RESEARCH PAPER

AI-Driven Identification of Therapeutic Targets and *In Silico* Screening of Natural Compounds Targeting Metabolic Reprogramming in Cervical Cancer

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Abstract

Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality among women worldwide despite significant advances in vaccination, screening, and therapeutic interventions. Persistent infection with high-risk human papillomavirus (HPV) initiates cervical carcinogenesis through disruption of tumor suppressor pathways, while metabolic reprogramming further promotes uncontrolled proliferation, invasion, and resistance to therapy. Conventional treatment strategies, including chemotherapy and radiotherapy, often exhibit limited specificity and are associated with severe adverse effects, highlighting the need for safer and more effective therapeutic alternatives. The present study proposes an integrated computational framework combining artificial intelligence, bioinformatics, network pharmacology, and molecular docking for the identification of potential therapeutic targets and natural inhibitors against cervical cancer. Publicly available genomic datasets were analyzed to identify cervical cancer-associated genes using preprocessing, feature selection, and Support Vector Machine (SVM)-based classification. Functional enrichment and pathway analyses were subsequently performed to identify key signaling pathways associated with tumor progression and metabolic dysregulation. Candidate phytochemicals with reported anticancer activity were collected from publicly available phytochemical databases and scientific literature. Drug-likeness, pharmacokinetic behavior, and toxicity profiles were evaluated using ADMET analysis prior to molecular docking. Selected compounds were docked against prioritized therapeutic protein targets to evaluate binding affinity and molecular interactions. The integrated computational workflow enabled systematic prioritization of disease-associated targets together with biologically relevant phytochemicals possessing favorable pharmacokinetic characteristics and strong predicted binding affinities. The study demonstrates that combining machine learning with network pharmacology and molecular docking provides an efficient strategy for accelerating natural product-based drug discovery. This framework offers a scalable, cost-effective, and environmentally sustainable approach for identifying promising therapeutic candidates targeting metabolic reprogramming in cervical cancer. The findings establish a computational foundation for future experimental validation and translational development of phytochemical-based anticancer therapeutics.

Keywords: Cervical cancer; Human papillomavirus; Machine learning; Support Vector Machine; Bioinformatics; Metabolic reprogramming; Phytochemicals; Network pharmacology; Molecular docking; ADMET; Drug discovery.

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1. Introduction

Cervical cancer continues to be one of the most frequent cancers among women all over the world today, posing serious public health problems especially in poorer regions where vaccination, screening and treatment are unavailable on a regular basis [1], [2].Persistent infection with the high-risk human papilloma virus (HPV), most notably HPV-16 and HPV-18, has been identified as the main cause of cervical cancer. The viral oncoproteins E6 and E7 work against the tumor suppressor proteins p53 and RB, thus causing the instability of the genome and the consequent growth of cells, their ability to evade apoptosis, and their transformation into cancer cells [3], [4], [5].The

growth of cancer can be explained not only by genetic changes within cells but also by changes in metabolism that allow cancer cells to thrive rapidly. This is known as metabolic reprogramming, which involves changes in the metabolism of glucose, amino acids, lipids, and mitochondria [6], [7]. One of the most studied metabolic phenomena of cancer is the Warburg effect, in which cancer cells use aerobic glycolysis instead of normal aerobic respiration for energy production [8], [9]. Changes in metabolism are regulated by several signaling cascades, including PI3K/AKT/mTOR, MAPK, p53, and HIF-1α that trigger tumor growth and make cancer cells more resistant to therapy [10], [11], [12]. Hence, metabolic enzymes targeted by these signaling pathways are considered potential therapeutic agents in cervical cancer treatment[13].

Traditional treatment methods like surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy have enhanced patient survival; however, these therapies have limitations which include systemic toxicity, multidrug resistance, relapse tumors, and lack of selectivity to cancer cells [1]. Due to these limitations, many researchers are investigating natural bioactive compounds as possible substitutes or adjuncts to conventional therapies. Phytochemicals from therapeutic plants have many biological properties like ability to act as antioxidants, anti-inflammatory, antiproliferative and promotes apoptosis [14]. Phytochemicals are much more appealing than synthetic anti-cancer medications as they can target multiple molecular targets at once while producing lower degree of toxicity [15].

Artificial Intelligence (AI), Machine Learning (ML), and Computational Biology have greatly benefited the initial phases of the process of finding a new drug as they have led to the seamless examination of huge biological datasets on a large scale. The algorithms used in ML are able to assist in the discovery of biomarkers, selection of therapeutic targets, and prediction of interactions involving drugs [16], [17] . One of the algorithms that is known for its efficiency is the Support Vector Machine or SVM algorithm due to its high level of stability as well as prediction [18]. Combination of pathway enrichment analysis with molecular docking and machine learning helps to find new drug candidates much faster and cheaper compared to standard techniques of drug discovery.

Network pharmacology has become a well-known systems biology methodology for the analysis of interactions among genes, proteins, pathways, and biologically active compounds. Unlike the traditional “one drug–one target” approach, network pharmacology acknowledges the intricate molecular interactions involved in multifactorial diseases, including cervical cancer [19], [20].When combined with molecular docking technologies, network pharmacology allows extensive identification of multitarget phytochemicals that can influence deregulated pathways [21], [22]. Although there have been important developments in computational oncology, most of the previously published studies have focused solely on machine learning, network pharmacology, or molecular docking. Only a limited number of studies have combined these complementary computational techniques into one framework to address metabolic reprogramming in cervical cancer [16], [23]. This shortcoming emphasizes the necessity of integrated computational methods for the identification of biologically significant therapeutic targets and screening of phytochemicals with advantageous pharmacokinetic profiles.

In order to fill this gap, this investigation presents a comprehensive computational workflow that includes machine learning gene prioritization, pathway enrichment analysis, network pharmacology, ADMET analysis, and molecular docking, providing a systematic approach to the identification of natural compounds targeting metabolic pathways related to cervical cancer. The utility of methodologies integrated in the proposed workflow should ultimately permit effective and speedy discovery of phytochemical drugs.

2. Material and methods

2.1 Study Design

The current research used an integrated methodology of in silico drug discovery to search for phytochemical agents that inhibit metabolic regulators implicated in cervical cancer. The approach integrated bioinformatics, machine learning, network pharmacology, and molecular docking to facilitate the process of identifying medicinal targets and screening for phytochemicals with promising antitumor effects. The workflow was aimed at simplifying large genomic datasets while enhancing the identification of lead compounds through a series of in silico studies [16], [17].

The research comprised four key phases: (i) identification and prioritization of genes related to cervical cancer by using public genomic databases and machine learning techniques, (ii) functional analysis of prioritized genes using pathways enrichment and protein–protein interaction methods, (iii) phytochemicals screening by drug-likeness and pharmacokinetics, and (iv) molecular docking to study protein–ligand interactions for the prioritized genes.

2.2 Data Sources and Computational Tools

Publicly available biomedical databases have been utilized to gather disease-related genes, protein structures, biological pathways, and phytochemical knowledge. GeneCards are used to pull genomic details related to cervical

cancer while STRING and KEGG ware utilized to carry out the analyses of protein interaction and pathway enrichment. The 3D protein structures were acquired from the Protein Data Bank (PDB), the stabilization of protein to bridge the gap is done using SWISS Model while the data regarding phytochemicals was obtained from PubChem. Machine learning analysis was carried out by means of kaggle dataset library and google colab while STRING was utilized to visualize the networks. PyRx integrated with AutoDock Vina was utilized to carry out molecular docking and study protein-ligand interactions with Discovery Studio Visualizer and PyMOL [19], [21].

Table 1: Databases and computational tools employed in the present study.

Tool/Database	Version	Purpose
Kaggle Dataset	-	SVM Model data collection
Google Colab	Cloud platform	Machine learning implementation (SVM)
GeneCards	-	Retrieval of cervical cancer-related genes
KEGG	-	Pathway enrichment analysis
STRING	12.0	Protein–protein interaction analysis
Cytoscape	3.10.1	PPI network visualization
GEPIA	2	Gene expression validation
PubChem	-	Phytochemical structure retrieval
RCSB PDB	-	Retrieval of Protein Structure
ADMETlab 2.0	2.0	ADMET and drug-likeness prediction
PyRx	0.8	Molecular docking
Discovery Studio Visualizer	2021	Protein–ligand interaction analysis
PyMOL	2.5	Prepare target protein structure before docking

2.3 Identification of Therapeutic Targets and Computational Screening

Genes contributing to cervical cancer (CC) were collected from several public databases and cleaned of duplicates using Microsoft Excel. After that, machine learning (ML) was applied to highlight possible target genes. The Support Vector Machine (SVM) model was selected due to its ability to classify large biological datasets properly [18]. The principal techniques of feature selection method were applied to eliminate redundancy and identify genes that contributed to better classification of diseases.

The selected genes went through Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses in order to identify their functions and related pathways. The next stage was Protein–protein Interaction (PPI) analysis performed using STRING database and visualized via Cytoscape in order to find hub genes that can be targeted for therapies [16], [22].Phytochemicals with anticancer effects were selected on the basis of literature review and using public databases. The screening was done by means of drug-likeness estimation and through the absorption, distribution, metabolism, and excretion (ADMET) properties analysis [21].

2.4 Molecular Docking and Interaction Analysis

The three-dimensional structures of the proteins that were intended to be explored were acquired from the Protein Data Bank and stabilized using SWISS Model, cleaned by removing water molecules, heteroatoms, and co-crystallized ligands using PyMol when necessary. The preparation of the receptor was done in order to make sure that the molecular docking needs of the ligand were met by adding the hydrogen atoms and etc. The ligand structures were

obtained from PubChem, converted to the required format, as well as minimized in energy prior to their use in the docking simulation.

The molecular docking was done utilizing AutoDock Vina through the PyRx software platform with the aim to determine the binding energy value. The binding energy was expressed in the form of the docking energy indicating the type of binding between the ligand and the protein [20], [21]. The data obtained through the docking simulation was visualized and analyzed with Discovery Studio Visualizer and PyMOL in order to identify the hydrogen bonding, hydrophobic interactions, stacking, and etc.The computational methodology supported the justification of selection of the biological targets and the phytochemical candidates selected for further testing.

3. Results

3.1 Machine Learning-Based Prioritization of Therapeutic Target Genes

Using a comprehensive machine learning-based screening algorithm, biologically significant genes associated with cervical cancer advancement were discovered. After filtering disease-related genes from open-source databases using the relevance score and Gene Information Content (GIFtS) values, the ultimate prioritization was done with the assistance of the Support Vector Machine (SVM) algorithm in order to select ten candidate genes, namely BRCA1, BRCA2, ATM, TP53, BRIP1, PALB2, CHEK2, MSH2, MSH6, and MLH1. These snatched genes are related mostly to DNA repair, cell-cycle control, and genomic integrity. They were thus considered targets of intervention in further analysis of pathways and molecular interactions being performed. The table containing the chosen genes can be found in Table 2. The SVM was applied to allow for prior selection of important genes for further computational processing and analysis.

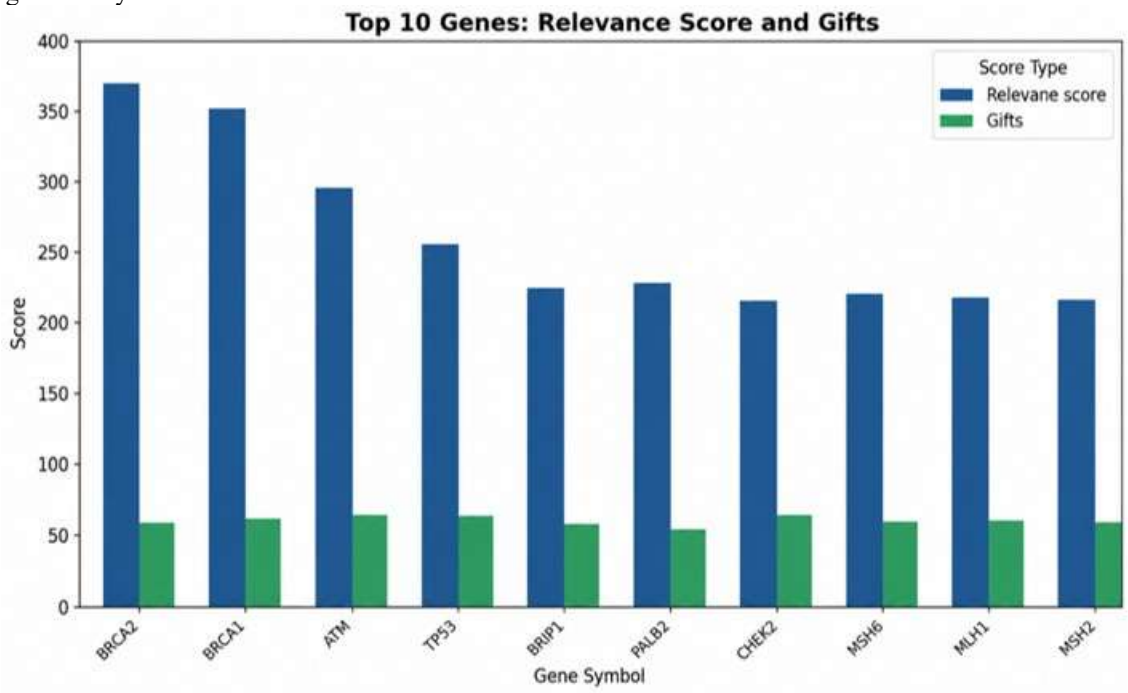

Figure 1: Chart of the top 10 candidate genes based on relevance and GIFtS scores, generated using Google Colab.

Table 2: Top-ranked therapeutic target genes identified through the SVM-based prioritization approach.

BRCA2	BRCA1	ATM	TP53	BRIO1
PALB2	MSH6	CHEK2	MSH2	MLH1

3.2 Pathway Enrichment and Gene Expression Analysis

Functional pathway analysis was conducted to assess the importance of the gene list for cervical cancer. This was demonstrated through KEGG pathway analysis of several shortlisted genes shown to be involved in cancer-associated cell communication pathways such as those of cell division, apoptosis, DNA repair, and metabolism. Glycolysis was noted to have been altered for the most part of the metabolic pathways with LDHA being identified as the most important glycolytic enzyme for cervical cancer development. Further enrichment analysis revealed to the

involvement of TP53 signaling and PI3K/AKT signaling pathway in connection to the metabolic reprogramming of the cells into tumors.

Gene expression analysis using the GEPIA platform further confirmed the findings of the computational analysis through the comparison of CESC samples to normal cervical tissue. Of the glycolytic genes analyzed and confirmed LDHA was found to have an increased level of expression compared to tumor free tissues, while the expression levels of the other LDH isoforms was relatively less distinct. This observation confirmed the decision to use LDHA as the main therapeutic target.

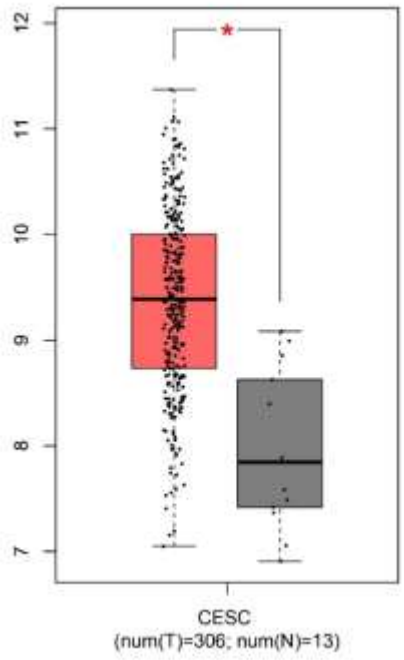

Figure 2: Differential expression analysis of LDHA in cervical squamous cell carcinoma using the GEPIA database, comparing tumour and normal tissue samples.

3.3 Protein–Protein Interaction Network Analysis

To explore the interactions between LDHA and other cancer-relevant proteins, we utilized the STRING database to develop a protein-protein interaction (PPI) network. This interaction network showed that LDHA had a close association with several key proteins involved in cellular metabolism, tumor suppression, hypoxia, and signaling. In particular, there was a clear interaction between LDHA and TP53, mTOR, and HIF1A, and there were connections with glycolytic enzymes such as PKM. This indicates that LDHA is part of a larger molecular network as opposed to being a single metabolic enzyme. The protein network is shown in Figure 3.

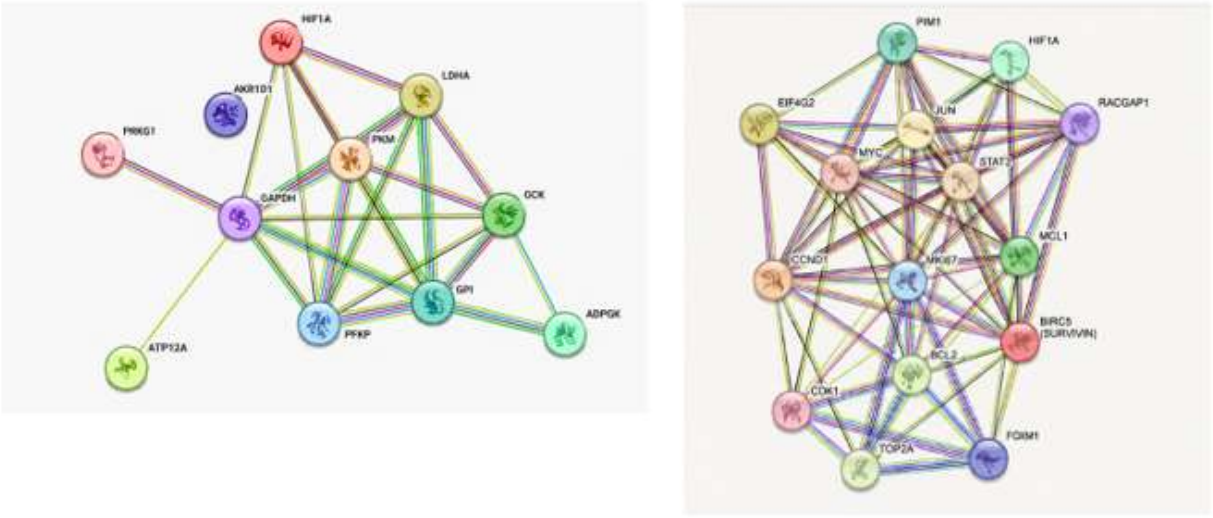

Figure 3: STRING protein–protein interaction network illustrating the association of LDHA with TP53, mTOR, HIF1A, PKM, and other regulatory proteins.

3.4 Selection of Phytochemicals for Computational Screening

After an extensive review of published scientific research as well as accessible databases describing various phytochemicals, ten compounds with anticancer activity were selected for further analysis. The list of these ten compounds includes Curcumin, Quercetin, Genistein, Resveratrol, Epigallocatechin Gallate, Apigenin, Luteolin, Kaempferol, Berberine, and Withaferin A. These specific compounds have been previously studied in regard to their ability to control various signaling pathways involved in cancer treatment and metabolic dysfunction. Before the analysis was conducted, all compounds were analyzed in terms of their structural characteristics and drug-like properties suitable for the interaction analysis that could be conducted later. The information about all selected compounds and the plants they were obtained from is summarized in Table 3.

Table 3: Top ten phytochemicals selected for molecular docking analysis, including their natural sources.

S.No.	Phytochemical	Plant source
1.	Curcumin	Curcuma longa
2.	Quercetin	Onion,apple
3.	Genistein	Glycine max
4.	Resveratrol	Vitis vinifera
5.	Epigallocatechin gallate	Camellia sinensis
6.	Apigenin	Chamomile
7.	Luteolin	Capsicum annuum
8.	Kaempferol	Brassica oleracea
9.	Berberine	Berberis vulgaris
10.	Withaferin a	Withania somnifera

3.5 Molecular Docking and Protein–Ligand Interaction Analysis

Following the identification of the target and screening of phytochemicals, the analysis of molecular docking was done in order to understand the binding interactions of LDHA with the phytochemicals selected. Removal of the non-essential structures ensured that the protein structure is presented for the docking simulations and the structure of the optimized protein is shown in Figure 4.

Withaferin A is the phytochemical that exhibits the maximum binding affinity towards LDHA which makes it a favorable compound for docking. The analysis of the docked complex showed that the ligand binds to the active site of LDHA and makes several important interactions with the amino acid components located nearby in their structure. In essence, the most important contributing factors in the stability of the predicted protein-ligand complex were hydrogen bond formation and hydrophobic interactions. Further analysis based on two-dimensional and three-dimensional showed that some important amino acids like HIS192 and ARG105 are involved in the binding of the ligand to the active site of the enzyme. The information about the binding conformation and interaction profile is shown in Figure 5.

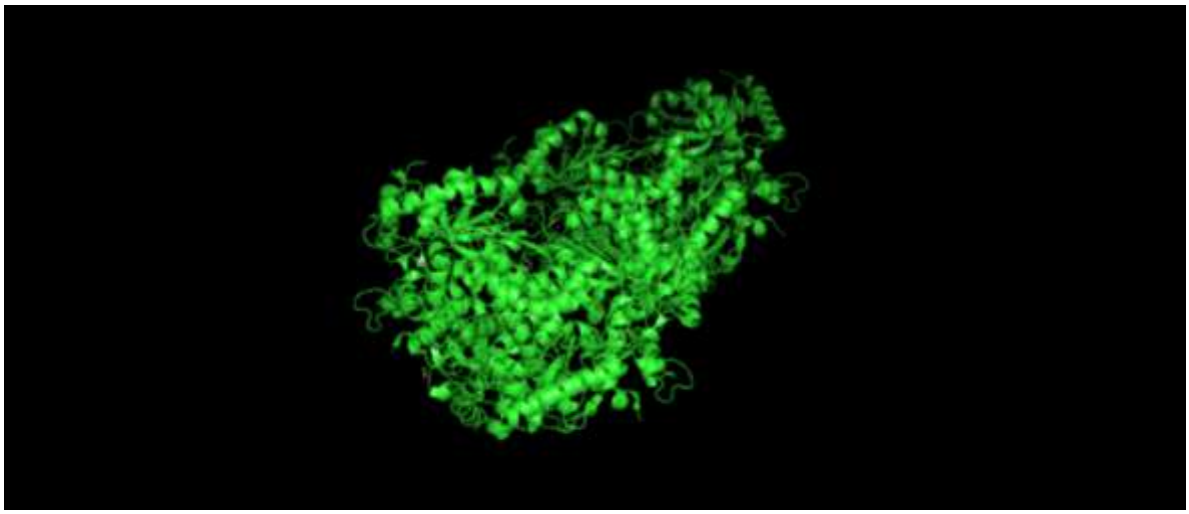

Figure 4: Three-dimensional structure of the LDHA protein prepared using PyMOL prior to molecular docking.

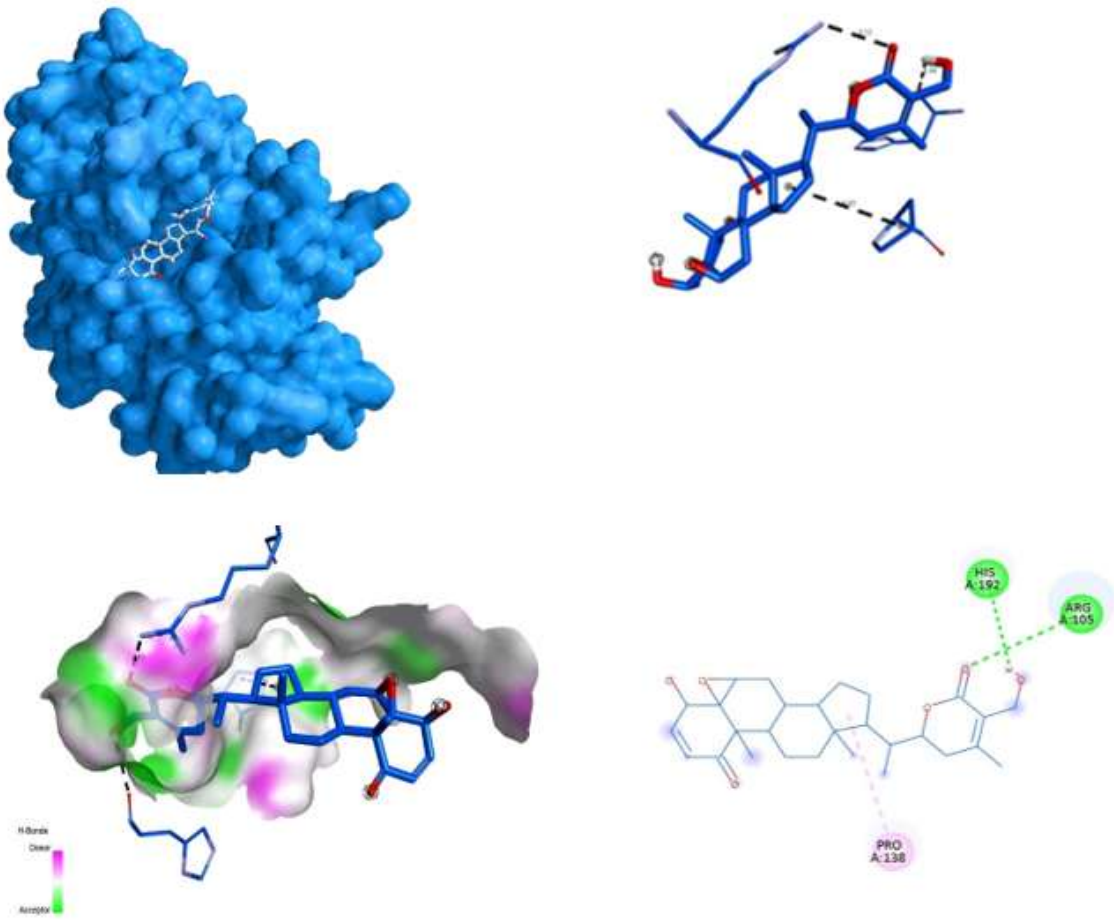

Figure 5: Two-dimensional and three-dimensional visualization of the interaction between Withaferin A and the LDHA active site generated using Discovery Studio Visualizer, illustrating hydrogen bonds and non-covalent interactions responsible for complex stabilization.

4. Discussion

4.1 Significance of LDHA as a Therapeutic Target in Cervical Cancer

The current research used a computational procedure to identify potential treatment targets related to cervical cancer metabolism, as well as to study phytochemicals able to exert an effect on these targets. Computational procedures identified LDHA (Lactate Dehydrogenase A) as a crucial enzyme in cervical cancer. Gene prioritization with the help of machine learning was done at the beginning of the research and implemented pathway enrichment, gene expression validation, and analysis of protein-protein interaction, showing that LDHA is at the center of the metabolic network in relation to cervical cancer. The research results support the latest studies claiming that metabolic enzymes are good drug targets due to their key role in the maintenance of tumor development and survival.

Tumour cells display a marked shift in metabolism to fuel their enhanced biosynthetic and energy requirements during the rapid rise in their proliferation. One of the most studied metabolic changes is the Warburg effect whereby cancer cells preferentially utilise aerobic glycolysis instead of oxidative phosphorylation even in the presence of oxygen. LDHA serves as the enzyme that converts pyruvate into lactate during glycolysis and thus helps to maintain the intracellular redox state and supply ATP continuously. High activity of LDHA has been related to increased tumour proliferation, angiogenesis, invasion, and therapies resistance in many types of cancer [8], [9].

The pathway enrichment analysis which is discussed in detail in the present theme confirmed that LDHA is linked with glycolysis and several other important cancer-associated signalling pathways, such as TP53-mediated regulation and the PI3K/AKT signalling pathway. At the same time, the STRING interaction network underlines that there exists significant interaction between LDHA and other regulatory proteins like TP53, mTOR, and HIF1A, which implies that LDHA is not just a mere metabolic enzyme but performs a crucial role in a complex signalling network

formed by other proteins. These findings are in accordance with the results provided in previous research that have shown that hypoxia signalling, mTOR activation, and alteration of metabolism are main contributing factors to the progress of cervical cancer due to high level of glycolytic activity [10], [11], [12].

Moreover, the RNA sequencing study suggests increased expression of LDHA in cervical cancer specimens relative to normal cervical samples, adding further evidence to its biological relevance. Its constant identification in various computational analyses only furthers its prospects of becoming a therapeutic target and implies that LDHA inhibition will disrupt the metabolic changes needed for cervical cancer development.

4.2 Potential of Withaferin A as a Natural LDHA Inhibitor

Withaferin A stood out as the most promising phytochemical query in the present study from the perspective of molecular docking, exhibiting the highest predicted interaction with LDHA. In terms of docking results, the study showed great binding ability, and structural visualization further confirmed the presence of the compound in the catalytic region of the enzyme due to the presence of multiple stabilizing interactions with crucial amino acid residues. The presence of hydrogen bonds along with hydrophobic interactions indicates that a stable protein–ligand complex has been formed that might interfere with the LDHA functioning.

The interaction patterns we have seen correlate with previous studies that have established the cancer-fighting properties of Withaferin A. Withaferin A, which is derived from the Withania somnifera plant, has been demonstrated to modulate numerous oncogenic pathways in processes such as cell cycle, apoptosis, oxidative stress, and metastasis. Withaferin A does not work through a specific molecular mechanism, as it produces various biological effects that make it a potential drug to treat difficult disorders, such as cancer [14].

Natural products that can interact with multiple signaling pathways have garnered significant attention because they might prevent the development of drug resistance that many selective inhibitors are prone to. Consequently, the high correlation that exists between Withaferin A and LDHA provides a rationale for further experimental studies to investigate the ability of Withaferin A to modulate the metabolism of cervical cancer.

4.3 Advantages of the Integrated Computational Workflow

A key improvement in the current study is to use more than one computational method in one study. Rather than using molecular docking exclusively, the current study also utilizes a gene prioritization method based on machine learning, bioinformatics, gene expression validation, protein-protein interaction testing, and pharmacological screening before performing molecular docking. The use of methods in this order ensures higher confidence in the process of target identification as molecular docking is carried out only for the proteins that have biological relevance.

The implementation of machine learning led to effective ranking of disease-related genes from big genomic data sets, significantly lowering the computational burden while enhancing the effectiveness of selecting meaningful candidates for therapy. Functional enhancement analysis offered biological background for the genes, while interactions between proteins helped find key elements in cervical cancer regulatory paths. At the end of molecular docking, we were able to discover the structure of how active substances interact with the chosen therapeutic target.

The overall computational approach is consistent with recent trends seen in drug discovery research where a range of complementary computational methods are used together to increase the efficacy and reliability in the process of lead compound identification [16], [17]. In this context, compared to traditional experimental screening methods, computational approaches effectively save both time and money while carrying out thorough screening of many candidates even before the experimental validation stage.

4.4 Limitations and Future Perspectives

Despite the present research being a full computational platform for selecting therapeutic targets and assessing phytochemicals, some limitations need to be stated. All findings are just based on silico studies, thus they must be confirmed in an experimental way. The molecular docking can evaluate the thermodynamic stability of the respective protein–ligand interactions but does not show the biological activity or therapeutic effects or clinical outcomes. The interaction of Withaferin A and LDHA has to be approved by using molecular dynamics methods in order to determine the stability of the complex at physiological level. Experimental studies should also involve enzyme inhibition tests as well as cervical cancer cell lines, gene expression tests, and animal models to be able to prove the validity of the computational studies' results.

In future research, it is possible to combine data from transcriptomic, proteomic, metabolomic, and clinical studies, which can help to identify future therapeutic targets by means of multi-omics analysis. The application of innovative AI-based models such as deep learning and explainable machine learning algorithms can boost predictive accuracy and help to discover new phytochemical agents against cervical cancer.

To summarize, this research presents an integrated framework, which provides a systematic methodology for finding biologically meaningful therapeutic targets and selecting natural compounds for studies. The study results may serve as a base for further experiments and have implications for the development of AI and computational biology.

5. Conclusion

The current research has constructed an integrated computational model utilized to identify therapeutic targets and screen natural products against the metabolic pathways linked to cervical cancer. By combining various techniques—including machine learning and bioinformatics, pathway enrichment analysis, gene expression validation, protein-protein interaction analysis, pharmacokinetic screening, and molecular docking, the research created a systematic process for finding potential phytochemical-based therapeutics. This integrated approach allowed the determination of relevant biological objectives while minimizing the complexity of analyzing vast genomic datasets.

Gene prioritization through machine-learning techniques has successfully identified ten candidate genes related to DNA repair, cell-cycle control, and genomic integrity. Further analysis via pathway enrichment and protein–protein interaction studies helped to show the significance of metabolic rewiring in cervical cancer development, with Lactate Dehydrogenase A (LDHA) being recognized as a possible target for therapy. Besides, gene expression data provided confirmation of LDHA physiological relevance because it has been found to be expressed at a higher level in tissues of cervical cancer compared to normal ones.

Out of all the phytochemicals tested, Withaferin A showed the best results in terms of binding to LDHA during the molecular-docking process. Visualization results indicated that Withaferin A formed a stable binding in the active site of the receptor protein through a series of hydrogen bonds and hydrophobic contacts, which implies its potential to influence the function of LDHA. These findings are supportive of the increasing interest in bioactive compounds that are obtained from plants as therapeutic agents targeting multiple proteins and provide a rationale for the study of Withaferin A as a therapeutic agent for cervical cancer.

The combination of machine learning and bioinformatics and molecular docking is a significant strength of this study. The proposed workflow, as opposed to the classical computational approach using docking alone, considers biologically important targets before starting on structural binding analysis and improves the first stage of candidate selection using rationales. Integration of computation approaches like this may be much quicker and less expensive than standard drug discovery techniques.

Even though the outcomes of the study are entirely based on computational analyses, it gives a good basis for future laboratory studies. Among the techniques that will be used in validation of therapeutic properties of Withaferin A against LDHA are enzyme inhibition assay and studies on cervical cancer cell lines, molecular dynamics simulations and animal studies. Future investigations may also use multi-omics datasets and state-of-the-art AI methods to build and expand the method of target selection.

In conclusion, this research establishes the fact that the combination of machine learning, bioinformatics and molecular docking represents an efficient solution in the search for new therapeutic targets and natural inhibitors in cervical carcinoma. The discovery of LDHA as one of the main metabolic targets and Withaferin A as a potential chemical compound is important for the development of therapies based on metabolism and contributes to the growing use of computational techniques in precision oncology.

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Ethical approval

The research conducted is not related to either human or animal use.

Conflict of interest

Authors declare no conflict of interest.