In Silico study of Wheatgrass constituents against Coronavirus COVID-19 Proteins

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Abstract

As a consequence of the COVID-19 pandemic, the virus associated with SARS-CoV-2 has emerged as an unparalleled global health crisis, marked by its extreme lethality and contagion. While vaccines offer a critical defense, they alone cannot guarantee a healthy future. Thus, alongside vaccine production, the development of effective treatments is imperative. This study is driven by the objective of exploring the therapeutic capabilities of specific chemical constituents found in Wheatgrass (Triticum aestivum Linn.) that hold potential for treating COVID-19. Seven distinct chemical constituents from Wheatgrass—namely, Ascobic acid (SWA00A), Rutin (SWA00B), Ferulic acid (SWA00C), quercetin (SWA00D), Luteolin (SWA00E), Apigenin (SWA00F), and Kaempferol (SWA00G)—were subjected to virtual screening.

The focus of this investigation encompassed COVID-19 viral proteins: 6lu7-SARS-CoV-2 main protease, 6zsl-SARS-CoV-2 helicase, 6w9c-papain-like protease of SARS-CoV-2, and 6m71-RNA-dependent RNA polymerase. As reference points, established drugs used in COVID-19 treatment, including Remdesivir, Darunavir, Ralimetinib, Berzosertib, Alpha-interferon, Arabinol, Chloroquine phosphate, Indinavir, Lopinavir, Ritonavir, Plegylated alfa interferon, and 2-chloro-2-deoxy-D-glucose, were employed as standards. Leveraging the PyRx Virtual Screening tool, molecular docking analyses were executed.

Among the seven chemical constituents evaluated, Rutin (SWA00B) showcased the most formidable binding affinity. This study's findings highlight the robust potential of Rutin, a component present in Wheatgrass, to inhibit key SARS-CoV-2 proteins. While Wheatgrass displays promising anti-SARS-CoV-2 properties, it's pivotal to underscore the necessity for further in-depth research to ascertain their efficacy within in vivo settings

Keywords: Wheatgrass, SARS-Cov-2, Molecular Docking, Rutin

INTRODUCTION

The Wuhan Municipal Health Commission initially reported a series of pneumonia cases in Wuhan, situated in Hubei Province. Subsequent investigations unveiled the cause of this pneumonia outbreak to be a novel coronavirus. The gravity of the situation escalated, prompting the World Health Organization (WHO) to declare a pandemic on March 12, 2020, due to the swift global dissemination of the SARS- CoV-2 virus and the increasing mortality attributed to Coronavirus Disease (COVID-19) [1, 2]. This emergence of COVID-19, a highly transmissible viral ailment triggered by the SARS-CoV-2 virus, instigated a nearly unprecedented global halt, resulting in over 3.8 million fatalities across the world. This calamitous toll ranks it as the most profound worldwide health crisis since the influenza pandemic of 1918 [3].

Throughout the course of this ongoing pandemic, SARS-CoV-2 has undergone evolutionary changes, giving rise to numerous variants. Among these, a select few have garnered the attention of the WHO as "variants of concern," largely due to their substantial impact on global public health. The WHO's latest epidemiological update records the emergence of five such variants of concern since the inception of the pandemic. These variants are identified as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta

(B.1.617.2), and Omicron (B.1.1.529) [3]. Currently, a diverse array of treatment options exists for COVID-19 management. These encompass antiviral medications such as molnupiravir, paxlovid, and remdesivir; anti-SARS-CoV-2 monoclonal antibodies like bamlanivimab/etesevimab and casirivimab/imdevimab; the anti-inflammatory drug dexamethasone; and immunomodulator agents such as baricitinib and tocilizumab. Many of these treatments have either received Emergency Use Authorization (EUA) from the FDA or are undergoing evaluation for COVID-19 treatment [4]. Despite the availability of vaccines, which hold promise in combatting the virus, a lasting cure remains uncertain, as the durability of vaccine efficacy is still undetermined. The utilization of medicinal plants in healthcare dates back thousands of years, with extensive global studies confirming their effectiveness. Indeed, some of these findings have even paved the way for the development of plant-derived medicinal treatments [5]. Nature has long been a source of remarkable therapeutic agents, and ancient civilizations used herbal plants to address conditions ranging from cancer to diabetes and atherosclerosis [6, 7]. This profound historical context underscores the enduring potential of natural remedies in the realm of modern medicine

Wheatgrass (Triticum aestivum) is the young grass of the common wheat plant. Notably nutrient-rich, this early-stage grass belonging to the wheat family boasts substantially higher levels of vitamins, minerals, and proteins compared to the mature seed kernels or grain products found in fully grown cereal plants [8]. Its significance as a dietary supplement has been acknowledged on a global scale [8, 9]. The grass derived from Triticum aestivum is particularly abundant in chlorophyll, amino acids, minerals, vitamins, and enzymes. The therapeutic attributes of its plant extracts primarily stem from the presence of bioactive components like phenols and flavonoids [8]. During the germination process, wheat sprouts undergo the synthesis of an array of vitamins, minerals, and phenolic substances, including flavonoids, rendering them at their peak antioxidant potential [9].

The diverse properties of this plant have proven to be advantageous; it possesses immunomodulatory, anti-inflammatory, antioxidant, diuretic, antibacterial, astringent, and anti-aging attributes. The application of this herb has demonstrated positive effects in addressing conditions such as acidity, colitis, kidney irregularities, atherosclerosis, and swelling [10].

The current study centers around a computational investigation of select chemical constituents present in Wheatgrass concerning their potential interactions with novel coronavirus proteins. Specifically, the proteins under scrutiny include the 6lu7 COVID-19 main protease, the 6zsl SARS-CoV-2 helicase, the 6w9c papain-like protease, and the 6m71 RNA-dependent RNA polymerase. In a prior study, our research had identified rutin as an inhibitor of PARP-1 [14]. Building upon this foundation, the present research delves into the assessment of certain chemical components sourced from Wheatgrass in relation to their interactions with proteins associated with SARS-CoV-2.

Material and Methods Insilico study

The term "insilico study" refers to a computational approach used to explore a chemical compound database in order to identify molecules that possess specific desired biological activities. In this study, we employed AutoDock Vina, which is integrated into PyRx 0.8 [35], to perform binding energy calculations. This technique involves using High Throughput Virtual Screening (HTVS) programs available through PyRx, which offers user-friendly graphical interfaces (GUIs). These programs utilize AutoDock to predict interactions between receptors and ligands. This method proves advantageous for comparing different ligands [36]. AutoDock Vina operates on the foundation of empirical scoring functions and has the added capability of automatically generating grid maps.

Preparation of Proteins:

The protein structures associated with SARS-CoV-2, denoted by their PDB IDs (6lu7, 6zsl, 6w9c, 6m71), were obtained from the Protein Data Bank (PDB) website (https://www.rcsb.org). These structures were visualized using Discovery Studio 4.0. Upon retrieval, the molecules were found in conjunction with water molecules and hetero-atoms. In order to prevent any interference during docking, Discovery Studio 4.0 was employed to eliminate these hetero-atoms and water molecules. Additionally, hydrogen atoms were introduced, and the modified structures were then saved in the PDB format.

Preparation of Ligands:

The 3D structures of the chemical constituents found in Wheatgrass and the standard drugs were sourced from the PubChem Database (https://pubchem.ncbi.nih.gov). These structures were acquired in the form of a structural data format (SDF). Subsequently, all of these structures underwent a minimization process using Open Babel, employing the Universal Force Field (UFF) as the force field and the conjugate gradients method as the optimization algorithm. This procedure was facilitated within PyRx 0.8.

Ligand protein docking

Docking procedures were executed using PyRx 0.8. Once the docking process was finalized, AutoDock preferences were extracted for both the ligand and the target, saved in the PDBQT format. The docking results, involving the protein and the ligand, were visualized through Discovery Studio 4.0. This allowed for a detailed analysis of the interactions between the ligand and the protein. Among the generated poses, the one with the lowest binding energy was selected as the most optimal interaction configuration

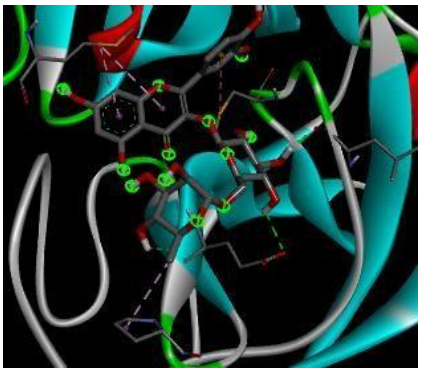
Results:

In silico studies were conducted utilizing PyRx to ascertain the binding affinity between proteins and molecules. Specifically, the proteins employed for this analysis included 6LU7, 6ZSL, 6W9C, and 6M71, alongside the delta variant protein 7V7Q and the Omicron spike protein, all derived from SARS-CoV-2. Detailed results of these investigations are outlined in Table

Table 1: Binding of ligands and standard with 6lu7-COVID-19 main protease.

Sr. No.	Protein	Binding Affinity			
1	6LU7 (SARS COV-2 main protease)	Chemical constituent		Standards	
		Ascobic acid	-5.1	Paxlovid	-6.5
		Rutin	**-9**	Molnupiravir	-7.4
		Ferulic acid	-6	Baricitinib	-6.4
		Quercetin	-7.3	Fluvoxamine	-6
		Luteolin	-7.4	Berzosertib	-8.1
		Apigenin	-7.8	Ralimetinib	-8.2
		Kaempferol	-7.1	Darunavir	-7.5
				Remdesivir	-6.6
				Alpha-interferon	-7.2
				Arabinol	-4.7
				Chloroquine Phosphate	-5.4
				Indinavir	-7.7
				Lopinavir Ritonavir mix structure	-7.5
				Plegylated alfa interferon	-4.3

				2-chloro-2-deoxy-D-glucose	-4.6



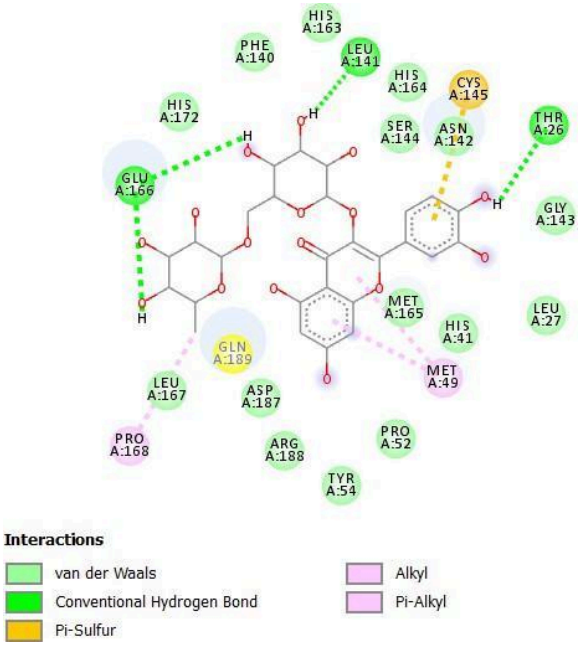


Figure 1: Molecular docking interaction of Rutin with 6LU7 (SARS COV-2 main protease.

Table 2: Binding of ligands with 6zsl-SARS-CoV-2 helicase.

Sr. No.	**Protein**	**Binding Affinity**			
1	6ZSL (SARS-CoV-2 helicase)	**Chemical constituent**		**Standards**	
		Ascobic acid	-5.5	Paxlovid	-7.3
		Rutin	**-9.3**	Molnupiravir	-8.3
		Ferulic acid	-6.4	Baricitinib	-7.5
		Quercetin	-8	Fluvoxamine	-5.9
		Luteolin	-7.8	Berzosertib	-8.6
		Apigenin	-7.8	Ralimetinib	-8.7
		Kaempferol	-7.7	Darunavir	-7.1

				Remdesivir	-8
				Alpha-interferon	-8.2
				Arabinol	-4.6
				Chloroquine Phosphate	-5.8
				Indinavir	-8.2
				Lopinavir Ritonavir mix structure	-7.9
				Plegylated alfa interferon	-4.6
				2-chloro-2 - deoxy-D-glucose	-5.3

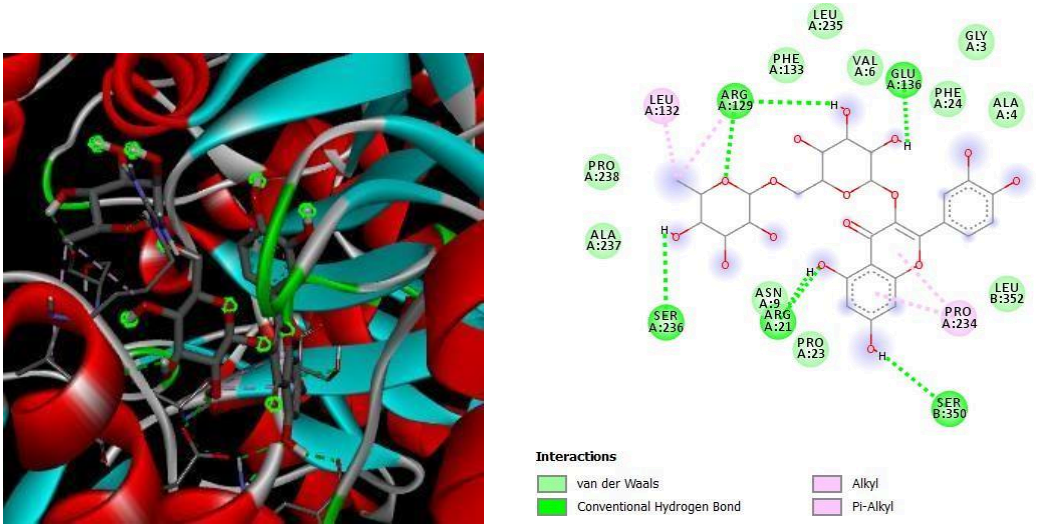
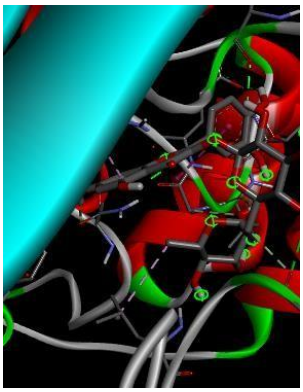


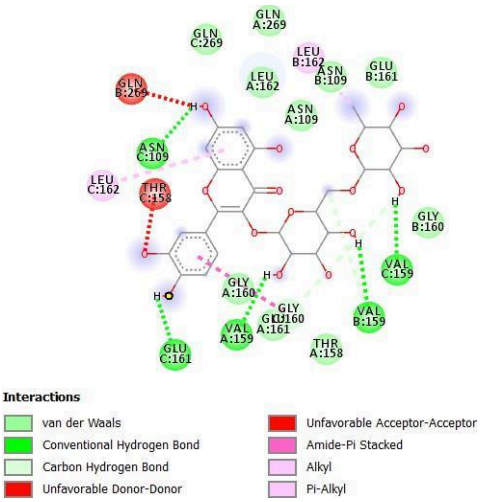
Figure 2: Molecular docking interaction of Rutin with 6ZSL (SARS-CoV-2 helicase).

Table 3: Binding of ligands with 6w9c-papain like protease of SARS CoV-2.

Sr. No.	Protein	Binding Affinity			
1	**6w9c-papain like protease of SARS CoV-2.**	**Chemical constituent**		**Standards**	
		Ascobic acid	-5.2	Paxlovid	-7.3

		Rutin	**-8.4**	Molnupiravir	-8.6
		Ferulic acid	-5.3	Baricitinib	-7.9
		Quercetin	-7	Fluvoxamine	-6.7
		Luteolin	-7.3	Berzosertib	-8
		Apigenin	-7.3	Ralimetinib	-7.1
		Kaempferol	-6.7	Darunavir	-6.5
				Remdesivir	-6.9
				Alpha- interferon	-7.6
				Arabinol	-4.8
				Chloroquine Phosphate	-4.6
				Indinavir	-7.2
				Lopinavir Ritonavir mix structure	-6.3
				Plegylated alfa interferon	-3.8
				2-chloro-2- deoxy-D-glucose	-5





6w9c

Figure 3: Molecular docking interaction of Rutin with 6w9c-papain like protease of SARS CoV-2.

Table 4: Binding of ligands with 6m71-RNA-dependent RNA polymerase.

Sr. No.	Protein	Binding Affinity			
1	**6m71-RNA-dependent RNA polymerase**	**Chemical constituent**		**Standards**	
		Ascobic acid	-5.6	Paxlovid	-6.5
		Rutin	**-9.5**	Molnupiravir	-8.1
		Ferulic acid	-5.5	Baricitinib	-6.4
		Quercetin	-7.4	Fluvoxamine	-6.2
		Luteolin	-7.6	Berzosertib	-8.1
		Apigenin	-7.4	Ralimetinib	-8.5
		Kaempferol	-7.1	Darunavir	-8.3
				Remdesivir	-8.3
				Alpha-interferon	-7.6
				Arabinol	-4.9
				Chloroquine Phosphate	-5.3
				Indinavir	-8.5
				Lopinavir Ritonavir mix structure	-7.8
				Plegylated alfa interferon	-4.3
				2-chloro-2-deoxy-D-glucose	-4.9

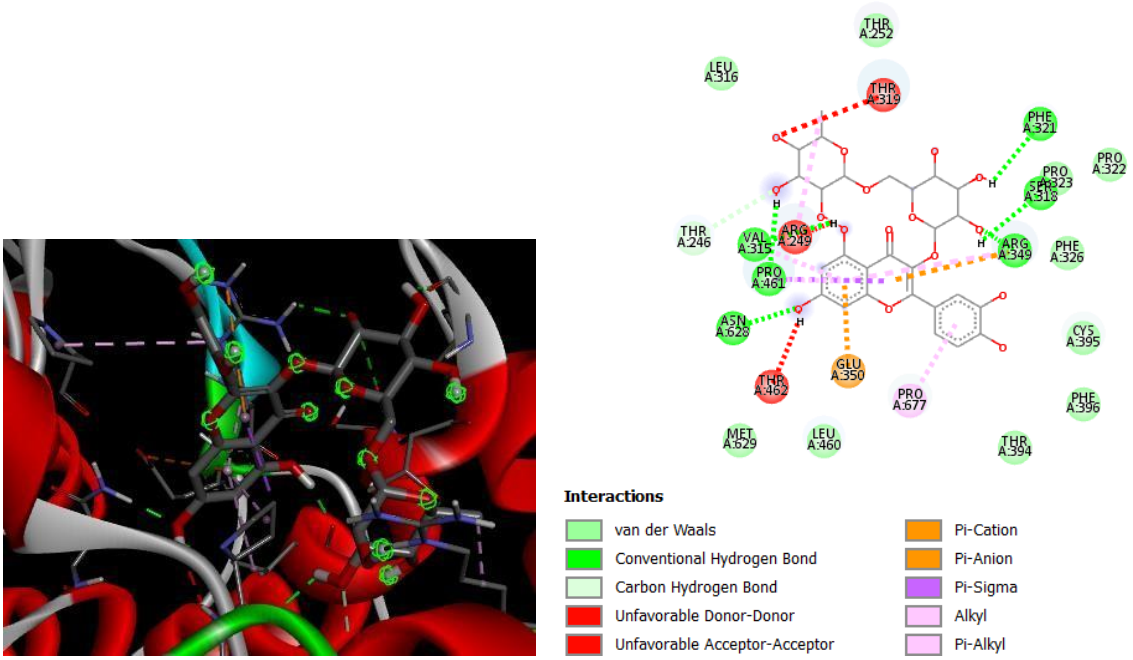


Figure 4: Molecular docking interaction of Rutin with 6m71-RNA-dependent RNA polymerase.

Table 5: Binding of Rutin with delta varient

Sr. No.	Protein	Binding Affinity			
1	**7v7q delta varient**	**Chemical constituent**		**Standards**	
		Rutin	-6.7	Paxlovid	-6.6
				Molnupiravir	-5.8
				Baricitinib	-6
				Fluvoxamine	-5.7

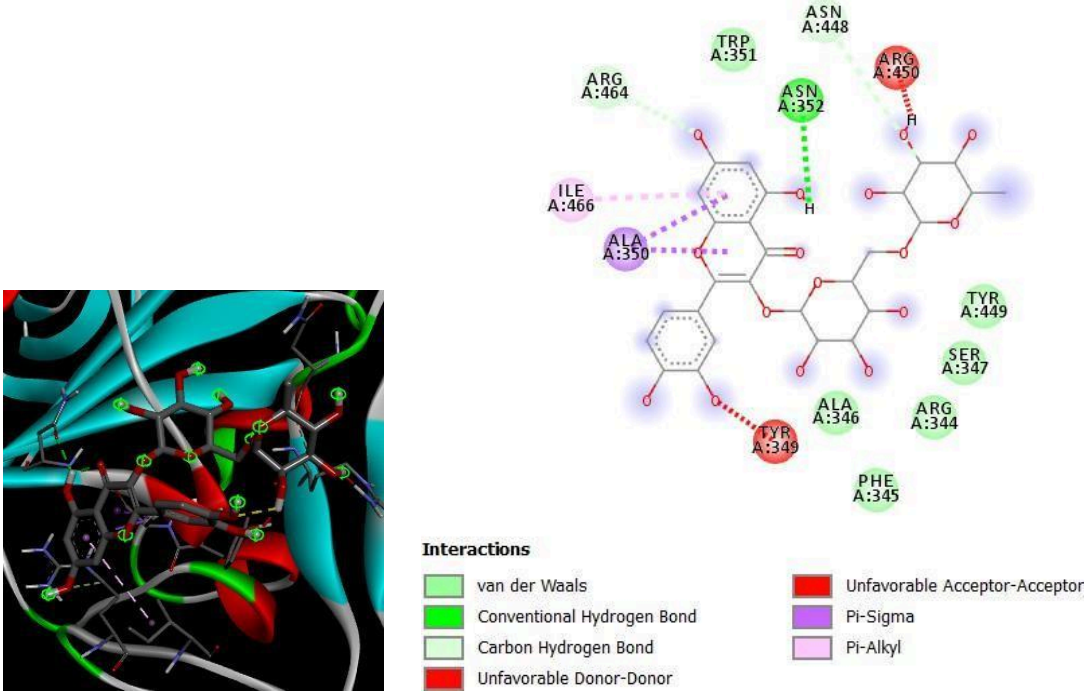


Figure 5: Molecular docking interaction of Rutin with 7v7q delta variant.

Table 6 : Binding of Rutin with omicron spike protein

Sr. No.	Protein	Binding Affinity			
1	**Omicron spike protein**	**Chemical constituent**		**Standards**	
		Rutin	-7.7	Paxlovid	-5.8
				Molnupiravir	-6
				Baricitinib	-5.8
				Fluvoxamine	-6.2

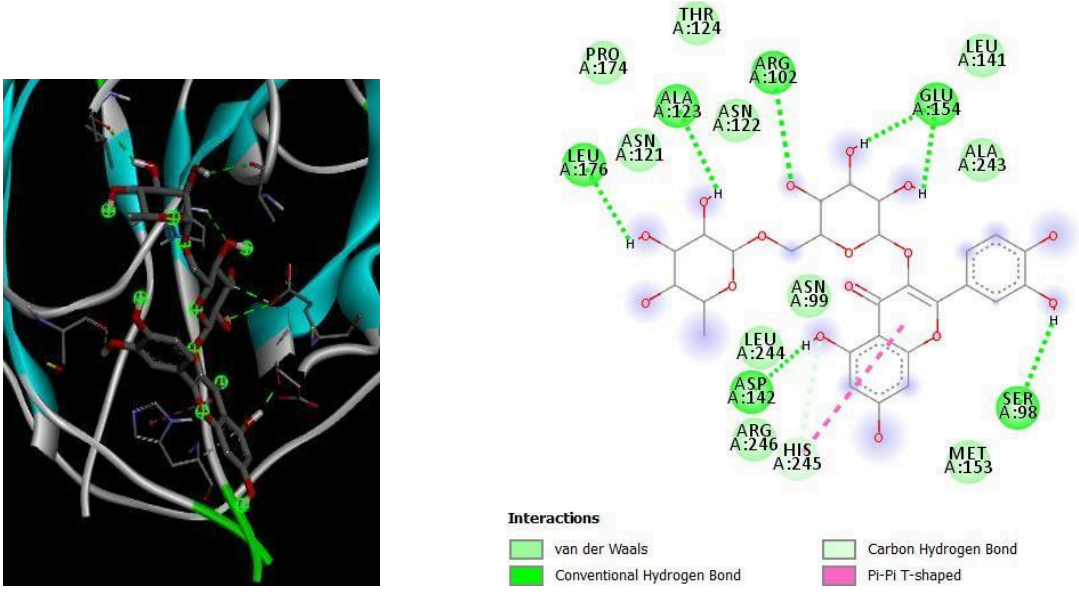


Figure 6: Molecular docking interaction of Rutin with Omicron spike protein

From the above result we can infer that SWA00B exhibited high binding affinity than that of standard drugs with SARS-COVID (6lu7-COVID-19 main protease, 6zsl-SARS-CoV-2 helicase, 6w9c-papain like protease of SARS CoV-2, 6m71-RNA-dependent RNA polymerase of SARS-COVID) proteins Binding energies of are as follows:

-9 kcal/mol against 6lu7 which is higher than the binding affinity of standard (Ralimetinib)

-9.3 kcal/mol against 6zsl which is higher than the binding affinity of standard (Ralimetinib)

-8.4kcal/mol against 6w9c which is higher than the binding affinity of standard (Berzosertib)

-9.5kcal/mol against 6m71 which is higher than the binding affinity of standard (Ralimetnib)

Discussion:

The virus responsible for the ongoing global pandemic has managed to infiltrate over 210 countries and territories, causing widespread concern. While experts initially theorized that the virus originated from animals and then transmitted to humans, there exists a plethora of conflicting reports regarding its true origin. Presently, treatment options for the virus are somewhat limited, primarily revolving around the utilization of antiviral agents like Remdesivir and Galidesivir [13].

In light of this critical situation, an intriguing avenue of investigation has emerged involving Wheatgrass and its potential antiviral properties against the SARS-CoV-2 virus. Numerous compounds with potential therapeutic applications have been scrutinized, and after a thorough review of the existing literature, a decision was made to assess the antiviral capabilities of seven specific chemical constituents—namely, ascorbic acid, Quercetin, Ferulic acid, Luteolin, Rutin, Kaempferol, and apigenin—found within Wheatgrass. Notably, the PyRx tool, employed for the analysis, pinpointed Rutin as the most suitable ligand among the selection, displaying a strong binding affinity towards proteins associated with SARS-CoV-2, specifically 6lu7, 6zsl, 6w9c, and 6m71.

Interestingly, Rutin, also known as Vitamin P within the realm of food processing, has earned recognition as an antioxidant. It has found extensive application in various complex vitamin supplements [13]. Chemically identified as 3,3’,4’5,7-pentahydroxyflavone-3-rhamnoglucoside, Rutin belongs to the flavonol subgroup of flavonoids and is naturally present in numerous plant species. Its pharmacological properties have been harnessed in human medicine and nutrition [15]. However, it is imperative to underscore that further comprehensive investigations centered around Rutin are necessary to unravel its complete potential.

In the interim, the consumption of Wheatgrass products—whether in the form of juice, powder, or tablets—holds promise as a preventive measure against SARS-CoV-2 infection. As research continues to shed light on the intricate interactions between natural compounds and viral infections, the avenue of Wheatgrass and its

constituents, particularly Rutin, presents an avenue worthy of dedicated exploration and further study.

Conclusion

In conclusion, the utilization of molecular docking analyses has proven to be instrumental in assessing the binding capabilities of certain chemical constituents found within Wheatgrass. Among the various compounds tested, SWA00B, specifically Rutin, has emerged as a highly promising candidate. This particular constituent demonstrated the most robust binding affinity when interacting with key proteins associated with the SARS-CoV-2 virus, including the 6lu7 COVID-19 main protease, the 6zsl SARS-CoV-2 helicase, the 6w9c papain-like protease of SARS-CoV-2, and the 6m71 RNA-dependent RNA polymerase of SARS-CoV-2. Notably, SWA00B exhibited superior binding affinity compared to all other ligands assessed in the study.

Given these findings, it is reasonable to propose that the Rutin-enriched fraction of Wheatgrass holds significant potential in offering protection against SARS-CoV-2 infection. However, it's essential to acknowledge that further investigations, particularly in vivo studies, are imperative to validate and reinforce the outcomes of this analysis. The pursuit of such research endeavors holds the promise of developing more potent therapeutic interventions for the management and control of SARS-CoV-2 infections. As we navigate the complexities of the ongoing pandemic, the exploration of natural compounds like Rutin offers a glimmer of hope in the quest for effective solutions against COVID-19.

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