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IN SILICO STUDY OF FLAVONOIDS AS POTENTIAL ANTAGONIST TARGETING NSP14 AND NSP15 OF SARS-CoV-2

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CANDIDATE'S DECLARATION

I Sanjoli, Roll Number: 2K21/MSCBIO/40, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled "**IN SILICO STUDY OF FLAVONOIDS AS POTENTIAL ANTAGONIST TARGETING NSP14 AND NSP15 OF SARS-CoV-2**" in the fulfillment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology,DTU, is an authentic record of my own carried out during the period from Jan to May 2023, underthe supervision of **Dr. Navneeta Bharadvaja**.

I have not applied for any other degree at this or any other University based on the information contained in this report. The following details about the related study have been approved in the SCI/SCI Scopus Index Conference:

Title of the Paper: "COMPUTATIONAL ANALYSIS OF POTENTIAL FLAVONOIDS TARGETING NSP14 OF SARS-COV-2 : A MOLECULAR DOCKING APPROACH"

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DEPARTMENT OF BIOTECHNOLOGY

CERTIFICATE

This is to certify that the Project dissertation titled "IN SILICO STUDY OF FLAVONOIDS AS POTENTIAL ANTAGONIST TARGETING NSP14 AND NSP15 OF SARS-CoV-2" which is submitted by Sanjoli Khare, 2K21/MSCBIO/40, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Sciences, is a record for the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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Abstract

Since December 2019, the continuing SARS-CoV-2 global pandemic has created a serious medical emergency and led the COVID-19 sickness to spread globally. This highly infectious virus spreads quickly across communities when it comes into intimate contact with an infected person or by respiratory aerosols. We concentrated our research efforts on finding possible therapeutic proteins for the exonuclease enzymes (nsp14 and nsp15) of SARS-CoV-2. To reduce immune-mediated responses brought on by the viral infection, our goal was to pinpoint flavonoids as enzyme antagonists. A thorough examination was carried out, including assessing the drug-likeness of 26 flavonoids and in silico molecular docking. The goal was to locate possible flavonoids that effectively bind to the target protein, opening up the possibility of additional research into these compounds as potential therapeutics. The flavonoids were gathered from research publications and COCONUT. Nobiletin, presented robust interactions with nsp14 due to their prolonged close contact and minimal binding energies of 7.27 kcal/mol, respectively. Isorhoifolin, Neoeriocitrin and Poncirin inhibited the activity of the nsp14 replication fork with binding affinity scores of - 7.9, -7.83 and -8.37 kcal/mol, respectively. Similarly, Casticin, Ganhuangenin, Olumiant and Nobiletin are the flavonoids that presented robust interactions with nsp15 due to their prolonged close contact and minimal binding energies of -7.96, -8.17, -8.06 and -7.93 kcal/mol, respectively. Potential SARS-CoV-2 flavonoids predicted by computation are known to have a variety of therapeutic benefits.

Keywords— Flavonoids, SARS-CoV-2, Nsp14, Molecular Docking, Toremifene, Nobiletin, Tipiracil, Casticin, Ganhuangenin, Olumiant

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CHAPTER-1

1. Introduction

The term "coronavirus disease 2019" (COVID-19) refers to an infectious condition brought on by the SARS-CoV-2 virus. In December 2019, news of the initial SARS-CoV-2 epidemic was released. Initially, it was thought to be a cluster of pneumonia cases of unclear cause. The genesis and evolution of SARS-CoV-2 might be attributed to bats, and SARS-CoV-2 could have developed spontaneously from bat coronavirus RaTG13 [1]. The infection swiftly spread across Wuhan and subsequently throughout China followed by the whole world.

Patients are the main source of infection, both symptomatic and asymptomatic. From mild to severe Fever, coughing, breathing problems, tiredness, loss of taste or smell, sore throat, and bodily aches are all possible COVID-19 symptoms. COVID-19 is classified into three stages based on illness severity: moderate, severe, and critical. Since its spread, SARS-CoV-2 is the source for extreme respiratory disease. Aside from that, there have been reports of significant cases of cardiac damage, coagulation disorders, and thrombotic consequences.[2]

SARS-CoV-2 viruses are enclosed viruses with a single-stranded RNA genome that is positive. [3] They are pleomorphic RNA viruses with crown-shaped peplomers that belong to the family Coronaviridae. [4]

The nucleocapsid protein is in charge of SARS's outer capsid, and the envelope protects the DNA. It is associated to three structural proteins: membrane protein (M), spike protein (S), and the protein that forms the envelope (E).

Non-structural proteins (nsps), encoded by the RNA genome, plays crucial roles in viral replication, evasion of the host immune response, and modulation of host cell functions and understanding their roles and interactions is critical for developing COVID-19 antiviral therapies and vaccines.[5]

There are about 16 NSPs found in SARS CoV-2. While nsp1 reduces host gene expression, reducing host antiviral protein synthesis and boosting viral multiplication, nsp2 and nsp4 aids in the evasion of the host immune response and may aid in viral replication and assembly [6]

One of the important nsp's is nsp3, also known as papain-like protease (PLpro). Nsp3 and Nsp5 are involved in the cleavage of the viral polyprotein into separate functional components. It also deubiquitinates, modulates the host immunological response, and promotes viral reproduction.[7]

Similarly, proteins, known as nsp7 and nsp8, constitute the Complex of RNA-dependent RNA polymerase. They are required for viral RNA replication because the RdRp complex generates new viral RNA molecules and nsp10 protein functions as a cofactor for the RdRp complex, increasing its activity in viral RNA production.

Likewise, Nsps 14,15 and 16 work together in a complex where nsp 14 works as a proofreader and helps in maintaining the fidelity of viral RNA replication, which reduces the incidence of mistakes in the viral genome and nsp15, also known as endoribonuclease (NendoU), is a viral RNA processing enzyme that may assist the virus elude detection by the host immune system whereas nsp16 protein is in charge of methylating the viral RNA cap structure. Methylation aids the virus in evading detection by the host immune system.[8]

Non-structural proteins possess tremendous importance in SARS-CoV-2 multiplication and survival within host cells. Therefore, understanding their roles and interactions is critical for developing COVID-19 antiviral therapies and vaccines. [9]. The research objective of this study is to investigate the potential of targeting non-structural proteins 14 (nsp14) and 15 (nsp15) of SARS-CoV-2 as candidates for molecular docking analysis. [10] By focusing on these specific proteins, it is aimed to explore their structural and functional properties and assess their potential as druggable targets for the development of novel antiviral therapeutics. [11] , [12]

Toremifene, which is FDA authorised for breast cancer, and Tipiracil, which is FDA approved for colorectal cancer, were utilised as controls for the docking study, which targeted NSP14 and NSP15 of SAR-CoV-2. The study wanted to analyze the reliability and correctness of our computational technique by integrating Toremifene and Tipiracil as controls in our docking analysis. Flavonoids, which have received a lot of interest in pharmaceutical research due to their health advantages and low side effects, are employed in this docking investigation. [14], [15]

Approximately 28 flavonoids with antiviral activities and reduced binding energies with target proteins were selected. In this investigation, two FDA-approved medicines for breast cancer and colorectal cancer, toremifene and tipiracil, were employed as control substances. There drugs were choosen because of their low binding energy and substantial interactions with nsp14 and nsp15, establishing a baseline for measuring the binding ability of flavonoids. The purpose of this project is to identify a medication to treat covid 19 by using flavonoids as a pharmacological option.

Chapter 2: Literature Review

2.1 Structure of SARS CoV-2

The SARS CoV-2 genomic sequence is a positive-sense RNA with a single-stranded genome which includes all of the genetic material required for viral replication and protein production. [16] From SARS to SARS-CoV-2, insights on structure, pathogenicity and immunity aspects of pandemic human coronaviruses. [17]

Mechanisms of SARS-CoV-2 entry into cells Other proteins found in the viral structure include Envelope (E) Protein, a tiny transmembrane protein that aids in the assembly and release of new viral particles, Membrane (M) protein that interacts with the viral nucleocapsid and envelope protein during viral assembly, Spike (S) Protein is a big glycoprotein that plays an important role in viral entrance into host cells by binding to the ACE2 receptor on human cell surfaces and Nucleocapsid protein (N), which binds to the viral RNA genome to create the viral nucleocapsid, aids in RNA packaging, viral replication, and host immune response control.[1]. Various replication complexes are also present in addition to those. Double-membrane vesicles (DMVs), which are specialist structures, where SARS-CoV-2 replicates in infected host cells. These DMVs are made from host cell membranes and act as places where viruses may replicate and assemble.

2.1.1. SARS CoV-2 antiviral therapy's potential molecular targets

The spike protein facilitates viral entry into host cells and can be blocked by neutralising antibodies or small molecule inhibitors [18] Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. [19] [20] The main protease (nsp5) [21] are vital for viral replication and polyprotein processing, [22] making them attractive targets for the development of protease inhibitors, [23]. Because it is necessary for viral RNA replication and transcription, the RNA-dependent RNA polymerase (nsp12) is a viable target for nucleotide analogues [24] and polymerase inhibitors. Due to their functions in RNA processing and host immune response regulation, other [26] non- structural proteins including nsp14 [27] and nsp15 have also been identified as possible targets. Also being investigated as possible targets for antiviral action are host elements implicated in viral entrance and replication, such as the ACE2 receptor and host proteases like TMPRSS2. [28] In order to effectively battle COVID-19, it is necessary to create targeted therapies that attempt to obstruct COVID-19 replication, entrance, and immune evasion. This is made possible by understanding the molecular targets of SARS-CoV-2. [29]

2.2 Viral proteins NSP14 and NSP15 as prospective molecular targets for CoV-2 antiviral treatment for SARS

NSP14 and NSP15 viral proteins have emerged as promising molecular targets for antiviral intervention against SARS-CoV-2. NSP14, also known as the exonuclease, is essential for proofreading viral RNA during replication, hence increasing the virus's replication fidelity. Targeting NSP14 may interfere with its proofreading function, increasing the likelihood of introducing mistakes into the viral genome, potentially lowering viral fitness and replication ability. NSP15, on the other hand, functions as an endoribonuclease and is involved in the digestion of viral RNA. [30]

Inhibiting NSP15 may prevent viral replication while also modulating the host immunological response. NSP14 and NSP15, due to their important roles in viral replication and RNA processing, present intriguing pathways for the development of antiviral therapies. Researchers hope to interfere with viral replication, damage viral RNA integrity, and reduce the pathogenicity of SARS-CoV-2 by targeting these proteins. The discovery of NSP14 and NSP15 as molecular targets opens the door to the development of new antiviral medicines and therapeutic approaches to attack COVID-19.

NSP 14 is dual-functioning in nature because it has an N-terminal exonuclease (ExoN) domain and a C-terminal part. The N-terminal exonuclease (ExoN) domain is thought to boost CoV RNA efficiency.[31]

The other protein is Nsp15, a member of the EndoU family with a C-terminal catalytic domain that is a crucial element of coronavirus pathogenesis that is highlighted in nsp15 mutant viruses. Coronaviruses with nsp15 mutations increase IFN production that is dependent on MDA5 and activate host dsRNA sensors. [32] [33]

2.3 Flavonoids as potential antiviral agents for the future

Flavonoids, a type of natural chemicals abundantly found in plants, have showed promise as possible antiviral medicines against several viral diseases, including SARS-CoV-2. They have a wide range of biological activities, including antiviral properties, making them intriguing therapeutic options.

Through preventing viral fusion and adherence to host cells, flavonoids can stop viral

entry. Inhibiting viral enzymes like RNA-dependent RNA polymerase or proteases, which are necessary for viral replication and assembly, can also stop viral replication. Additionally, flavonoids have immunomodulatory characteristics that allow them to control how the host immune system reacts to viral infections. In order to lessen the inflammation brought on by viral infections, they can increase the generation of antiviral cytokines, promote the activity of immune cells, and display antioxidant properties.

Flavonoids have been investigated for their potential inhibitory effects on viral entry, replication, and inflammation associated with COVID-19 in the setting of SARS-CoV-2. Potential interactions between flavonoids and viral proteins, such as the spike protein, major protease (Mpro), and RNA-dependent RNA polymerase (RdRp), have been discovered by molecular docking studies. [34] While further research is required to prove flavonoids' efficacy against SARS-CoV-2, their all-natural makeup, minimal toxicity, and variety of antiviral routes make them attractive candidates for inquiry. Flavonoids have the potential to be powerful antiviral medicines that might help in the creation of cures and preventative measures for viral diseases like COVID-19. [35]

A library of 25 flavonoids was meticulously compiled for the current study from a variety of sources, including research journals, scientific databases, and botanical references. A thorough review and exploration of the literature was carried out in order to identify flavonoids with diverse structural properties and potential antiviral properties. Flavonoids from diverse plant sources, such as fruits, vegetables, and medicinal plants, were included to guarantee a comprehensive representation of chemical variety within the collection. The selection of these flavonoids was based on their reported bioactivity, antiviral potential against other viral infections, and their ability to interact with viral targets of interest, including viral proteins involved in replication and host cell interaction. The work

intends to completely examine their potential as antiviral medicines against SARS-CoV-2 by including this varied group of flavonoids, as well as providing insights into their structure-activity connections and binding interactions with viral targets.

Nobiletin	Licuraside	Isorhoifolin	Cernuoside
Casticin	Ganhuangenin	Olumiant	Hesperidin
Neohesperidin	Amentoflavone	Daidzen	Formononetin
Morin	Genistein	Sovaldi	Naringin
Neoeriocitrin	Iristectorigenin A	Poncirin	Acacetin
Afzelechin	Amurensin	Astragalin	Baicalein
Bractein	Castillicetin	castilliferol	wogonin

1.TABLE List of flavonoid compounds taken.

2.4 Molecular docking as a computational tool.

Molecular docking simulates the binding process between a ligand and a target protein, allowing researchers to evaluate the strength and quality of the binding as well as predict the binding pose and affinity.[36] Identification of potential drug candidates, lead compound optimisation, and comprehension of the molecular mechanisms underlying ligand-target interactions all depend on this knowledge. Molecular docking employs algorithms and scoring functions to assess the complementarity between the ligand and target, taking into account factors such as shape, electrostatics, and hydrophobicity. By eliminating the need for time-consuming experimental screening, molecular docking speeds up the process of finding new drugs by screening enormous chemical libraries and

offering insights into ligand-target interactions. [37] But it's crucial to remember that molecular docking is a computational method, and its conclusions should be confirmed by empirical research. Molecular docking is frequently employed in drug discovery to speed the identification and optimization of promising drug candidates and acts as a vital tool in drug discovery, supporting the rational design and development of new therapeutic medicines.

2.5 Control Compounds used in Molecular Docking Analysis

For the molecular docking analysis in this study, two FDA-approved medications, Toremifene and Tipiracil, were chosen as control compounds.

Toremifene, a selective estrogen receptor modulator, has been approved for the treatment of breast cancer and has shown potential antiviral activity against certain viruses. According to one study, the interaction with NSP14 has the potential to be inhibitory in three ways: first, it appears to cause steric interference between toremifene and any functional ligands, as well as impairing base interaction in the contributing pocket, and finally, it shows a fairly high affinity of -7.8 during the virtual screening procedure. Toremifene was repurposed as one of the antiviral medications against COVID-19 because of these factors. [38]

Contrarily, **Tipiracil**, a thymidine phosphorylase inhibitor, is used in conjunction with other medications to treat colorectal cancer. Tipiracil suppresses SARS-CoV-2 Nsp15 by interacting with the uridine, which binding pocket in the enzyme's active site, according to crystallographic, biochemical, and whole-cell examinations. [39] Due to their well-

established pharmacological profiles and well-known binding properties, these FDA-approved medications were selected as control compounds. The docking analysis aims to provide a benchmark for assessing the binding energies and interactions of other ligands with the target proteins of interest by using Toremifene and Tipiracil as controls.

Chapter 3:

Tools and Materials used in the molecular docking analysis.

For the current inquiry, we used software such as SwissDock, Biovia Discovery Studio, UCSF Chimaera, SwissDock ADME, as well as other bioinformatics tools and biological databases including PubMed, PubChem, and PDB (Protein Data Bank).

1.] SwisDock- The programme used in molecular docking to predict the binding affinities and modalities of small molecules (ligands) with target proteins. It is based on protein-ligand interaction. [40]

2.] Biovia Discovery Studio- A software package for computational drug discovery and molecular treatment to visual 2D and 3D diagrams of molecules and analyze their binding interactions.[41]

3.] UCSF Chimaera- The molecular visualization and analysis software suite offers tools for molecular modelling, interactive 3D visualization, and structural data analysis. [42]

4.] Protein Database Bank- The Protein Data Bank (PDB), repository that serves as a global resource for three-dimensional structural data of biological macromolecules, especially proteins.[43]

Chapter 4:

Methodology

4.1 Preparation and Refinement of Protein

The Protein Database (PDB) was used to derive the structures of the target proteins NSP14 (7R2V) and NSP15 (7RB0). Biovia discovery studio was employed for the clarification of the protein's structural details. This was utilised to remove water molecules, ligands, and heteroatoms. Non-polar hydrogens were then added, and the process was finished using a Gasteiger charger. The protein's active areas were also discovered using Biovia Discovery Studio. The protein that was produced was stored in PDB format.

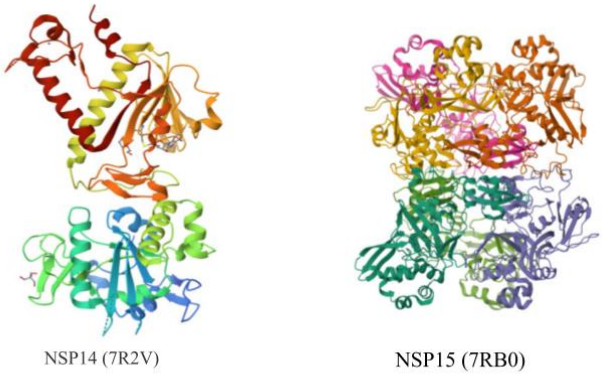


Fig.1 Structure of NSP14 (7R2V) and NSP15 (7RB0) (Source- PDB)

4.2 Preparation of Flavonoids as ligand library

Toremifene (PubChem ID:3005573) and Tipiracel (PubChem ID:6323266), two FDA-approved medications used as controls, and a number of flavonoids were retrieved in SDF format via PubChem. Later, they were transformed into Mol2 format with the aid of the Biovia discovery studio.

4.3 Molecular Docking

Molecular docking was accomplished using the Swiss dock. (http://www.swissdock.ch/) [44] Targets in PDB format for proteins and ligands in Mol2 format are both accepted by Swiss dock. First, a protein was molecularly docked with the drugs Toremifene and Tipiracil as a control, and the binding energy was recorded along with a 3D and 2D diagram of the protein-ligand interaction.

The 2D and 3D structural diagrams of the protein-ligand interaction were generated using Biovia Discovery Studio and UCSF Chimaera (http://www.cgl.ucsf.edu/chimera/)[45]. The target protein was then docked with the 25 different flavonoids that were collected as samples after this phase.

4.4 Docking Analysis

By contrasting different flavonoids' binding energies with Toremifene and Tipiracil and looking at the interaction between proteins and ligands, numerous flavonoids were studied. Toremifene-equivalent or higher-binding flavonoids were chosen (Fig. 3 shows 2D diagrams of the shortlisted flavonoids' interactions with proteins as ligands). To

determine if particular flavonoids might make excellent candidates for pharmacological development, Lipinski's Rule of Five was studied. Swiss ADME (http://www.swissadme.ch/) Identification of Cyanobacteria-Based Natural Inhibitors Against SARS-CoV-2 Druggable Target ACE2 Using Molecular Docking Study, ADME and Toxicity Analysis and Molinspiration (https://molinspiration.com/cgi-bin/properties) were used to investigate the Bioavailability score and Bioactivity.

Chapter 5:

Results

5.1 Docking analysis of Flavonoid-NSP14 interactions

5.1.1 Binding affinity and scoring analysis of Flavonoid-NSP14 interactions.

The comparison of the docking results between the NSP 14 receptor molecule and the conventional drug Toremifene and various shortlisted Flavonoids was performed. Isorhoifolin, Monoxerutin, Neoeriocitrin, Narcissoside, Poncirin, Engeletin, Iristectorigenin A, Cosmosiin, Silymarin, Nobiletin are among the few shortlisted flavonoids which have greater or comparable binding energies with Toremifene. The binding energies of Toremifene and various shortlisted flavonoids are tabulated below (TABLE II.) The bioavailability scores of flavonoids are mentioned in TABLE II.

Table 2. Comparison of Binding energies of different flavonoids and their respective Bioavailability scores for NSP14 (Using Swiss dock and Swiss ADME)

Flavonoid	Binding Energy (Kcal/mol)	Bioavailability Score
Iristectorigenin A	-7.19	0.55

Isorhoifolin	-7.9	0.17
Neoeriocitrin	-8.18	0.17
Poncirin	-8.19	0.17
Nobiletin	-7.27	0.55

5.1.2 ADMET Analysis.

Refer to TABLE III for a summary of the flavonoid analysis on the different Lipinski parameters. In TABLE II, several flavonoids' bioavailability ratings are listed. Nobiletin has high bioactivity and bioavailability ratings and also adhere to Lipinski's rule of five.

Using factors like a compound's molecular weight, lipophilicity (logP), and the quantity of hydrogen bond donors and acceptors, Lipinski's Rule of Five, a guiding principle in the field of drug discovery, establishes criteria to evaluate the likelihood of a compound's success as an orally administered drug.

The molecular interactions of the flavonoid Nobiletin are shown in Figs. 1 and 2, respectively, as radar plots and 3D structures.

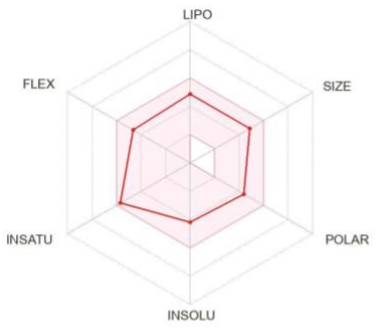
Table 2. In silico pharmacokinetics of ligands (in NSP14) (using Swiss ADME)

Flavonoid	Weigt (g/mol)	Hydrogen bond donor	LogP	Molar Refractivity	Hydrogen bond acceptor
Iristectorigenina	330.29 g/mol	3	2.73	86.97	7
Isorhoifolin	578.52 g/mol	8	2.98	137.33	14
Neoeriocitrin	596.53 g/mol	9	2.15	136.94	15
Poncirin	594.56 g/mol	7	3.02	139.38	14

Table.2 Bioactivity of Flavonoids (NSP14) (Using Molinspiration)

Flavonoids	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Nobiletin	-0.13	-0.04	0.09	0	-0.22	0.11
Isorhoifolin	0.05	-0.32	-0.01	-0.03	0.01	0.24
Neoeriocitrin	0.07	-0.5	-0.3	0.04	0.07	0.17
Iristectorigenin A	-0.22	-0.62	0.01	0.04	-0.67	0.03
Poncirin	0.05	-0.52	-0.31	-0.08	0.06	0.15

5.1.3 Radar plots of potential flavonoids



Nobiletin

Fig. 2 Radar plots of Nobiletin (Source- Swiss ADME)

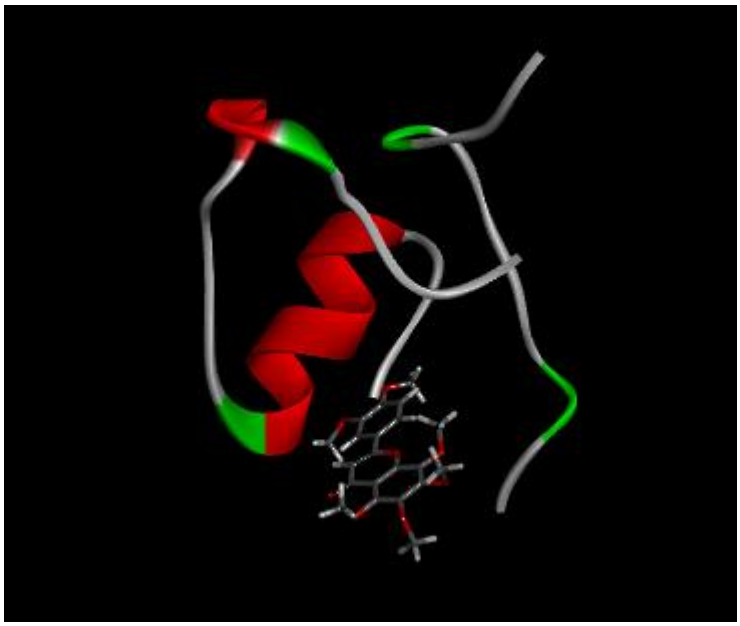


Fig.3 Molecular Interactions of Flavonoid Nobiletin with NSP14. (Source- UCSF Chimera)

5.2 Docking analysis of Flavonoid-NSP15 interactions

5.2.1 Binding affinity and scoring analysis of Flavonoid-NSP15 interactions.

The docking data between the NSP 15 receptor molecule, the control medication Tipiracil, and the several selected flavonoids were compared. The few flavonoids that have been nominated and exhibit binding energies that are higher or comparable to those of Tipiracil include **Licuraside, Isorhoifolin, Cernuoside, Casticin, Ganhuangenin, Neohesperidin, Amentoflavone, Sovaldi, Naringin, Olumiant, Hesperidin and Nobiletin**. The table below (TABLE II) lists the binding energies of Tipiracil and the

several flavonoids that made the short list. In TABLE II, several flavonoids' bioavailability ratings are listed.

Table 2. Comparison of Binding energies of different flavonoids and their respective Bioavailability scores. (NSP15) (Using Swiss dock and Swiss ADME)

Flavonoids	**Binding energies**	**Bioavailability scores**
Licuraside	-9.18	0.55
Isorhoifolin	-9.22	0.55
Cernuoside	-8.6	0.55
Casticin	-7.96	0.55
Ganhuangenin	-8.17	0.55
Neohesperidin	-8.51	0.55
Amentoflavone	-8.08	0.55
Sovaldi	-9	0.55
Naringin	-9.44	0.55
Olumiant	-8.06	0.55
Hesperidin	-8.53	0.55
Nobiletin	-7.93	0.55

5.2.1. ADMET Analysis

Refer to TABLE III for a summary of the flavonoid analysis on the different Lipinski parameters. In TABLE II, several flavonoids' bioavailability ratings are listed. Casticin,

Ganhuangenin, Olumiant and Nobiletin has high bioactivity and bioavailability ratings and also adhere to Lipinski's rule of five.

Using factors like a compound's molecular weight, lipophilicity (logP), and the quantity of hydrogen bond donors and acceptors, Lipinski's Rule of Five, a guiding principle in the field of drug discovery, establishes criteria to evaluate the likelihood of a compound's success as an orally administered drug.

The molecular interactions of the flavonoid Casticin, Ganhuangenin, Olumiant and Nobiletin are shown in Figs. 1 and 2, respectively, as radar plots and 3D structures.

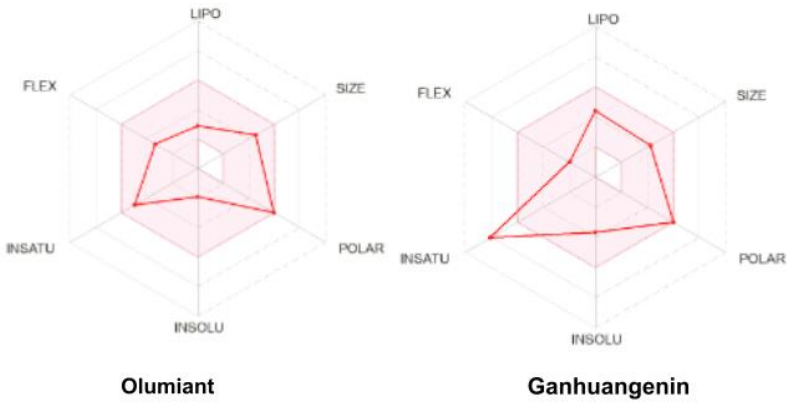
Table 3. In silico pharmacokinetics of ligands (NSP15) (using Swiss ADME)

Flavonoids	**Weight (g/mol)**	**Hydrogen bond donor**	**LogP**	**Hydrogen bond acceptor**
Casticin	374.34 g/mol	2	2.51	8
Ganhuangenin	346.29 g/mol	4	1.69	8
Olumiant	371.42 g/mol	1	0.55	7
Nobiletin	402.39 g/mol	0	3.96	8

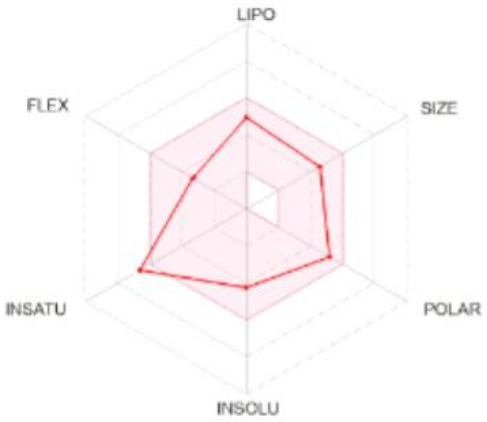
Table 4. Bioactivity of Flavonoids (Using Molinspiration)

Flavonoids	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Nobiletin	-0.13	-0.04	0.09	0	-0.22	0.11
Olumiant	0.27	-0.12	0.62	-0.76	-0.03	0.11
Ganhuangenin	-0.05	-0.01	0.09	0.16	-0.24	0.15
Casticin	-0.14	-0.27	0.13	0.01	-0.34	0.12

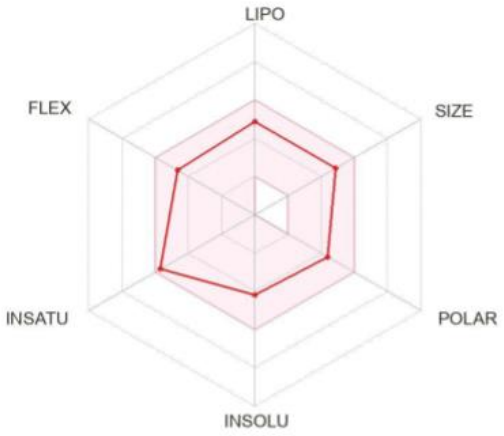
5.2.1 Radar plots of potential flavonoids



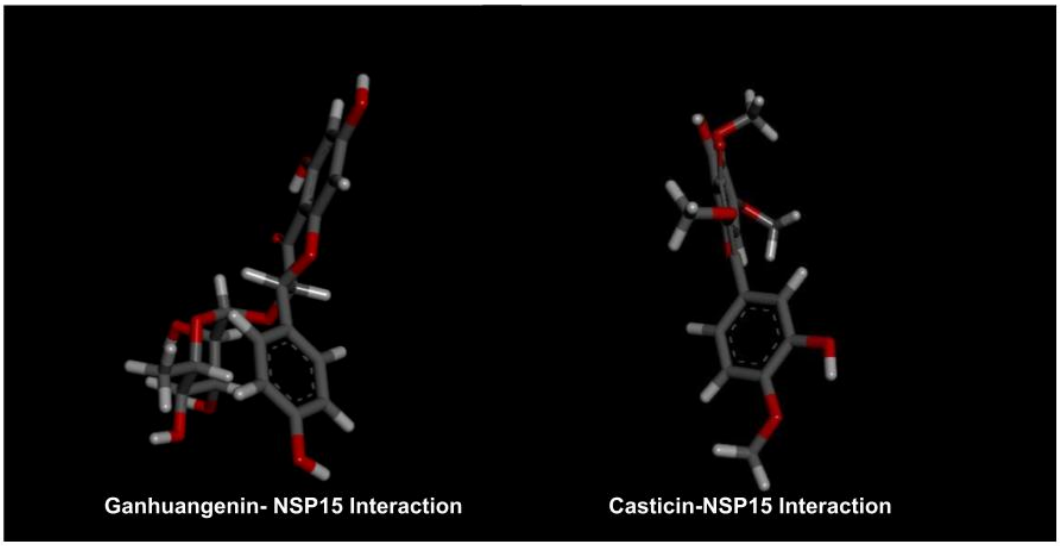
Olumiant **Ganhuangenin**



Casticin



Nobiletin



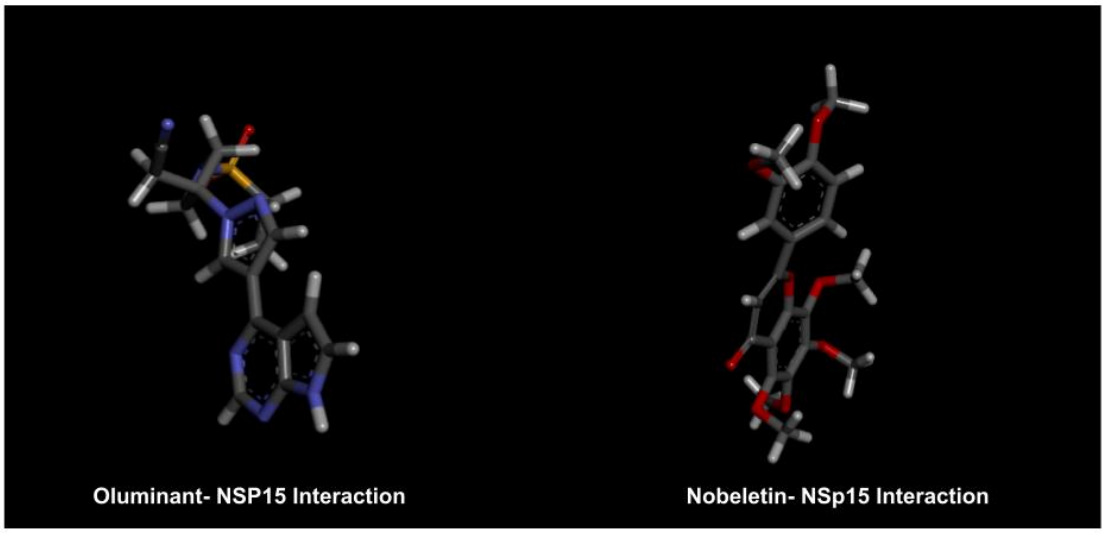


Fig 4. Molecular Interactions of Flavonoids Nobiletin, Oluminant, Ganhuangenin and Casticin with target protein. (Source- UCSF Chimera)

Chapter 6:

Discussion

When nsp14 and nsp15 proteins are docked with toremifene, tipiracil, and 28 flavonoids, vital information about the proteins' potential as inhibitors is revealed. Both Toremifene and nsp14, as well as Tipiracil and nsp15, exhibit high binding energies and favourable interactions, which point to their substantial affinity and possible inhibitory effect. The major chemical factors of binding may be understood by analysing the individual amino acid residues involved in the binding and the type of interactions. The 28 flavonoids' docking results also revealed information on their possible interactions and binding affinities with nsp14 and nsp15, substances with high binding energies and good interactions

6.1 Insights into flavonoid-NSP14 interactions

Nsp14 and flavonoid interaction results identify Nobelitin as the standout compound as potential candidate for drug discovery. Nobiletin, an antioxidant found in citrus fruits like tangerines and oranges, belongs to the polymethoxyflavone subclass. In several cellular and animal models, it has been demonstrated to have antioxidant properties by scavenging free radicals and lowering oxidative stress. Numerous methoxy groups are connected to the flavone backbone of nobiletin, which has shown potential anticancer properties.

Nobiletin is a focus of current research because of its variety of biological functions, which also draw attention to its potential medicinal uses. To completely comprehend its molecular targets and the processes behind its health-promoting actions, more research is

required. However, nobiletin is an interesting flavonoid with potential health advantages due to its complex biochemistry and citrus fruit origins.

6.2 Insights into flavonoid-NSP15 interactions

Nsp15 and flavonoid interaction results identify Casticin, Ganhuangenin, Olumiant and Nobiletin as the standout compound as potential candidate for drug discovery.

The medicinal plant flavonoid casticin, which is found in Artemisia species and Vitex species (commonly known as chaste tree), has a unique chemical structure that is characterised by hydroxyl and methoxy groups connected to a flavone backbone.

The Chinese herb Scutellaria baicalensis, often known as Huang Q, has a root that contains a substance called ganhuangenin, which has a unique chemical structure with hydroxyl and methoxy groups connected to a flavone backbone. By removing free radicals and lowering oxidative stress, ganhuangenin also exhibits antioxidant effects. Additionally, by preventing cell development, triggering apoptosis, and restraining tumour growth, it has demonstrated potential anticancer properties.

6.3 Comparison with previous studies and findings

Insights into the antiviral activities of flavonoids are gained by contrasting the results of the current study with those of earlier research on possible flavonoids for SARS-CoV-2. For instance, a study by Chen et al. (2020) revealed quercetin, a flavonoid that has been the subject of much research, to have antiviral properties by preventing viral replication and lowering virally-induced inflammation. The inhibitory effects of baicalein, a flavonoid derived from Scutellaria baicalensis, on viral entry and replication were emphasised in another work by Li et al. (2020).

The new study's findings may be compared to those of other studies to confirm that flavonoids may have antiviral properties that are effective against SARS-CoV-2. Additionally, it supports the choice of particular flavonoids for continued research and eventual development as antiviral medicines. It is crucial to remember that more experimental research and clinical trials are required to demonstrate the effectiveness and security of these flavonoids as prospective treatments for SARS-CoV-2.

Chapter 6:

Conclusion

For the creation of drugs with a structural basis, the interaction between the protein and ligand is crucial. The current investigation used the NSP14 and NSP15 of SARS CoV-2 receptor and discovered many flavonoids with higher binding energies than the already-approved repurposed drug Toremifene and Tipiracil respectively. Additionally, pharmacokinetic and drug-likeness analyses were performed on the flavonoids with substantial binding energies.

In the case of NSP14**,** Nobiletin, satisfied the pharmacokinetic and binding energy requirements, making them acceptable therapeutic agents. Similarly, in the case of NSP15, Casticin, Ganhuangenin, Olumiant and Nobiletin has high bioactivity and bioavailability ratings and also adhere to Lipinski's rule of five and hence are potential drug targets.

Flavonoids are organic substances that are often found in a variety of foods, including fruits, vegetables, and herbs. They have a number of pharmacological benefits that make them desirable for medication development. They have demonstrated antiviral and antibacterial action, preventing microbial growth. In addition, it has been noted that flavonoids alter important cellular processes involved in viral infection and immunological response. They are intriguing targets for the development of new SARS-CoV-2 medicines due to their capacity to target numerous viral pathogenesis-related mechanisms. To completely understand their unique modes of action and assess their effectiveness and safety as antiviral medicines in the setting of COVID-19, more study is required.

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CERTIFICATE

This is to certify that the Project dissertation titled "IN SILICO STUDY OF FLAVONOIDS AS POTENTIAL ANTAGONIST TARGETING NSP14 AND NSP15 OF SARS-CoV-2" which is submitted by Sanjoli Khare, 2K21/MSCBIO/40, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Sciences, is a record for the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

Place: Delhi

Date:

30/05/2023

Prof. Pravir Kumar

Head of the Department (HOD)
Department of Biotechnology

Navneeta Bharadwaj 30/5/23

Dr. Navneeta Bharadwaj

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Department of Biotechnology

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CANDIDATE'S DECLARATION

I Sanjoli, Roll Number: 2K21/MSCBIO/40, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled "**IN SILICO STUDY OF FLAVONOIDS AS POTENTIAL ANTAGONIST TARGETING NSP14 AND NSP15 OF SARS-CoV-2**" in the fulfillment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology,DTU, is an authentic record of my own carried out during the period from Jan to May 2023, underthe supervision of **Dr. Navneeta Bharadvaja**.

I have not applied for any other degree at this or any other University based on the information contained in this report. The following details about the related study have been approved in the SCI/SCI Scopus Index Conference:

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