In silico Screening of Food Bioactive Compounds to Predict Potential Inhibitors of COVID-19 Main protease (M^{pro}) and RNA-dependent RNA polymerase (RdRp)

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Abstract

As novel corona virus (COVID-19) infections has spread throughout the world, world health organization (WHO) has announced COVID-19 as a pandemic infection. Henceforth investigators are conducting extensive research to find possible therapeutic agents against COVID-19. Main protease (Mpro) that plays an essential role in processing the polyproteins that are translated from the COVID-19 RNA becomes and RNA-dependent RNA polymerase (RdRp) that catalyzes the replication of RNA from RNA template as a potential targets for in silico screening of effective therapeutic compounds to COVID-19. In this study we used COVID-19 Docking Server to predict potential food bioactive compounds to inhibit Mpro and RdRp. The results showed that Phycocyanobilin, Riboflavin, Cyanidin, Daidzein, Genistein are potent inhibitor bioactive

compounds to Mpro and RdRp in comparison to antiviral drugs. Though, further in vitro and/or in vivo research is required to validate the docking results.

Introduction

The novel coronavirus nCoV has recently appeared as a human pathogen in the city of Wuhan, China, which causes COVID-19 with symptoms; fever, cough, severe respiratory illness, and pneumonia. According to the World Health Organization (WHO), as of 28 March 2020, there had been >574,444 confirmed cases with 26,654 deaths. Till now, no specific treatment for COVID-19 is available and researchers are working on identification of potential therapeutic compounds. Some studies investigated potential of combinations of human immunodeficiency virus protease inhibitor lopinavir/ritonavir to treat COVID-19 [1]. Liu et al. (2020) have successfully established crystal structure of main protease (Mpro) or chymotrypsin-like protease (3CLpro) from COVID-19, and deposited in the Protein Data Bank (PDB) for public access [2]. This enzyme plays a key role in processing of translated polyproteins [3]. Xu et al. (2020) reported that nelfinavir was identified as the best potential inhibitor against COVID-19 Mpro, based on docking studies among among 4 drug compounds (nelfinavir, pitavastatin, perampanel, and praziquantel) [4]. In addition, RNA-dependent RNA polymerase (RdRp), a key enzyme in virus replication is another target to find therapeutic agents to COVID-19 [5]. Literature studies reported that antiviral drug Remdesivir as a potent inhibitor to virus replication [5].

Food bioactive compounds mainly present in fruits, vegetables, whole grains and legumes, provide health benefits in addition to basic nutritional value [6]. Epidemiological studies show that high intake of bioactive compounds (such as; vitamins, phytochemicals, and mainly phenolic compounds, such as flavonoids and carotenoids) has a positive influence on human health and could reduce the risk of diseases [7]. In the present study, we investigated the binding affinity of food bioactive compounds (Phycocyanobilin, Riboflavin, Cyanidin, Daidzein, Genistein,

Catechin, Resveratrol, Curcumin, Astaxanthin, B-carotene, Gingerol, Vanillin, Eugenol, Thymol) towards Mpro and RdRp to screen potential inhibitors of COVID-19.

Methodology

To test binding affinity of selected bioactive compounds against COVID-19 Mpro, docking studies are performed with online COVID-19 Docking Server [6]. In this server various proteins of COVID-19 virus are available. Which targets virus replication and virus attachment to host cell. In this study we selected M^{pro} and RdRp as targets for docking studies. The input ligand files of selected bioactive compounds and antiviral compounds were downloaded from Chemical Entities of Biological Interest (ChEBI) in SDF file format. For docking, the server used Autodock Vina as docking engine [6].

Results and Discussion

Table 1 depicts binding energies obtained from docking Mpro and RdRp with ligands; current anti-viral drugs and bioactive compounds from various food sources. For Mpro, the results show phycocyanobilin docked with best score with binding energy of -8.6 Kcal/mol followed by Riboflavin (-7.9 Kcal/mol), Cyanidin (-7.9 Kcal/mol), Daidgein (-7.8 Kcal/mol) and Genistein (-7.6 Kcal/mol). In comparison, antiviral drugs showed binding energies in order of Remdesivir (-8.1 Kcal/mol), Nelfinavir (-7.9 Kcal/mol) and Lopinavir (-7.9 Kcal/mol).

In case of RdRp, Phycocyanobilin again show best score with binding energy of -9.3 Kcal/mol followed by Riboflavin (-.9.0 Kcal/mol) and Cyanidin (-8.8 Kcal/mol) Kcal/mol, Genistein (-8.6 Kcal/mol) and Daidgein (-8.4 Kcal/mol). In case of antiviral drugs, Lopinavir have high score (-9.7, Kcal/mol) followed by Nelfinavir (-9.3, Kcal/mol), and Remdesivir (-9.0, Kcal/mol). Interestingly, in comparison to anti-viral drugs, phycocyanobilin showed superior binding affinity

and Riboflavin, Cyanidin, Daidzein & Genistein showed comparable binding affinity, which makes them possible potent inhibitors to Mpro and RdRp and thereby COVID-19.

In conclusion, the results revealed that Phycocyanobilin, Riboflavin, Cyanidin, Daidzein, Genistein are predicted as potential bioactive compounds to treat COVID-19. Since these bioactive compounds are derived from natural food materials, further studies for approval are not mandatory. However to validate these docking results and to understand exact impact of selected bioactive compounds further in vitro and/or in vivo studies with novel corona virus will be recommended.

Table 1: Molecular docking results of bioactive compounds or antiviral drugs with COVID-19 main protease (Mpro) and RNA dependent RNA polymerase (RdRp)

Source	**Compounds**	**Mpro Binding energy (Kcal/mol)**	**RdRp Binding energy (Kcal/mol)**
Chemical	Remdesivir	-8.1	-9.0
Chemical	Nelfinavir	-7.9	-9.3
Chemical	Lopinavir	-7.9	-9.7
Spirulina	Phycocyanobilin	**-8.6**	**-9.3**
Eggs, meat, fruits and vegetables	Riboflavin	**-7.9**	**-9.0**
Grapes and berries	Cyanidin	**-7.9**	**-8.8**
Legumes	Daidzein	-7.8	-8.4
Legumes	Genistein	-7.6	-8.6

Green tea	Catechin	-7.3	-8.4
Grapes and berries skin	Resveratrol	-7.0	-7.3
Turmeric	Curcumin	-7.0	-8.1
Microalgae	Astaxanthin	-7.0	-8.2
Fruits and Vegetables	β-carotene	-6.5	-7.8
Chili Pepper	Capsaicin	-6.2	-7.3
Ginger	Gingerol	-6.1	-6.6
Vanilla	Vanillin	-5.0	-6.4
Cloves	Eugenol	-4.9	-6.1
Thyme	Thymol	-4.8	-6.9

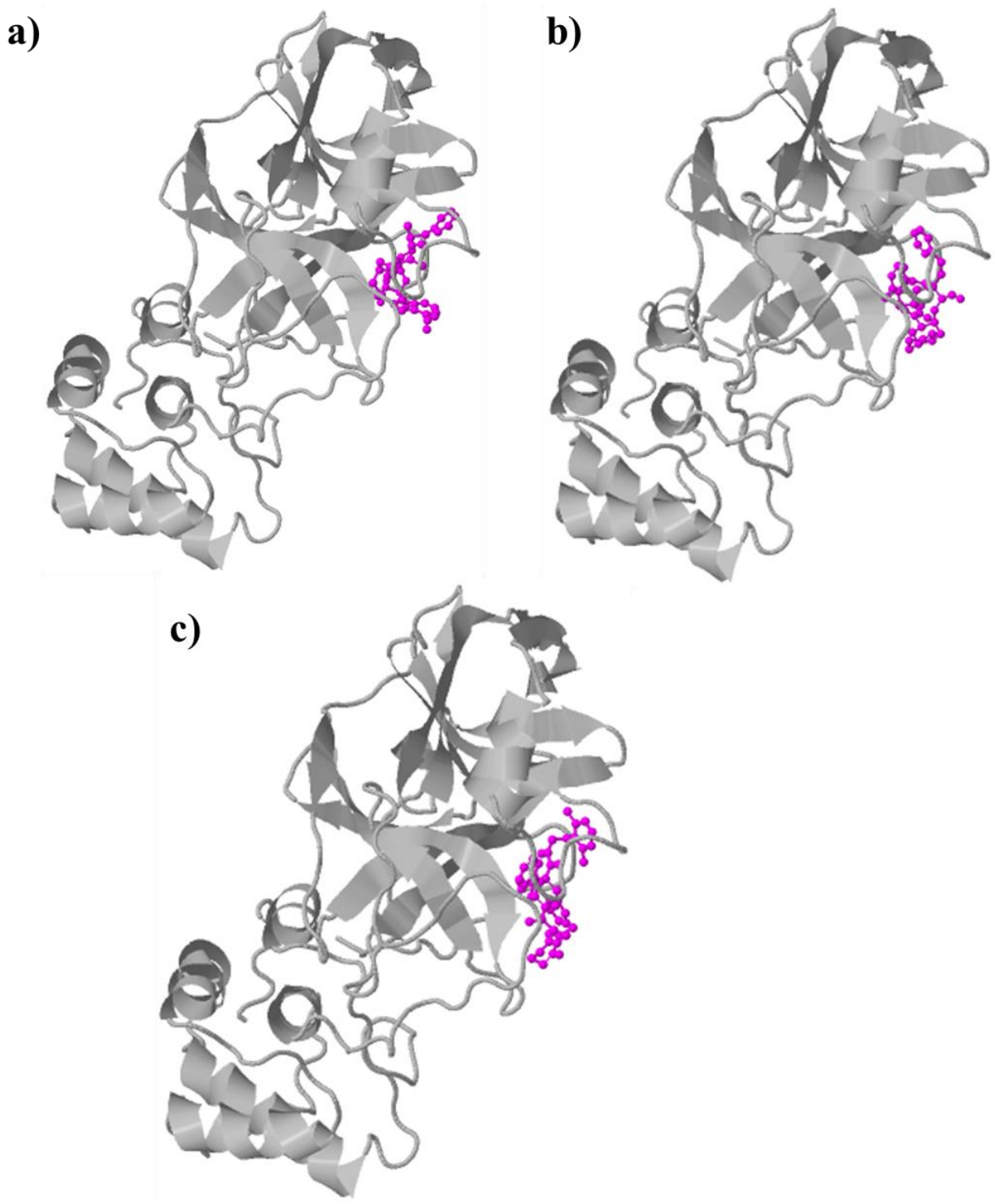

Figure 1: Best docked model visualization of antiviral drugs with M^{pro}; a) Remdesvir b) Nelfinavir c) Lopinavir

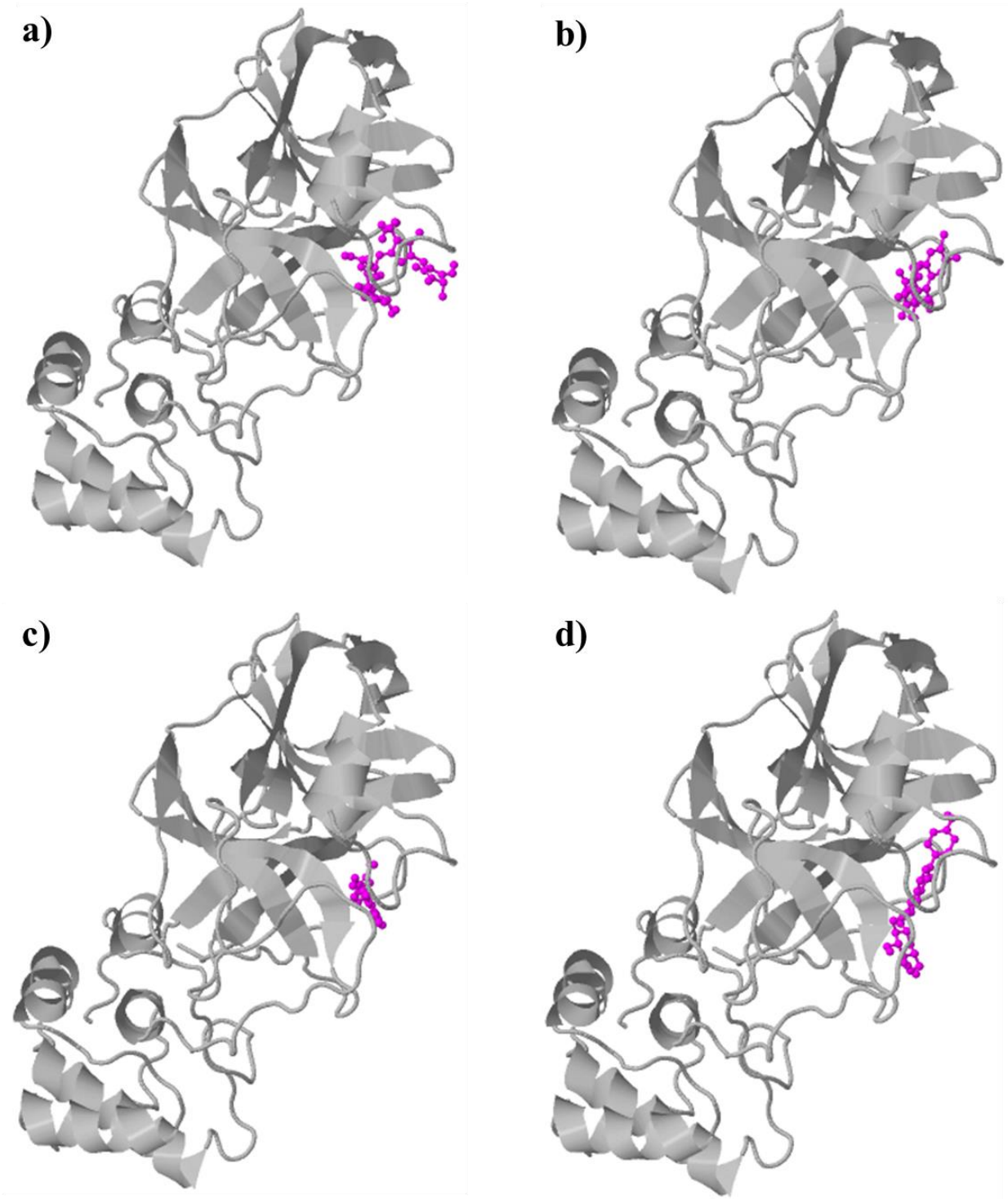

Figure 2: Best docked model visualization of bioactive compounds with M^{pro}; a) Phycocyanobilin b) Riboflavin c) Cyanidin d) Daidzein

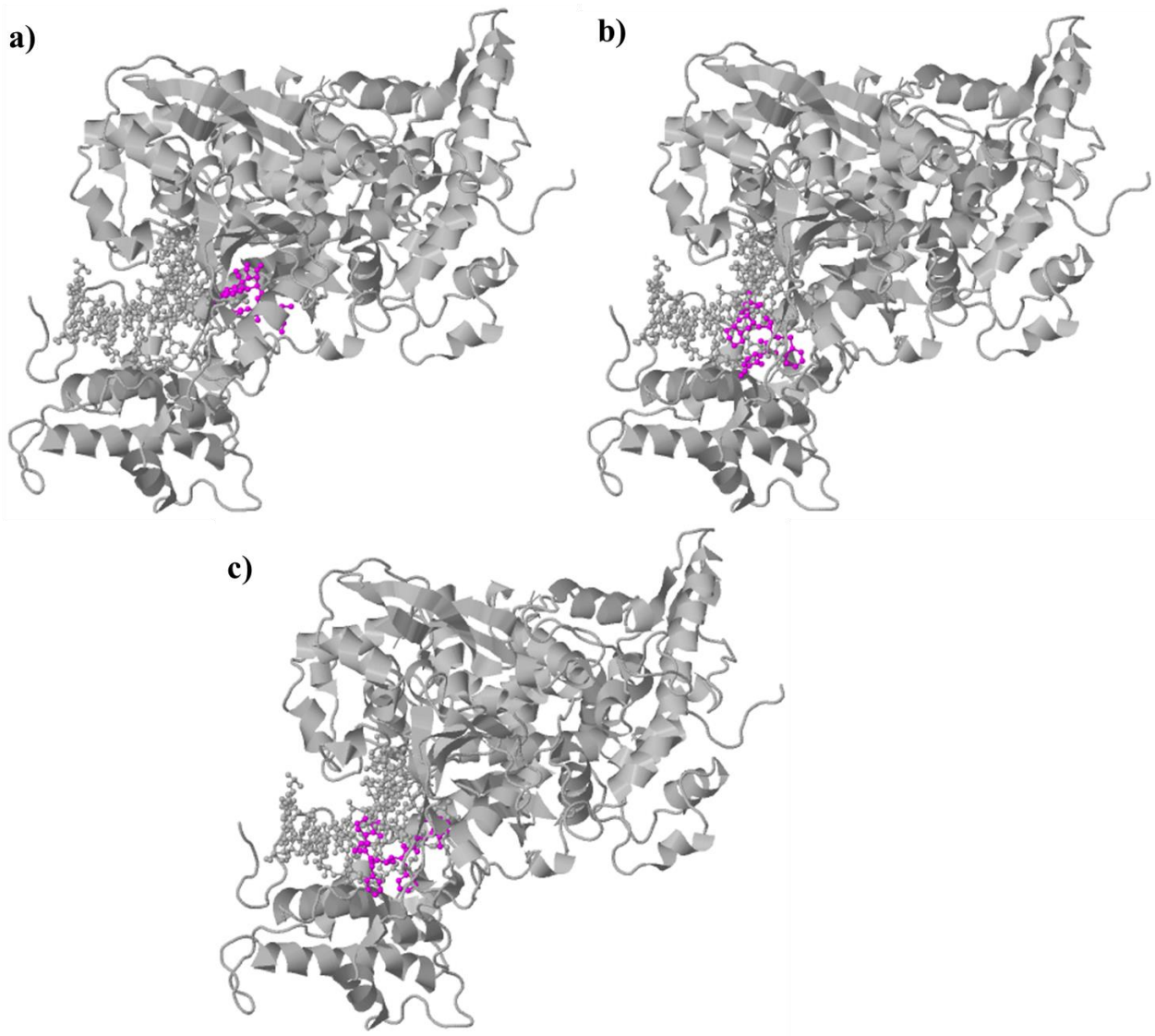

Figure 3: Best docked model visualization of antiviral drugs with RdRp; a) Remedesvir b) Nelfinavir C) Lopinavir

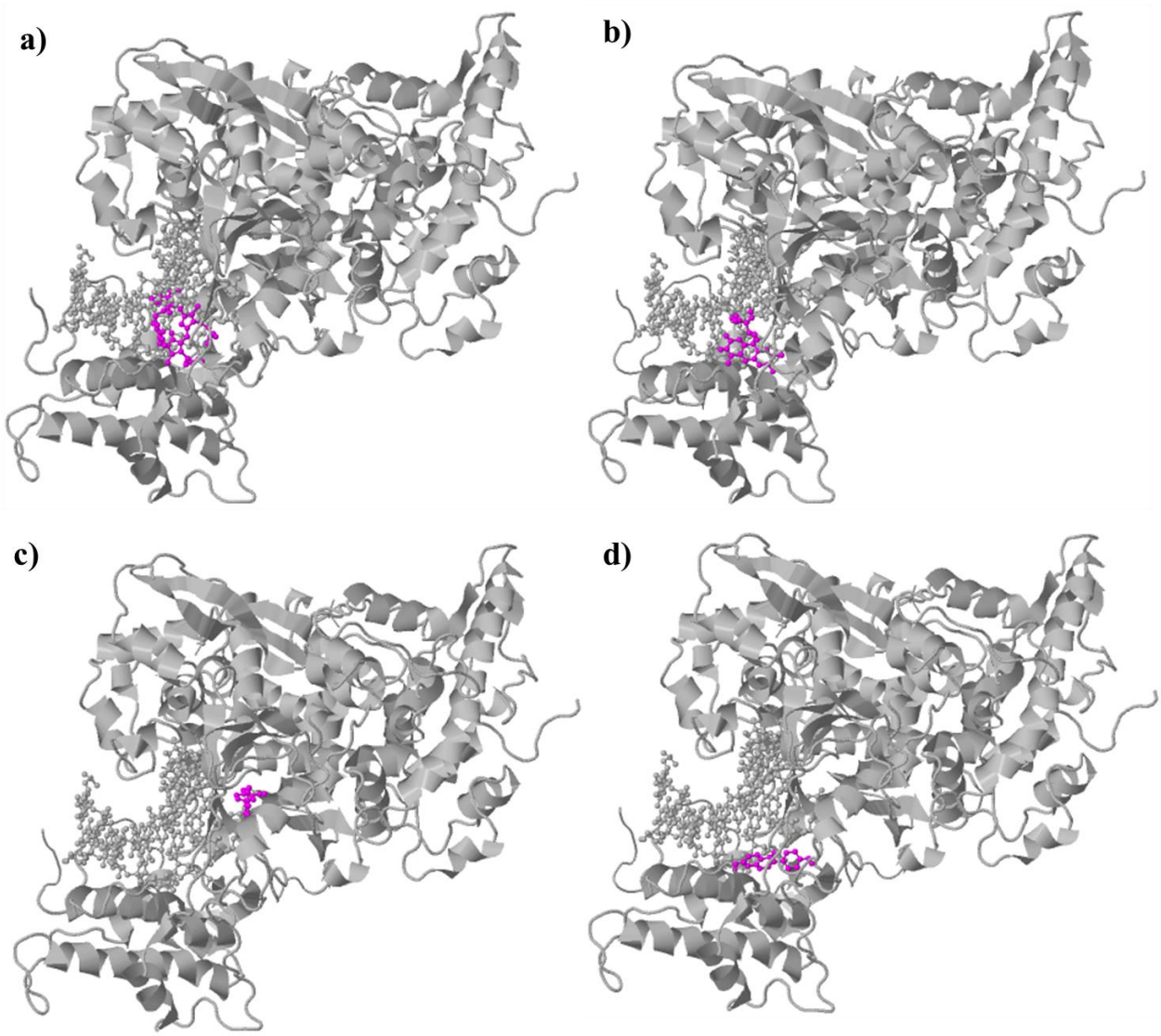

Figure 4: Best docked model visualization of bioactive compounds with RdRp; a) Phycocyanobilin b) Riboflavin c) Cyanidin d) Daidzein

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Note: There are no conflicts to declare

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