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Research Article

Network pharmacological approach to predict the herbal drug targets in Measles Virus infection

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Abstract: The measles virus, which is spread by aerosols, kills a significant number of individuals and infects many children each year. It was previously believed to replicate in the respiratory epithelium before spreading, but it has now been shown to employ signaling lymphocytic activation molecule family member 1 as a receptor to initially infect airway dendritic cells and macrophages. The measles virus replicates quickly in lymphatic organs once these cells carry the infection there after navigating the respiratory epithelium. Here, we mainly aimed to the selected dataset which is publicly available and is related to measles infection where we had seven different types of cell lines and performed in-silico analysis of the gene expression patterns and the altered signaling pathways and finally, compared them between the cell lines. In this case, we selected a set of differentially expressed genes (DEGs) and prepared the protein-protein interaction and the inferred pathways network. In the DEGs and pathways network, we analyzed those proteins which are highly connected in terms of proteins and the biological functions. After predicting the set of proteins, we performed docking profiling of herbal drugs Curcumin, Resveratrol, Myricetin, and Diosmin with the predicted leading proteins. We conclude that Diosmin as the potential putative drugs against ITGA2, VAV3, and CCND2.

Keywords: Measles virus; Lung Cancer; identification of target proteins; herbal drugs; molecular docking

1. Introduction

One kind of cancer that starts as lung cell growth is lung cancer and are the two spongy organs in the chest that regulate breathing. Lung cancer is the leading cause of cancer-related deaths worldwide. Smokers are more prone to develop lung cancer. The risk of lung cancer increases with the number of cigarettes smoked over a lengthy period of time. Even if you have smoked for a long period, quitting significantly lowers your risk of developing lung cancer. Lung cancer can even strike people who have never smoked. It is one kind of malignant tumor that originates in the lung is lung carcinoma, which is another name for lung cancer[1-8]. Lung cancer is caused by genetic damage to the DNA of airway cells, which is often caused by smoking cigarettes or breathing in dangerous chemicals. When injured airway cells have the ability to multiply unchecked, a tumor may develop. If treatment is not received, tumors spread throughout the lung and affect lung function. Through metastasis, lung cancers eventually spread to other parts of the body. Early-stage lung cancer often shows no symptoms and can only be detected by medical imaging. As the cancer progresses, the majority of patients experience nonspecific respiratory problems such coughing, dyspnea, or chest pain. Additional symptoms depend on the location and size of the tumor. People who are suspected of having lung cancer typically undergo a series of imaging tests to determine the location and size of any lesions. To get a conclusive diagnosis of lung cancer, a pathologist must examine a biopsy of the suspicious tumor under a microscope. Based on the cells from which the tumor originates, a pathologist can classify the tumor and detect malignant cells. About 15% of cases are small-cell lung cancer (SCLC), with the remaining 85% being non-small-cell lung cancers, or NSCLC, which are composed of adenocarcinomas, squamous-cell carcinomas, and large-cell carcinomas[9-17]. After a diagnosis, more imaging and biopsies are carried out to determine the stage of the cancer and gauge its spread.

Other important risk factors for lung cancer development include immunologic dysfunction, genetic predisposition, underlying nonmalignant lung disease, occupational carcinogens, air pollution, radon, and environmental

exposure to cooking fumes and tobacco smoke. A viral etiology for lung cancer has been proposed, although it remains controversial. The viruses that have been suggested include human papillomavirus (HPV), Epstein-Barr virus (EBV), simian virus 40 (SV40), BK virus, JC virus, and human cytomegalovirus (HCMV). Measles virus (MV), an aerosol-transmitted virus, kills over 120,000 people year and infects roughly 10 million children. Although it was long thought to be replicated in respiratory epithelium, it was recently shown to use signaling lymphocytic activation molecule (SLAM, CD150) as a receptor to first infect macrophages and dendritic cells of the airways. Once the virus has passed through the respiratory epithelium, these cells carry it to lymphatic organs, where it multiplies quickly. How and where the virus re-enters the airways is yet unknown. However, several cancer cell lines have been shown to be either permissive for wt MV infection or not[18-22]. Moreover, the Jaagsiekte sheep retrovirus-related retrovirus has been associated with bronchioloalveolar cancer in sheep, despite the fact that it has not been found in humans. MV may be connected to the etiology of Hodgkin's lymphoma, according to a recent study, and there are some cases in the literature that suggest MV may be connected to lung cancer[2, 23-27]. Measles is a common RNA virus. It may lead to a persistent viral infection, and many cell lines that are consistently infected have been examined. It has been suggested that only the modified virus is capable of causing persistent infection, not the wild-type virus. Compared to normal lung tissue, lung cancer samples have been found to overexpress Pirh2, and MV phosphoprotein may inhibit Pirh2's ability to ubiquitinate the cell cycle regulator p53. Moreover, CD46, a protein that inhibits cell membrane complement and acts as an MV receptor, is overexpressed in lung cancer cells. The goal of the current study was to determine whether patient biopsies for non-small cell lung cancer (NSCLC) could include MV. Furthermore, we examined several clinicopathological and demographic traits in patients with NSCLC and their correlation with the expression of p53, Pirh2, and MV antigens in the tumor tissue[28].

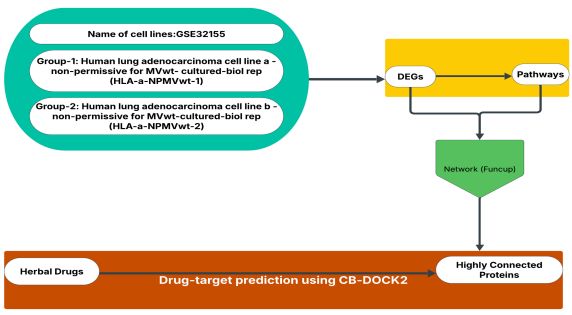
Genetic aberrations and epigenetic changes in the human body have a significant impact on suppressor genes (genes encoding proteins, whose function is to inhibit cell growth and differentiation and to maintain cell stability; mutations in these genes lead to uncontrolled cell proliferation) and proto-oncogenes (genes that promote cell growth, which can become oncogenes due to mutation). The growth and migration of cancer cells are aided by these modifications. However, this is only one step in the process. When homeostasis is preserved, the immune system has a very strong ability to detect, locate, and destroy cancer cells. However, these cells have developed several defense mechanisms that allow them to avoid immune system monitoring. Therefore, the second potential pathway in the etiology of cancer, including lung cancer, should be considered any disturbances in the human body that impact the immune system's ability to function[1, 4, 29-49].

To identify the molecular mechanisms of herbal medications, researchers have created a number of systems or network pharmacological techniques in recent years. These research use the "herb to ingredient to target" approach, which entails gathering the constituents of herbal medications first, then using in silico ligand-based target prediction techniques to identify the compounds' possible targets on a proteome-wide scale after in vivo validation. A more thorough knowledge of the pharmacological foundation of herbal medications has been made possible by these investigations. The biochemical characteristics of herbal medications and the disadvantage of ligand-based techniques, such as the fact that many components of some herbal medications are yet unknown, limit the effectiveness of this strategy. When there are few known binding ligands for a target, ligand-based methods frequently produce subpar prediction results[50-59].

Thus, we developed the goal to work on the MV genes and the herbal drug-target for the continuation of our previous study[60]. For this purpose, the gene expression dataset (GSE32155[61]) for various lung cancer cell lines was selected from the Gene Expression Omnibus (GEO), which is publically available (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE32155). Gene expression profiling was then carried out. Afterwards, we predicted the enriched pathways for the differentially expressed genes (DEGs). In this study, we performed network-level analysis where we predicted the top genes in terms of connection with the genes and the pathways and targeted with the herbal drugs Curcumin, Resveratrol, Myricetin, and Diosmin by using CB-DOCK2.

2. Methods

2.1. Data collection: This work is in continuation of our previously published work[62](Figure 1). The Gene Expression Omnibus (GEO), which is openly accessible (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE32155), provided the gene expression dataset (GSE32155) for several lung cancer cell lines that was selected for this study. Seven sample groups, each consisting of three biological replicates of one of the seven cell lines, are created from the 21 samples in the collection dataset.



by network preparation.

After that, gene expression profiling was done. Next, the enriched pathways for the genes that were differentially expressed (DEGs) were anticipated. Fold change and p-value are the two criteria we use to classify the genes as DEGs. We consider a gene to be up-regulated if its fold change is greater than 2.0 and its p-value is less than 0.05, and down-regulated if its fold change is less than -2.0 and its p-value is less than 0.05. Finally, we evaluated the immunological signaling pathways and DEGs of the immune system that we carefully selected. Only routes with p-values less than 0.05 were deemed enriched in the pathway analysis. Since many genes were found to fall within these ranges, we chose to be more stringent and only include the top DEGs in the analysis.

2.2. Data processing and analysis: In order to forecast the fold change and p-values for each gene, we first created group names for the various cell lines and used the built-in tool GEO2R on the GEO webpage. To forecast the DEGs between two groups, we compared one group with another. Additionally, the enriched pathways were predicted using the GECIP toolkit[63]. We mapped out every DEG associated with the immune system/signaling pathways after predicting the DEGs and enriched pathways.

2.3. Receptor and ligand preparation

After network- level analysis, five highly connected genes were selected. The 3D structure of the targeted proteins was collected from AlphaFold3, a powerful tool offers highly accurate and fast predictions of protein structures and complex bimolecular interactions[64-67]. For ligand screening, we chose four known herbal drugs (Curcumin, Resveratrol, Myricetin, and Diosmin), which are considered for treating different human diseases including cancer and infectious diseases. These drug compounds are natural, have low toxicity, and possess strong antioxidant, anti-inflammatory, and anti-cancer properties that can help inhibit cancer cell growth, induce apoptosis. The 2D structure of these drugs were retrieved from PubChem[54, 68], a publicly accessible database that provides detailed information on chemical compounds, their structures, properties, biological activities[7, 8, 58, 69, 70].

2.4. Molecular docking

Molecular docking was performed to determine the interactions between protein and ligand. Publicly available docking tool called CD-DOCK2[71] was used for accurate and efficient molecular docking. This tool allows to predict small molecules like drugs or natural compounds to interact with target proteins. It helps in identifying potential drug candidates by simulating binding affinities and interaction patterns. In CD-DOCK2, good ligand–protein interactions are determined by evaluating key factors such as low binding energy scores (the lower the score, the better the binding affinity), the presence of stable hydrogen bonds and hydrophobic interactions with active site residues, a low RMSD value (preferably below 2.0 Å), and proper ligand positioning within the predicted binding pocket without steric clashes.

3. Results

3.1. Network-level understanding and analysis: We performed the gene expression analysis of all the seven cell lines and selected top 200 DEGs (100 up and 100 down) and afterwards plotted venn diagram to show the number of genes common between different groups or cell lines. In this study, we selected the network of DEGs between the two groups only (Figure 1). This network was mapped out for protein-protein interactions (PPIs) from PPI network database (FunCoup) and then linked the associated KEGG pathway with the related protein (Figure 2). Here, we arranged the nodes (protein) based on connectivity where we clearly observed that there are certain proteins which potentially act as the master regulator of the major signaling pathways and the proteins. CCND2, LEF1, ITGA2, CREB5, and VAV3 were among them (Figure 2). These proteins potentially associate

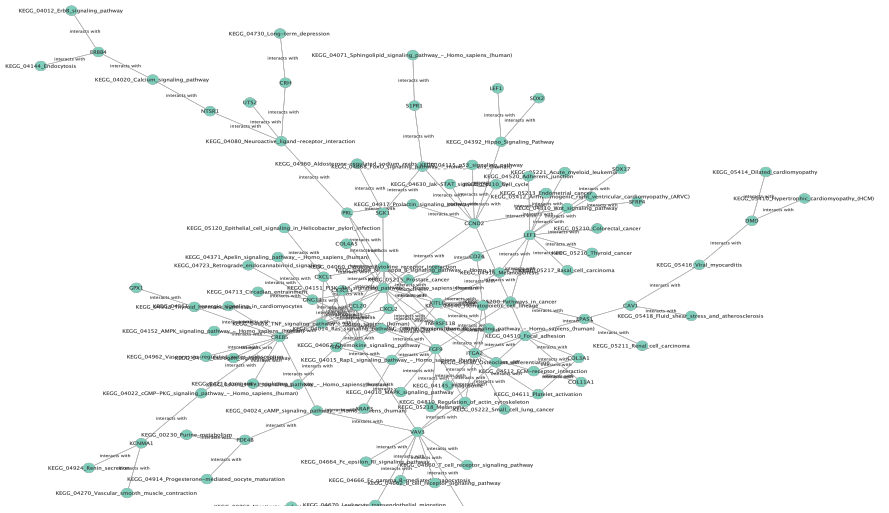


Figure 2. Network of the DEGs inferred proteins and the associated pathways. Here. We presented the network for the inferred proteins of DEGs of the two groups only and the associated pathways. Human lung adenocarcinoma cell line a - non-permissive for MVwt (Grp 1) and human lung adenocarcinoma cell line b - non-permissive for MVwt (Grp 2).

linked to the trivial signaling pathways associated with different human diseases including infectious disease, and cancers. These pathways are cell cycle, p53 signaling, hippo signaling, Wnt signaling, PI3K-Akt signaling, JAK-STAT signaling, FoxO signaling, pathways in cancer, AMPK signaling, TCR/BCR signaling, NK cell-mediated cytotoxicty, and more.

3.2. Network-pharmacological approach to predict the potential drugs and the targets: After network analysis, we performed the docking profiling of herbal drugs (Curcumin, Resveratrol, Diosmin, and Myricetin) and the top-ranked proteins (CCND2, LEF1, ITGA2, CREB5, and VAV3) in the network. Thus, we performed docking for the combination of the selected drugs and the predicted putative targets. The medications and target proteins that were prepared for molecular docking in order to anticipate the binding locations were compiled in Figure 3.

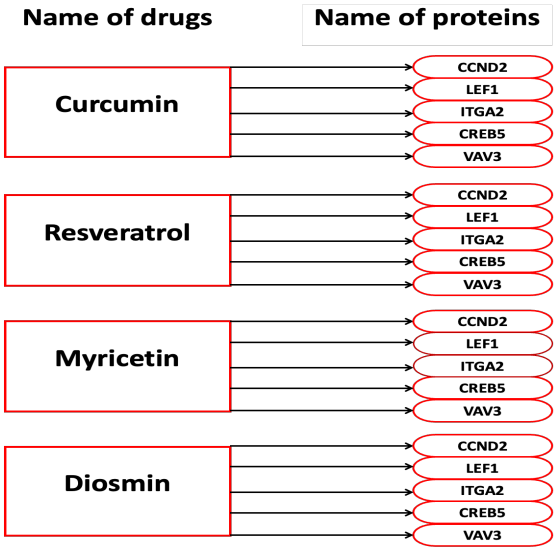


Figure 3. Drug-target combination. Here, we summarized the drugs and the target proteins which were processed for molecular docking to predict the binding sites.

For this purpose, we used CB-DOCK2 to perform docking and selected the top binding cavity (pocket) which displayed lowest binding affinity (delta G). In our results, we observed that Diosmin with ITGA2 and Diosmin with VAV3 displayed as the most optimal possibility as the drug-targets with the binding affinity of -10.9 and -10.6 kcal/mol, respectively (Table 1). The binding affinity of Diosmin with CCND2 was -9.1 kcal/mol. Myricetin had binding affinity of -9.0 kcal/mol with VAV3. The binding affinity of Myricetin with ITGA2 was -8.5 kcal/mol. The lowest binding affinity was for Curcumin with CREB5 and that was -5.9 kcal/mol. The other combination of drugs and the targets were between these values. Thus, the analysis of binding affinity of drugs and the target proteins leads to the conclusion that Diosmin as the potential herbal drug among all these four herbal drugs for these selected five proteins CCND2, LEF1, ITGA2, CREB5, and VAV3. All the binding affinity of the drugs and the targets were presented in Table 1.

Table 1. The list of drugs and the target proteins with their respective binding affinity.

Serial	Drug-ligand complex	Binding affinity energy (kcal/mol)
1	Curcumin :: CCND2	-6.4
2	Curcumin :: LEF1	-7.3
3	Curcumin :: ITGA2	-7.6
4	Curcumin :: CREB5	-5.9
5	Curcumin :: VAV3	-7.9
6	Resveratrol :: CCND2	-6.2
7	Resveratrol :: LEF1	-6.1
8	Resveratrol :: ITGA2	-6.6

9	Resveratrol :: CREB5	-5.3
10	Resveratrol :: VAV3	-7.5
11	Myricetin :: CCND2	-6.8
12	Myricetin :: LEF1	-6.7
13	Myricetin :: ITGA2	-8.5
14	Myricetin :: CREB5	-5.5
15	Myricetin :: VAV3	-9.0
16	Diosmin :: CCND2	-9.1
17	Diosmin :: LEF1	-8.1
18	Diosmin :: ITGA2	-10.9
19	Diosmin :: CREB5	-6.6
20	Diosmin :: VAV3	-10.6

After analyzing the binding affinity of all the binding cavity, we also analyzed the binding sites and explored the structures with binding representations (Figure 4).

3.3. Exploration of the binding sites: Finally, we explored the structures of the binding cavities for the drugs and the targets (Figure 4). In the structural exploration of the drug-target binding cavities, we observed that there exist potential difference for different drug-target combinations. Diosmin and Myricetin displayed much higher and dense binding sites for most of the target proteins compared to the other combinations of drugs and targets while curcumin and resveratrol displayed lesser number of binding sites.

Thus, we conclude that there was potential difference in binding affinity, binding sites, number of binding sites, and binding sites in terms of amino acids and the drug components.

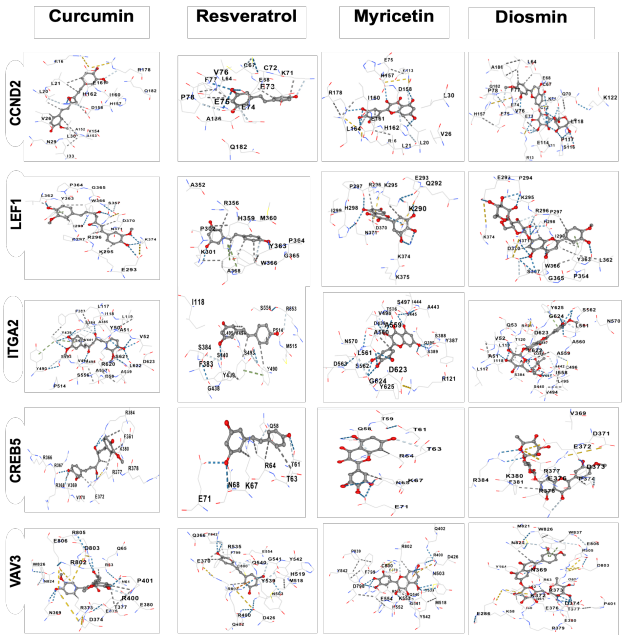


Figure 4. Structural representation of the binding sites for all the drug-target combinations.

4. Dicussion: This work is continuation of our previous study[62]. In order to comprehend the effects of measles infection (MV) on the immune system, we previously reported a comparative analysis of gene expression and pathway enrichment analysis across several cell lines. Urinary Bladder Squamous Carcinoma Cell Line: Non-permissive for MVwt, Urinary Bladder Transitional Cell Carcinoma Cell Line: Non-permissive for MVwt, and Urinary Bladder Grade 3 Carcinoma Cell Line: Permissive for MVwt were the three sets of

bladder cell lines that had PI3K-Akt and cytokine signaling in common. The two groups (Urinary Bladder Squamous carcinoma cell line: non-permissive for MVwt and Urinary Bladder Grade 3 Cell Line: Permissive for MVwt) shared neuroactive ligand-receptor interaction signaling. They also shared ECM, focal adhesion, CAMs, and pluropotency of stem cell signaling. Both the urinary bladder transitional cell carcinoma cell line (Group 4) and the urinary bladder squamous carcinoma cell line (Group 3), which were non-permissive for MVwt, exhibited hippocampal signaling. Rap1, leukocyte transendothelial migration, and actin cytoskeleton modulation were unique to groups 4–7 (grade 3 carcinoma cell line, which is permissive for MVwt, and transitional cell carcinoma cell line, which is non-permissive for MVwt). In this case, we discover that ECM, focal adhesion, and CAMs, along with pluropotency of stem cells, were the most significant signaling pathways for the groups (urinary bladder transitional cell carcinoma cell line, which is not permissive for MVwt, and urinary bladder grade 3 carcinoma cell line, which is permissive for MVwt). Lung cancer cell lines a and b, which are non-permissive for MVwt (Group 1 and Group 2, respectively), were the only ones that exhibited APC, RAP1, NK cells, cAMP, RAS, TNF, and neuroactive ligand-receptor signaling—all of which are mostly associated with the immune system. Human lung papillary adenocarcinoma cell line a, which is permissive for MVwt (Group 6), and lung adenocarcinoma cell line a, which is non-permissive for MVwt (Group 1), were specifically found to have enriched ECM. Focal adhesion, PI3K-Akt, Rap1, and cAMP signaling were enriched for lung adenocarcinoma cell line a, which is non-permissive for MVwt (Group 1), lung adenocarcinoma cell line b, which is non-permissive for MVwt (Group 2), and lung bronchioalveolar carcinoma cell line, which is permissive for MVwt (Group 5). Specifically, there were increased levels of APC, Wnt, NK, cytokines, TNF, and neuroactive ligand-receptor signaling in lung adenocarcinoma cell line a, which is non-permissive for MVwt (Group 1), and lung adenocarcinoma cell line b, which is non-permissive for MVwt (Group 2). We might infer that non-permissive lung adenocarcinoma cell lines might be immune system-sensitive because of the intimate relationship between these pathways and the immune system. ECM, MAPK, and modification of actin cytoskeleton signaling pathways were enriched for the cell lines lung adenocarcinoma cell line b, which is non-permissive for MVwt (Group 2), and lung bronchioalveolar carcinoma cell line, which is permissive for MVwt (Group 5).

Here, we continued our previous work[62] by extending the study to network pharmacological approach where we prepared the network of DEGs for selected group and of pathways. Afterwards, we selected the key genes which potentially connects major and more signaling pathways and these genes were CCND2, LEF1, CREB5, ITGA2, and VAV3. After selecting these genes we predicted the respective 3D protein structures and processed for therapeutic target prediction. For this purpose, we used Curcumin, Resveratrol, Myricetin, and Diosmin to target the the selected five proteins where we observed that Diosmin and Myreiceting could potential drugs to target these proteins.

MV is the most contagious virus in humans. Unlike most respiratory viruses, MV does not instantly infect epithelial cells when it reaches a new host. Before being sent to lymphatic organs for proliferation, MV passes via the epithelium of immune cells. Then, infected immune cells simultaneously send large amounts of virus to the airways. However, there is no information available regarding MV replication in airway epithelia. In early study[72], primary cultures of human airway epithelial cells (HAE) from lung donors that had undergone appropriate differentiation were used to model it. In HAE, MV spreads straight from cell to cell, forming infectious foci that grow for three to five days, stabilize for a few days, and then disappear. Since transepithelial electrical resistance remains constant during the course of HAE infection, we hypothesized that MV infectious sites might detach while epithelial function is preserved. They extracted apical washes and separated the virus's cell-associated and cell-free components using centrifugation after confocal imaging confirmed that infectious centers eventually separated from HAE. The virus titers in the cell-associated fraction were nearly ten times greater than those in the supernatant. In shifted infection centers, ciliary beating persisted and apoptotic markers were difficult to detect, suggesting that their metabolism is still functioning.

Lung cancer cells, particularly those of NSCLC, have been shown to express nectin-4. We previously developed a recombinant MV that is unable to bind Nectin-4 but can engage its primary receptor, signaling lymphocyte activation molecule (SLAM). Breast cancer cells are infected and destroyed by this virus (rMV-SLAMblind) both in vitro and in a subcutaneous xenograft form. It is yet unknown how well rMV-SLAMblind works against other cancer types and in other tumor models that better represent disease. Previous studies have investigated the anti-tumor activity of this virus against lung cancer cells using a modified form of the virus that encodes green fluorescent protein (rMV-EGFP-SLAMblind). They found that rMV-EGFP-SLAMblind successfully infected nine human lung cancer cell lines, and that the infection reduced the viability of six of the cell lines. Tumor growth was suppressed when the virus was applied to subcutaneous tumors in xenotransplanted animals. Moreover, rMV-EGFP-SLAMblind may target scattered tumor masses in the lungs of xenotransplanted animals. These results suggest that rMV-SLAMblind shows promise as a lung cancer treatment and is an oncolytic for the disease[61, 73, 74]. Since there hasn't been much research done in this area up to this point, we used the publicly available dataset from several cell line types to present our study in a novel approach, exploring the DEGs and enriched pathways that are either mutually shared or completely cell line specific.

5. Conclusions: Lastly, we draw the conclusion that there may be variations in binding sites, binding affinity, and the quantity of binding sites depending on the amino acids and medication ingredients. Myricetin and diosmin seem to be

the two possible medications that target the proteins CCND2, LEF1, ITGA2, CREB5, and VAV3. We also consider that this approach will be worth milestone for further exploration of the MV infections in a number of human diseases.

Author Contributions: Conceptualization, S.I. and R.A.; methodology, S.I. and R.A.; software, S.I. and R.A.; validation, S.I. and R.A.; formal analysis, S.I. and R.A.; investigation, S.I.; resources, S.I.; data curation, S.I.; writing—original draft preparation, S.I. and R.A.; writing—review and editing, S.I. and R.A.; visualization, S.I.; supervision, S.I.; project administration, S.I.; funding acquisition, S.I. and R.A. All authors have read and agreed to the published version of the manuscript.

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