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Docking studies of Vitamin C, Vitamin E, Damnacanthal and Scopoletin with human lens gamma D-crystalline

Satyanarayana Rentala[1], Sudhakar Konada[1]*, Ramakrishna Chintala[2], Lakshmi Narasu Mangamoori[3], Suryanarayana Murthy Upadhyayula[4] & Sarva Mangala Dhurjeti[1]

[1]Department of Biotechnology, GITAM Institute of Technology, GITAM University, Rushikonda, Visakhapatnam – 530 045, INDIA; [2]Department of Environmental Studies, GITAM Institute of Science, GITAM University, Rushikonda, Visakhapatnam – 530 045, INDIA; [3]Department of Biotechnology, Institute of Science and Technology, Jawaharlal Nehru Technological University, Hyderabad – 500085, INDIA; [4]Associate professor of ophthalmology, Rajiv Gandhi Institute of Medical Sciences, Srikakulam, Andhra Pradesh, INDIA; Sudhakar Konada – Email: sudha.1930@gmail.com; 09032456487, Office: 0891-2840246; *Corresponding author

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Abstract:
Vitamin C, Vitamin E, scopoletin and damnacanthal are the major constituents of Noni (*Morinda citrifolia*). These compounds are known to have good medicinal properties and they are known to act as antioxidants. Loss of vision in elderly is due to opaqueness of the lens proteins such as gamma-D-crystallin during oxidative stress conditions. Therefore, it is of importance to find the potential interaction of Vitamin C, Vitamin E, Scopoletin and Damnacanthal with the lens protein gamma-D-crystallin. Hence, their physical binding to gamma-D crystallin (PDB ID: 2G98) was evaluated using molecular and structural docking procedures. Results show the potential binding of all the above anti-oxidants to gamma-D-crystalline with equal affinity. Thus, the role of cumulative anti-oxidant effect in Noni fruit juice through their potential yet predicted interaction with the lens protein gamma-D-crystallin is implied for cataract treatment.

Key words: Cataract formation, Oxidative stress, gamma-D-crystallin, Anti-oxidants, Docking scores.

Background:
Oxidative stress is the one of the leading causes of cataract due to imbalance between oxidants and antioxidants in favor of oxidants in the human body **[1].** In order to maintain tight homeostatic control of reactive oxygen species (ROS) and prevent oxidative stress, external supplementation with dietary antioxidants or herbal preparations may prove useful. The major proteins maintaining the lens transparency are crystallins representing up to 90% of the soluble lens proteins **[2]**. Human gamma-D-crystallin (γD-crys) is one of the most abundant γ-crystallins in the lens and a significant component of the age-related cataract due to its misfolding. Any changes occurred in γD-crys gene (CRYGD) would result in non-functional protein **[3].** As shown in **(Figure 1)**, γD-crys is a monomeric protein composed of two structurally homologous domains.

Each domain is composed of intercalated double β-sheet key motifs a characteristic structural feature of the βγ-crystallin superfamily. The duplicated domains connected by a linker peptide form a highly conserved hydrophobic interface that plays a crucial role in determining long-term stability **(Figure 1).** External supplementation of Noni fruit juice (*Morinda.citrifolia*) includes nutraceuticals and dietary supplements such as vitamin C, vitamin E, Scopoletin, Damnacanthal and many more compounds **[3-9].** In this paper, we investigated some of the anti-oxidants present in Noni fruit

juice to bind with gamma-D-crsytalline and found that these anti-antioxidants have considerable binding affinity for human gamma-D-crsytallin.

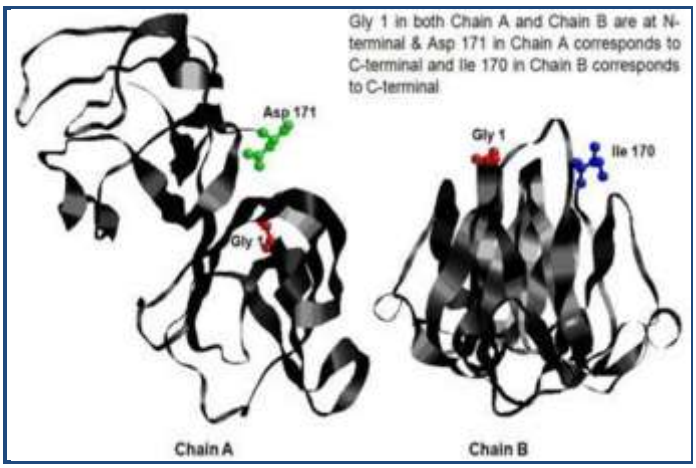

Figure 1: X-Ray diffraction structure of human Gamma-D-Crystalline in lens. The above protein was drawn using Accelerys Discovery Studio (R) (http://accelrys.com/). C- and N- terminal amino acids were shown in ball-stick model. N-terminal Gly1 (shown in red colour) was selected in chains A and B, C-terminal Asp171 (shown in green colour) in chain A, Ile 170 (shown in blue colour) in chain B were shown.

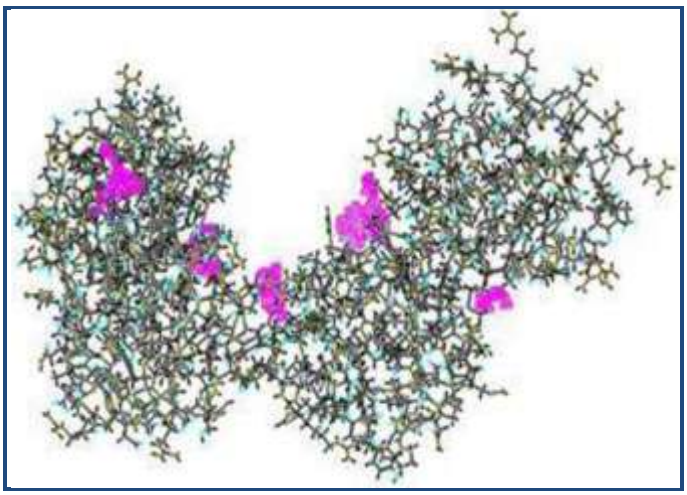

Figure 2: Gamma-D-Crsytalline with five cavities. Gamma-D-Crystallin (PDB ID: 2G98) was searched for cavities using MoleGro Virtual Docker software. Five cavities were generated. The five cavities were shown in pink colour. Ligands were docked into these five cavities.

Methodology:

Tools employed

Protein Data Bank server (PDB:www.rcbs.org/pdb) **[10],** Whatif server (http: //swift.cmbi.ru.nl/ servers/html/ index.html) **[11],** ACD chemsketch and MoleGro Virtual Docker and viewer, preparation of Human Gamma D-crystalline structure was downloaded from PDB server. The ID generated was 2G98. The structure of the protein was optimized using Whatif server and was used for further analysis. Vitamin C, Vitamin E, Damnacanthal and Scopoletin, structures were constructed using ACDchemsketch 12.01 software. The three dimensional structure of these compounds was optimized using ACDchemsketch - structure optimization wizard.

Docking studies of Vitamin C, Vitamin E, Scopoletin and Damnacanthal with Human lens gamma- D-Crystalline (2G98): The protein was imported into MoleGro Virtual Docker version 4.0.2.0 and surface was created. Cavities were detected in the protein surface. Five cavities were found and they were represented in green color as shown in **(Figure 2)**. Vitamin C, Vitamin E, Damnacanthal and Scopoletin were saved individually into MoleGro Virtual Docker software in ".mol" format. These ligands were docked into all the cavities to produce five docking sites with different amino acid sequence. The MolDock scores and root mean square deviation (RMSD) values were calculated.

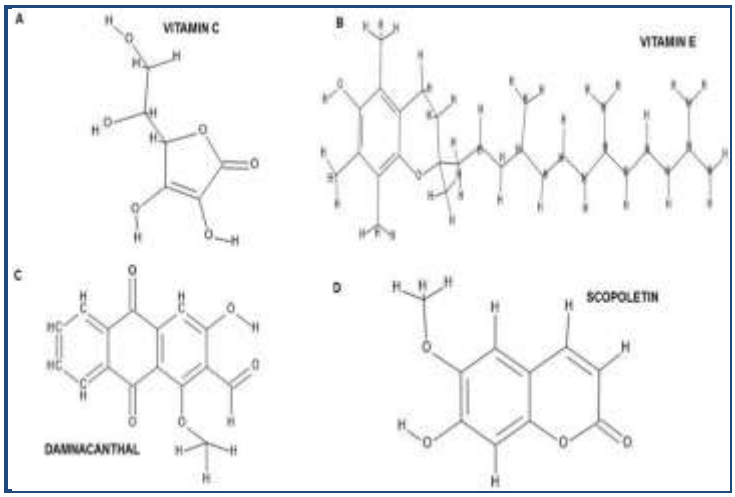

Figure 3: Two dimensional structures of Vitamin C, Vitamin E, Damnacanthal and Scopoletin. Figure 3A is Vitamin C, Figure 3B is Vitamin E, Figure 3C is Damnacanthal and Figure 3D is Scopoletin. All the above figures were drawn in Accelerys Draw 4.1 ®

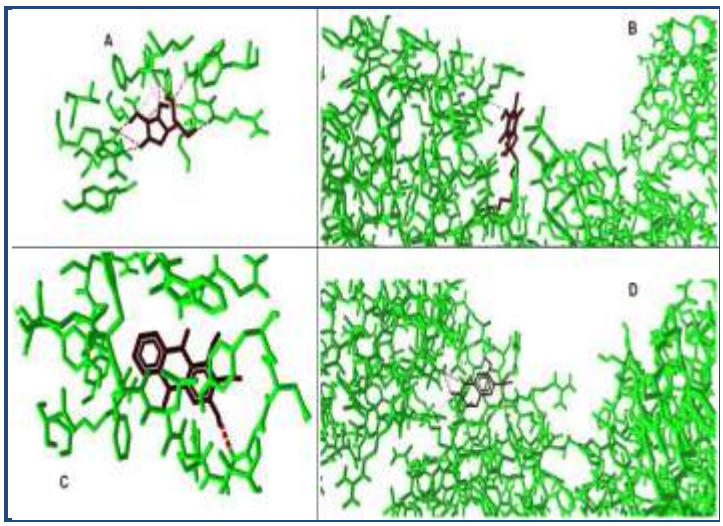

Figure 4: Docking of Vitamin C, Vitamin E, Damnacanthal and Scopoletin within the cavities of gamma-D-crystallin. Docking studies of Vitamin C with gamma-D-crystallin was shown in figure **(A)**. Docking studies of Vitamin E with gamma-D-crystallin was shown in figure **(B).** Docking studies of Damnacanthal with gamma-D-crystallin was shown in figure

(C). Docking studies of Scopoletin with gamma-D-crystallin was shown in Figure **(D**). Hydrogen bonds were shown in dotted lines.

Results and Discussion:

Optimization of three dimensional structures of gamma-D-crsytalline and its ligands (Vitamin C, Vitamin E, Damnacanthal and Scopoletin)

The optimized structure of gamma-D-crsytalline with five cavities was shown in **(Figure 2**). The protein was subjected to detect cavities using MoleGro Virtual Docker version 4.0.2.0. Vitamin C, Vitamin E, Damnacanthal and Scopoletin were optimized using ACDChemSketch version 12.01. The optimized structures in two dimensional conformations were shown in **(Figures 3A, 3B, 3C & 3D)**.

Docking studies of Vitamin C, Vitamin E, Damnacanthal and Scopoletin with gamma-D-crsytalline

Docking of Vitamin C, Vitamin E, Damnacanthal and Scopoletin within the cavities of gamma-D-crsytalline generated five poses with unique chemical arrangement. The docking studies within the cavity structures were shown in **(Figures 4A, 4B, 4C & 4D)**. Docking results of Vitamin C, Vitamin E, Damnacanthal and Scopoletin were shown in **Table 1 (see supplementary material).** The MolDock Scores and cavity volume of Pose 1 was high in all the docking experiments; the structure in the pose1 was superior to other poses.

The present investigation emphasize that Vitamin C, Vitamin E, Damnacanthal and Scopoletin docked into pose 1, which is said to be the best fit for PDB Id: 2G98, leading to least MolDock scores and re-rank scores. Corresponding amino acid sequence and MolDock scores were also shown in **(Table 1)**. This implies that the structures in pose 1, are firmly bound with gamma-D-crystalline, making the protein more active. This may lead to deactivation of mutated gamma-D-crystalline. This report suggests that anti-oxidants present in Noni have strong binding affinity towards gamma-D-crystallin. This investigation supports the anti-oxidant and cataract treating effects of Noni fruit juice.

Conclusion:

In conclusion, our work highlights the importance of studying docking parameters of Vitmain C, Vitamin E, Damnacanthal and Scopoletin into gamma-D-crystallin. The findings in the present investigation lead to the application of Vitmain C, Vitamin E, Damnacanthal and Scopoletin during age related, oxidative stress induced loss of vision problems. Further, anti-oxidant activities of Vitmain C, Vitamin E, Damnacanthal and Scopoletin must be examined separately in in vitro and in vivo animal models. Thus, a careful selection of the appropriate tools and experimental approaches for analyzing the roles of Vitmain C, Vitamin E, Damnacanthal and Scopoletin during oxidative stress induced cataract treatment is required.

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Supplementary material:

Table1: **Docking parameters of Vitamin C, Vitamin E, Damnacanthal and Scopoletin with gamma-D-crystallin (PDB: 2G98).** Proximity of amino acid sequences, MolDock scores, Rerank scores and RMSD values were shown in the Table. The maximum volume for the cavities of pose 1 was taken into consideration in all the cases for better docking with proximal amino acids in the cavities

S. No	Ligand	Cavity Volume	Amino acid sequence [Proximity]	Mol dock score	Rerank score	RMSD	H Bond
1	Vitamin C	89.088 Proximity value 2.65	Arg-58, Leu-57, Met-69, Tyr-62	-62.7865	-53.9438	31.2078	-12.4463
2	Vitamin E	91.136 Proximity value 2.65	Arg-58, Leu-57, Met-69	-107.315	-82.3691	30.8974	-1.64539
3	Scopoletin	88.064 Proximity value 2.65	Arg-58, 167, Leu-57, Met-69, Phe-56, Tyr-62	-61.1952	-61.5999	28.3689	-2.00817
4	Damnacanthal	82.944 Proximity value 2.69	Arg-58, 167, Leu-57, Met-69, Phe-56, Tyr-62	-61.1952	-61.5999	28.3689	-2.00817