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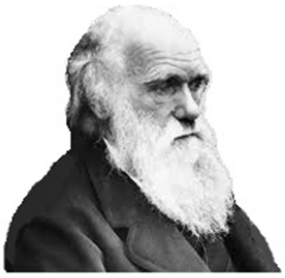

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Discovery of skin lightening agents in *Curcuma longa* using computational methods

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ABSTRACT

Curcuma longa has been reported to impart fairness to human skin traditionally. However, the empirical evidence of this report has barely being actualized. Efforts were made by using Molecular Docking approach and Adsorption Distribution Metabolism Excretion and Toxicity (ADMET) analysis to identify the potential compounds responsible for imparting fairness. The results showed that the hit compounds - Turmerone, curlone, 6-Octadecenoic acid (Z)-, Ar-turmerone, 9-Octadecenoic acid and Hexanoic acid, 5-oxo-,ethyl ester were the most abundant compounds with percentages 16.7 %, 9.31 %, 9.19 %, 7.98 %, 6.65 % and 5.24 % have more stable binding affinity on the human tyrosinase-related protein 1 and ADMET analysis proved these hit compounds to be skin friendly.

***Keywords*:** Skin lightening, computational methods, binding affinity, toxicity

1. INTRODUCTION

Evidence from empirical studies consistently demonstrates that people in less developed countries perceive light or white complexion as more desirable or superior, especially amongst women. Multinational firms have for the past few years actively promoted the assumption that having lighter skin results in greater success (Lee et al., 2020 & Bukhari et al., 2014). While certain substances have been demonstrated to be helpful in skin whitening, others have raised safety issues. For instance, hydroxyquinone and mercury compounds have been connected to kidney and neurological problems. In response, some countries in Africa recently passed a

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resolution urging a regional ban on cosmetics containing the skin-bleaching ingredient hydroquinone (Lei et al., 2016).

Natural skin-lightening chemicals are chemical substances that, when applied to human skin, have a tendency to affect skin fairness. These chemical substances prevent melanin which absorbs ultraviolet rays from the sun from developing. Tyrosinase inhibition is a mechanism by which a few commonly used skin-whitening agents prevent the formation of melanin, preventing the polymerization of dihydroxyindole. For example, kojic acid can suppress the activity of dihydroxyindole acid oxidase and tyrosinase.

Tyrosinase is a member of the metalloenzyme family of polyphenol oxidases that is found in a variety of organisms and has specialized roles in melanogenesis. Melanosome membranes include a multifunctional glycoprotein called tyrosinase, which is a type 3 copper-containing membrane-bound glycoprotein. Melanin inhibition can be achieved mainly through suppression of tyrosinase activity.

Curcuma longa (turmeric) is a spice that has a deep, golden orange colour and is known for giving food flavour, colour, and nutrition. It is regarded as a powerful skin-lightening and glow-revealing substance that can lessen hyperpigmentation, blemishes, and dark spots (Jakubczyk et al., 2016).

Considering the deleterious effects of artificial skin lighteners on human health, and the craze for fair skin among black people, it has become pertinent to search for friendlier compounds especially from the plant kingdom that can impact the same effect at very low risk. Majority of the times, crude extracts of the plants were employed for reducing melanin concentration; the precise chemicals in question responsible for the act have not yet been accurately identified. Thus, identifying these natural skin lightening molecules could serve as an alternative to synthetic bleaching compounds.

2. COMPUTATIONAL TECHNIQUES

The structure and reactivity of molecules are studied in two branches of computational chemistry: molecular mechanics and quantum mechanics. Performing geometry optimizations, computing the vibrational frequencies of molecules resulting from interatomic motion within the molecule, and computing the energy, or properties related to the energy, of a specific molecular structure are the basic types of calculations they both perform (Chidiebere et al., 2021).

The structures and characteristics of molecules are predicted using molecular mechanics simulations (Nwofora et al., 2022). These techniques are distinguished by the specific force fields that they use to simulate the interactions between atomic species. Calculations for molecular mechanics are dependent on nuclei interactions and do not directly address the electrons in a molecular system (Park et al., 2021). However, through parameterizations, electron effects are implicitly incorporated into the force fields. Because of the approximations employed in molecular mechanical calculations, the approaches can be used in very large systems with thousands of atoms (Rupsa et al., 2020).

One of the most important techniques for modeling molecules and materials is electronic structure theory, which uses quantum mechanics rather than classical physics as the basis for calculations (Bulat et al., 2021). The Schrödinger equation, which can be expressed as Eq. 1, is solved to give the energies and structures of molecules.

$$i\hbar\frac{\partial}{\partial t}\psi(x,t) = \left[-\frac{\hbar^2}{2m}\frac{\partial^2}{\partial x^2} + V(x,t)\right]\psi(x,t) \quad (1)$$

where, $\psi(x,t)$ is a wave function, a function that assigns a complex number to each point x at each time t. The parameter m is the mass of the particle, and $V(x,t)$ is the potential that represents the environment in which the particle exists. The constant i is the imaginary unit, and ħ is the reduced Planck constant, which has units of action (energy multiplied by time) (Warshel et al., 2014).

2. MATERIALS AND METHODS

2. 1. Materials

2. 1. 1. Apparatus

Conical flask (150 ml), beaker (200 ml), and funnel

2. 1. 2. Reagents

70 % Ethanol, distilled water

2. 1. 3. Instruments

Mixer grinder, spectrophotometer (Model: 7890 GC and 5977B MSD, Agilent Technologies, USA), weighing balance and rotary evaporator.

2. 1. 4. Softwares and Data Bases

AutoDock Vina in PyRx software version 0.8, Open Babel Software, ADMETsar 2 server, PubChem data base, Protein Data Bank

2. 2. Methods

2. 2. 1. Sample Preparation and Identification of Phytochemicals in the Crude Extract of *Curcuma longa*

Dried rhizomes of turmeric were purchased from an open market and were crushed in a ceramic mortar to a fine pulp. 1g of it was macerated in 20 mL ethanol (70 %) and the mixture was left to stand for 24 hours. The sample was filtered and the crude extract-solvent mixture was separated using a rotary evaporator. The phytochemicals in the sample were identified using a Gas Chromatography-Mass Spectrometer (GC-MS) (Model: 7890 GC and 5977B MSD, Agilent Technologies, USA), using the method as described by Duru (Duru et al., 2021). The eluates were compared with the National Institute of Standard and Technology (NIST) mass spectrum library of compounds.

2. 2. 2. Computational Methods

2. 2. 2. 1. Ligand Preparation

The 3D structure-data files (SDF) of the identified phytochemicals from the crude extracts of *Curcuma longa* were downloaded from the PubChem database. They were minimized by

utilizing the Universal Force Field at 200 steps in the PyRx virtual screening tool before being changed into AutoDock ligands (pdbqt) which were then used for docking analysis.

2. 2. 2. 2. Receptor Preparation

The human tyrosinase-related protein 1 (PDB ID: 5M8O) was identified in the literature and downloaded from Protein Data Bank (PDB). The chain A of the human tyrosinase-related protein 1 (PDB ID: 5M8O) with a resolution 2.50 Å was used as the target for the study. After removing the interfering crystallographic water molecules and cocrystallized ligand, UCSF Chimera 1.14 was used to minimize the protein's energy. At 300 steepest descending steps, the protein was minimized at 0.02 Å. The conjugate gradient steps were 10 steps at 0.02 Å and 10 update. Dock Prep was also used to add Gasteiger charges in order to achieve a suitable structural conformation.

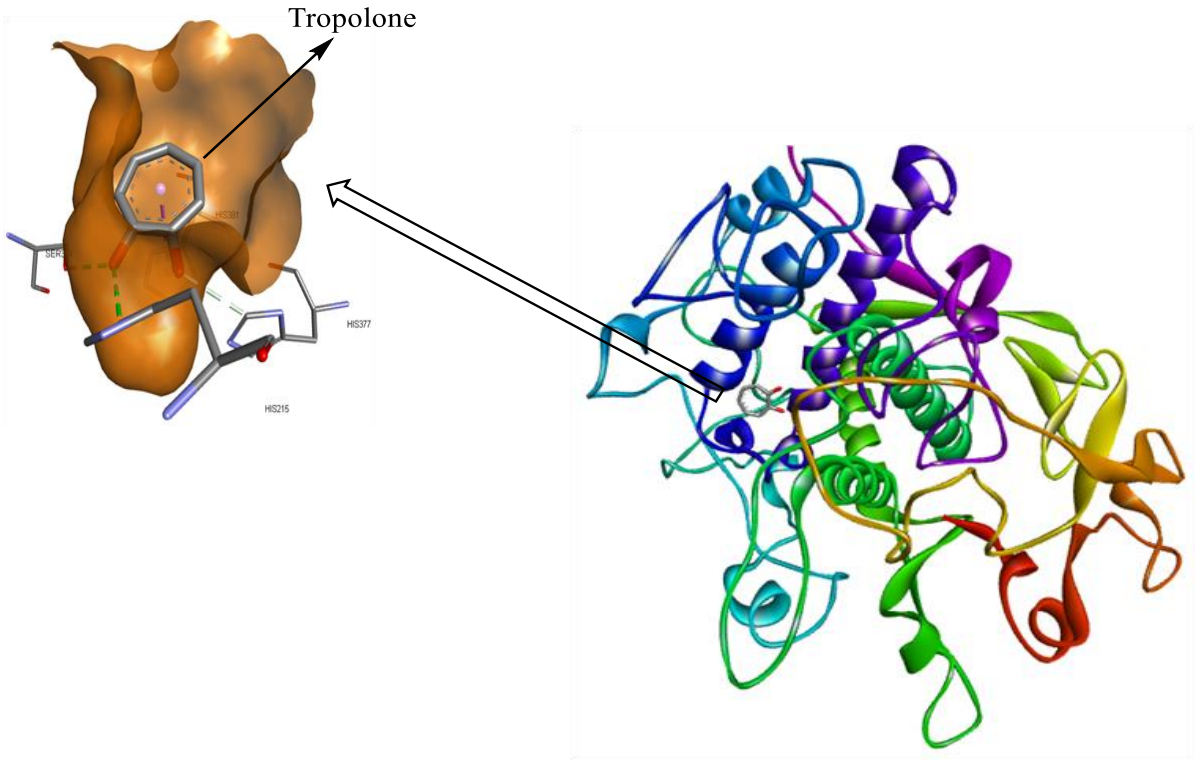


Figure 1. The cocrystallized ligand at the active site of the human tyrosinase enzyme

2. 2. 2. 3. Docking Studies

Phytochemical compounds from *C. longa* were screened by docking them on specific binding pockets of 5M8O protein and ranking them according to their binding energies. AutoDock Vina in PyRx software was used to multiplex the docking of the ligands and protein (Tsao et al., 2020 & Johnson et al., 2020). The Heat Map of the data was seen by utilizing the Conditional Formatting feature, and the molecular docking results were arranged on an Excel spreadsheet.

2. 2. 3. Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Analysis

The toxicity characteristics of the hit compounds from *Curcuma longa* were examined using the ADMETsar 2 server (Duru et al., 2021).

3. RESULTS AND DISCUSSION

3. 1. GC-MS Analysis

Gas chromatography and mass spectrometry are two analytical techniques that can be combined to identify various chemicals in a test sample (Duru et al., 2021). The GC-MS chromatogram of *C. longa* crude extract is shown in Figure 2. The percentages of the identified compounds and their structures are shown in Table 1.

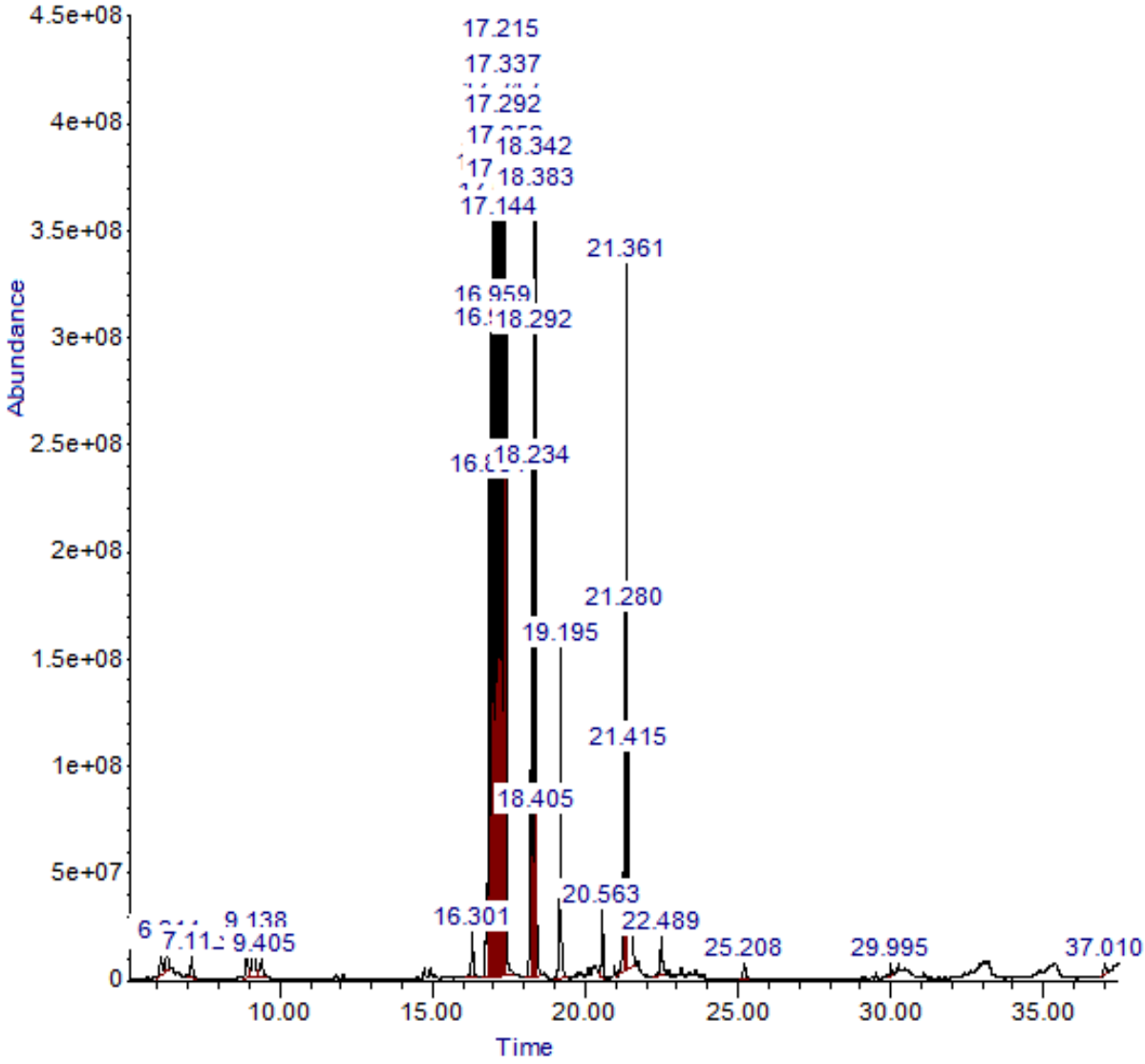
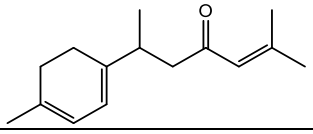
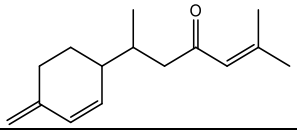
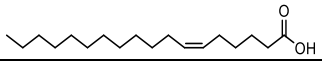
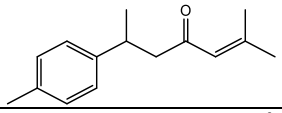
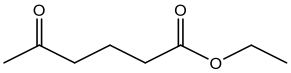
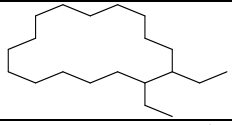
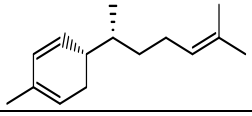
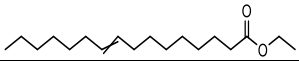
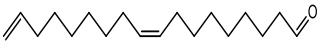
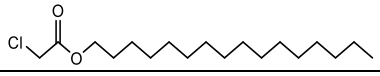
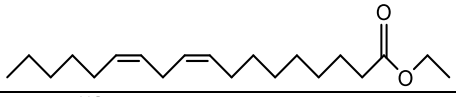
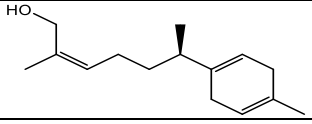
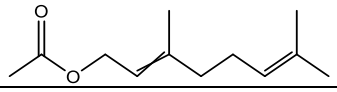
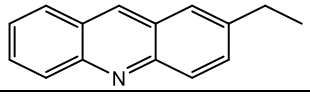
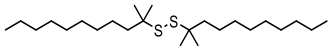
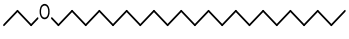
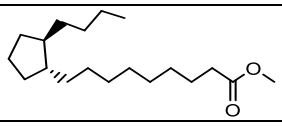
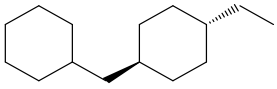


Figure 2. GC-MS chromatogram of *C. longa* crude extract

Table 1. Percentage and chemical structure of the identified compounds in *C. longa*

Phytochemical Compounds	Percentage (%)	Chemical Structure
Turmerone	16.70	
Curlone	9.31	
6-Octadecenoic acid, (Z)-	9.19	
Ar-turmerone	7.98	
9-Octadecenoic acid	6.65	
Hexanoic acid, 5-oxo-, ethyl ester	5.24	
5-Octadecene, (E)-	4.46	
Hexadecanoic acid, ethyl ester	4.39	
Cyclohexadecane, 1,2-diethyl-	4.08	
1,3-Cyclohexadiene, 5-(1,5-dimethyl-4-hexenyl)-2-methyl-, [S-(R*,S*)]-	3.83	
1-Octadecene	3.70	
Ethyl 9-hexadecenoate	3.49	
9-Octadecenoic acid, (E)-	2.65	
9,17-Octadecadienal, (Z)-	2.24	
Acetic acid, chloro-, hexadecyl ester	2.09	
Linoleic acid ethyl ester	1.90	
(R,Z)-2-Methyl-6-(4-methylcyclohexa-1,4-dien-1-yl)hept-2-en-1-ol	1.88	

2,6-Octadien-1-ol, 3,7-dimethyl-, acetate	1.55	
11-Tetradecen-1-ol, (E)-	1.08	
2-Ethylacridine	0.86	
Disulfide, di-tert-dodecyl	0.85	
Docosyl propyl ether	0.79	
Methyl trans-9-(2-butylcyclopentyl)nonanoate	0.71	
Cyclohexane, 1-(cyclohexylmethyl)-4-ethyl-, trans-	0.46	

Turmerone, curlone, 6-Octadecenoic acid (Z)-, Ar-turmerone, 9-Octadecenoic acid and Hexanoic acid, 5-oxo-, ethyl ester were the most abundant compounds with percentages 16.7 %, 9.31 %, 9.19 %, 7.98 %, 6.65 % and 5.24 % respectively. The main sesquiterpene extracted from turmeric is turmerone. According to reports, it is more successful in treating lung cancer (Magisetty, 2021).

Sesquiterpenoids, commonly known as curlone or 2,6-dihydroxybenzoquinone, are a subclass of chemical substances. It is a natural substance that has attracted interest recently because of its possible uses in scientific research. It has been demonstrated that this substance, which is present in many plants including coffee, tea, and cocoa, has a variety of biochemical and physiological effects. Its potential as an antioxidant is one intriguing area. Strong antioxidant activity in Curlone, as demonstrated by studies, may make it helpful in the prevention and treatment of disorders linked to oxidative stress. Curlone has also been demonstrated to have antibacterial and anticancer characteristics, which may be helpful in the creation of novel treatments for various diseases (Adamczak et al., 2020).

Cis-6-octadecenoic acid, commonly referred to as cis-9-octadecenoic acid, is a naturally occurring fatty acid that may be found in the bodies of many different species, including humans. It is an essential part of the cell membrane and takes part in a variety of metabolic processes. Due to its abundance in both plant and animal sources, it is also an important part of the human diet. There are many uses for cis-6-octadecenoic acid in scientific studies. It serves as a substrate for a range of biochemical and physiological investigations as well as the synthesis of numerous enzymes and hormones. Additionally, it is employed in the research of metabolic procedures like the regulation of gene expression and the oxidation of fatty acids. It is also applied to research lipid metabolism and how particular disorders are affected by it (Agrawal et al., 2022).

The main bioactive component of the herb *Curcuma longa* is aromatic (ar-) turmerone. Ar-turmerone may be effective in treating neurodegenerative diseases because it reduces microglia activation, according to some research. Ar-turmerone is a viable future therapeutic

candidate to enhance regeneration in neurological diseases since it inhibits microglia activation and promotes NSC proliferation (Agrawal et al., 2022).

The chemical compound known as 9-octadecenoate, often referred to as 18:1, N-9, or octadec-9-enoic acid, is a member of the group of substances known as long-chain fatty acids. These are aliphatic fatty acids having a tail made up of 13–21 carbon atoms. It has been found in a variety of biofluids, including blood and urine. Octadec-9-enoic acid takes involvement in a variety of enzymatic processes (Arghya et al. 2020).

In order to characterize how small molecules behave in the binding site of target proteins and to shed light on basic biochemical processes, the molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level (Rupsa et al., 2020). By introducing a molecule (ligand) into the preferred binding site of the target specific area of the protein (receptor) primarily in a non-covalent manner to build a stable complex of potential efficacy, it is an appealing scaffold to understand ligand-receptor interaction mechanisms. The binding energy, free energy, and stability of complexes can be suggested using the information gleaned through the docking procedure. As of now (Rupsa et al., 2020), the docking technique is used to forecast the tentative binding characteristics of the ligand-receptor complex.

The binding energies (docking scores) of phytochemical compounds from *C. longa* to the protein linked to human tyrosinase were used to score them. Table 2 presents the results.

The compounds in *C. longa* with better binding affinity include ar-turmerone, Turmerone, 2-Ethylacridine, (Z)-Beta-Curcumene-12-ol, Curlone, and L-Zingiberene from *C. longa*.

Table 2. Binding energy values of the identified phytochemicals from the studied plants.

Compound	Ligand CID	Binding Energy (kcal/mol)	Source
Ar-turmerone	558221	-6.6	Turmeric
Turmerone	558173	-6.6	Turmeric
2-Ethylacridine	610161	-6.5	Turmeric
(Z)-Beta-Curcumene-12-ol	91710638	-6.3	Turmeric
Curlone	196216	-6.3	Turmeric
L-Zingiberene	521253	-6.1	Turmeric
2H-Benzotriazole, 2-ethyl-	590090	-5.6	Turmeric
Cyclohexane, 1-(cyclohexylmethyl)-4-ethyl-, trans-	143232	-5.6	Turmeric
Tropolone	10789	-5.5	Control
2,6-Octadien-1-ol, 3,7-dimethyl-, acetate	1549026	-5.3	Turmeric

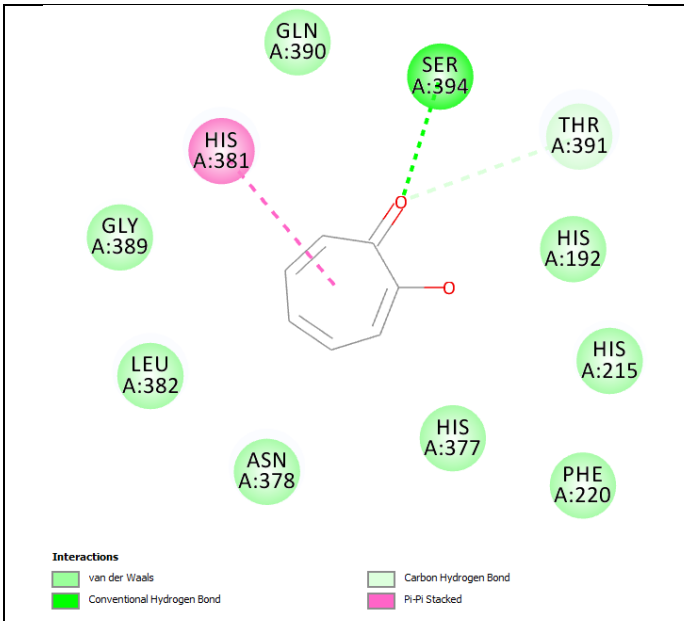
Methyl trans-9-(2-butylcyclopentyl)nonanoate	14389759	-5.2	Turmeric
11-Tetradecen-1-ol, (E)-	1712011	-5.1	Turmeric
9-Octadecenoic acid	637517	-5.1	Turmeric
Hexadecanoic acid, ethyl ester	12366	-5.0	Turmeric
Hexanoic acid, 5-oxo-, ethyl ester	84130	-5.0	Turmeric
6-Octadecenoic acid, (Z)-	5281125	-4.9	Turmeric
Hydroquinone	72376322	-4.9	Synthetic
9,17-Octadecadienal, (Z)-	5365667	-4.8	Turmeric
Ethyl 9-hexadecenoate	5364759	-4.8	Turmeric
1-Octadecene	8217	-4.8	Turmeric
Linoleic acid ethyl ester	5282184	-4.6	Turmeric
1. 5-Octadecene, (E)-	5364598	-4.6	Turmeric
Acetic acid, chloro-, hexadecyl ester	104090	-4.4	Turmeric
Docosyl propyl ether	20189717	-3.2	Turmeric
Disulfide, di-tert-dodecyl	117981	-1.6	Turmeric
Cyclohexadecane, 1,2-diethyl-	536940	1.3	Turmeric

3. 2. Protein-Ligand interactions

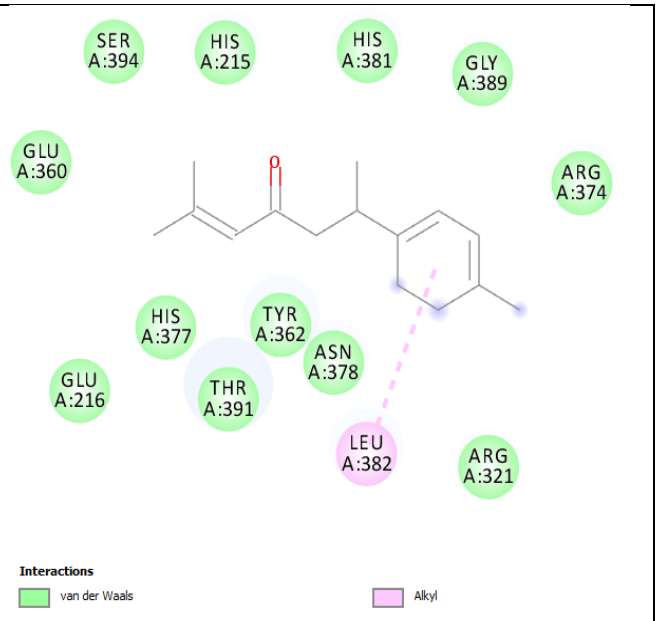
As a result of molecular recognition between proteins that interact with one another or with other molecules, a protein-ligand complex forms. A protein-ligand is a complex comprising a protein associated with a ligand. Figure 3 shows the 2D interactions of the amino acid moiety of the human TYRP1 compounds from *C. longa* and *S. aromaticum*.

The interactions between the cocrystallized ligand and the hit compounds at the TYRP1 enzyme binding pocket were compared, and the results are shown in Table 3. The main molecules interacting with the amino acid residues in the enzyme were the hydroxyl (OH) and carbonyl (C = O) functional groups.

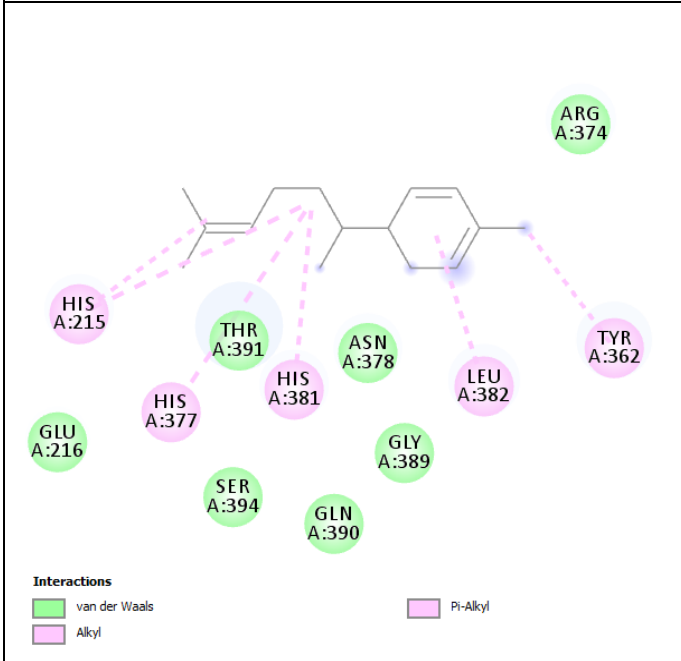
Hydrogen bonds have been found between the TYRP1 enzyme and the hit compounds interactions with this enzyme. However, small compounds that engage with protein sites through hydrogen bonds are more stable at the binding sites of the proteins (Duru et al., 2021 & Rupsa et al., 2020).



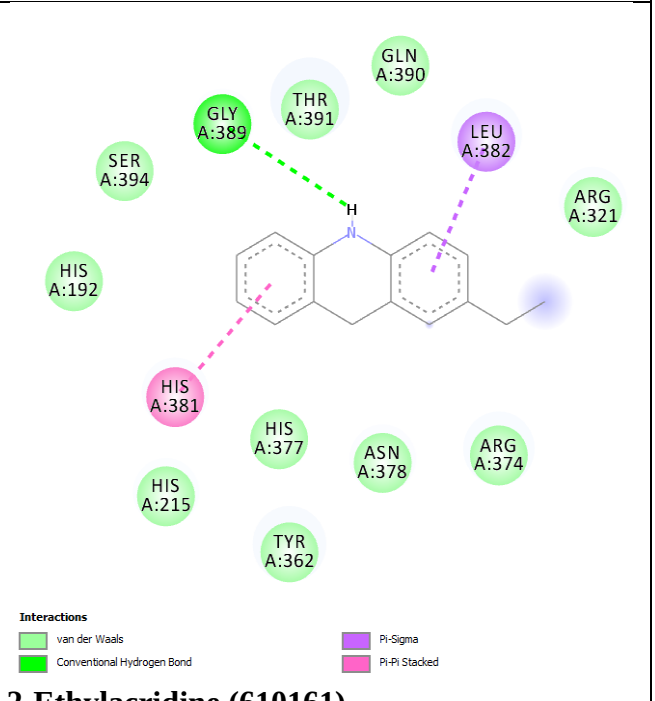
Tropolone (10789)



Turmerone (558173)



1,3-Cyclohexadiene, 5-(1,5-dimethyl-4-hexenyl)-2-methyl-, [S-(R*,S*)]- (521253)



2-Ethylacridine (610161)

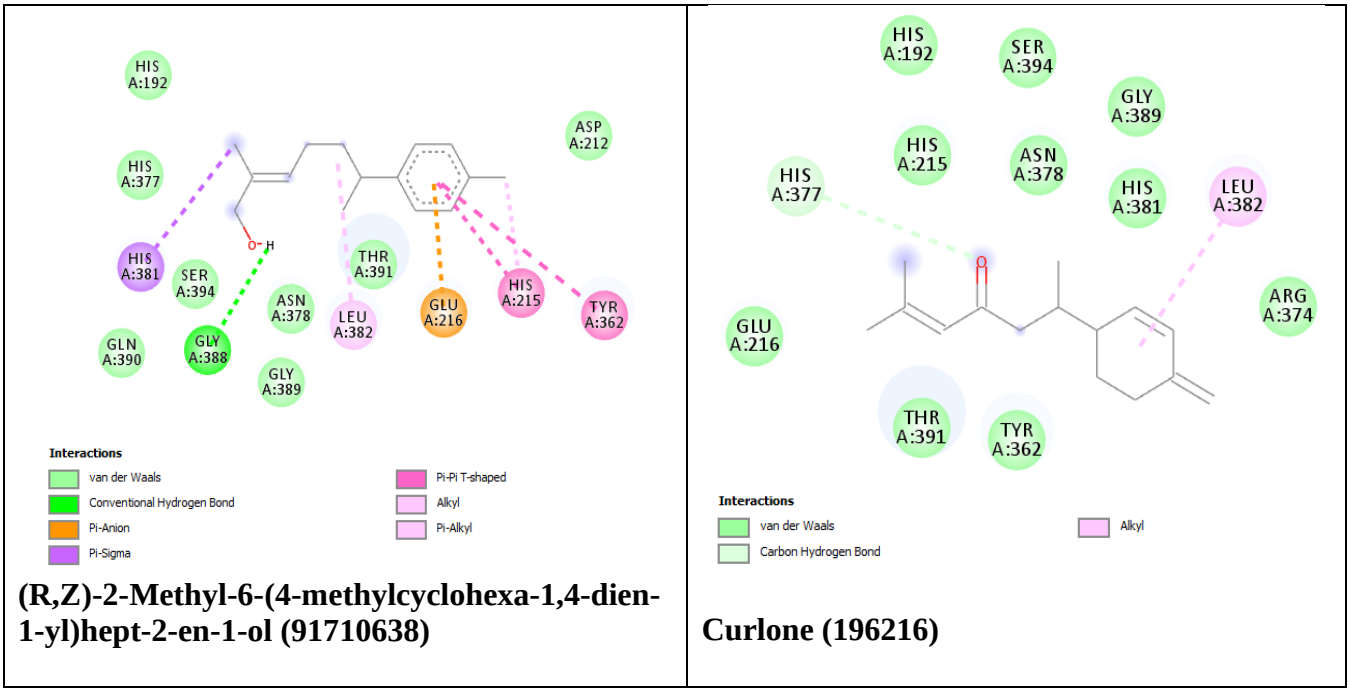


Figure 3. 2D-view of protein-ligand interaction for the compounds with the best binding affinity

Table 3. Protein-ligand interaction comparison

Compound	Hydrogen bond	Van der Waals	Carbon-hydrogen	Pi-pi stacked
Tropolone	SER394	HIS192; HIS215; PHE220; HIS377; ASN378; LEU382; GLY389; GLN390	THR391	HIS381
Turmerone	-	HIS215; GLU216; ARG321;GLU360; TYR362; ARG374; HIS377; ASN378; HIS381; GLY389; THR391; SER394	-	-
2-Ethylacridine	GLY389	HIS192;ARG3212; HIS215; TYR362; ARG374; HIS377; ASN378; GLN390; THR391;SER394	-	HIS381

(R,Z)-2-Methyl-6-(4-methylcyclohexa-1,4-dien-1-yl)hept-2-en-1-ol	-	HIS192; ASP212; HIS377; ASN378; GLY389; GLU390; THR391; SER394	-	-
Curlone	-	HIS192; HIS215; GLU216; TYR362; ARG374; ASN378; HIS381; GLY389; THR391; SER394	HIS377	-
1,3-Cyclohexadiene, 5-(1,5-dimethyl-4-hexenyl)-2-methyl-, [S-(R*,S*)]-	-	GLU216; ARG374; ASN378; GLY389; GLU390; THR391; SER394	-	-

3. 3. ADMET Analysis

Table 4 shows the results of absorption, distribution, metabolism, excretion, and toxicity (ADMET) qualities, which demonstrate the pharmacokinetics and pharmacodynamics features. The hit compounds' drug-likeliness was predicted using Lipinski's rule of five, which takes into account a complex balancing act of different molecular properties and structural features like lipophilicity, electronic distribution, hydrogen bonding properties, molecule size, and flexibility, as well as the presence of different pharmacophores that affect a molecule's behavior in a living organism. A good drug candidate, however, shouldn't transgress more than one of the guidelines (Lipinski, 2016).

Table 4. ADMET properties for skin sensitivity of the selected eight compounds and the control with best binding affinity.

Compounds	Carcinogenicity (binary)	Eye corrosion	Mitochondrial toxicity	Nephrotoxicity	Respiratory toxicity	Skin corrosion	Skin irritation	Skin sensitisation	Water solubility
C2	+	-	-	+	-	-	+	+	-3.20
C3	-	-	-	-	-	-	+	+	-3.23
C4	-	-	-	-	-	-	+	+	-2.43
C5	-	-	-	+	-	-	+	+	-2.72
C6	-	-	-	-	-	-	+	+	-3.39

C7	-	-	-	+	+	-	+	+	-5.31
CT	-	+	-	+	-	+	+	+	-0.23

Key: C2 = Ar-turmerone, C3 = Turmerone, C4 = 2-Ethylacrine, C5 = (Z)-Beta-Curcumene-12-ol, C6 = Curlone, C7 = Longifolene-(V4) CT = Hydroxyquinone

The range of solubility was between -5.31 and -0.23. Compounds can be categorized, nevertheless, based on their solubility values (Log S); those with solubility values of 0 and higher are extremely soluble, those in the range of 0 to -2 are soluble, those in the range of -2 to -4 are mildly soluble, and those less than -4 are insoluble (Duru *et al*., 2022). With solubility values of -1.99 and -0.23, respectively, C1 and CT are both soluble. The solubility values for C2, C3, C4, C5, and C6 are respectively -3.20, -3.23, -2.43, -2.72, and -3.39. However, according to the ADMET characteristics listed in Table 4, C1 was found to be negative for skin sensitization, eye corrosion, mitochondrial toxicity, nephrotoxicity, and carcinogenicity (binary). While skin irritation and skin sensitization revealed positive results in C2, C3, C4, C5, C6, C7, C8, and CT. It suggests that C1 would be a more skin-friendly chemical.

4. CONCLUSION

Many phytochemicals were identified in *C. longa*, however, few had a good binding affinity on the targeted protein (TYP 1). The selected hit compounds were proven to have no detrimental effect on human skin through ADMET analysis. Thus *C. longa* could be an alternative to synthetic chemicals such as hydroquinone, compounds containing mercury etc.

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