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# The Role of Curcumin on Rhinovirus (HRV14) Protein Inhibition by Targeting Host and Viral Proteins

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**Abstract:** This *in-silico* analysis aims to explain curcumin's effects and how (HRV14) protein may cure the common cold fever. Human rhinoviruses predominantly cause the common cold and are responsible for the manifestation of maximum upper respiratory tract viral infections. Human rhinovirus belongs to the Picornaviridae family and is part of the genus *Enterovirus*. More than 150 HRV variants are categorized as species A, B, and C. Exacerbations of chronic obstructive pulmonary disease, asthma, and cystic fibrosis have also been linked to rhinoviruses. In this research work, turmeric is selected as the plant source, and curcumin is a phytochemical constituent selected for the *in-silico* analysis against the common cold. Humans have relied on plants for medicinal purposes since the dawn of time. *Curcuma longa* L. is the scientific name for turmeric, which belongs to the family Zingiberaceae of plants. It is grown in almost every country on this planet, with the majority of production taking place in Asia, Europe, North America, and the United States. It is a common spice and aromatic crop, and dried seeds are used in various foods, medicines, and beverage formulations. It has many therapeutic properties, such as anti-carcinogenic, anti-diabetic, hypocholesterolemic, anti-microbial, and antioxidant activities. In this research, an *in silico* analysis of curcumin against rhinovirus capsid protein HRV14 was performed using Auto Dock Vina software. The ligands were successfully bound to the active site of the rhinovirus capsid protein HRV14 and showed no toxicity and good drug scores. So, the study signifies that this ligand may be tried clinically and may act as a potential drug applicant against the common cold.

**Keywords:** rhinovirus; common cold; phytochemicals; turmeric (*Curcuma longa* L.); *in-silico* analysis.



## 1. Introduction

The common cold is a self-limiting, acute viral illness that affects the upper respiratory tract, including the nose, sinuses, pharynx, and larynx. The virus is transmitted by direct or indirect hand contact with an infected person's secretions or by inhaling the secretions and virus as an aerosol [1]. Rhinovirus infection mainly targets bronchial epithelial cells. More than half of all upper respiratory system infections are caused by HRVs. The illness is known as a common cold, and it normally lasts 5–7 days. Nasal congestion, sneezing, coughing, and a sore

throat are some of the symptoms. However, 12-32 percent of HRV infections in children under the age of four are asymptomatic [2]. According to information from the Centers for Disease Control and Prevention (CDC), the common cold can be caused by various respiratory viruses [3,4]. Human rhinovirus, human parainfluenza viruses, common human coronaviruses, respiratory syncytial virus, human metapneumovirus, and adenovirus are among the viruses that can cause colds. Sinus, ear infections, and asthma have also been linked to rhinoviruses [5]. It is the general cause of the common cold and the worsening of asthma and COPD [6]. HRVs have a single-stranded positive-sense RNA genome and are non-enveloped (Figure 1, Figure 2 (A), Figure 2 (B)). An icosahedral protein capsid made up of 60 copies of each of the four viral proteins VP1-VP4 protects the genome [2,7]. More than 150 HRV variants are categorized as species A, B, and C based on phylogeny [8]. Such flu symptoms appear similar to even a cold, but they are usually more severe and less likely to have a sinus infection. Some evidence supports the use of surgical masks [9-13]. There seems to be no cure, but the symptoms can be managed. When taken soon after the onset of side effects, zinc can help to shorten the duration and severity of symptoms [14-18].

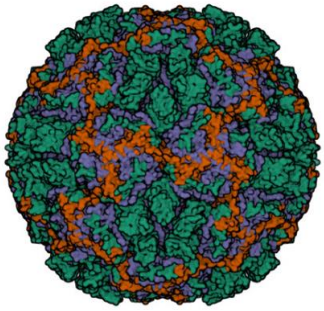
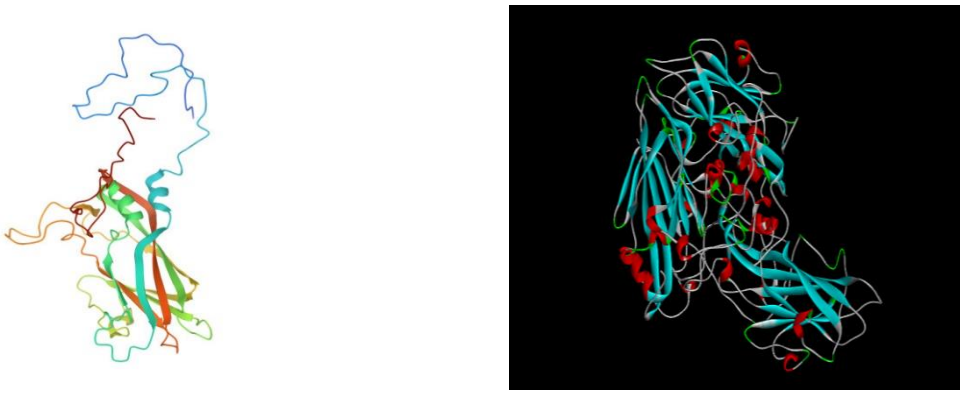


**Figure 1.** Icosahedral HRV14 rhinovirus protein capsid.



**(a)** **(b)**

**Figure 2.** 3D structures of HRV14 rhinovirus capsid protein using **(a)** PubChem; **(b)** BIOVIA Discovery Studio.

Plants have the inborn quality to treat diseases and integrate numerous non-enzymatic rust inhibitors or antioxidants competent in devaluating ROS-induced oxidative damage. WHO approximates that 80% of people still believe in herbal medication for their requirements primarily because they have fewer negative effects and work better with the body and endure them. Medicinal plants include all those plants used as herbs and contain substances used for therapeutic purposes. These plants might eventually result in the creation of new drugs for the presence of some compounds that serve as pharmacological precursors. These plants include *Aloe vera*, *Camellia sinensis*, *Curcuma longa*, *Mentha pulegium*, *Nigella sativa*, *Allium sativum*, *Zingiber officinale*, *Artemisia absinthiu*, and many other plants. So, those plants with medicinal properties that qualify as therapeutic agents or drugs are considered medicinal plants

[19,20]. We favor plants because there are so many of them that make it simple to treat illness without any adverse effects. Higher plants' antioxidant defense system comprises enzymes and low-molecular-weight substances (alkaloids, flavonoids, vitamins, and other phytochemicals) [21-24]. As a component of their enzymatic defense system, plants neutralize, eliminate, or scavenge oxy-intermediates [25-27]. Turmeric (*Curcuma longa* L.), a popular South Asian spice, is a member of the ginger family Zingiberaceae having three main curcuminoids, namely curcumin, bis-desmethoxycurcumin, and desmethoxycurcumin (Figure 3 and Figure 4) [28, 29].

**Figure 3.** *Curcuma longa L.* (turmeric).

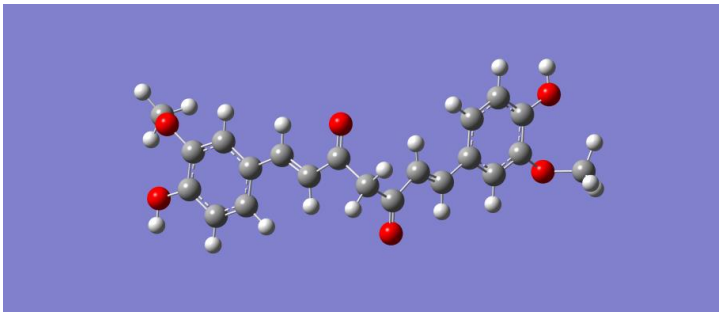


**Figure 4.** Chemical structure of curcumin using GuassView 4.1.

## 2. Materials and Methods

*2.1. Ligand selection and filtration.*

Curcumin from *Curcuma longa* L. was taken as a ligand for docking analysis. The three-dimensional coordinates for ligands were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov).

*2.2. Drug likeness and toxicity prediction of the ligands.*

The pharmacologically active substituents are characterized by calculating steric, hydrophobic, electronic, and hydrogen bonding properties as well as by the drug-likeness score. The drug-likeness score theory helps optimize pharmaceutical and pharmacokinetic properties, such as chemical stability, solubility, distribution profile, and bioavailability. These parameters are responsible for about 60 percent of failures of all drugs in the clinical phases. So the prediction of OSIRIS property explorer (https://www.organic-chemistry.org) explores the drug-likeness of the select ligands (Table 1). The molecular descriptors have developed as rationally predictive and informative, for example, Lipinski's Rule-of-Five. Lipinski's rule of five describes the important molecular properties required for the drug's pharmacokinetics. Lipinski's rule states that the drug to have a good pharmacokinetic profile should not have more than one violation of the following criteria: (i) not more than 5 hydrogen-bond donors,

(ii) not more than 10 hydrogen-bond acceptors, (iii) molecular weight should be less than 500 daltons (Da), and (iv) the partition coefficient (log P) not greater than 5 [30-34] (Table 2).

**Table 1.** Toxicity analysis of the screened ligands generated by Osiris property explorer.

| Ligand Number | Ligand CID | Mutagenic | Tumorigenic | Irritant | Reproductive |
|---|---|---|---|---|---|
| 1 | 969516 | No | No | No | No |

**No**: These ligands possess no high-risk or medium-risk fragments.
**Mutagenic:** Whether the ligand has any fragment that can cause mutation.
**Tumorigenic**: Whether the ligand has any fragment that can cause tumors.
**Irritant**: Whether the ligand has any fragment that can cause irritation.
**Reproductive effect**: Whether the ligand has any fragment that can cause any reproductive effect.

**Table 2.** Lipinski's rule requires important molecular properties for the drug's pharmacokinetics.

| Compound name | H-bond donor count | H-bond acceptor count | Partition coefficient (XLogP) | No. of rotational bonds | Molecular Weight (G/mol) | Lipinski's rules |
|---|---|---|---|---|---|---|
| Curcumin | <5 | <10 | <5 | 2 | <500 | Pass |

*2.3. Protein preparation.*

The three-dimensional crystallographic structures of rhinovirus (common cold) were retrieved from the RCSB PDB database (https://www.rcsb.org) and were used for further processing. In protein structure modification initially requires various tasks such as insertion of atoms missing in incomplete residues, deletion of alternate confirmations, missing loop region modeling, protonation of titrable residues, prediction of pKa (a measure of negative logarithm of the dissociation constant of an acid), providing standardized atom names and removal of water molecules or heteroatoms and addition of hydrogen atoms. The preparation of proteins was performed with the aid of CHARMM force fields [35-38].

*2.4. Protein-ligand docking.*

Discovery Studio 2.0 (Accelrys, USA) (http://www.3dsbiovia.com) was employed for the *in silico* and post-docking visualization. The molecular docking study was completed by a Discovery Studio LibDock program that revealed the bioactive binding sites of receptors. In LibDock, two protein site features, polar and apolar, are available and are called hotspots. Further, curcumin interacted with the polar and apolar sites of receptors. Additionally, to identify specific interacting residues of the receptor with a bound ligand, a 2D diagram of the docking study was carried out.

*2.5. Visualisation*

The protein target was validated with AutoDockVina (http://autodock.scripps.edu/resources/adt), an open-source software designed by Dr. Oleg Trott. This docking process was based on root mean square deviation (RMSD) value determination. The RMSD value less than 2Å was used for considering the best docking position between 1NCQ and ligands, and the schematic diagrams of protein-ligand interactions were prepared using BIOVIA Discovery Studio.

## 3. Results

The data gathered from the respondents were examined with the targets and objectives of the study in view, and the aftereffects of the evaluation and investigation in accordance with the study's objectives are exhibited under the accompanying headings.

*3.1. In silico analysis of curcumin against common cold 'HRV14' protein.*

Fifteen flavonoids were evaluated for their pharmacokinetic profile based on Orisis property explorer and Lipinski's rule of five using MedChem Designer software. Out of those 15, Ligand CID No. 969516, i.e., curcumin, is selected for further studies as it passes both tests. Curcumin binds with the target site (HRV14).

The present study subjected curcumin to molecular docking at the active site of rhinovirus (HRV14) protein structures. The docking results showed that curcumin interacted with HRV14 with a good docking score of 93.14 Kcal/mol (Table 3). The curcumin compound's methoxyphenyl group is involved in forming hydrogen bonds with the Ser175, Tyr197, Ser126, Val188, and Pro189 amino acids of the HRV14 enzyme. In molecular docking analysis, different types of bond interactions, such as hydrogen bond interaction, hydrophobic bond interaction, Van der Walls interaction, and π-π bond interaction, were also examined with their amino acids' residues (Figure 5). We found that Met221, Val191, Ser126, Pro174, Ala150, Val176, and Phe186 were involved in binding with the active site pocket of HRV14. Our results were similar to previous molecular docking studies [39].

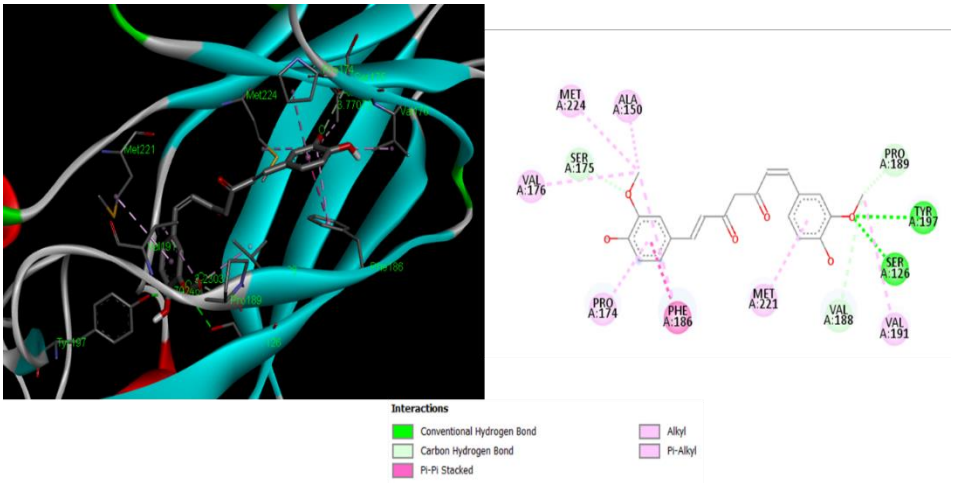



**Figure 5.** 3D and 2D poses shows binding interactions of curcumin with the HRV14 enzyme (common cold).

**Table 3.** Molecular docking of curcumin with HRV14 enzyme (common cold).

| Structure | Docking score (Kcal/mol) | Hydrogen bond | | Hydrophobic interactions amino acid |
|---|---|---|---|---|
| | | Amino acid | Bond length (Å) | |
| Curcumin | 93.18 | O14-Tyr197<br>C13-Pro189<br>C14-Val188<br>O34-Ser175 | 2.70246<br>3.23032<br>3.65591<br>3.77072 | Met221, Val191, Ser126, Pro174, Ala150, Val176, Phe186 |

*3.2.Hydrogen bonding interactions.*

Curcumin inhibits the viral protease by forming multiple essential hydrogen bonds with its amino acid constituents.O14-Tyr197: With a length of 2.70246 Å, this bond demonstrates a robust interaction that maintains curcumin binding to the protease active site.C13-Pro189: This

contact helps ensure that curcumin is positioned correctly within the protease, with a bond length of 3.23032 Å.C14-Val188: Curcumin is additionally anchored by this bond, which is located at 3.65591 Å, increasing its inhibitory potency.O34-Ser175: A further stabilizing interaction is highlighted by the bond length of 3.77072 Å, assuring strong binding.

*3.3.Hydrophobic interactions.*

Curcumin's binding affinity is also significantly influenced by hydrophobic interactions. Met221, Val191, Ser126, Pro174, Ala150, Val176, and Phe186 are important residues in these interactions. Through these interactions, the curcumin inhibitory effect is enhanced by stabilizing it within the hydrophobic regions of the viral protease. The compound's efficacy and toxicity profile support the ongoing efforts to develop curcumin as a medicinal countermeasure.

## *4.* Discussion

This is the first study to compare curcumin's efficacy in treating human rhinovirus. Curcumin, a polyphenolic molecule produced from spice turmeric, has drawn attention for its broad-spectrum antiviral capabilities; this study was the first to assess its efficacy. 93.18 Kcal/mol is the docking score for curcumin, which indicates that it has significant potential in suppressing Human Rhinovirus (HRV14). This score indicates a significant binding affinity, indicating that curcumin inhibits the lifecycle of HRV14 by efficiently interacting with important viral proteins. Due to the widespread nature of rhinovirus infections and their influence on world health, which are the primary causes of colds, the inhibition of Human Rhinovirus (HRV14) by curcumin is especially noteworthy. The process of determining a tiny molecule's preferred orientation when it is coupled to a second molecule's binding site is known as molecular docking. It is one of the methods for creating structure-based drugs that is most commonly employed.

## 5. Conclusions

From the *in-silico* analysis, we concluded that curcumin taken for virtual screening effectively binds with the rhinovirus capsid protein 1NCQ. So, this may be a potential drug candidate against the common cold as it has no toxicity and possesses a good drug score. The bioactive compounds present in curcumin can be traced to its medicinal uses, but more research and analysis are needed. This bioactive compound making is crucial in medicine because it helps reduce reliance on synthetic medicines and several costly therapies for diseases. The issues that have appeared as a result of the analysis and discoveries have, thus far, reopened the way to fresh research. It's dreadful to say that all has been done, that vital data has been acquired and presented, but there is still room to learn about more phytocompounds, evaluate them, and test them on a variety of new emergent maladies around the world to eradicate them. *In vitro*, investigations make it easier to develop pharmaceuticals and learn about the therapeutic benefits of nutri-compounds from plants like curcumin without harming living organisms. As a response, using commercial software and web tools, the *in-silico* approach used in this study aided in the discovery of ligands for the common cold. This technique saves money and time by decreasing the cost and time it takes to design a treatment and assess its likelihood before entering clinical trials.

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## Conflicts of Interest

The authors declare no conflict of interest.

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