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Melanin and its Precursors as Effective Antiviral Compounds: with a Special Focus on SARS CoV2

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Abstract

Melanins are ubiquitous pigment which plays a diverse role in organisms ranging from bacteria to human beings. Its unique properties made it an important compound for study in diverse fields from electronics to drug discovery. Melanin and precursors have proved to be good antiviral candidate against many viruses. It has shown to inhibit replication of HIV-1 and HIV-2. Insilico studies proved that it can also interact with furin protein which is an important protein in SARS CoV2 pathogenesis. Our present study proved that melanin precursors like 5,6-dihydroxyindole-2-carboxylic acid (DHICA) and l-3,4-dihydroxyphenylalanine (L DOPA) strongly interacts with the spike protein of the CoV2. All these studies prove melanin and its precursors could be utilized as effective antiviral compounds

Keywords

Melanin. L DOPA. DHICA. Antiviral. SARS CoV2

Introduction

Melanins are polyphenolic compounds distributed in most life forms which basically involve in the protection of the organism. Its UV absorptive property enables the organism to escape from the UV mediated cell damage. While for organism like bacteria, melanin helps them to escape from the host immune system as the pigment have good antioxidant activity which enables them to escape from the ROS mediated immune responses inside the host organism. Though to the host it is a negative aspect, the production of melanin increases the virulence of the pathogenic organism [1]. Apart from all these functions, melanins are considered to be an important component in human body. They play crucial role in energy transmission in tissues and organs like skin, retina, inner ear and nervous system. Disturbances in melanin metabolism can lead to Parkinson's disease, senile macular degeneration and senile deafness. Melanin metabolism is shown to be altered in Alzheimer's as well as Down syndrome patients. So apart from its protective role melanin plays an important role in maintaining human health [2].

Melanins commercially available can be of two forms, synthetic as well as biological. Both have somewhat similar properties and either can be utilized in melanin-based experiments and products. Biological melanin is usually extracted and purified from ink sacs of Sepia as well as produced by microorganisms like bacteria and fungi. This commercial melanins are usually utilized for its cosmetological applications as it can enhance sun protective factor in sun protective creams and lotions. Its effectiveness in being as a component in electronics like solar cell and batteries to drug delivery and anti-cancer activity has been proved in the laboratory level and not yet been commercialized. So, the melanin still remains as a less explored compound with enormous potential due to its diverse properties [3].

Melanins, namely Eumelanin, Pheomelanin and Allomelanins are synthesized by diverse biosynthetic pathways. Melanin synthesis mostly begin from amino acid tyrosine which is further converted to l-3,4- dihydroxyphenylalanine (DOPA) by tyrosinase. DOPA further oxidizes to form DOPAquinone and then to DOPAchrome. DOPAchrome further converted to the important building blocks that makes up melanin, DHI (5, 6-dihydroxyindole) and DHICA (5,6-dihydroxyindole-2-carboxylic acid). Both components further polymerized to for eumelanin. During this biosynthetic pathway if thiols like cysteine or glutathione, DOPAchrome will react with them and form 5-S-cysteinylDOPA (5-S-CD) which further polymerized to for pheomelanin. Rest of the melanin subtypes are included in a

heterogenous group called allomelanins. This includes DHN-melanin, homogentisic acid (pyomelanins), γ-glutaminyl-4-hydroxybenzene (GHB-melanin), catechols, 4-hydroxyphenylacetic acid etc. Allomelanins are seen predominantly in plants, bacteria and fungi and its precursor may not be tyrosine in most cases [4].

Whichever be the precursor molecules, melanins usually exhibit similar biophysical properties. Melanins had shown diverse activities like antibacterial, antibiofilm [5], antioxidant, anti-inflammatory [6] and so on makes then major biomolecule to exploit extensively. Antiviral potential of melanin is least explored so far. Synthetic soluble DOPA melanin had shown to inhibit the replication of human immunodeficiency virus types 1 and 2 (HIV-1 and HIV-2) in vitro. Melanin found to block the infection by the cell free virus. Melanin inhibited the binding of HIV-1 envelope surface glycoprotein to the MT-2 lymphoblastoid cell lines [7]. L-DOPA the precursor in eumelanin synthesis was found to inhibit West Nile Virus multiplication in cell culture. L-DOPA significantly reduced the production of infectious virus in all cell types tested [8]. Plant melanins were found to have and patented anti-viral activity against influenza viruses, herpes simplex virus type 2, HIV-1, and vaccinia virus. DHICA, the major building block of melanin was found to inhibit RNA dependent DNA polymerase and HIV-1 integrase. Its structural analogue Arbidol is used in the treatment SARS CoV 2 [9].

SARS CoV2 is the root cause of the pandemic COVID-19 which is still causing threat to the world by taking the life of millions of people. The disease is mainly characterized with mild to severe respiratory illness. There is no approved drug yet shown fully effective in controlling the virus. Clinal trials of few drugs like chloroquine, remdesivir, arbidol, and favipiravir is still ongoing. In silico studies proved that melanin, eumelanine, L-dopaquinone and L-DOPA binds to the active site of furin protein, which have a significant role in the viral entry [10]. Spike glycoprotein of SARS CoV2 plays an important role in viral entry to the host cells [11]. Binding of Spike glycoprotein with human cellular receptor angiotensin-converting enzyme 2 (ACE2) is considered to be the crucial step in the viral entry. Drugs which can interfere with these interactions could be one of the important areas we should focus in developing SARS CoV2 antiviral drugs [12]. Interaction of melanin precursors like DHICA and L DOPA is analyzed using molecular docking the current study.

SARS-CoV-2 D614G 1-RBD up Spike Protein (PDB ID :7KDL) retrieved from the Protein Data Bank [13] was used in the study. Since this is a homotrimer protein, we focused on chain A only. Protein structure obtained from the PDB was not suitable in its native state for molecular docking [14]. Therefore, the protein structure was optimized with Schrödinger's Protein Preparation Wizard. In that proper bond orders, the addition of hydrogen atoms and missing residues, correction of formal charges to the hetero groups, and generation of ionization states at physiological pH (7.0) were corrected [15]. The water molecules were present in most crystal protein structure. Consequently, water molecules were deleted. Finally, the protein structure was minimized using OPLS_2005 force field [16].

The generation of a defined grid-box on the protein's active site is a prerequisite for prospective molecular docking studies. Thus, the active site was defined as an enclosing box (36×36×36 Å) at the centroid of the active site, which a smaller secondary box was created as default and centered around the potential binding site using Receptor Grid Generation wizard [17]. The scaling of van der Waals radii was set to defaults where scaling factor was 1.0 Å and the partial atomic charge was less than 0.25 as a cut-off. No rotatable groups were selected and no constraints were defined.

The 3-dimensional structural coordinates of L DOPA (6047) and DHICA (119405) molecules were retrieved in SDF format from PubChem database. The LigPrep and EpiK were applied to expand protonation and tautomeric states at pH 7.0±2.0 for each molecule using LigPrep wizard. The chirality of ligands was determined from their three-dimensional structures.

Molecular Docking is the binding orientation of small molecules to their protein targets in order to predict the affinity and activity of the small molecules, hence, plays an important role in the structure-based drug design [18]. The Glide v11.9 module was used to estimate the binding interactions between the target protein and ligands [19]. The molecular docking was performed using extra precision (XP) mode. The interactions between the receptor and phytochemical were calculated as Glide scores, i.e., G-scores, based on the following equation.

Glide score = 0.065×vdW +0.130×Coul + Lipo + Hbond+ Metal + BuryP + RotB + Site

Were,

vdW =van der Waals energy,

Coul =Coulomb energy,

Lipo = lipophilic term derived from hydrophobic grid potential,

Hbond = hydrogen-bonding term,

Metal = metal-binding term,

BuryP = penalty for buried polar groups,

RotB = penalty for freezing rotatable bonds, and

Site = polar interactions present in the active site.

Molecular docking has been performed with a flexible ligand and a rigid receptor, the most popular method in use pharmaceutical research. Here, we use Glide v11.9 from Schrodinger team for receptor ligand docking.

In the current study, binding interaction of L DOPA (6047) and DHICA (119405) with SARS-CoV-2 D614G 1-RBD up Spike Protein were analysed. The results showed that DHICA molecules showed high docking score (-3.679 k/cal) and energy with 2 hydrogen bond interactions (**Figure 1A**). Stable hydrogen bonds are observed between DHICA and Gln 314 of the spike protein. Meantime L DOPA interacted with SARS-CoV-2 D614G 1-RBD up Spike Protein with -3.088 k/cal and produce 3 hydrogen bonds within 3 A0 distance (**Figure 1B**). Strong hydrogen bonds are observed between L DOPA with Ile 312 and Gln 314. Gln 314 plays an important role in interacting with drug compounds. In earlier reports Gln 314 of spike protein is found to form strong hydrogen bonds with potential inhibitors such as Digitoxin [20] and Epigallocatechin gallate [21]. Similar interactions are observed between spike and DHICA and L DOPA reveals their potential to inhibit the spike protein. How these interactions are going to affect with spike and ACE2 needs to be investigated further. Hence, more insilico studies and further invitro studies are needed to confirm whether these melanin precursors DHICA and L DOPA could be used as antiviral drugs against SARS CoV2.

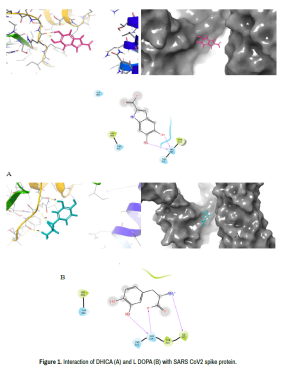

Figure 1. Interaction of DHICA (A) and L DOPA (B) with SARS CoV2 spike protein.

Conclusion

Antiviral drugs are the need of the hour because many viral diseases are emerging and becoming threat to humans in this decade. Melanin and its biosynthetic precursors were found to inhibit a wide range of viruses like HIV, Influenza, West Nile virus etc. could be exploited further in developing antiviral drugs. SARS CoV2 is still a threat to human life since 2019, production of effective antivirals against it is the most needed thing. Melanin and its precursors found to inhibit furin protein and our study proves that it can also interact with spike protein. These all indicates melanin and its precursors could be utilized in development antivirals against SARS CoV2.

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