5.9	-7.7	-6
beta-Amyrin	-9.5	-7.3	-10.5
Flavanomarein	-9.2	-8.2	-10.1
Okanin	-9.2	-6.9	-8.5
Abiesin	-10.2	-8.7	-11.5
3-Carene	-6.1	-5.9	-6.1
alpha-Pinene	-5.6	-4.7	-5.8
Carvone	-6.7	-4.9	-6.1
beta-Pinene	-6.1	-5.2	-5.7
Epigallocatechin gallate	-8.9	-7.8	-10.5
Betuin	-9	-7	-9.4
L-Rhamnose	-6.6	-5.6	-5.8
alpha-Amyrin	-9.2	-7.6	-10.2
Bauerenol	-9.8	-7.6	-10
Lupeol	-8.3	-7.2	-9.8
Ehretinine	-7.5	-5.7	-7.4
Allantoin	-6.5	-5.6	-6.4

Bronianone	-8	-6.7	-10.3
Sanguinarine	-9.4	-7.4	-9.9
Protopine	-9.6	-7.8	-10.6
Oxyhydrastinine	-7.6	-6.2	-6.9
Cryptopine	-8.7	-7	-8.4
Myristic acid	-5	-4	-5.1
Corydine	-7.3	-6.2	-8.7
Coptisine	-8.8	-7.7	-10.3
Cherubine	-9.5	-7.5	-9.7
Chelerythrine	-8.1	-6.8	-8.9
6-([1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6H-furo(3,4-g][1,3]benzodioxol-8-one	-10.8	-7.5	-10.4
Kaempferol-7-rhamnoside	-10.1	-8.8	-10.6
Cucurbitacin I	-8.5	-7.6	-9.7
Cucurbitacin E	-9.4	-6.8	-9.2
3-Methylthiopropylamine	-3.2	-3.1	-3.3
Neophytadiene	-6.5	-4	-5.8
Glycerides, C14-18	-4.7	-4.8	-4.3
beta-Bisabolene	-7.3	-5.8	-6.5
0-Cymene	-6.5	-5.3	-5.9
6,10,14-Trimethylpentadecan-2-one	-6.3	-4.4	-5.2
Dillapiol	-5.9	-5	-6.2
Carvacrol	-6.6	-5.3	-6.4
Elemicin	-6.5	-4.9	-5.7
1-Heptadecanol	-9.6	-3.9	-4.8
2-Hexanone	-4.3	-4.1	-4.6
Heptacosane	-7.2	-3.9	-6.1
Pinocarvone	-6.4	-4.6	-5.8
Malvalic acid	-5.5	-4.4	-5.8
Pipertenone	-7	-5.5	-6
Myristicn	-5.5	-5	-6.2
Eugenol	-6.6	-5	-6.1
Bicyclogermacrene	-6.7	-5.3	-7.2
(25,4R)-p-Mentha-1(7), 8-dien-2-ol	-6.9	-6.2	-6.2
beta-Copaene	-10	-9.1	-8.6
(Z)-alpha-Bisabolene	-6.4	-5.1	-6.6
(E)-alpha-bisabolene	-6.8	-6.1	-6.6
Ent-13-epi-manoyl oxide	-7.2	-6.2	-8.3
(R)-4-Isopropylcyclohex-2-enone	-6.1	-4.2	-6
gamma-Terpinene	-6.5	-5.7	-5.5
Geranyl formate	-6.2	-5.3	-5.4
Neomenthyl acetate	-6.5	-4.9	-6
p-Mentha-1,8-dien-4-ol	-6.5	-5.4	-5.8
Citronellyl formate	-6.2	-4.6	-5.4
Myrtenal	-5.1	-4.5	-5.9
Pentadecanal	-4.4	-4	-5.2

Methyl linoleate	-6.5	-4.5	-5.6
Thiamine	-6.4	-5.4	-7.2
Stearic acid	-6.4	-5.5	-6.1
Methyl oleate	-7	-5.4	-6.1
Undecanal	-5.3	-4.1	-4.7
Ethyl stearate	-6.4	-5.5	-6.1
Palmitic acid	-4.1	-4.6	-5.3
beta-Cubebene	-6.9	-6.3	-7.5
1,4-Dimethoxybenzene	-5.1	-4.9	-4.9
Ethyl octanoate	-4.9	-4	-5.1
Vitamin E	-5.3	-6.2	-8
Phenethyl 2-methylbutyrate	-6.3	-5.7	-5.9
Riboflavin	-7.3	-7.9	-9.2
Sterculic acid	-7	-4.2	-5.3
Ethyl palmitate	-6.8	-5.2	-6
Citronellyl propionate	-6.4	-4.5	-5.6
Ethyl tetradecanoate	-5.9	-3.7	-5.5
Ethyl linoleate	-6.5	-5.5	-6.3
Phenethyl isobutyrate	-6.9	-5.5	-6
2-Dodecanone	-4.5	-4.1	-4.9
(27,6E)-Famesal	-5.4	-4.9	-6.1
Germacra-1(10),5-dien-4-ol	-6.6	-5.6	-7.3
Neryl acetate	-5.8	-5.4	-5.5
2-Methoxy-4-vinylphenol	-6.3	-6.2	-5.8
9-Hexadecenoic acid	-5.8	-4.9	-5.9
Palmitoleic acid	-4.4	-3.8	-5.4
Vernolic acid	-6.4	-4.5	-5.8
Humulene	-6.4	-5.1	-6.7
Oleic acid	-4.7	-4.8	-5.4
Undecyl acetate	-5.2	-4.2	-4.8
Linolenic acid	-5.3	-4.7	-5.4
Pentyl 3-methylbutanoate	-4.9	-4.4	-5
beta-Caryophyllene	-7.1	-5.5	-6.8
Limonene	-6.3	-4.6	-5.5
D-Glucuronic Acid	-6.9	-5.9	-6.5
Linoleic acid	-5	-4.6	-5.5
alpha-Copaene	-6.5	-5.6	-7.4
Butyl decanoate	-5.2	-4.3	-5.2
Butyl nonanoate	-5.9	-4.2	-5
Pentyl octanoate	-5.7	-3.6	-4.9
2-Methylbutyl heptanoate	-4.5	-4.1	-5.1
2-Methylbutyl nonanoate	-5.9	-3.9	-5.6
2-Methylbutyl octanoate	-4.7	-4	-5.7
Citronellyl isovalerate	-6	-4.9	-5.7
Decyl propionate	-5.4	-4.2	-5.2
Quercetin	-7.8	-7.4	-9.2

Dodecyl propionate	-4.8	-4.6	-5.1
Isoamyl phenylacetate	-6.4	-4.3	-5.7
Isobutyl nonanoate	-5.5	-4.7	-5.3
Nonyl octanoate	-5.8	-4.3	-5.6
Octyl valerate	-5.7	-4.4	-5.2
Propyl decanoate	-5.6	-4	-5.1
2-Dodecenyl acetate	-4.7	-4.5	-5.2
2-Phenylethyl valerate	-6.6	-5.2	-5.5
alpha-Terpinyl acetate	-7	-5.7	-6.2
beta-Sitosterol	-8.4	-6.2	-9.1
Nicotinic acid	-5.4	-5.1	-5.9
Epoxyoleic acid	-5.9	-4.6	-5.8
Myricetin	-9.1	-7.4	-8.9
1-Triacontanol	-7.1	-4.6	-5.6
Tetracosane	-6.9	-5.6	-5.5
beta-sitosterol-3-0-beta-d-glucoside	-9.2	-7.2	-10.4
Ambrettolic acid	-3.9	-4.4	-6
Cholesterol	-9.1	-6.3	-8.8
Cyanidin	-8.5	-7.1	-8.9
Farnesol	-5.1	-5.1	-6.2
Campesterol	-8.7	-6.5	-9.2
Oxalic acid	-4.3	-4.1	-4.5
Ergosterol	-9.1	-6.8	-9.5
Stigmasterol	-8.6	-6.7	-9.6
beta-D-Glucose	-6.5	-6	-5.7
beta-Sitosterol-beta-D-glucoside	-8	-7	-8.9
Daucosterol	-8.5	-7.1	-9.1
Geranylacetone	-5.7	-5.1	-5.9
Isoamyl acetate	-5.1	-4.6	-5
Cephalin	-6.3	-5.4	-6.2
Octyl butyrate	-5.7	-4.3	-4.9
Hexanal	-4.3	-3.9	-4.4
D-Glucose	-6.3	-6	-5.8
1-Decanol	-5.1	-4.1	-4.5
1-Dodecene	-4.7	-4.2	-4.4
Decyl acetate	-5.8	-4.3	-5.2
Dodecyl acetate	-4	-3.8	-5.2
1-Octanol	-4.6	-4.2	-4.6
Spathulenol	-7.1	-5.5	-7.3
Butyl acetate	-4.6	-4.2	-4.7
2-Decanone	-5.2	-4.2	-3.8
Methacrolein	-3.7	-3.4	-3.8
(27,6E)-Farnesol	-7.3	-5.5	-6.3

Table S2: ADMET properties of the compounds-

Phytochemical Name	GI Absorption	Solubility	Lipinski	BBB permeant
Flavylium	High	7.03e-02 mg/ml ; 3.39e-04 mol/l	Yes	Yes
Thiamine	High	1.28e+00 mg/ml ; 4.83e-03 mol/l	Yes	No
Riboflavin	Low	1.85e+01 mg/ml ; 4.93e-02 mol/l	Yes	No
D-Glucose	Low	2.55e+03 mg/ml ; 1.41e+01 mol/l	Yes	No
D-Galacturonic Acid	Low	6.09e+02 mg/ml ; 3.14e+00 mol/l	Yes	No
Triterpenoids	High	3.08e-03 mg/ml ; 6.51e-06 mol/l	Yes	No
D-Galactose	Low	2.55e+03 mg/ml ; 1.41e+01 mol/l	Yes	No
L-Rhamnose	High	4.72e+02 mg/ml ; 2.88e+00 mol/l	Yes	No
Myristic acid	High	1.11e-02 mg/ml ; 4.86e-05 mol/l	Yes	Yes
Glycerides, C14-18	High	7.26e-02 mg/ml ; 2.52e-04 mol/l	Yes	Yes
Malvalic acid	High	7.71e-03 mg/ml ; 2.75e-05 mol/l	Yes	Yes
Pentadecanal	High	7.38e-03 mg/ml ; 3.26e-05 mol/l	Yes	Yes
Methyl linoleate	High	3.14e-03 mg/ml ; 1.07e-05 mol/l	Yes	No
Stearic acid	High	5.26e-04 mg/ml ; 1.85e-06 mol/l	Yes	No
Methyl oleate	High	1.43e-03 mg/ml ; 4.83e-06 mol/l	Yes	No
Undecanal	High	1.57e-01 mg/ml ; 9.20e-04 mol/l	Yes	Yes
Ethyl stearate	Low	1.82e-04 mg/ml ; 5.83e-07 mol/l	Yes	No
Palmitic acid	High	2.43e-03 mg/ml ; 9.49e-06 mol/l	Yes	Yes
beta-Cubebene	Low	2.00e-02 mg/ml ; 9.81e-05 mol/l	Yes	Yes
Ethyl octanoate	High	4.23e-01 mg/ml ; 2.45e-03 mol/l	Yes	Yes
Sterculic acid	High	4.78e-03 mg/ml ; 1.62e-05 mol/l	Yes	No
Ethyl tetradecanoate	High	4.22e-03 mg/ml ; 1.65e-05 mol/l	Yes	Yes
2-Dodecanone	High	9.12e-02 mg/ml ; 4.95e-04 mol/l	Yes	Yes
Neryl acetate	High	1.22e-01 mg/ml ; 6.22e-04 mol/l	Yes	Yes
Palmitoleic acid	High	5.02e-03 mg/ml ; 1.97e-05 mol/l	Yes; 0 violation	Yes
Humulene	Low	2.17e-02 mg/ml ; 1.06e-04 mol/l	Yes; 1 violation: MLOGP>4.15	No
Oleic acid	High	1.09e-03 mg/ml ; 3.85e-06 mol/l	Yes; 1 violation: MLOGP>4.15	No
Linolenic acid	High	4.64e-03 mg/ml ; 1.67e-05 mol/l	Yes; 1 violation: MLOGP>4.15	Yes
beta-Caryophyllene	Low	2.78e-02 mg/ml ; 1.36e-04 mol/l	Yes; 1 violation: MLOGP>4.15	No

Limonene	Low	4.33e-02 mg/ml ; 3.18e-04 mol/l	Yes; 0 violation	Yes
alpha-Copaene	Low	2.84e-02 mg/ml ; 1.39e-04 mol/l	Yes; 1 violation: MLOGP>4.15	Yes
Butyl decanoate	High	2.98e-02 mg/ml ; 1.30e-04 mol/l	Yes; 0 violation	Yes
Butyl nonanoate	High	6.42e-02 mg/ml ; 2.99e-04 mol/l	Yes; 0 violation	Yes
Pentyl octanoate	High	6.42e-02 mg/ml ; 2.99e-04 mol/l	Yes; 0 violation	Yes
2-Methylbutyl heptanoate	High	2.34e-01 mg/ml ; 1.17e-03 mol/l	Yes; 0 violation	Yes
Citronellyl isovalerate	High	2.99e-02 mg/ml ; 1.24e-04 mol/l	Yes; 0 violation	Yes
Decyl propionate	High	5.72e-02 mg/ml ; 2.67e-04 mol/l	Yes; 0 violation	Yes
Dodecyl propionate	High	1.23e-02 mg/ml ; 5.05e-05 mol/l	Yes; 0 violation	Yes
Isoamyl phenylacetate	High	1.07e-01 mg/ml ; 5.16e-04 mol/l	Yes; 0 violation	Yes
Isobutyl nonanoate	High	4.37e-02 mg/ml ; 2.04e-04 mol/l	Yes; 0 violation	Yes
Propyl decanoate	High	5.24e-02 mg/ml ; 2.44e-04 mol/l	Yes; 0 violation	Yes
alpha-Terpinyl acetate	High	8.69e-02 mg/ml ; 4.43e-04 mol/l	Yes; 0 violation	Yes
beta-Sitosterol	Low	5.23e-06 mg/ml ; 1.26e-08 mol/l	Yes; 1 violation: MLOGP>4.15	No
Epoxyoleic acid	High	8.06e-03 mg/ml ; 2.70e-05 mol/l	Yes; 0 violation	Yes
Myricetin	Low	3.14e-01 mg/ml ; 9.88e-04 mol/l	Yes; 1 violation: NHorOH>5	No
Ambrettolic acid	High	4.96e-02 mg/ml ; 1.84e-04 mol/l	Yes; 0 violation	Yes
Cyanidin	High	7.15e-01 mg/ml ; 2.49e-03 mol/l	Yes; 0 violation	No
Farnesol	High	1.50e-02 mg/ml ; 6.74e-05 mol/l	Yes; 0 violation	Yes
Campesterol	Low	1.16e-05 mg/ml ; 2.90e-08 mol/l	Yes; 1 violation: MLOGP>4.15	No
Ergosterol	Low	7.63e-05 mg/ml ; 1.92e-07 mol/l	Yes; 1 violation: MLOGP>4.15	No
Stigmasterol	Low	1.43e-05 mg/ml ; 3.46e-08 mol/l	Yes; 1 violation: MLOGP>4.16	No
beta-D-Glucose	Low	2.55e+03 mg/ml ; 1.41e+01 mol/l	Yes; 0 violation	No
beta-Sitosterol-beta-D-glucoside	Low	1.15e-05 mg/ml ; 2.00e-08 mol/l	Yes; 1 violation: MW>500	No
Daucosterol	Low	1.15e-05 mg/ml ; 2.00e-08 mol/l	Yes; 1 violation: MW>501	No
Geranylacetone	Low	1.15e-05 mg/ml ; 2.00e-08 mol/l	Yes	No
Isoamyl acetate	High	2.04e-01 mg/ml ; 1.05e-03 mol/l	Yes	Yes
Cephalin	High	2.06e+00 mg/ml ; 1.58e-02 mol/l	Yes	Yes
Octyl butyrate	Low	1.87e+04 mg/ml ; 6.26e+01 mol/l	Yes	No
Hexanal	High	1.40e-01 mg/ml ; 6.98e-04 mol/l	Yes	Yes
Decyl acetate	Low	4.63e-03 mg/ml ; 2.75e-05 mol/l	Yes	No
Dodecyl acetate	High	1.11e-01 mg/ml ; 5.53e-04 mol/l	Yes	Yes
Spathulenol	High	9.40e-01 mg/ml ; 7.22e-03 mol/l	Yes	Yes

Butyl acetate	High	1.51e-01 mg/ml ; 6.83e-04 mol/l	Yes	Yes
Methacrolein	High	3.14e-01 mg/ml ; 2.01e-03 mol/l	Yes	Yes
beta-Farnesene	High	1.50e-02 mg/ml ; 6.74e-05 mol/l	Yes	Yes
Tetradecadienyl acetate	High	1.03e-02 mg/ml ; 4.59e-05 mol/l	Yes	Yes
Tetradecenyl acetate	High	7.11e-03 mg/ml ; 2.82e-05 mol/l	Yes	Yes
Hexyl propionate	High	2.04e-02 mg/ml ; 9.01e-05 mol/l	Yes	Yes
Hesperidin	Low	7.59e-05 mg/ml ; 1.68e-07 mol/l	Yes	No
(-)-Bornyl acetate	High	3.07e-02 mg/ml ; 1.14e-04 mol/l	Yes	No
(-)-Limonene	Low	4.90e-02 mg/ml ; 3.60e-04 mol/l	Yes	Yes
Taraxerol	Low	4.24e-02 mg/ml ; 3.11e-04 mol/l	Yes	Yes
beta-Amyrin	Low	1.93e-06 mg/ml ; 4.52e-09 mol/l	Yes	No
Flavanomarein	Low	9.34e-07 mg/ml ; 2.19e-09 mol/l	Yes	No
Okanin	Low	2.69e-05 mg/ml ; 5.89e-08 mol/l	Yes	No
Abiesin	Low	2.40e-06 mg/ml ; 5.62e-09 mol/l	Yes	No
alpha-Pinene	Low	3.96e-05 mg/ml ; 6.82e-08 mol/l	Yes	No
Carvone	High	4.26e+00 mg/ml ; 1.30e-02 mol/l	Yes	No
beta-Pinene	Low	4.90e-02 mg/ml ; 3.60e-04 mol/l	Yes	Yes
Epigallocatechin gallate	Low	4.24e-02 mg/ml ; 3.11e-04 mol/l	Yes	Yes
alpha-Amyrin	Low	6.74e-02 mg/ml ; 4.95e-04 mol/l	Yes	Yes
Bauerenol	Low	9.48e-06 mg/ml ; 2.14e-08 mol/l	Yes	No
Lupeol	Low	2.94e-06 mg/ml ; 6.89e-09 mol/l	Yes	No
Ehretinine	Low	8.87e-06 mg/ml ; 1.94e-08 mol/l	Yes	No
Allantoin	Low	2.94e-06 mg/ml ; 6.89e-09 mol/l	Yes	No
Bronianone	Low	9.83e-07 mg/ml ; 2.30e-09 mol/l	Yes	No
Sanguinarine	Low	5.23e-06 mg/ml ; 1.26e-08 mol/l	Yes	No
Protopine	High	1.16e-01 mg/ml ; 4.21e-04 mol/l	Yes	Yes
Oxyhydrastinine	Low	7.55e+02 mg/ml ; 4.77e+00 mol/l	Yes	No
Cryptopine	High	1.93e-03 mg/ml ; 5.80e-06 mol/l	Yes	Yes
Corydine	High	2.62e-02 mg/ml ; 7.41e-05 mol/l	Yes	Yes
Coptisine	High	1.35e+00 mg/ml ; 6.56e-03 mol/l	Yes	Yes
Chelerythrine	High	6.31e-02 mg/ml ; 1.85e-04 mol/l	Yes	Yes
Kaempferol-7-rhamnoside	High	9.72e-03 mg/ml ; 3.03e-05 mol/l	Yes	Yes
Cucurbitacin I	High	1.82e-03 mg/ml ; 5.03e-06 mol/l	Yes	Yes
Cucurbitacin E	High	1.89e-03 mg/ml ; 5.42e-06 mol/l	Yes	Yes
Neophytadiene	Low	3.63e-01 mg/ml ; 8.39e-04 mol/l	Yes	No
beta-Bisabolene	Low	1.80e-02 mg/ml ; 3.51e-05 mol/l	Yes	No

Dillapiol	Low	4.74e-05 mg/ml ; 1.70e-07 mol/l	Yes	No
Carvacrol	Low	2.61e-03 mg/ml ; 1.28e-05 mol/l	Yes	No
Elemicin	Low	2.08e-02 mg/ml ; 1.55e-04 mol/l	Yes	Yes
Pinocarvone	High	4.24e-01 mg/ml ; 2.04e-03 mol/l	Yes	Yes
Eugenol	Low	9.84e-08 mg/ml ; 2.58e-10 mol/l	Yes	No
Bicyclogermacrene	High	1.11e+00 mg/ml ; 7.38e-03 mol/l	Yes	Yes
beta-Copaene	High	1.91e-01 mg/ml ; 9.93e-04 mol/l	Yes	Yes
(Z)-alpha-Bisabolene	High	5.69e-01 mg/ml ; 3.47e-03 mol/l	Yes	Yes
(E)-alpha-bisabolene	Low	3.94e-02 mg/ml ; 1.93e-04 mol/l	Yes	No
Ent-13-epi-manoyl oxide	High	1.04e+00 mg/ml ; 6.81e-03 mol/l	Yes	Yes
(R)-4-Isopropylcyclohex-2-enone	Low	2.00e-02 mg/ml ; 9.81e-05 mol/l	Yes	Yes
gamma-Terpinene	Low	2.48e-03 mg/ml ; 1.21e-05 mol/l	Yes	No
Geranyl formate	Low	2.48e-03 mg/ml ; 1.21e-05 mol/l	Yes	No
Neomenthyl acetate	Low	1.42e-03 mg/ml ; 4.89e-06 mol/l	Yes	No
p-Mentha-1,8-dien-4-ol	High	1.73e+00 mg/ml ; 1.25e-02 mol/l	Yes	Yes
Citronellyl formate	Low	4.79e-02 mg/ml ; 3.52e-04 mol/l	Yes	Yes
Myrtenal	High	1.18e-01 mg/ml ; 6.48e-04 mol/l	Yes	Yes
Farmesyl acetate	High	6.61e-03 mg/ml ; 2.50e-05 mol/l	Yes	yes
Citral	High	5.67e-01 mg/ml ; 3.73e-03 mol/l	Yes	Yes
alpha-Famesene	low	5.54e-03 mg/ml ; 2.71e-05 mol/l	Yes	No
Nonanoic acid	High	4.85e-01 mg/ml ; 3.06e-03 mol/l	Yes	Yes
1-Tetradecene	low	1.01e-03 mg/ml ; 5.13e-06 mol/l	Yes	No
Ambrettolide	High	3.31e-03 mg/ml ; 1.31e-05 mol/l	Yes	Yes
4-Methyl-2,3-dihydrofuran	High	1.29e+01 mg/ml ; 1.53e-01 mol/l	Yes	Yes
Dihydrofamesol	High	1.18e-02 mg/ml ; 4.98e-05 mol/l	Yes	Yes
Pindrolactone	low	7.59e-05 mg/ml ; 1.68e-07 mol/l	Yes	no
quercetin	high	2.11e-01 mg/ml ; 6.98e-04 mol/l	Yes	no
Friedeln	low	9.34e-07 mg/ml ; 2.19e-09 mol/l	Yes	no
3-Carene	low	4.90e-02 mg/ml ; 3.60e-04 mol/l	Yes	yes
betaine	low	5.20e+01 mg/ml ; 4.44e-01 mol/l	Yes	no
Chelirubine	high	1.82e-03 mg/ml ; 5.03e-06 mol/l	Yes	yes
6-([1,3]dioxolo[4,5-g]isoquinolin-5-yl)-6H-furo(3,4-g][1,3]benzodioxol-8-one	high	1.26e-02 mg/ml ; 4.98e-05 mol/l	Yes	yes

3-Methylthiopropylamine	high	3.51e+01 mg/ml ; 3.33e-01 mol/l	Yes	yes
o-Cymene	low	2.08e-02 mg/ml ; 1.55e-04 mol/l	Yes	yes
6,10,14-Trimethylpentadecan-2-one	high	2.18e-03 mg/ml ; 8.11e-06 mol/l	Yes	no
1-Heptadecanol	high	1.41e-03 mg/ml ; 5.50e-06 mol/l	Yes	no
2-Hexanone	high	7.38e+00 mg/ml ; 7.37e-02 mol/l	Yes	yes
Heptacosane	high	9.84e-08 mg/ml ; 2.58e-10 mol/l	Yes	
Pipertenone	high	9.87e-01 mg/ml ; 6.57e-03 mol/l	Yes	yes
Myricetin	low	3.14e-01 mg/ml ; 9.88e-04 mol/l	Yes	no
(25,4R)-p-Mentha-1(7),8-dien-2-ol	high	1.04e+00 mg/ml ; 6.81e-03 mol/l	Yes	yes
1,4-Dimethoxybenzene	high	7.02e-01 mg/ml ; 5.08e-03 mol/l	Yes	yes
Vitamin E	low	1.08e-06 mg/ml ; 2.50e-09 mol/l	Yes	no
Phenethyl 2-methylbutyrate	high	1.29e-01 mg/ml ; 6.24e-04 mol/l	Yes	yes
Ethyl palmitate	high	8.75e-04 mg/ml ; 3.07e-06 mol/l	Yes	yes
Citronellyl propionate	high	1.07e-01 mg/ml ; 5.02e-04 mol/l	Yes	yes
Ethyl linoleate	high	1.47e-03 mg/ml ; 4.78e-06 mol/l	Yes	yes
Phenethyl isobutyrate	high	1.45e-01 mg/ml ; 7.53e-04 mol/l	Yes	yes
Farnesol	high	1.50e-02 mg/ml ; 6.74e-05 mol/l	Yes	yes
2-Methoxy-4-vinylphenol	high	2.31e-01 mg/ml ; 1.54e-03 mol/l	Yes	yes
9-Hexadecenoic acid	high	5.02e-03 mg/ml ; 1.97e-05 mol/l	Yes	yes
Vernolic acid	high	1.62e-02 mg/ml ; 5.46e-05 mol/l	Yes	yes
Pentyl 3-methylbutanoate	high	6.21e-01 mg/ml ; 3.60e-03 mol/l	Yes	yes
D-Glucuronic Acid	low	6.09e+02 mg/ml ; 3.14e+00 mol/l	Yes	yes
Linoleic acid	high	2.49e-03 mg/ml ; 8.87e-06 mol/l	Yes	yes
2-Methylbutyl nonanoate	high	5.06e-02 mg/ml ; 2.21e-04 mol/l	Yes	yes
2-Methylbutyl octanoate	high	1.09e-01 mg/ml ; 5.09e-04 mol/l	Yes	yes
Quercetin	high	2.11e-01 mg/ml ; 6.98e-04 mol/l	Yes	yes
Nonyl octanoate	high	2.91e-03 mg/ml ; 1.08e-05 mol/l	Yes	yes
Octyl valerate	high	6.42e-02 mg/ml ; 2.99e-04 mol/l	Yes	yes
2-Dodecenyl acetate	high	3.54e-02 mg/ml ; 1.56e-04 mol/l	Yes	yes
2-Phenylethyl valerate	high	1.12e-01 mg/ml ; 5.43e-04 mol/l	Yes	yes
Nicotinic acid	high	6.81e+00 mg/ml ; 5.53e-02 mol/l	Yes	yes
1-Triacontanol	low	4.66e-08 mg/ml ; 1.06e-10 mol/l	Yes	no
Tetracosane	low	1.06e-06 mg/ml ; 3.13e-09 mol/l	Yes	no

beta-sitosterol-3-0-beta-d-glucoside	low	1.15e-05 mg/ml ; 2.00e-08 mol/l	Yes	no
Cholesterol	low	1.54e-05 mg/ml ; 3.97e-08 mol/l	Yes	no
Oxalic acid	high	6.02e+01 mg/ml ; 6.69e-01 mol/l	Yes	yes
1-Decanol	high	1.06e-01 mg/ml ; 6.72e-04 mol/l	Yes	yes
1-Dodecene	low	4.63e-03 mg/ml ; 2.75e-05 mol/l	Yes	no
1-Octanol	high	9.40e-01 mg/ml ; 7.22e-03 mol/l	Yes	yes
2-Decanone	high	3.14e-01 mg/ml ; 2.01e-03 mol/l	Yes	Yes
(27,6E)-Farnesol	high	1.50e-02 mg/ml ; 6.74e-05 mol/l	Yes	Yes
Cannabiscitrin	Low	5.93e-01 mg/ml ; 1.23e-03 mol/l	No	No
Acetoside	Low	8.36e-01 mg/ml ; 1.34e-03 mol/l	No	No
Jaceoside	Low	5.60e-02 mg/ml ; 1.14e-04 mol/l	No	No
Sophoraflavonoloside	Low	7.97e-01 mg/ml ; 1.31e-03 mol/l	No	No
Orientin	Low	9.00e-01 mg/ml ; 2.01e-03 mol/l	No	No
Isoquercitrin	Low	4.23e-01 mg/ml ; 9.10e-04 mol/l	No	No
Eruberin B	Low	8.03e-01 mg/ml ; 1.25e-03 mol/l	No	No
Eruberin C	Low	3.61e-01 mg/ml ; 5.51e-04 mol/l	No	No
Quercitrin	Low	2.08e-01 mg/ml ; 4.64e-04 mol/l	No	No
Aconitine	Low	2.63e-01 mg/ml ; 4.07e-04 mol/l	No	No
Veratrine	Low	1.28e-01 mg/ml ; 2.17e-04 mol/l	No	No
Nicotiflorin	Low	9.31e-03 mg/ml ; 1.57e-05 mol/l	No	No
Narcissin	Low	1.92e-01 mg/ml ; 3.07e-04 mol/l	No	No
Rutin	Low	3.08e-01 mg/ml ; 5.05e-04 mol/l	No	No
Meratin	Low	2.44e+00 mg/ml ; 3.89e-03 mol/l	No	No
Spiraeoside	Low	1.07e-01 mg/ml ; 2.29e-04 mol/l	No	No
Hyperoside	Low	4.23e-01 mg/ml ; 9.10e-04 mol/l	No	No
Quercetin 3-Sambubioside	Low	1.23e+00 mg/ml ; 2.06e-03 mol/l	No	No
Quercimeritrin	Low	4.23e-01 mg/ml ; 9.10e-04 mol/l	No	No
Cyanin	Low	1.35e+01 mg/ml ; 2.21e-02 mol/l	No	No
Cyanidin 3-sophoroside	Low	1.83e+00 mg/ml ; 2.99e-03 mol/l	No	No
Quercetin 3-diglucoside	Low	2.44e+00 mg/ml ; 3.89e-03 mol/l	No	No
Cyanin chloride	Low	2.74e+00 mg/ml ; 4.23e-03 mol/l	No	No

Alpha-Carotene	Low	4.19e-09 mg/ml ; 7.80e-12 mol/l	No	No
Quercetin-3,7-diglucoside	Low	1.49e+00 mg/ml ; 2.38e-03 mol/l	No	No
Kaempferol 3-xylosylglucoside	Low	1.02e+00 mg/ml ; 1.76e-03 mol/l	No	No
Gossypitrin	Low	5.93e-01 mg/ml ; 1.23e-03 mol/l	No	No
Hydnowightin	Low	1.67e-04 mg/ml ; 2.60e-07 mol/l	No	No
Amentoflavone	Low	9.63e-05 mg/ml ; 1.79e-07 mol/l	No	No
Ajugamacrin B	Low	1.96e-02 mg/ml ; 3.31e-05 mol/l	No	No
Ajugapantin A	Low	1.87e-01 mg/ml ; 3.39e-04 mol/l	No	No
Folic Acid	Low	1.09e+01 mg/ml ; 2.48e-02 mol/l	No	No
Reserpine	High	1.08e-03 mg/ml ; 1.77e-06 mol/l	No	No
Rescinnamine	High	4.97e-04 mg/ml ; 7.82e-07 mol/l	No	No
Strictosidine	Low	3.72e-01 mg/ml ; 7.00e-04 mol/l	No	No
Glomeratose A	Low	1.44e+01 mg/ml ; 2.56e-02 mol/l	No	No
Swertiaside	Low	1.03e+00 mg/ml ; 2.07e-03 mol/l	No	No
Rescinnamidine	High	7.53e-04 mg/ml ; 1.18e-06 mol/l	No	No

Thesis

ORIGINALITY REPORT

5%	2%	2%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to California Southern University Student Paper	1%
2	Submitted to University of Greenwich Student Paper	1%
3	journals.innovareacademics.in Internet Source	1%
4	Submitted to Central University of Himachal Pradesh, Dharamshala Student Paper	<1%
5	dugi-doc.udg.edu Internet Source	<1%
6	Submitted to University of York Student Paper	<1%
7	Submitted to University of Western Australia Student Paper	<1%
8	academic.oup.com Internet Source	<1%
9	app.bighubitservices.in Internet Source	<1%

10	espace.curtin.edu.au Internet Source	<1%
11	McDonald, C.B.. "Structural basis of the differential binding of the SH3 domains of Grb2 adaptor to the guanine nucleotide exchange factor Sos1", Archives of Biochemistry and Biophysics, 20081101 Publication	<1%
12	Sohaib Hourfane, Hicham Mechqoq, Fatima Errajouani, João Miguel Rocha, Noureddine El Aouad. "In Vitro and In Silico Evaluations of Boswelliacarterii Resin Dermocosmetic Activities", Cosmetics, 2022 Publication	<1%
13	Smit, Nico, Jana Vicanova, and Stan Pavel. "The Hunt for Natural Skin Whitening Agents", International Journal of Molecular Sciences, 2009. Publication	<1%

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	On		