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REPURPOSING OF BUDESONIDE IN HUMAN PAPILLOMAVIRUS [HPV] RELATED INFLAMMATION

***Kashid Pratiksha Vinod, Sabale Shruti Bharat, Gholap Prachi Vikas, Doifode Usha Pratap, Ghodake Aditi Laxman, Dr. Nikunj Solanki**

India.

***Corresponding Author: Kashid Pratiksha Vinod**

India.

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ABSTRACT

Human Papillomavirus (HPV) infection, particularly by high-risk types HPV-16 and HPV-18, is a major driver of cervical cancer, which ranks as the fourth most common cancer worldwide. These viruses contribute to carcinogenesis by manipulating host cellular mechanisms and immune responses to promote chronic inflammation, immune evasion, and tumor progression. The viral oncoproteins E6 and E7 disrupt tumor suppressor pathways, alter cytokine production, and interfere with immune signaling, creating a proinflammatory and immunosuppressive environment that fosters persistence of infection and malignant transformation. Addressing this complexity, systems biology and meta-analysis approaches have enabled identification of inflammation- associated gene signatures distinctive to HPV-16 and HPV-18 infected cervical cancers. These signatures allow classification of patients based on individual molecular differences, paving the way for precision medicine. The study leveraged gene signature reversal and network pharmacology to screen and repurpose anti- inflammatory drugs that target these subtype-specific inflammation pathways. Molecular docking validated the physical binding potential of these novel drug candidates to key inflammatory proteins implicated in HPV-associated carcinogenesis. Drugs such as betamethasone and methylprednisolone were identified for HPV-16, daphnetin and phenylbutazone for HPV-18, and others for both subtypes, offering tailored therapeutic options aimed at modulating chronic inflammation driving cervical cancer. Moreover, Budesonide—a glucocorticoid with potent anti-inflammatory and immunomodulatory effects— has emerged as a promising repurposed drug candidate. AI-based computational tools including machine learning, molecular docking, and network pharmacology facilitated the prediction of Budesonide's interactions with HPV-induced inflammatory pathways and key gene targets, offering deeper molecular insight into its therapeutic potential. This integrated AI and systems biology approach highlights a shift from conventional therapies targeting HPV replication alone to combinatorial treatments that address the inflammatory microenvironment crucial for cancer progression.

KEYWORDS: Moreover, Budesonide—a glucocorticoid with potent anti-inflammatory and immunomodulatory effects— has emerged as a promising repurposed drug candidate.

INTRODUCTION

Human Papillomavirus (HPV), especially types 16 and 18, is a virus that can cause cervical cancer, one of the most common cancers worldwide. These two types of HPV make special proteins called E5, E6, and E7. These proteins change how cells normally work: they interfere with how cells grow, how the immune system fights infections, and how damaged cells die. Because of these changes, the virus can stay in the body for a long time and sometimes cause cancer. The proteins made by HPV affect important systems inside our cells that control inflammation (which is how the body reacts to injury or infection) and the immune system's defenses.

HPV makes infected cells harder for the immune system to detect, allowing these cells to multiply uncontrollably.

This infection also causes long-lasting inflammation by activating certain pathways and chemicals in the body, including NF-κB, COX-2, IL-1β, IL-6, and TNF-α. This ongoing inflammation helps cancer cells grow, make new blood vessels to bring them nutrients, and avoid being destroyed by the immune system. Scientists studied which genes are active during HPV 16 and 18 infections to find signs of this inflammation. Using these gene patterns, they searched for anti-inflammatory drugs that could block the harmful effects caused by the virus.

Computer programs showed that some drugs, like betamethasone and methylprednisolone, may work well against HPV-16, while others like daphnetin and phenylbutazone may be better for HPV-18. Some drugs might help with both types. Budesonide is a medicine usually used to treat asthma and other diseases caused by inflammation. It can reduce inflammation and influence the immune system. Researchers used artificial intelligence and computer models to predict how budesonide might fight the inflammation caused by HPV and which genes it affects.

Budesonide: A corticosteroid primarily used for asthma, COPD, and inflammatory bowel disease. It acts by suppressing pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β.

Need for Repurposing: Drug repurposing reduces time, cost, and risk in drug development — especially valuable for HPV-related diseases where no direct anti-inflammatory therapy exists.

AI in Drug Repurposing: Artificial intelligence enables prediction of new drug- disease links through data-driven insights from molecular databases, gene expression profiles, and interaction networks.

Drug repurposing, also known as drug repositioning, is a modern approach that identifies new therapeutic uses for existing drugs. It offers a cost-effective and time-saving alternative to traditional drug discovery, as the safety profiles of repurposed drugs are already well established. Artificial intelligence (AI), network pharmacology, and in silico modeling are now widely used to identify potential drug-disease interactions for repurposing.

Budesonide, a well-known glucocorticoid with strong anti-inflammatory and immunomodulatory properties, has shown potential for repurposing in HPV- related inflammation. Traditionally used for asthma, inflammatory bowel disease, and respiratory disorders, budesonide works by inhibiting cytokine release, reducing immune cell activation, and suppressing inflammatory Recent computational and network-based studies suggest that budesonide may target inflammatory mediators and HPV-induced signaling pathways, thereby reducing tissue damage and viral persistence. Using AI and network-based approaches can help predict budesonide's interactions with HPV-related host proteins and inflammation-associated genes, providing new insights into its therapeutic potential.

Role of AI and Computational Drug Repurposing

AI algorithms analyze large biological datasets to discover hidden drug–disease connections. Machine learning (ML) and deep learning (DL) models predict drug efficacy based on molecular fingerprints, target interactions, and gene expression profiles.

AI-Based Strategies

1. Machine Learning Models

Use data from DrugBank, PubChem, and ChEMBL to predict drug– target affinity. Algorithms: Random Forest, Support Vector Machine, XGBoost.

2. Deep Learning Networks

Deep neural networks analyze omics data (transcriptomics, proteomics) to map drug effects.

3. Natural Language Processing (NLP)

Text-mining of scientific literature for drug–disease correlations.

4. In Silico Modeling and Docking Studies

In silico molecular docking helps visualize and predict the binding affinity of budesonide to HPV-related proteins.

Software and Tools Used

AutoDock Vina or PyRx – for molecular docking. Discovery Studio or Chimera – for visualization.
SwissADME – for pharmacokinetic and drug-likeness analysis. ProTox-II – for toxicity prediction.
ADMETlab – for absorption, distribution, metabolism, excretion, and toxicity profiling.

PROCESS

1. Retrieve protein structures (e.g., NF-κB, IL-6 receptor) from Protein Data Bank (PDB).
2. Prepare budesonide structure (PubChem).
3. Perform docking to predict binding interactions.
4. Analyze docking scores and hydrogen bond interactions.

Expected Results

Budesonide exhibits strong binding affinity toward inflammation-related targets, supporting its potential role in modulating HPV-induced inflammatory responses.

AI-Based Predictive Workflow for Budesonide Repurposing

Sr.no	Process	Tools/Database
1	Data collection [genes, proteins, drugs]	Genecards, PubChem DrugsBank
2	Docking validation	Autodock Vina, PyRx
3	AI model training	TensorFlow, PyTorch
4	Network analysis	Cytoscape, STRING
5	Toxicity & ADMET analysis	ADMETlab, pkCSM

Future Prospects

Integration of AI and CRISPR-based screening could validate molecular targets experimentally.

Multi-omics AI models will enhance precision in predicting anti- inflammatory drug responses.

Clinical translation: Combining budesonide with antiviral or immunotherapeutic regimens may improve outcomes in HPV- associated diseases.

Limitations

- Lack of clinical validation for AI-predicted targets.
- Variability in omics datasets may affect prediction accuracy.
- HPV strain-specific differences in inflammation pathways may alter response.
- Integrate AI-driven multi-omics data to refine target prediction.
- Conduct in vitro and in vivo validation studies.
- Explore nano-formulation of Budesonide for localized delivery to cervical tissue.
- Employ machine learning to predict combination therapy outcomes with antiviral or immunomodulatory drugs.
- Clinical trials assessing anti-inflammatory and antiviral effects in HPV-positive patients.

CONCLUSION

AI and network-based repurposing of budesonide reveal its promising potential in mitigating HPV-related inflammation.

Budesonide's well-established safety, anti-inflammatory efficacy, and molecular interactions with HPV-related targets make it a viable candidate for further preclinical and clinical investigation. Combining AI prediction, network pharmacology, and in silico modeling establishes a comprehensive pipeline for future drug repurposing in viral-induced inflammatory diseases.

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