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Molecular Docking-Based Analysis of Rauvolfia Serpentina Alkaloids Targeting HPV E1 and L1 Proteins for Antiviral Therapeutic Potential

Pavani J Bharadwaj*

Abstract

Human papillomavirus (HPV) is a major cause of cervical cancer and other epithelial cancers. E1 and L1 proteins are crucial to the virus's life cycle. E1, a viral helicase, is essential for HPV DNA replication, and L1 is the main structural capsid protein that builds the virion and infects target cells. Targeting these proteins offers a promising strategy to inhibit viral proliferation. In this context, Rauvolfia serpentina, a medicinal plant known for its wide range of pharmacological effects and high alkaloid content, appears to be a promising natural source for therapeutic agents. This work investigates the molecular interactions between HPV E1 and L1 proteins and phytoconstituents from Rauvolfia serpentina using molecular docking techniques. The ability of alkaloids like ajmaline, serpentine, and sandwicine to bind to the target proteins' active sites was assessed. According to the docking studies, these bioactive substances have favorable binding energies and establish stable molecular interactions with key residues in the E1 and L1 proteins. Ajmaline, in particular, demonstrated strong affinity for the E1 helicase domain, which may indicate inhibition of viral replication. Likewise, ajmaline demonstrated strong interaction with L1, suggesting potential disruption of viral entry and capsid formation. This study provides computational evidence that Rauvolfia serpentina contains compounds capable of interacting with and potentially inhibiting critical HPV proteins. These results highlight the need for further experimental studies to validate the antiviral potential of the identified phytocompounds. The findings underscore the potential of plant-derived molecules in developing alternative therapeutic strategies against HPV infection, especially by targeting essential viral proteins through molecular interactions.

Keywords: Ajmaline, Anticancer, Cervical Cancer, Human Papillomavirus, Molecular Docking, Oncoproteins, Rauvolfia serpentina, Sandwicine, Serpentine

INTRODUCTION

Human papillomavirus (HPV) is a small, non-enveloped, double-stranded DNA virus that primarily infects epithelial cells of the skin and mucous membranes. The virus comprises numerous genotypes that differ in their transmissibility and oncogenic potential [1]. Transmission occurs mainly via direct contact, making HPV one of the most prevalent sexually transmitted infections (STIs) worldwide. Based on their cancer-causing ability, HPV genotypes are classified into high-risk and low-risk types. High-risk variants include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 [2], whereas low-risk types, most commonly HPV 6 and 11, are mainly associated with genital warts [1]. High-risk HPV types are strongly linked to cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers, with HPV 16 and 18 accounting for over 70% of cervical cancer cases [2]. While most infections are transient and cleared by the host

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immune system within 6 months to 2 years, a subset of infections may persist, inducing cellular abnormalities that can progress to cervical cancer [1].

The established connection between HPV infection and cervical cancer has driven the World Health Organization (WHO) to implement a global strategy aimed at eliminating cervical cancer through vaccination, screening, and treatment of precancerous lesions [3]. Although infections are often asymptomatic, some may present as genital warts, which, despite being benign, can lead to physical discomfort and psychological distress [4]. Epidemiological data suggest that HPV contributes to over 90% of cervical cancer cases globally. Prevalence varies geographically, with asymptomatic infections affecting 57.7% of women in Eastern Asia, 32.3% in Eastern and Southern Africa, and 3.7% in Western Europe, primarily among individuals under 25 years of age. In men, prevalence ranges from 17.2% in South Africa to 3.2% in parts of Asia. Risk factors include multiple sexual partners, human immunodeficiency virus (HIV) infection, and homosexual behavior, with the infection burden disproportionately higher in low- and middle-income countries [5].

Vaccination remains the most effective preventive approach, as established HPV infections are difficult to eliminate due to the virus residing in deep epithelial layers. Available vaccines include a bivalent formulation targeting HPV 16 and 18, a quadrivalent vaccine covering HPV 6, 11, 16, and 18, and a 9-valent vaccine offering the broadest coverage [5]. However, vaccine efficacy decreases when administered post-infection, since vaccines primarily prevent viral entry rather than clear existing infections. Furthermore, high costs and limited financial support restrict access in several regions [5], highlighting the need for alternative therapeutic strategies.

Medicinal plants have historically provided bioactive compounds with therapeutic potential against infectious and non-infectious diseases. Several plant-derived metabolites demonstrate antiviral activity, including compounds effective against influenza [6] and HIV [7]. Plant metabolites have also inspired clinically relevant antiviral drugs, such as oseltamivir, derived from shikimic acid extracted from star anise (*Illicium verum Hook.f.*) [8]. Indole-3-carbinol from cruciferous vegetables exhibits anti-estrogenic effects in cervical cells [9], ursolic acid shows anti-mutagenic and apoptosis-inducing activity [10], resveratrol from grape skins modulates the cell cycle and enhances radiosensitivity in cervical tumor cells [11], and gingerol, the main bioactive component of ginger, exhibits antioxidant and anticancer properties, suppressing colorectal carcinogenesis [12].

Rauwolfia serpentina, an evergreen shrub in the Apocynaceae family, is native to tropical and subtropical regions of Asia, including India, Bangladesh, Sri Lanka, the Himalayas, Burma, and Indonesia [13]. Commonly known as Sarpagandha or Snake root, it contains pharmacologically active secondary metabolites, particularly indole alkaloids concentrated in the roots and rhizomes [14]. Traditionally, *R. serpentina* has been used in Ayurvedic and Siddha medicine to treat hypertension, insomnia, epilepsy, anxiety, schizophrenia, gastrointestinal disorders, and menstrual irregularities. Phytochemical studies report alkaloids, phenols, tannins, and flavonoids [15]. Among its constituents, serpentine acts as a topoisomerase II inhibitor with antipsychotic activity, and peroxidase catalyzes its formation from ajmalicine. Given the global burden of chronic diseases and the need for therapeutics with fewer side effects and broader acceptability, *R. serpentina* has emerged as a promising candidate due to its wide range of pharmacological effects, including antioxidant, anticancer, antidiuretic, antiarrhythmic, antidysentery, antidiarrheal, antihypotensive, anticontractile, and tranquilizing activities [16].

This *in silico* study investigates interactions between bioactive phytochemicals and HPV target proteins. Three-dimensional models of the HPV E1 and L1 proteins were generated using the PyRx server, followed by structural optimization and energy minimization through the Energy Minimization Server. Molecular docking with selected natural ligands was performed using AutoDock to assess binding interactions with the E1 and L1 oncoproteins [17].

METHODS

Retrieval of Protein

The three-dimensional crystal structures of the pentamer structure of Major Capsid Protein L1 of Human Papillomavirus type 16 (PDB ID 2R5H) and the hexameric helicase of papillomavirus E1 (PDB ID 2GXA) were retrieved from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (https://www.rcsb.org/) in PDB format. The missing residues were modeled. Proteins 2R5H and 2GXA were resolved using X-ray diffraction, with resolutions of 3.70 Å and 3.15 Å, respectively [18].

Retrieval of Ligands

A literature survey and search on open-access Dr. Duke's Phytochemical and Ethnobotanical databases revealed that approximately 40 molecules were reported from *R. serpentina*. Of these, structural information for 28 molecules was collected from the databases [19], and the canonical Simplified Molecular Input Line Entry System (SMILES) and PubChem ID of the selected ligands were documented. The ligands were downloaded in Structure Data File (SDF) format (https://pubchem.ncbi.nlm.nih.gov/) [19], out of which 21 molecules were considered.

Pharmacological Studies

Swiss ADME (http://www.swissadme.ch/) analysis assesses ligands' pharmacological qualities based on their physicochemical characteristics, such as lipophilicity, saturation, insolubility, flexibility, size, and polarity [20]. The ligands were then filtered using Lipinski's Rule of Five, Pan-Assay Interference Compounds (PAINS), gastrointestinal (GI) absorption, and bioavailability.

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis facilitates drug discovery. ADMET properties are crucial for determining pharmacological efficacy as a possible candidate for pharmaceutical research and for identifying drug-like features. The ADMET analysis was performed using ADMETlab 2.0, an online server (https://admetmesh.scbdd.com/) [21]. Based on the docking data, the ligands with the higher negative binding affinity were selected for ADMET analysis. After being retrieved from PubChem, the top six ligands' canonical SMILES were evaluated using ADMET in the ADMETlab 2.0 website.

Protein Purification

To purify proteins 2R5H and 2GXA, water molecules were removed because their free energy did not match their crystallographic structure. All water molecules were completely removed before docking because they could have an impact on the outcome. To simplify the protein structure, all other extra chains were eliminated, leaving only the A-chains. To improve the quality of the purified protein, polar hydrogen atoms were added, and the prebound heteroatoms and complexed ligands were removed from the protein structure. Protein purification was accomplished using BIOVIA DS Discovery Studio [22]. The PDB sum generator website (https://www.ebi.ac.uk/thorntonsrv/databases/pdbsum/Generate.html) was used to perform Ramachandran plot analysis and secondary structure prediction on the purified structures [23].

Validation of Protein Structure

The Ramachandran plot is used to assess the quality of a protein based on the torsion angles (Psi and Phi) in a protein structure. The number of amino acid residues found in the permitted, prohibited, and favorable regions is displayed using Ramachandran plot statistics [24]. Using the PDBsum generator (https://www.ebi.ac.uk/thorntonsrv/databases/pdbsum/create.html), the Ramachandran plot and secondary structure of a protein were obtained from the stored purified protein files.

Molecular Docking

The purified proteins (2R5H) and (2GXA) were uploaded into PyRx as macromolecules, and the plant's phytocompounds were loaded into PyRx as ligands. The ligands were converted from SDF to PDB format using OpenBabel [25]. Grid dimensions for the center were formed and chosen for the

active site. The ligands were docked independently against 2R5H major capsid protein L1 using the PyRx web server, and energy was reduced. In the PyRx software, the ligands adopt nine different conformations to attain the best binding conformation with the protein. The degree of binding is evaluated based on the binding affinity. The lowest binding affinity indicates the best docking conformations; therefore, the top six ligands with the lowest binding affinity scores at zero root mean square deviation values (RMSD) were visualized in the DS Biovia Discovery Studio. From the docking analysis, the most effective compounds were 3,4,5-trimethoxybenzoic acid, ajmaline, isosandwicine, papaverine, sandwicine, and serpentine.

Visualization

The interactions between the phytocompounds and the active sites of the target proteins were analyzed and visualized using Biovia Discovery Studio. This software enables detailed two-dimensional and three-dimensional representations of protein–ligand interactions. Interacting amino acids and types of interactions, such as non-bonding interactions, bond distances, and bond types, were evaluated. This provided crucial information for analyzing the binding affinity and stability of the complexes.

RESULT

Protein Structure Analysis

The Ramachandran plot is a valuable tool for assessing the energetically favorable conformational space of amino acid torsion angles (ϕ and ψ) within a protein structure. For alpha-synuclein, the Ramachandran plot generated using PROCHECK (see Figure 1 and Figure 2) indicates that 82.6% of the residues are located within the most favored regions, represented in red, which correspond to sterically permissible conformations. Notably, no residues (0.0%) were found in disallowed regions. Among the 262 total residues, 235 are non-glycine and non-proline, 11 are glycine, 9 are proline, and 7 represent terminal residues (see Figure 1).

The Ramachandran plot for the 2R5H protein (see Figure 3) showed 71.9% of residues in the most favored regions and 0.6% in disallowed regions, supporting the structural reliability of the model. The remaining 6.7% are distributed within additionally allowed sub-regions. Out of a total of 419 residues, 360 are non-glycine and non-proline, 30 are glycine, 25 are proline, and 4 are terminal residues (see Figure 3).

According to the secondary structure prediction provided by PDBsum, protein 2GXA (see Figure 2) is predicted to contain 2 beta-sheets, 1 beta-hairpin, 7 beta-strands, 13 helices, 18 helix–helix interactions, 21 beta-turns, and 1 gamma turn. Similarly, the secondary structure of protein 2R5H (see Figure 4) comprises 8 beta-sheets, 6 beta-hairpins, 7 beta-bulges, 25 beta-strands, 11 helices, 2 helix–helix interactions, 41 beta-turns, and 6 gamma turns.

Physicochemical Properties of Selected Phytochemicals

The physicochemical characteristics of the selected phytocompounds were examined to understand their behavior and to support the assessment of their safety profiles. These properties were analyzed using the SWISS-ADME web server, and the findings are presented accordingly. Based on the SWISS-ADME evaluation, all the investigated phytocompounds exhibited favorable physicochemical features.

SWISSADME Analysis and ADMET Analysis

Important requirements for a compound to be employed in drug products include its physicochemical features, absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, Lipinski's rule of 5, and PAINS (Pan-Assay Interference Compounds) filters. For the production of medicine with the fewest side effects, toxicity prediction and aggregate data are also crucial. Therefore, the phytocompounds retrieved from *Rauvolfia serpentina* (R. serpentina) were subjected to pharmacological studies to determine their drug-like properties.

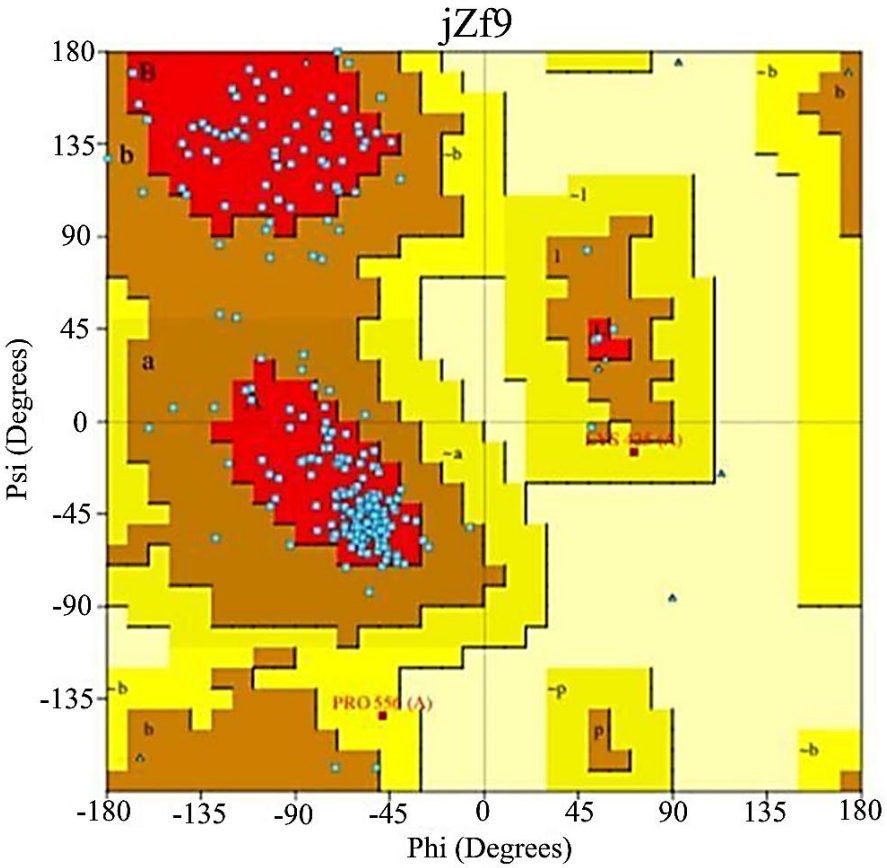

Figure 1. Ramachandran plot of protein 2GXA.

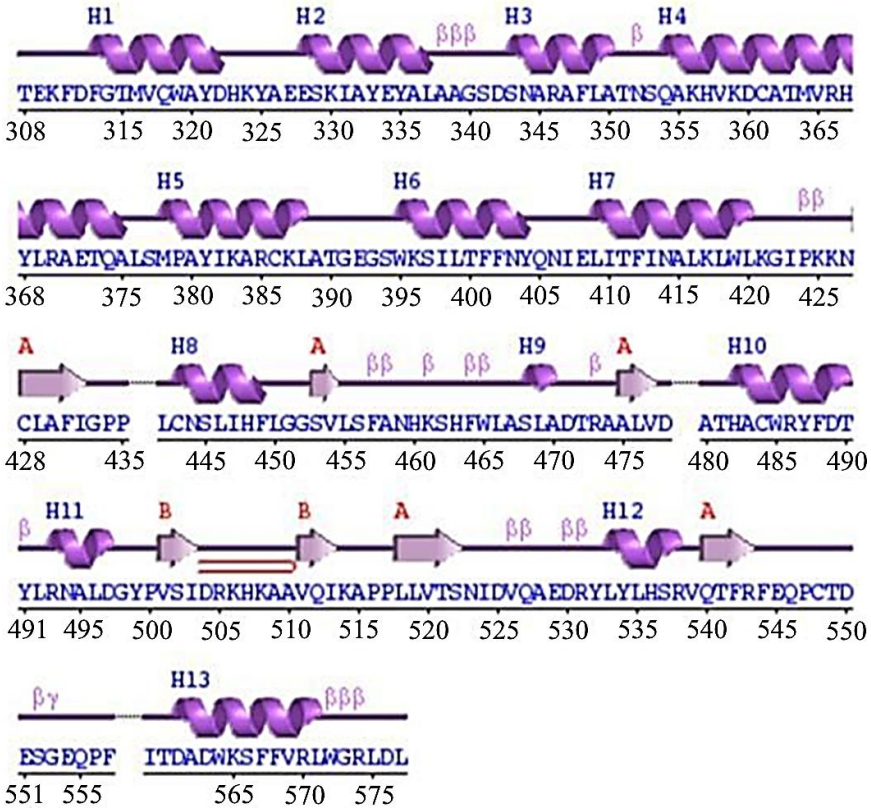

Figure 2. Secondary structure of protein 2GXA.

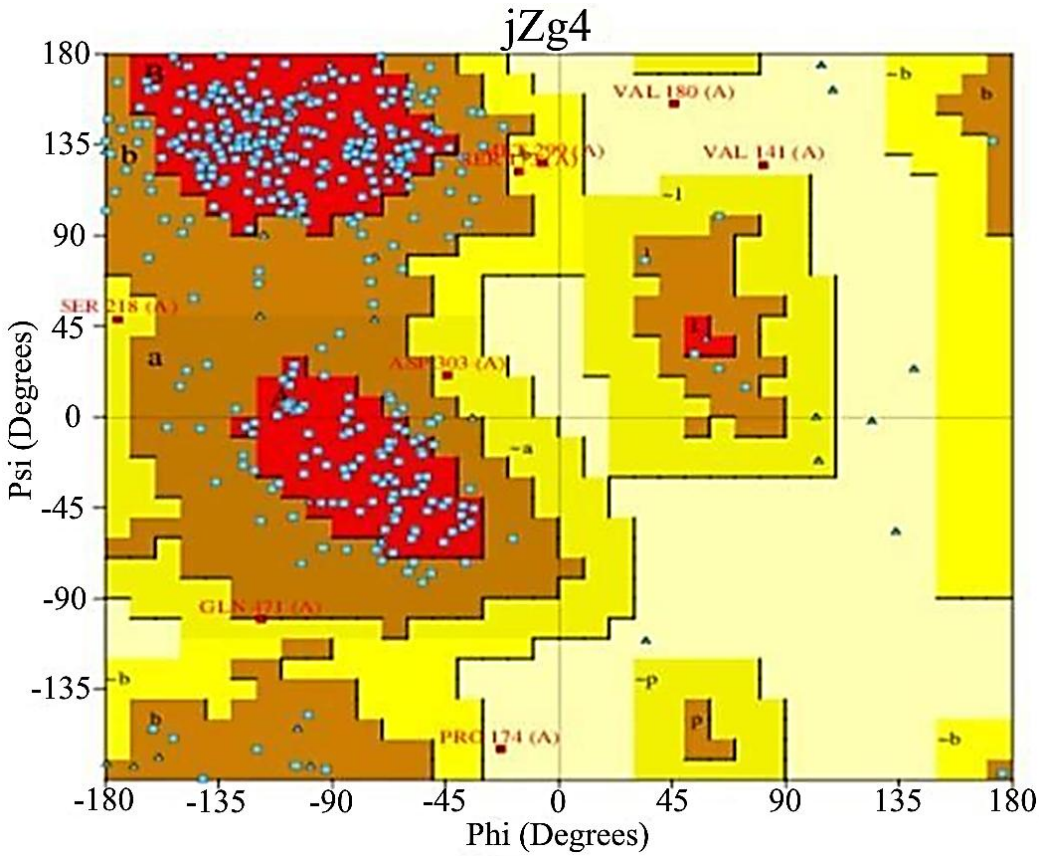

Figure 3. Ramachandran plot of protein 2R5H.

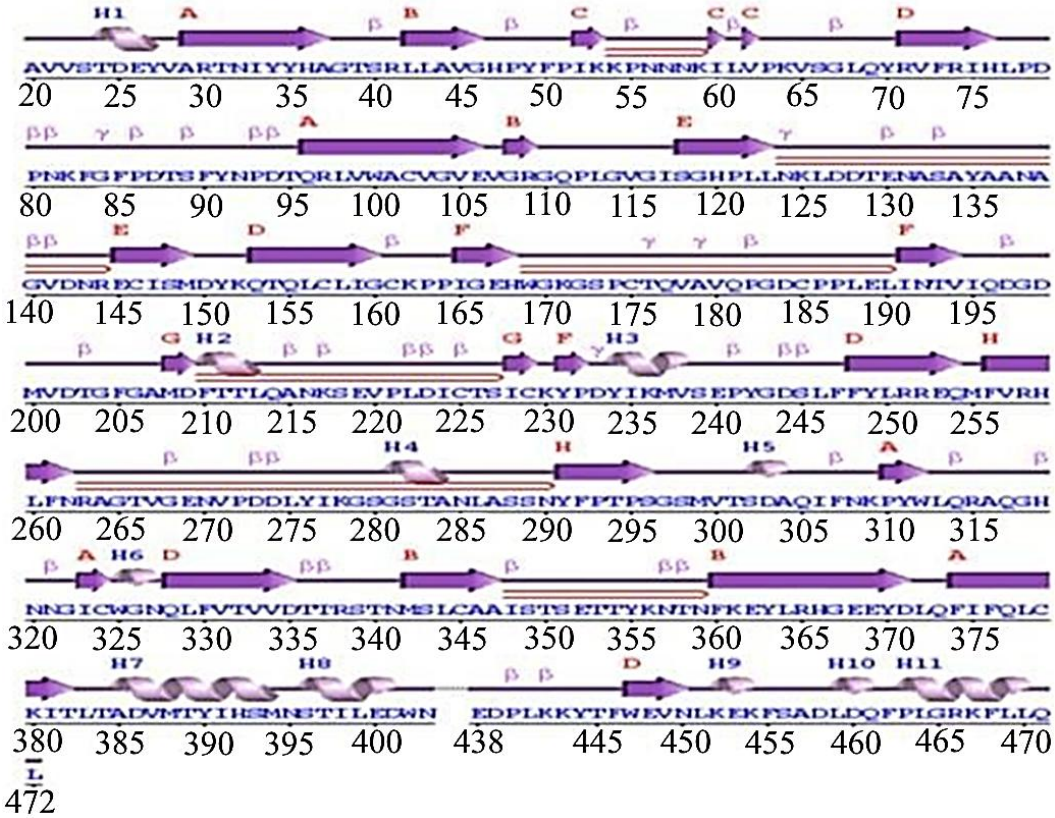

Figure 4. Secondary structure of protein 2R5H.

Pharmacological Studies

The phytoconstituents from *R. serpentina* were subjected to physicochemical screening based on the parameters listed in Table 1, and the physicochemical properties of the top ligands are listed in Table 2.

Lipinski and PAINS Filter Analysis

The Lipinski rule has five parameters (see Table 3), and a compound must adhere to at least four of them. As per the results (see Table 4), it is evident that the top six ligands fulfill Lipinski's Rule of 5 without any violations, as well as the PAINS rule.

ADME Analysis

An ADME analysis has four key characteristics. The extent of the substance's intracranial movement is constrained by the Blood-Brain Barrier (BBB). This information is essential for creating a medicine. The amount of gastrointestinal (GI) absorption should be substantial to maximize the drug's efficacy. In addition, the material must be easily soluble. Lower negative solubility levels are consequently accepted. As per the results (see Table 5), it is evident that all the ligands have high gastrointestinal absorption, and they also have good solubility and bioavailability.

Toxicity Prediction

The following are some of the key characteristics of toxicity prediction. The human Ether-à-go-go-Related Gene (hERG), Hepatotoxicity (H-HT), Drug-Induced Liver Injury (DILI), Ames test, Rat Oral Acute Toxicity (ROA), and Carcinogenicity parameters were evaluated using ADMETLAB (admetlab3.scbdd.com/server/evaluationCal) to determine the toxicity of the top six ligands (see Table 6). FDAMDD was not used in this analysis.

Table 1. Parameters for physicochemical properties.

Properties		Optimal Range
Lipophilicity	xLogP	−0.7–+5.0
Size	MW	150–500 g/mol
Polarity	TPSA	20–130
Saturation	Sp3 hybridization	Not<0.25
Flexibility	Rotatable bonds	Not more than 9

Table 2. Physicochemical properties.

Ligands	MW	Fraction Csp3	Rotatable bonds	TPSA	Lipophilicity
3,4,5-trimethoxybenzoic acid	212.2	0.3	4	64.99	1.45
Ajmaline	326.43	0.7	1	46.94	1.81
Isosandwicine	442.5	0.58	3	121.54	-0.91
Papaverine	339.39	0.25	6	49.81	2.95
Sandwicine	326.43	0.7	1	46.94	1.81
Serpentine	349.4	0.33	2	55.2	3.08

Table 3. Lipinski rule parameters.

Properties	Optimal Range
MW	150–500 daltons
MlogP	<4.15
H donors	<5
H acceptors	<10
MR	40–130

Table 4. Data for the properties of the PAINS and Lipinski rule obtained using SwissADME.

Ligands	MW	MLogP	H Donors	H Acceptors	PAINS	Molar refractivity
3,4,5-trimethoxybenzoic-acid	212.2	0.8	1	5	0	52.88
Ajmaline	326.43	2.67	2	3	0	99.87
Isosandwicine	442.5	1.67	4	7	0	124.29
Papaverine	339.39	1.78	0	5	0	97.16
Sandwicine	326.43	2.67	2	3	0	99.87
Serpentine	349.4	2.21	1	3	0	100.49

Table 5. ADME data obtained using SwissADME.

Ligands	BBB	GI Absorption	PGP Substrate	Solubility (LOGSw-SILICOS IT)
3,4,5-trimethoxybenzoic-acid	Yes	High	No	-2.16
Ajmaline	Yes	High	Yes	-2.25
Isosandwicine	No	High	Yes	-2.25
Papaverine	Yes	High	Yes	-7.1
Sandwicine	Yes	High	Yes	-2.25
Serpentine	Yes	High	Yes	-4.93

Table 6. Toxicity analysis.

Ligands	hERG	H-HT	DILI	Ames	ROA	Carcinogenicity
3,4,5-trimethoxybenzoic-acid	0.049	0.5	0.705	0.287	0.307	0.445
Ajmaline	0.243	0.566	0.559	0.609	0.404	0.463
Isosandwicine	0.159	0.505	0.661	0.589	0.36	0.232
Papaverine	0.281	0.541	0.579	0.475	0.387	0.682
Sandwicine	0.182	0.587	0.296	0.677	0.678	0.28
Serpentine	0.346	0.511	0.934	0.751	0.802	0.706

Molecular Docking and Virtual Screening

The outcomes of the molecular docking and virtual screening conducted using PyRx software are presented in Tables 7 and 8. The binding affinities of all the screened ligands towards the 2R5H and 2GXA protein targets were determined. For subsequent evaluation, the docking pose exhibiting the highest binding energy, along with optimal RMSD/ub and r/lb values, was selected. Phytocompounds with a binding energy of −6.2, such as ajmaline, sandwicine, and serpentine, showed the most favorable negative binding energies (see Tables 9 and 10). Therefore, these three were considered for further analysis. The ligand ajmaline demonstrated the lowest binding with both target proteins (2R5H and 2GXA), but with different binding energies. Therefore, the binding interactions of ajmaline with 2R5H and 2GXA were visualized. From the 2D and 3D interaction diagrams, it is evident that the ligand interacts with the protein by establishing bonds with significant amino groups, such as PHE, LEU, PRO, CYS, TRP, ASP, GLN, LYS, and GLY.

Table 7. Docking score of 2GXA protein with selected ligands.

Ligands	PUBCHEM ID	Binding affinity with 2GXA
Ajmaline	441080	-7.9
Sandwicine	15559808	-7.6
Serpentine	73391	-7.3
Papaverine	4680	-7.2
3,4,5-trimethoxybenzoic acid	8357	-5.3
Isosandwicine	134828126	-4.5

Table 8. Docking score of 2R5H protein with selected ligands.

Ligands	PUBCHEM ID	Binding affinity with 2R5H
Ajmaline	441080	-7.6
Sandwicine	15559808	-7.3
Serpentine	73391	-6.9
Papaverine	4680	-6.3
3,4,5-trimethoxybenzoic acid	8357	-5.1
Isosandwicine	134828126	-5

Table 9. Docking score of the top three ligands with protein 2GXA.

Ligands	PUBCHEM ID	Binding affinity with 2GXA
Ajmaline	441080	-7.9
Sandwicine	15559808	-7.6
Serpentine	73391	-7.3

Table 10. Docking score of the top three ligands with protein 2R5H.

Ligands	PUBCHEM ID	Binding affinity with 2R5H
Ajmaline	441080	-7.6
Sandwicine	15559808	-7.3
Serpentine	73391	-6.9

DISCUSSION

Cancer is a leading cause of morbidity and mortality globally and remains a significant barrier to increasing life expectancy. In 2020, approximately 19.3 million new cancer cases and 10 million deaths were reported [26]. Human papillomaviruses (HPVs) are DNA viruses that specifically infect epithelial cells, and their replication is closely linked to epithelial differentiation. Over 200 HPV genotypes have been identified, each exhibiting distinct tissue tropism and infection characteristics. HPV infections contribute to a variety of lesions, including genital warts, hand and foot lesions, and are implicated in cancers such as cervical, esophageal, head and neck, brain, and lung malignancies. Differences in clinical outcomes, traditional risk factors, and higher prevalence in certain populations, and geographic regions have heightened interest in studying HPV infections.

Human Papillomaviruses (HPVs) belong to the Papillomaviridae family and are highly adapted to their hosts, enabling the evasion of immune responses. Most of the more than 200 characterized HPV types infect humans, with cervical cancer being the primary outcome of persistent HPV infection in women. While Papillomaviridae members share similar genome organization and capsid structure, sequence variations and amino acid differences give rise to distinct HPV groups. HPV genomic DNA consists of three regions of unequal size; the early proteins `$E_6$` and `$E_7$` play critical roles in cervical carcinogenesis. The viral capsid comprises 72 pentameric capsomeres made of `$L_1$` protein units, each associated with an `$L_2$` protein. Integration of HPV DNA into the host genome dysregulates oncoprotein expression: `$E_6$` promotes degradation of the tumor suppressor `p53` via the formation of a complex with `$E_6$`-associated protein (`$E_6$AP`), while `$E_7$` binds cyclin-dependent kinase inhibitors, disrupting cell cycle control. Viral replication occurs in basal epithelial cells and requires early proteins `$E_1$` and `$E_2$`, with `$E_2$` acting as a transcriptional regulator for `$E_6$` and `$E_7$`. HPV replication involves a rolling-circle integration mechanism [26].

Plants have long served as valuable sources of bioactive compounds with therapeutic potential, particularly in oncology. Between 1981 and 2014, nearly 49% of anticancer agents were derived from plant sources [27]. *Rauvolfia serpentina* (L.) Benth. ex Kurz, commonly referred to as Sarpagandha or Indian Snakeroot, is an important medicinal shrub of the Apocynaceae family. It is native to moist deciduous forests in South and Southeast Asia, including India, Bangladesh, Sri Lanka, Myanmar, and

Malaysia; the genus *Rauvolfia* encompasses over 100 species worldwide [28]. Cultivation of this plant has increased considerably, and its stems and leaves, along with roots, are widely used in agricultural and pharmaceutical applications due to their rich content of bioactive alkaloids [29].

R. serpentina contains a diverse array of indole alkaloids, including ajmaline, ajmalinine, reserpine, rauwolscine, serpenticine, isoajmaline, rawolfinine, renoxycine, rescinamine, reserpilline, serpentine, sarpagine, and tetraphyllicine, which are reported to have therapeutic potential against various conditions such as hypertension, insomnia, gastrointestinal disorders, eye diseases, fever, wounds, asthma, splenic and uterine complications, malaria, pneumonia, headaches, and dermatological issues [30]. Alkaloids are unevenly distributed within the plant, with the root bark containing the highest concentration—approximately 90%—compared to only 1.7–3.0% in the root [30]. Leaves contain comparatively fewer alkaloids than roots. Several alkaloids from *R. serpentina*, including reserpine [31], yohimbine, and serpentine [32], have been investigated *in vitro* for their anticancer properties.

In this study, 21 phytocompounds were selected based on their pharmacological applications. The ligands 3,4,5-trimethoxybenzoic acid, ajmaline, isosandwicine, papaverine, sandwicine, and serpentine exhibited the highest binding affinity against the targeted proteins 2GXA and 2R5H. The top three ligands (ajmaline, sandwicine, and serpentine) were subsequently selected for further visualization. These interactions were visualized using Dassault Systèmes BIOVIA Discovery Studio.

An overall analysis of the `2D` structure of the top three ligands involved in docking with 2R5H of ajmaline (see Figure 5) revealed the implication of GLN:69, LYS:64, ASP:197, and TRP:447 as the amino acids present. Docking with 2R5H of sandwicine (see Figure 6) indicated the presence of TYR:135, ALA:287, SER:288, and ALA:139. For the serpentine ligand (see Figure 7), the amino acids found were ALA:136, ALA:287, ALA:139, and LEU:286.

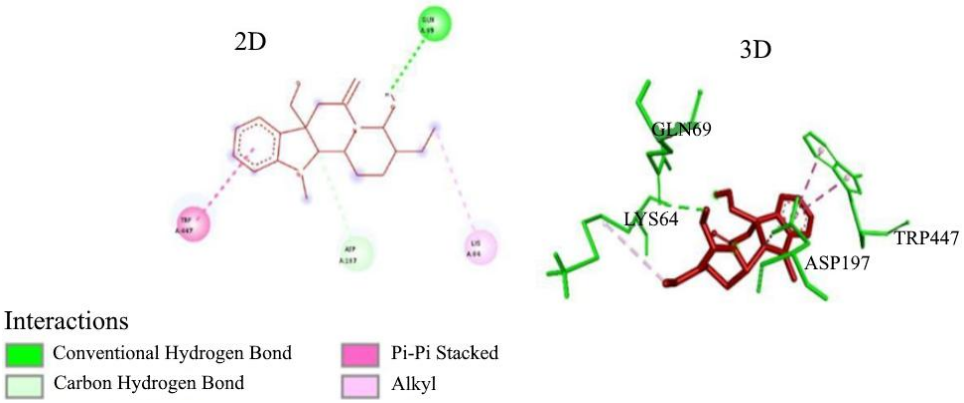

Figure 5. Visualization of molecular interactions of protein 2R5H with the Ajmaline ligand.

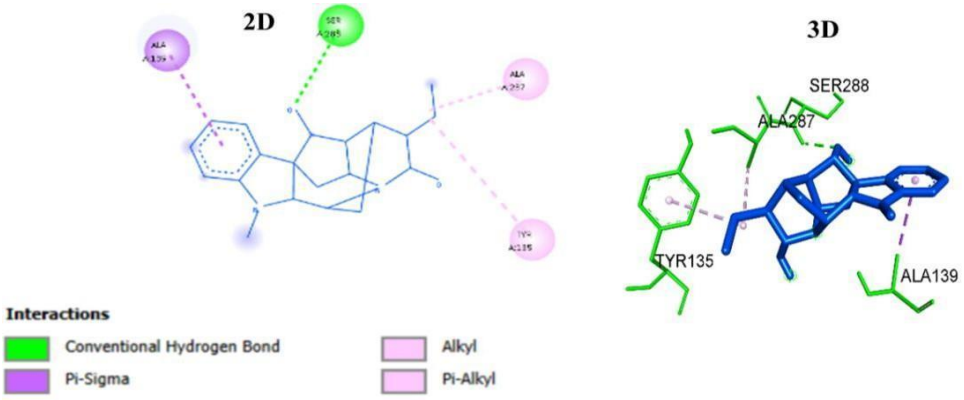

Figure 6. Visualization of molecular interaction of protein 2R5H with the Sandwicine ligand.

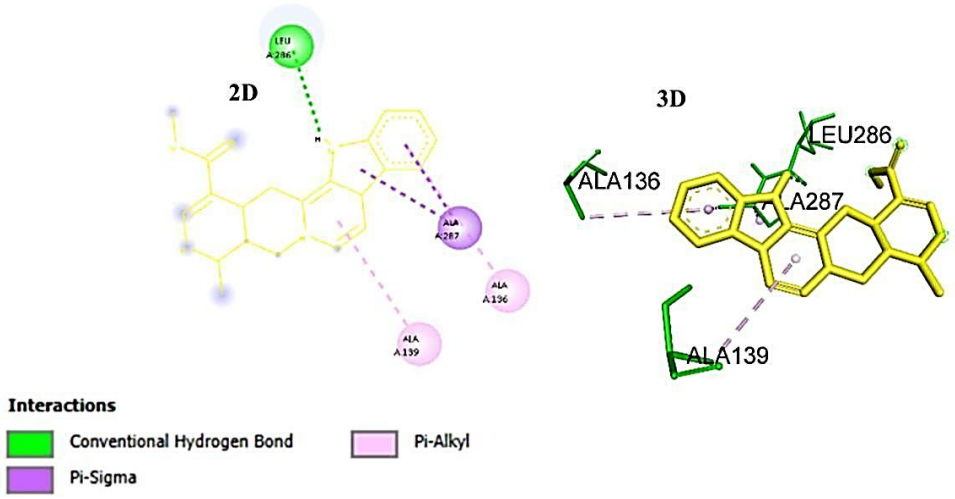

Figure 7. Visualization of molecular interaction of protein 2R5H with the Serpentine ligand.

Analysis of the `2D` structure of the top three ligands involved in docking with 2GXA. For ajmaline (see Figure 8), the amino acids identified were LEU:442, PHE:544, PRO:434, PRO:435, CYS:443, and GLY:433. For the sandwicine ligand (see Figure 9), the presence of ASP:478, CYS:443, THR:521, PHE:431, and GLY:433 was indicated. For the serpentine ligand (see Figure 10), the amino acids found were ASP:478, ASN:523, and THR:521.

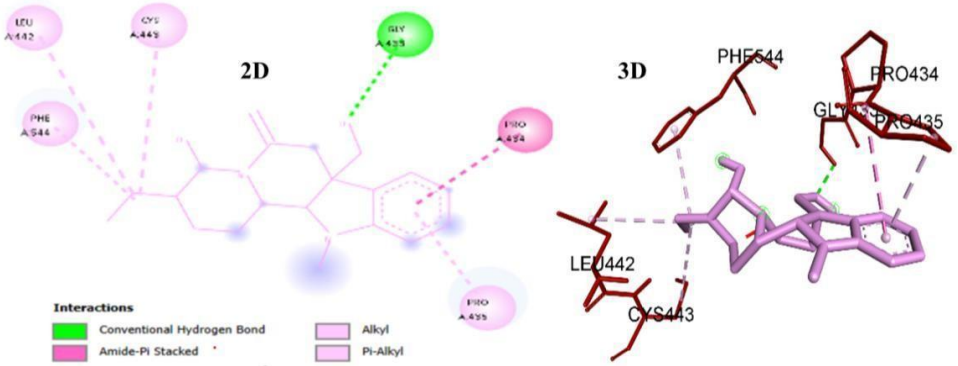

Figure 8. Visualization of molecular interaction of protein 2GXA with the Ajmaline ligand.

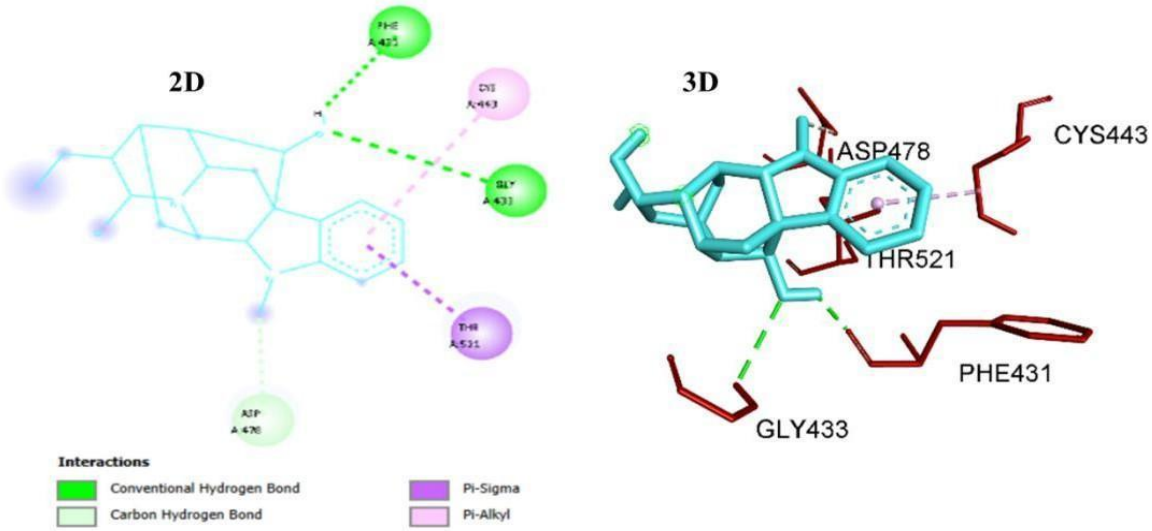

Figure 9. Visualization of molecular interactions of protein 2GXA with the Sandwicine ligand.

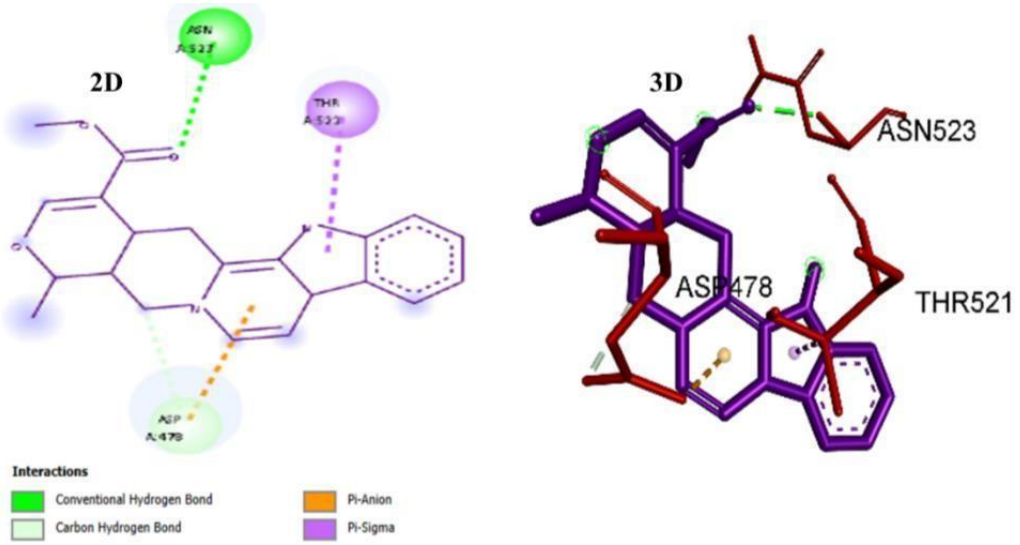

Figure 10. Visualization of molecular interaction of protein 2GXA with the Serpentine ligand.

Furthermore, *in silico* testing of the top six compounds was conducted to predict their drug-likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) characteristics. The results are listed in (see Tables 1-6).

CONCLUSION

The findings of this study highlight the potential of *Rauvolfia serpentina* derivatives—Ajmaline, Sandwicine, and Serpentine—as promising therapeutic agents, particularly against Human Papillomavirus (HPV) associated cervical cancer. Among the tested ligands, Ajmaline exhibited the strongest binding affinities with both target proteins 2GXA and 2R5H, recording binding energies of -7.9 and -7.6 kcal/mol, respectively, as detailed in (see Tables 7 and 8). The observed interaction strength and stability highlight its potential to serve as an effective inhibitor. The high negative binding affinities, coupled with favorable pharmacological parameters, indicate that these plant-derived compounds possess significant therapeutic potential. As interest in plant-based drug discovery continues to rise, such bioactive compounds from medicinal plants may pave the way for innovative and more natural approaches to disease prevention and treatment. This study supports the role of phytochemicals in future drug development and their potential in combating HPV-induced cervical cancer.

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List of Abbreviations

ADMET	Chemical absorption, distribution, metabolism, excretion, and toxicity
CSV	Comma-Separated Values
GI	Gastrointestinal absorption
SDF	Structure Data File
PDB	Protein Data Bank
MR	Molar refractivity
MW	Molecular weight
PAINS	Pan-Assay Interference Compounds
SMILES	Simplified Molecular Input Line Entry System

RMSD	Root mean square deviation
UB	Upper bound
LB	Lower bound
BBB	Blood-brain barrier

REFERENCES

1. Giannone G, Giuliano AR, Bandini M, Marandino L, Raggi D, Earle W, et al. HPV vaccination and HPV-related malignancies: impact, strategies and optimizations toward global immunization coverage. Cancer Treat Rev. 2022;111:102467.
2. Herbster S, Paladino A, de Freitas S, Boccardo E. Alterations in the expression and activity of extracellular matrix components in HPV-associated infections and diseases. Clinics. 2018;73:e551s.
3. Šali A, Blundell TL. Comparative protein modelling by satisfaction of spatial restraints. J Mol Biol. 1993;234(3):779–815.
4. Dell G, Wilkinson KW, Tranter R, Parish J, Brady RL, Gaston K. Comparison of the structure and DNA-binding properties of the E2 proteins from an oncogenic and a non-oncogenic human papillomavirus. J Mol Biol. 2003;334(5):979–991.
5. Wang Y, Coulombe R, Cameron DR, Thauvette L, Massariol MJ, Amon LM, et al. Crystal structure of the E2 transactivation domain of human papillomavirus type 11 bound to a protein interaction inhibitor. J Biol Chem. 2004;279(8):6976–6985.
6. Abbate EA, Voitenleitner C, Botchan MR. Structure of the papillomavirus DNA-tethering complex E2: Brd4 and a peptide that ablates HPV chromosomal association. Mol Cell. 2006;24(6):877–889.
7. Kim SS, Tam JK, Wang AF, Hegde RS. The structural basis of DNA target discrimination by papillomavirus E2 proteins. J Biol Chem. 2000;275(40):31245–31254.
8. Gasteiger J, Marsili M. A new model for calculating atomic charges in molecules. Tetrahedron Lett. 1978;19(34):3181–3184.
9. Yuan F, Chen DZ, Liu K, Sepkovic DW, Bradlow HL, Auborn K. Anti-estrogenic activities of indole-3-carbinol in cervical cells: implication for prevention of cervical cancer. Anticancer Res. 1999;19(3A):1673–1680.
10. Novotný L, Vachalkova A, Biggs D. Ursolic acid: an anti-tumorigenic and chemopreventive activity. Minireview. Neoplasma. 2001;48(4):241–246.
11. Zoberi I, Bradbury CM, Curry HA, Bisht KS, Goswami PC, Roti JL, et al. Radiosensitizing and anti-proliferative effects of resveratrol in two human cervical tumor cell lines. Cancer Lett. 2002;175(2):165–173.
12. Manju V, Nalini N. Chemopreventive efficacy of ginger, a naturally occurring anticarcinogen during the initiation, post-initiation stages of 1,2-dimethylhydrazine-induced colon cancer. Clin Chim Acta. 2005;358(1–2):60–67.
13. Yaffe D, Forrest LR, Schuldiner S. The ins and outs of vesicular monoamine transporters. J Gen Physiol. 2018;150(5):671–682.
14. Biradar N, Hazar I, Chandy V. Current insight to the uses of Rauwolfia: a review. Res Rev J Pharmacogn. 2016;3(3):1–4.
15. Kumari R, Rathi B, Rani A, Bhatnagar S. Rauvolfia serpentina L. Benth. ex Kurz.: phytochemical, pharmacological and therapeutic aspects. Int J Pharm Sci Rev Res. 2013;23(2):348–355.
16. Gawade BV, Fegade SA. Rauwolfia (reserpine) as a potential antihypertensive agent: a review. Int J Pharm Phytopharmacol Res. 2012;2(1):46–49.
17. Reddy JM, Verma P, Agrawal I, Vyas M, Sahu SK. Molecular docking studies of chemical constituents of Rauwolfia serpentina on hypertension. In: BIO Web Conf. 2024;86:01044.
18. Ugai T, Sasamoto N, Lee HY, Ando M, Song M, Tamimi RM, et al. Is early-onset cancer an emerging global epidemic? Current evidence and future implications. Nat Rev Clin Oncol. 2022;19(10):656–673.

19. Ryder-Burbidge C, Diaz RL, Barr RD, Gupta S, Nathan PC, McKillop SJ, et al. The burden of late effects and related risk factors in adolescent and young adult cancer survivors: a scoping review. Cancers. 2021;13(19):4870.
20. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7(1):42717.
21. Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C, et al. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Res. 2021;49(W1):W5–W14.
22. Jejurikar BL, Rohane SH. Drug designing in Discovery Studio.
23. Zhou AQ, O'Hern CS, Regan L. Revisiting the Ramachandran plot from a new angle. Protein Sci. 2011;20(7):1166–1171.
24. Tam B, Sinha S, Wang SM. Combining Ramachandran plot and molecular dynamics simulation for structural-based variant classification: using TP53 variants as model. Comput Struct Biotechnol J. 2020;18:4033–4039.
25. Kondapuram SK, Sarvagalla S, Coumar MS. Docking-based virtual screening using PyRx tool: autophagy target Vps34 as a case study. In: Molecular Docking for Computer-Aided Drug Design. Academic Press; 2021. p. 463–477.
26. Roy AC, Prasad A, Priya K, Das P, Singh S, Ghosh C, et al. Anticancer effect of antioxidant-rich methanolic extract of Rauvolfia serpentina (L.) Benth. ex Kurz leaves in HepG2 and HeLa cells: a mechanistic insight. Biocatal Agric Biotechnol. 2023;50:102674.
27. Majolo F, Delwing LK, Marmitt DJ, Bustamante-Filho IC, Goettert MI. Medicinal plants and bioactive natural compounds for cancer treatment: important advances for drug discovery. Phytochem Lett. 2019;31:196–207.
28. Singh A, Rani R, Sharma M. Medicinal herbs of Punjab (India). In: Biol Forum. 2018;10:10–27.
29. Agarwal K, Mohapatra S, Behera B. Journal of biodiversity and conservation. In: Proceedings of National Seminar "Indigenous Knowledge & Conservation of Threatened Medicinal Plants". 2019;30:31.
30. Alshahrani MY, Rafi Z, Alabdallah NM, Shoaib A, Ahmad I, Asiri M, et al. A comparative antibacterial, antioxidant, and antineoplastic potential of Rauwolfia serpentina (L.) leaf extract with its biologically synthesized gold nanoparticles (R-AuNPs). Plants. 2021;10(11):2278.
31. Hong B, Su Z, Zhang C, Yang Y, Guo Y, Li W, et al. Reserpine inhibit the JB6 P+ cell transformation through epigenetic reactivation of Nrf2-mediated anti-oxidative stress pathway. AAPS J. 2016;18:659–669.
32. George BP, Chandran R, Abrahamse H. Role of phytochemicals in cancer chemoprevention: insights. Antioxidants. 2021;10(9):1455.

