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Original Article

Uncovering the Therapeutic Potential of Panchavalkala: An *in silico* Approach on Cervical Cancer

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ABSTRACT

Background: Among all cancer that affect women worldwide, cervical cancer ranks third behind colorectal and breast cancer, with 5,69,000 new cases reported each year, that requires novel therapeutic strategies in addition to Holistic treatments. **Objectives:** In *Ayurveda*, the *Panchavalkala* is used for wound healing activity and studies have proven that it is effective in Cytotoxic activity. Hence, using bioinformatics, this study uncovers the role of *Panchavalkala*, to assess the mode of action in Cervical cancer. **Materials and Methods:** *Panchavalkala's* phytochemicals were procured from databases. Absorption, Metabolism, Distribution, Excretion and Toxicity screening of the phytochemicals were done. Targets related to plants and disease were obtained and overlapping targets were found. Common targets were used to predict KEGG pathways and topological analysis was done. Docking was done with the phytochemical having highest degree and hub genes and binding affinity was calculated. **Results:** 124 overlapping targets, 10 pathways and 18 phytochemicals were obtained by performing topological analysis. Corosolic acid had highest binding affinity towards AKT1 with -12.1 kcal/mol as binding affinity. Pathways in cancer had 50 common targets and had highest count in the KEGG pathways. **Conclusion:** *Panchavalakala* is told as Cytoprotective, but its mechanism of action was inconclusive, with *in silico* analysis the preliminary mechanism was justified. Further pre-clinical and clinical assessment is required to consider the phytochemical and the combination as a first line treatment in cervical cancer.

Keywords: Bioinformatics, *Panchavalakala*, Pathway, Phytochemicals, Target.

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INTRODUCTION

The primary cause of chronic HPV infection is cervical cancer (Okunade K S, 2020). The incidence of cervical cancer appears to be related to the prevalence of HPV in the population. In countries with a high incidence of cervical cancer, the prevalence of chronic HPV is approximately 10% to 20%, whereas in low-incidence countries it is 5% to 10% (Parkin M *et al*., 2002). Although effective, treating cervical cancer presents several difficulties. Reproductive possibilities may be limited due to fertility loss resulting from surgical treatments like hysterectomy. Notwithstanding these disadvantages, new therapy modalities such as integrative medicine and customized therapies are contributing to better patient results.

In classics single formulation with multiple indications has been addressed, the network pharmacology approach enables us to comprehend how a medicine functions specifically on a single ailment. A traditional formulation named *Panchavalkala* (preparation containing five plants bark), which comprises of equal proportion of the barks from *Ficus glomerata (Udumbara), Ficus lacor (Plaksha), Ficus religiosa (Ashwattha), Ficus benghalensis (Vata),* and *Thespesia populnea (Pareesha)*, which has references in classics for the management of vaginal diseases, leucorrhoea, and endometriosis-related issues among women (Aphale *et al*., 2021). Recent research has shown that aqueous extract of *Panchavalkala* (preparation containing five plants bark) has anticancer properties against HPV-positive cervical cancer cell lines, reducing the cells' viability (Aphale *et al*., 2018). This formulation is being studied for understanding the multi-targeted mechanisms of action, supporting its relevance in holistic medicine and modern oncology through *in silico* approach.

Network pharmacology is an *in silico* method that has surfaced to help explain drug pharmacokinetics with multiple targets, (Vohra, 2022) it is an integrative method that illuminates the reasons behind the synergistic therapeutic activities of traditional drugs by creating a "protein-compound/disease-gene" network (Chandran *et al*., 2017). Employing this tool will enable us to ascertain what pathways are active under certain conditions,

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describes how genes, proteins, and metabolites interact and predict the effect of drug therapies or gene alterations.

MATERIALS AND METHODS

Preparation of Panchavalkala Kashaya

Panchavalkala Kashaya is traditionally prepared by taking 5 g of each drug, and adding 16 parts of water, i.e., 400 mL reducing it to one-eighth of the original volume i.e., 50 mL to obtain the decoction. It is specifically indicated in *Yonidhawana* (vaginal wash) in various gynecological conditions, where it helps in cleansing, reducing inflammation and promoting local healing of the vaginal tissues. The polyherbal combination makes it effective in maintaining vaginal hygiene and managing infections naturally (Paradakara H.S.S, 2016). The outline of the methodology followed is illustrated in Figure 1 in a flowchart.

Ethical statement

Since the research study did not involve any human or animal participants, obtaining ethical committee approval was not required.

Statistical analysis

The *p*-value was not derived from our calculations. It was obtained from Genecard and other databases.

Bioactive compounds and targets related to plants

Plant databases: 1. Dr. Dukes (Duke *et al.*, 1992) and 2. IMPPAT (Mohanraj K *et al.*, 2018) (IMPPAT: A curated database of Indian Medicinal Plants, Phytochemistry and Therapeutics) was used to acquire the phytochemicals related to the plant and the specific part. The obtained phytochemicals related SMILIES were obtained from Pub Chem database (Kim *et al.*, 2025). The SMILIES obtained were uploaded into AMDET Lab 3.0 (Fu L *et al.*, 2024). Then based on 4 parameters the obtained Phytochemicals were filtered, they were: Drug Likeliness, Human Intestinal Absorption, F 30 (Bio-availability - 30%) and Cytotoxicity. The obtained phytochemicals SMILIES Bioavailability into Swiss Target Prediction for acquiring targets related to the specific phytochemicals (Gfellar *et al.*, 2014).

Extraction of gene related to disease and finding overlapping targets

The Gene ID's related to disease were extracted from Gene cards database (Stelzer *et al.*, 2016). The cutoff score was kept till 7 in Gene cards. The targets related to the disease was also attained from Human Protein Atlas (HPA) (Thul P J *et al.*, 2017) followed by that both disease targets and compound related targets were found from Venny 2.1.0 (Oliveros *et al.*, 2015).

Protein interaction

Overlapping targets were uploaded into STRING (Szklarczyk *et al.*, 2013) database and the Protein network was constructed between the nodes. The network was then transferred to Cytoscape 3.10.3 (Shannon *et al.*, 2003) and the final interaction was developed to assess the degree of interaction between the nodes. The top 10 targets were assessed using Cyto Hubba (Chin *et al.*, 2014) and the calculation of the score was done using the app.

Enrichment pathway

DAVID Bioinformatics (Sherman *et al.*, 2021) was used to find out the Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway enrichment. Followed by these the top 10 pathways were plotted in SR plot and the P value and score analysis was done (Tang *et al.*, 2023). The *p*-value was not derived from our calculations. It was obtained from Genecard and other databases. Enrichment analysis of the top 10 KEGG pathways were done and the data regarding the role of the top 10 KEGG pathways in relation to the disease were obtained through literature research.

Network Development

Network design was done using Cytoscape 3.10.3 (Shannon P *et al.*, 2003) to show how phytochemicals, target protein molecules, and a selected pathways are connected. The Network Analyzer program was used to combine and analyse several networks. A number of characteristics, including colour, node size, and form, were used to improve the network's visual representation. Based on degree, the phytochemicals that had the most significant impact on a certain disease pathway were examined.

Molecular docking

After the topological analysis the compounds and the targets were sorted on the basis of degree and followed by that the compounds and targets having highest degree were chosen and further docking was done. The target's PDB ID were downloaded from RCS PDB (Burley S K *et al.*, 2023) and the compound 3D structures were downloaded from PubChem. (Mohanraj K *et al.*, 2018) Followed by this the hetero atoms were removed in Biovia, (Dassault 2021) water molecules were removed, hydrogen bonds were added and kollman charges were added from Autodock tool 1.5.7 (Morris *et al.*, 2009). After this the binding affinity was assessed in PyRx software (Dallakyan S *et al.*, 2015) and the visualisation of the target - compound interaction was done in Biovia.

RESULTS

Plant targets

The name of the 5 *Ficus glomerata (Udumbara), Ficus lacor (Plaksha), Ficus religiosa (Ashwattha), Ficus benghalensis (Vata), and Thespesia populnea (Pareesha)*, were entered into the plant databases and the part was specified as "bark", because *valkala*

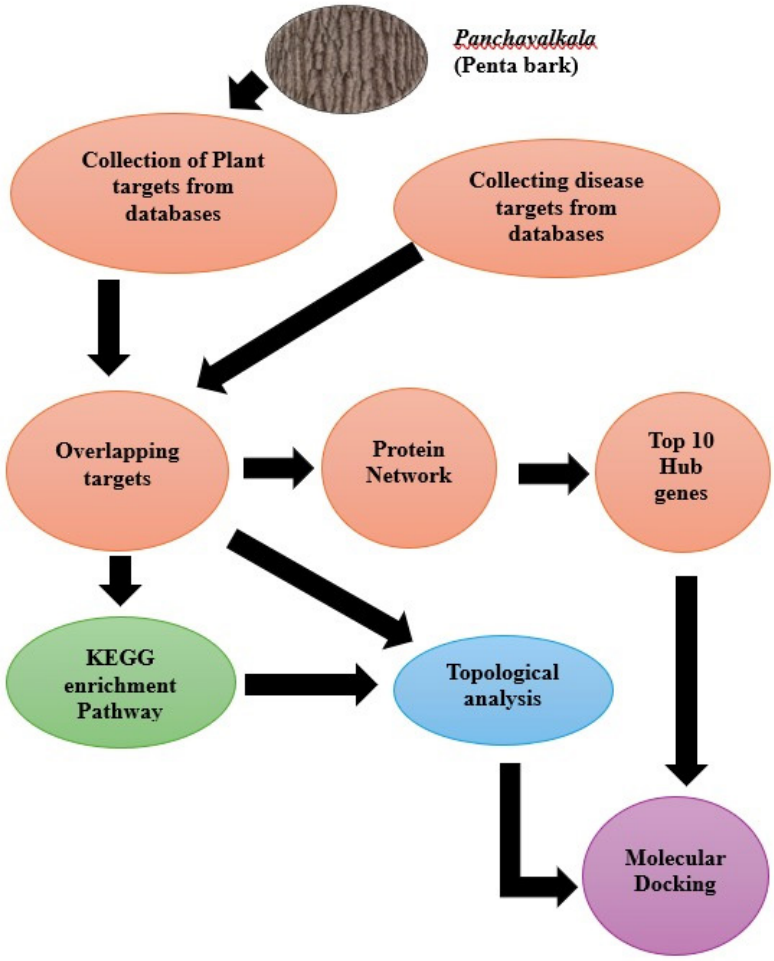

Figure 1: Workflow of the methodology adopted.

in Sanskrit means bark. In total the plant had *Ficus religiosa* - 40, *Ficus bengalhensis* - 60, *Ficus racemosa* - 27, *Thespesia populnea* - 51 and *Ficus glomerata* - 25 phytochemicals. In total there were 203 phytochemicals present and after removing duplicates a total of 87 phytochemicals were present. After screening drug likeliness with a medium score of 0.5, human intestinal absorption, F 30% and Cytotoxicity with a medium score of 0.499999 in ADMET lab 3.0, 17 phytochemicals were obtained. The 17 phytochemicals were 1-[2-(Benzyloxy)-6-hydroxyphenyl] ethan-1-one, 1H-Benzimidazole-1-methanol, 2,3-Dimethylacrylic acid, (E)-2,6-Dimethoxyphenol 3,4-Dihydroxybenzoic acid, Corosolic acid, Ferulic acid , Jasmone, Mansonone C, Mansonone D, Mansonone E, Mansonone F, Methyl ferulate, Sesquiterpenes, Sinapyl alcohol, Thespon, Vogelin E. There were a total of 1615 targets obtained from Swiss Target Prediction and after removing duplicates we got 590 targets related to the combination.

Disease targets and Overlapping targets

The targets related to "Cervical cancer" was obtained from the two databases Gene cards and Human Protein Atlas (HPA). In Gene cards a total of 322 targets were obtained after applying a cutoff score of 7 and in HPA 1908 targets were obtained. After removing the duplicate targets from both the database a total of 2230 targets were obtained. With 590 compound targets and the 2230 disease targets, a total of 124 overlapping targets were found from Venny 2.1.0. The overlapping targets are shown in Figure 2.

Protein network

These 124 targets were uploaded into STRING database and the interaction between the nodes were assessed in Cytoscape 3.10.3 and the network was constructed on the basis of edges interaction. Top 10 targets were attained from Cytohubba and the score was calculated, among these 10 Hub genes, AKT1 had a score of 3.79627281858069, followed by that BCL2 with a score of 3.79627281857858 and other genes had consecutive scores. The top 10 Hub genes were: AKT1, BCL2, HIF1A, STAT3, BCL2L1, SRC, MTOR, CASP3, ESR1 and CTNNB1. The PPI network of targets is shown in Figure 3 and the top 10 hub genes are illustrated in Figure 4.

Enrichment pathway

The common targets 124 were then uploaded into DAVID Bioinformatics for KEGG pathway analysis, with the selection as Official Gene symbol and Species as "*Homo sapiens*" a total of

156 pathways were attained. Among this based on the count and P value the top 10 KEGG pathways were analysed and they were plotted into SR plot for further investigation. Pathways in cancer had the highest count with 50 that implies that our common targets are highly involved in this pathway, 40.3228% and a *p* value of 3.349, which signifies the role of this pathway in our disease, illustrated in Figure 5.

Target - Compound - Pathway analysis

The 124 targets, 18 phytochemicals and 10 pathways were then uploaded into Cytoscape 3.10.3, and the topological analysis was done between the targets, compounds and pathways. Figure 6 depicts the network between the pathways, overlapping targets and pathways. The phytochemicals showed a degree layout and edge betweenness of 101, EGFR had the highest edge betweenness of 17, followed by that MAPK8 with 16 and MAPK1 with 15 as their edge betweenness. But these targets were not there among the top 10 hub genes.

Molecular Docking

Molecular docking analysis was done with 5 compounds and 5 top hub genes AKT1, CASP3, BCL2, STAT3 and SRC. The molecular docking had shown that Corosolic acid had highest binding affinity towards most of the targets. It had shown -12.1 kcal/mol towards AKT1, -7.6 kcal/mol, -7.8 kcal/mol towards CASP3, -10 kcal/mol towards SRC and -10 kcal/mol towards STAT3. -4.4 kcal/mol was the lowest binding affinity seen from 2,6-Dimethoxyphenol towards CASP3. Table 1 depicts binding affinity of targets and compounds, and the visualisation of the compound-target is shown in Figure 7.

DISCUSSION

Dysplasia, in which aberrant cervical cells first arise, is the precursor to Cervical Cancer (CC), which, if left untreated, can progress to invasive malignancy. The most successful approach worldwide is prevention through routine cervical screening and HPV immunization. For prognosis counselling and therapeutic guidance, accurate staging is essential (National cancer institute 2023).

Recent years have seen a tremendous advancement in CC treatment, with numerous therapeutic techniques like as, Surgery in various early-stage cancers, Radiotherapy like (EBRT, IMRT, Brachytherapy), Chemotherapy as supportive therapy along with surgery and radiotherapy and the agent used is Cisplatin and immunotherapy has been discovered as new treatment for cervical cancer (Burmeister *et al.*, 2022).

A study using a mouse papilloma model revealed that the aqueous extract of *Panchavalkala* (preparation containing five plants bark) (five barks) had anticancer activity in cervical cancer cell lines such as SiHa and HeLa. By altering HPV E6/E7 oncoproteins and tumour suppressors, this caused apoptosis. Furthermore, this medication demonstrated immunomodulatory potential. This study used both vitro and *in vivo* methods to demonstrate *Panchaavalkala (preparation containing five plants bark)*'s effectiveness as a powerful anti-cervical cancer medication (Aphale S *et al.*, 2021). It was discovered that the exact mechanism

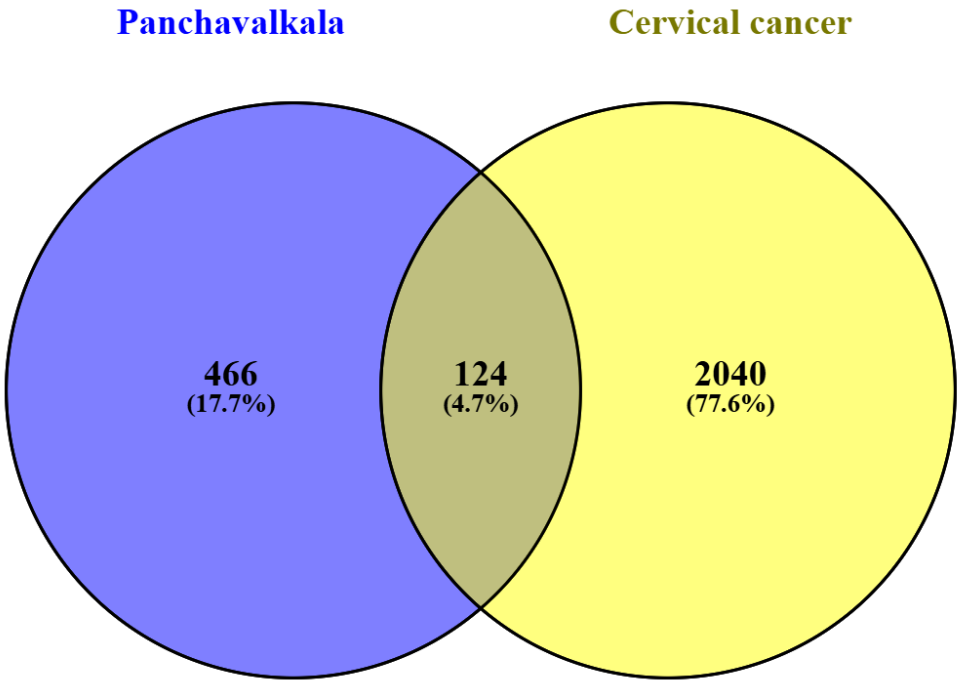

Figure 2: Overlapping targets between *Panchavalkala* targets and cervical cancer disease targets.

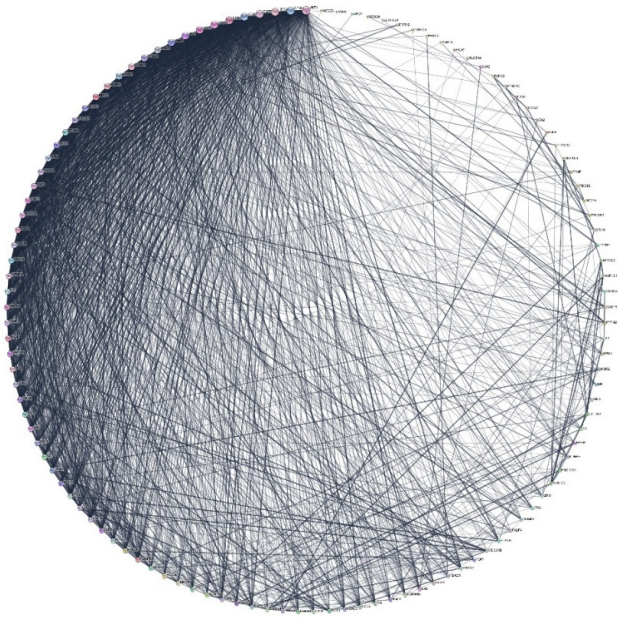

Figure 3: PPI network.

Table 1: Binding affinity of phytochemicals with their targets.

Binding affinity (kcal/mol)					
Phytochemical	**Targets**				
	AKT1	**BCL2**	**CASP3**	**SRC**	**STAT3**
PDB ID	(3O96)	(4IEH)	(2H5I)	(2SRC)	(6NJS)
Sesquiterpenes	-8	-6.7	-6	-7.2	-6.6
Corosolic acid	-12.1	-7.6	-7.8	-10	-10
2,6-Dimethoxyphenol	-5.2	-5.2	-4.4	-5.3	-5.1
1H-Benzimidazole-1-methanol	-6.2	-5.5	-5.2	-5.9	-6
1-[2-(Benzyloxy)-6-hydroxyphenyl] ethan-1-one	-9	-6.9	-6.1	-7.2	-7.7

behind its anti-cancer action was unknown. To date, no *in silico* (network pharmacology) research has been conducted to prove the fundamental mechanism of *Panchavalkala* (*preparation containing five plants bark*) in CC.

After screening phytochemicals and docking them with disease targets, we discovered that corosolic acid, 1-[2-(Benzyloxy)-6-h ydroxyphenyl] ethan-1-one, and sesquiterpenes had the highest binding affinities to disease targets AKT1, SRC, and STAT3, therefore they were discussed.

Corosolic acid has anticancer effects through the following mechanisms: 1. ER stress pathway by activating pro-apoptotic signalling; 2. Lipid peroxidation mediated cell death; and 3. Mitochondrial caspase pathways: When HeLa and CaSki cervical cancer cells are treated with corosolic acid, CA caused S-phase arrest, mitochondrial dysfunction, caspase-mediated apoptosis, cell cycle arrest, and by suppressing PI3K/Akt, a survival pathway in CC (Zhao J *et al.*, 2021).

1-[2-(Benzyloxy)-6-hydroxyphenyl] ethan-1-one, is derivative of Acetophenone. An MTT cytotoxic assay was carried out to find out the anticancer potential of the acetophenone derivatives by employing HeLa (Cervical cancer cell), MCF-7 (Breast cancer cell), A-549 (Lung cancer), SMMC-7541 (Liver cancer) cells. This depicted strong cytotoxic effects against HeLa cancer cells, indicating strong cytotoxic effects of the Acetophenone compounds (Ahmadpourmir H *et al.*, 2024).

Cervical cancer can be effectively prevented by using sesquiterpene lactones. When EM23, a sesquiterpene, is applied to CaSki and SiHa cells, it inhibits the proliferation of cancer cells by targeting thioredoxin reductase (TrxR), which leads to the accumulation of Reactive Oxygen Species (ROS) and mitochondrial dysfunction, ultimately causing apoptosis. EM23 also boosts the ASK1-JNK pathway, which encourages apoptotic autophagy, and decreases Akt/mTOR signalling. When it comes to treating cervical cancer, sesquiterpenes appear to be promising as multi-target medications (Shao F Y *et al.*, 2016).

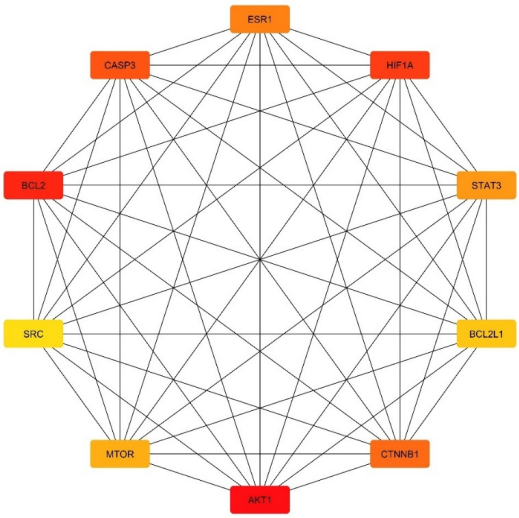

Figure 4: Top 10 Hub genes.

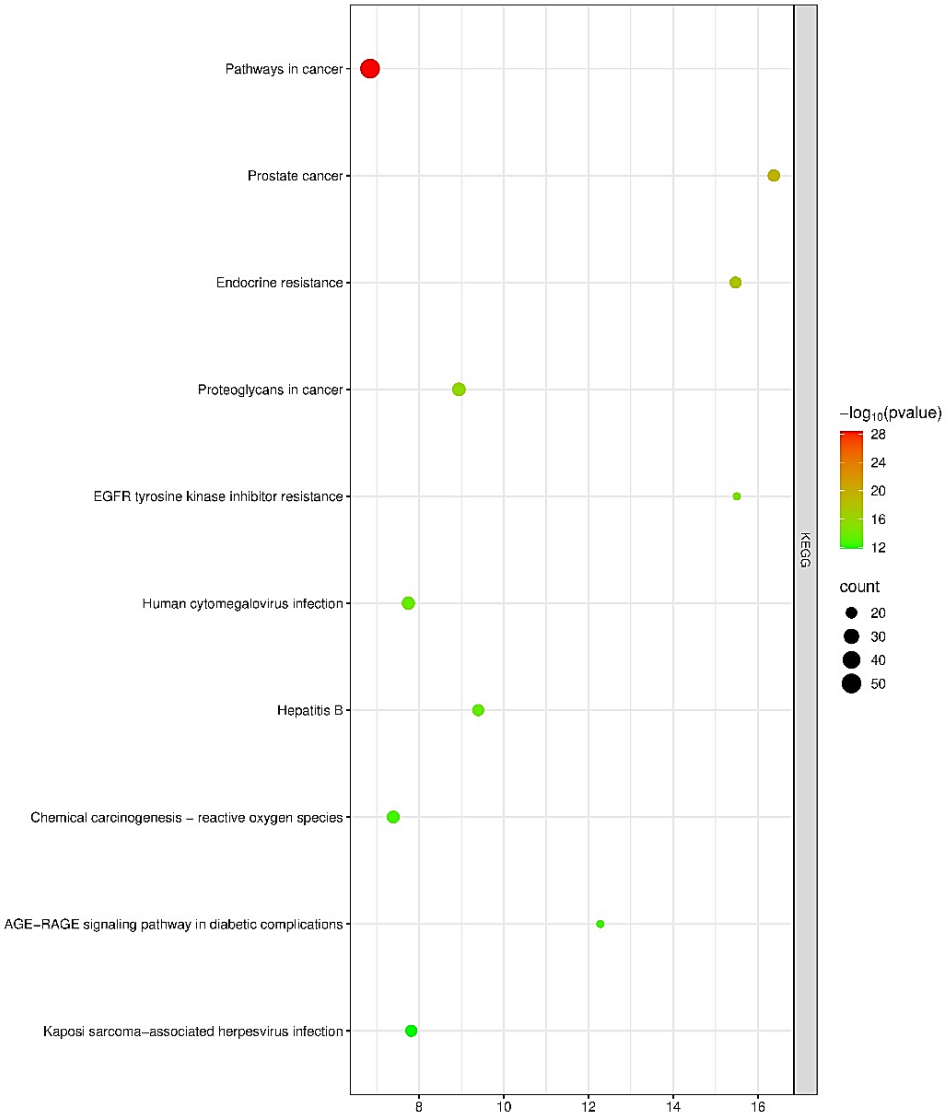

Figure 5: Enrichment bubble of Top 10 pathways.

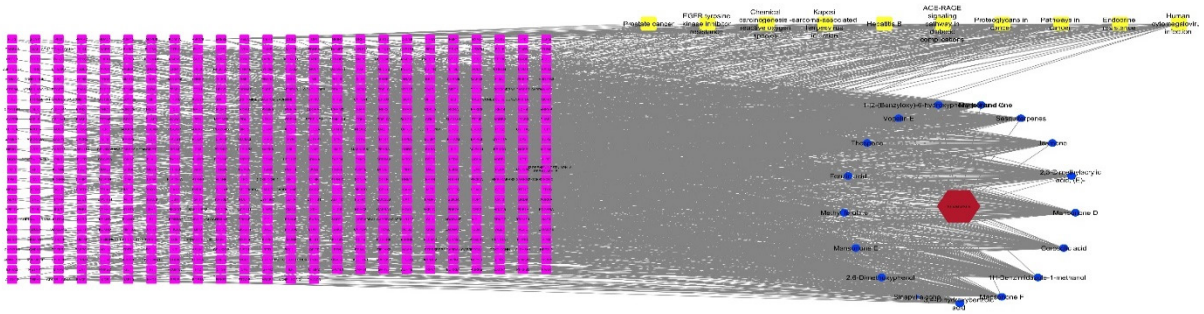

Figure 6: Merged Network of Target - Compound - Pathway.

The increased AKT1 gene in CC accelerates the growth of tumors and improves cell invasion, proliferation, and the Epithelial-Mesenchymal Transition (EMT). TGF-β triggers this, and the circ-AKT1/miR-5p axis controls it; in this case, circ-AKT1 promotes AKT1 expression and sponges miR-942-5p. It is a key oncogenic factor and a crucial disease target in the pathophysiology and treatment of cervical cancer because of its activity, which promotes the growth of cervical cancer (Ou R *et al*., 2020).

Cervical cancer progression is associated with SRC, a non-receptor tyrosine kinase. Proliferation, increased apoptosis, and cell cycle arrest in the G0/G1 phase are the results of SRC inhibition by the selective inhibitor PP2 in HeLa (HPV positive) and C33A (HPV negative) cells. SRC uses the ERK pathway to promote the development of cancer cells, as evidenced by these effects, which were followed by decreased phosphorylation of ERK1/2 and c-Fos and increased c-jun signal (Song *et al*., 2017).

STAT3, an oncogene, is widely expressed in cervical cancer and stimulates the development of tumors, metastases, proliferation, and clones. By inhibiting the Beclin-1/PIK3C3 complex via the Bcl-2-Beclin-1 axis, it has a negative impact on autophagy by reducing autophagic activity. By boosting autophagy, lowering Bcl-2, and raising Beclin-1, STAT3 ablation prevents cervical cancer from growing. Because it partially suppresses autophagy, which encourages the growth and survival of cervical cancer, STAT3 is thus a potential therapeutic target (Wu L *et al*., 2022).

Pathways in cancer is a collective entity which includes many pathways which involve development and progression of cancer namely, 1. PI3K/AKT/mTOR pathway, 2. MAP-Kinase pathway, 3. Wnt/β-catenin pathway. As upon screening and adding the phytochemicals and disease targets to the discussion section, we observed that a large number of phytochemicals function via the PI3K/AKT/mTOR pathway. Thus, we have considered this pathway for discussion.

HPV oncoproteins e6/e7 frequently cause PIK3CA mutations, PI3K amplification, and PTEN loss, which all contribute to the hyperactivation of the PI3K/AKT/mTOR pathway. This p-AKT and p-mTOR activation triggers chemoradiation resistance and proliferation. This can therefore be linked to this pathway as both a target and a predictive biomarker (Zhang *et al*., 2019).

Docking was carried out to determine the binding affinity of the phytochemicals and targets. Of the five phytochemicals that were selected for docking, we discovered that corosolic acid had the highest binding affinity with the disease target AKT1 (3O96) with a relatively low binding energy of -12.1 kcal/mol. The same phytochemical also showed binding affinity with the disease target SRC (2SRC) and STAT3 (6NJS) with a binding energy of -10 kcal/mol, which was higher than any of the compounds we had selected for docking. Corosolic acid has shown highest binding affinity towards selected targets in docking, this suggests that extract of the Phytochemical from the main compound formulation i.e. *Panchavalkala (preparation containing five plants bark)* should be studied exclusively in CC to check its efficacy in Clinical trial. This suggests that *Panchavalkala (preparation containing five plants bark)* treats CC altogether. Good binding affinity for the disease targets has also been demonstrated by the other phytochemicals that have been docked.

In order to determine *Panchavalkala (preparation containing five plants bark)*' s activity in CC, the study just looked at a few databases; no *in vitro* or *in vivo* research was conducted to support this. As the databases continue to be updated, their reliability will be in uncertain.

CONCLUSION

Our study demonstrated that *Panchavalkala (preparation containing five plants bark)*-mediated management of CC was a complicated process involving a variety of phytochemicals, disease targets, and disease pathways by using network pharmacology and molecular docking. *Panchavalkala (preparation containing*

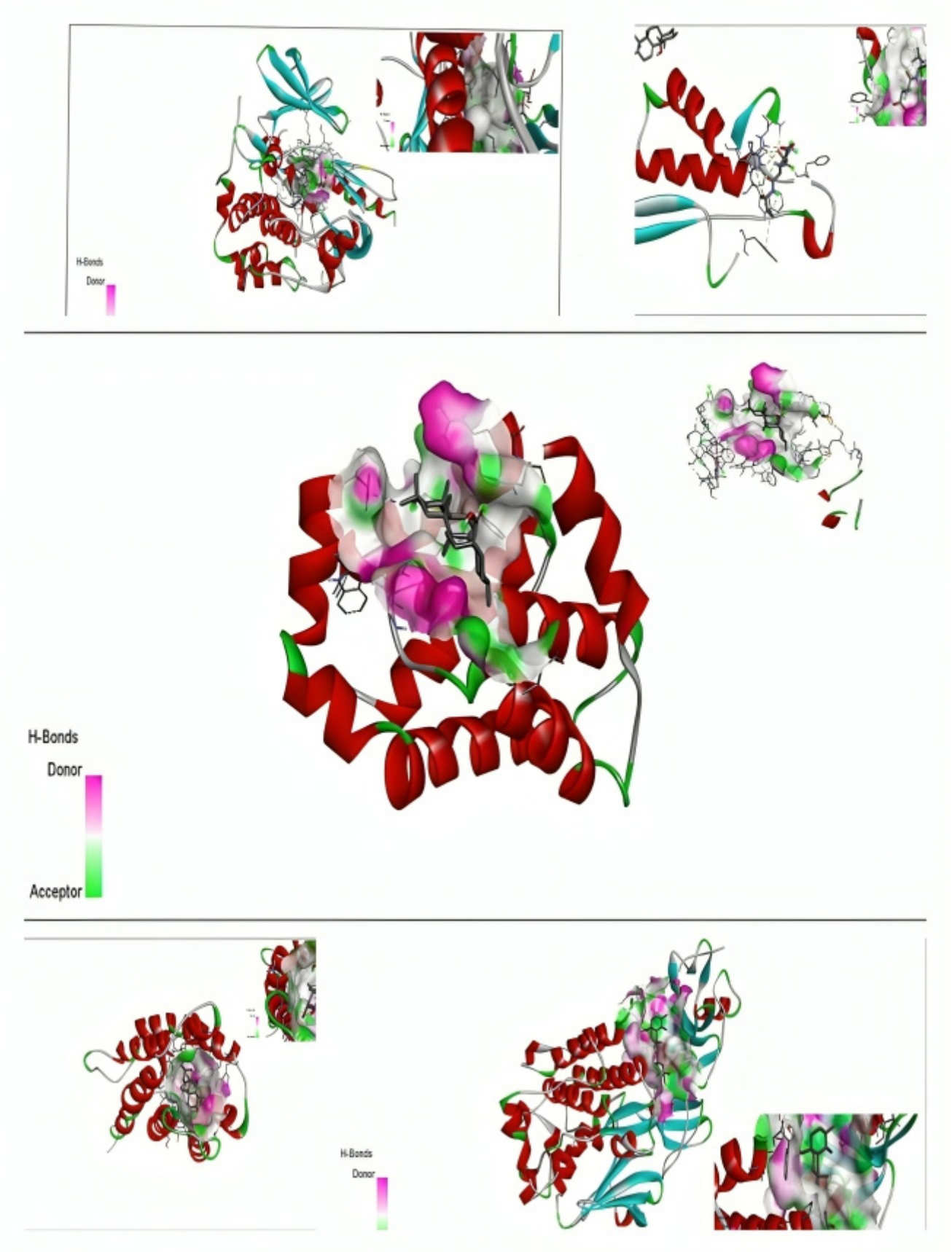

Figure 7: Docking visualisation of the ligand and the target, the top most two targets are CASP3, BCL2. The centre one is AKT1, the lower most two are SRC and STAT3.

five plants bark) controls cancer cell proliferation, metastasis, and chemotherapy resistance through the PI3K/AKT/mTOR pathway, which also includes AKT1, STAT3, and SRC in the treatment of CC. These compounds, disease targets, and pathways serve as an outline for CC clinical trials and treatment, as well as a theoretical framework for CC medication development.

ABBREVIATIONS

CC: Cervical Cancer; **HPA:** Human Protein Atlas; **PDB ID:** Protein Data Bank ID; **RCS PDB:** RCSB Protein Data Bank; **EBRT:** External Beam Radiation Therapy; **IMRT:** Intensity-Modulated Radiation Therapy; **EMT:** Epithelial-Mesenchymal Transition; **ADMET:** Absorption, Metabolism, Distribution, Excretion and Toxicity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

R S Hiremath- Conceptualization, Revising the manuscript.

Rashmi Motnalli- Data procuring, Interpretation of results, Preparation and Revising manuscript.

Sri Venkata Krishnan V - Designing the study, Preparation of Manuscript.

Santosh N- Interpretation of results and Revising manuscript.

SUMMARY

Cervical cancer is 4th most common cancer with around 6,60,000 new cases and 350,000 deaths in 2022. Though there are various treatment modalities for management of cervical cancer in modern pharmacology, they produce numerous side effects in day-to-day lifestyle. On the other hand, in *Ayurveda*, the bark of five trees known as *Panchavalkala* is mentioned as anti-cytotoxic action in classical texts, to elucidate the role of the *Panchavalkala* and to understand the mode of action *in silico* analysis was performed. The targets related to the phytochemicals of the 5 plants were obtained from the databases, they were combined, and duplicates were removed and finally 590 targets were obtained. From disease databases a total of 2230 targets were procured and after overlapping both the Phyto and disease targets, 124 overlapping common targets were obtained. After exporting the common targets, the top 10 hub gene targets were analyzed, and ranking was given. KEGG enrichment analysis was done on the top 10 pathways with pathways in cancer as the topmost. Topological analysis was done followed by molecular docking was done on targets like AKT1, SRC, BCL2, CASP3 and STAT3, with corosolic acid, a phytochemical in the formulation that had highest binding affinity of -12.1 kcal/mol against AKT1. Though this computational pharmacology may serve as a preliminary analysis for the formulation's (*Panchavalakala*) mode of action, further analysis on animal and human participants will be required to validate the statement that was obtained during the study.

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