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Anticancer Medicinal Plants, In-silico Docking and Binding Energy Studies of Podophyllotoxin and Curcumin

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ABSTRACT

Natural products have been central to oncology, yielding approved drugs such as paclitaxel, vinca alkaloids, camptothecin derivatives and epipodophyllotoxins. This review summarizes fifty medicinal plants with reported anticancer properties, highlighting key phytochemicals, proposed mechanisms (e.g., microtubule disruption, topoisomerase inhibition, apoptosis/ferroptosis induction, anti-angiogenesis, immune modulation) and the level of evidence (approved drug, clinical, or preclinical). The intent is an educational, non-prescriptive overview to support hypothesis generation and responsible translational research.

Key words: Cancer, Medicinal Plants, Phytochemicals, Herbal Medicines

Introduction

Cancer remains a leading cause of global mortality. The International Agency for Research on Cancer revealed that the incidence and the mortality rate of cancer are

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increases day by day [1]. It is estimated that in 2030, the incidence of the cancer will be 26 million and 17 million cancer deaths per year [2].Despite significant advances in targeted therapy and immuno-oncology, drug resistance, toxicity, and cost continue to limit outcomes. Medicinal plants have provided a rich pharmacopeia for oncology. Several cornerstone chemotherapeutics are plant-derived or semisynthetic derivatives that are taxanes from Taxus, vinca alkaloids from Catharanthus, and topoisomerase inhibitors derived from camptothecin and podophyllotoxin are used for cancer therapy. Most of the plants exhibit in-vivo or in-vitro anticancer activity [3]. This review article exhibit the data on medicinal plants having anticancer effects, their Phytoconstituents and mechanisms of action.

Methodology

A narrative, evidence-weighted survey of peer-reviewed literature (2010–2024) was performed using terms such as “medicinal plants anticancer” and “plant-derived anticancer drugs”. Priority was given to authoritative reviews, monographs, and clinical summaries. Evidence level was categorized as: Approved (marketed anticancer drug or derivative), Clinical (human studies/monographs with clinical end points), or Preclinical (in vitro/in vivo only).

The molecular docking study was conducted to evaluate “podophyllotoxin and curcumin” bioactive phytochemicals derived from *Podophyllum hexandrum / P. peltatum* and *Curcuma longa* against the 5XLT and 9FPX target proteins respectively. The 3D structures of the compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov) and optimized through energy minimization before conversion into PDBQT format using Auto Dock Tools. The crystal structures of the target proteins (5XLT and 9FPX) were obtained from the RCSB PDB (https://www.rcsb.org/structure/5XLT) and (https://www.rcsb.org/structure/9FPX) respectively. The water molecules were removed and adding polar hydrogen atoms. A grid box was generated accordingly. Docking simulations were performed using AutoDock Vina, generating multiple conformations for each ligand. The best binding poses were selected based on binding free energy, inhibition constant, and key molecular interactions. Re-docking of the native ligand was performed to validate the docking protocol, ensuring an RMSD value below 2.0 Å. Visualization and interaction analysis were performed by using Discovery Studio, version v25.1.0.24284, to interpret the binding site of the ligands. Overall, the docking study explain the binding interaction of the ligands (curcumin and podophyllotoxin) and the target protein (5XLT and 9FPX) their binding energy.

Results

Table 1 summarizes medicinal plants with anticancer relevance. For each entry, the principal compounds, a concise mechanism/target or cancer focus, the evidence level, and sample references are listed. Moreover, **the 2D and 3D interaction diagrams of podophyllotoxin and curcumin with the target proteins 5XLT and 9FPX are presented in Figures 1, 2, 3, and 4, respectively. In the molecular docking study, the** highest negative binding energy indicated the strongest binding affinity of the ligands (podophyllotoxin and curcumin) with the proteins molecules (**5XLT and 9FPX). The binding energy of both ligands and proteins** are presented in table no 2

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and 3.

Table no.1. Anticancer medicinal plants

No.	Plant (Scientific / Common)	Key Compound(s)	Mechanism / Cancer Focus	Evidence (Sample Refs)
1	Taxus brevifolia (Pacific yew)	Paclitaxel (taxanes)	Microtubule stabilization; breast/ovarian and others	Approved [4,7]
2	Camptotheca acuminata (Happy tree)	Camptothecin → irinotecan/topotecan	Topoisomerase I inhibition; colorectal/others	Approved [4,7]
3	Catharanthus roseus (Madagascar periwinkle)	Vincristine, Vinblastine	Microtubule disruption; leukemias/lymphomas	Approved [4,7]
4	Podophyllum hexandrum / P. peltatum	Podophyllotoxin → etoposide/teniposide	Topoisomerase II inhibition; multiple tumors	Approved [4,7]
5	Cephalotaxus harringtonia/fortunei	Homoharringtonine (omacetaxine)	Protein synthesis inhibition; CML	Approved [8]
6	Curcuma longa (Turmeric)	Curcumin	NF-κB/STAT3 modulation; apoptosis/chemosensitization	Clinical/Preclinical [9]
7	Nigella sativa (Black seed)	Thymoquinone	ROS modulation; apoptosis; anti-metastatic	Clinical/Preclinical [10]
8	Camellia sinensis (Green tea)	EGCG, catechins	Cell cycle arrest; anti-angiogenesis; chemoprevention	Clinical/Preclinical [11]
9	Salvia miltiorrhiza (Danshen)	Tanshinone IIA, salvianolic acids	Anti-angiogenesis; apoptosis; EMT inhibition	Clinical/Preclinical [12]
10	Scutellaria baicalensis (Baikal skullcap)	Baicalein, baicalin	Cell cycle arrest; apoptosis; PI3K/AKT	Preclinical [13]
11	Artemisia annua (Sweet wormwood)	Artemisinin/derivatives	Ferroptosis/apoptosis; repositioned interest	Clinical/Preclinical [14]
12	Boswellia serrata (Indian	Boswellic acids (AKBA)	Anti-inflammatory; pro-apoptotic;	Clinical/Preclinical [15]

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	frankincense)		anti-angiogenic	
13	Withania somnifera (Ashwagandha)	Withaferin A, withanolides	Proteasome/NF-κB /STAT3; apoptosis	Clinical/Preclinical [16]
14	Azadirachta indica (Neem)	Limonoids, nimbolide, polyphenols	Apoptosis; inhibition of NF-κB/Notch; chemoprevention	Preclinical [17]
15	Vitis vinifera (Grape)	Resveratrol	SIRT1/AMPK activation; anti-angiogenesis; EMT	Clinical/Preclinical [18]
16	Silybum marianum (Milk thistle)	Silymarin complex	Hepatoprotective; anti-proliferative; STAT3	Clinical/Preclinical [19]
17	Panax ginseng (Asian ginseng)	Ginsenosides (Rg3, Rh2)	Immune modulation; apoptosis; anti-angiogenesis	Clinical/Preclinical [20]
18	Glycyrrhiza glabra (Licorice)	Glycyrrhizin, liquiritigenin	MAPK/ERK; apoptosis; chemopreventive signals	Preclinical [21]
19	Berberis/Coptis spp.	Berberine	AMPK activation; cell-cycle arrest; anti-metastatic	Clinical/Preclinical [22]
20	Rosmarinus officinalis (Rosemary)	Carnosic/rosmarinic/ursolic acids	Anti-angiogenesis; apoptosis; NF-κB	Preclinical [23]
21	Allium sativum (Garlic)	Allicin, DAS, DADS	Detox enzymes; chemoprevention; apoptosis	Clinical/Preclinical [24]
22	Zingiber officinale (Ginger)	[6]-Gingerol, shogaols	Anti-inflammatory; apoptosis; invasion inhibition	Preclinical [25]
23	Brassica oleracea (Broccoli)/Brassicaceae	Sulforaphane, I3C/DIM	Nrf2 activation; HDAC inhibition; chemoprevention	Clinical/Preclinical [26]
24	Punica granatum (Pomegranate)	Ellagitannins (punicalagin), urolithins	Anti-proliferative; PSA kinetics in prostate CA	Clinical/Preclinical [27]
25	Olea europaea (Olive)	Oleuropein, hydroxytyrosol	Anti-proliferative; antioxidant; EMT modulation	Preclinical [28]

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26	Ginkgo biloba	Terpene lactones, flavonols	Oxidative stress modulation; limited antitumor data	Preclinical [29]
27	Piper nigrum (Black pepper)	Piperine	Bioavailability enhancer; apoptosis; PI3K/AKT	Preclinical [30]
28	Capsicum annuum (Chili pepper)	Capsaicin	TRPV1-linked apoptosis; anti-angiogenesis	Preclinical [31]
29	Glycine max (Soy)	Genistein, daidzein	Hormone-responsive tumors; epigenetic effects	Clinical/Preclinical [32]
30	Phyllanthus emblica (Emblica, Amla)	Ellagic acid, emblicanin, gallic acid	Apoptosis; antioxidant; anti-invasion	Preclinical [33]
31	Andrographis paniculata	Andrographolide	NF-κB/STAT3 inhibition; apoptosis; immunomodulation	Clinical/Preclinical [34]
32	Hedyotis diffusa (Oldenlandia)	Iridoids, flavonoids	Traditional oncology adjuvant; apoptosis	Preclinical/Traditional [35]
33	Tinospora cordifolia (Guduchi)	Diterpenoids, alkaloids	Immunomodulatory adjunct; radio-protection	Preclinical [36]
34	Moringa oleifera	Isothiocyanates, quercetin	Apoptosis; oxidative stress modulation	Preclinical [37]
35	Annona muricata (Soursop)	Acetogenins (annonacin)	Complex I inhibition; potent cytotoxicity (toxicity concerns)	Preclinical [38]
36	Solanum nigrum (Black nightshade)	Solamargine, solasonine	Apoptosis; autophagy; hepatoprotective context	Preclinical [39]
37	Curcuma zedoaria (White turmeric)	Curzerenone, zedoarone	Anti-metastatic; apoptosis	Preclinical [40]
38	Boerhavia diffusa	Boeravinones	Topoisomerase inhibition;	Preclinical [41]

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	(Punarnava)		anti-metastatic signals	
39	Hemidesmus indicus	2-hydroxy-4-methoxybenzaldehyde	Apoptosis; anti-angiogenic signals	Preclinical [42]
40	Plumbago zeylanica (Ceylon leadwort)	Plumbagin	ROS generation; NF-κB inhibition; apoptosis	Preclinical [43]
41	Paeonia lactiflora (Peony)	Paeoniflorin	EMT/angiogenesis modulation; apoptosis	Preclinical [44]
42	Tripterygium wilfordii (Thunder god vine)	Triptolide, celastrol	Transcriptional suppression; potent but toxic	Preclinical [45]
43	Houttuynia cordata	Polysaccharides, quercitrin	Immunomodulation; anti-metastatic	Preclinical [46]
44	Garcinia mangostana (Mangosteen)	Xanthones (α-, γ-mangostin)	Apoptosis; anti-angiogenesis	Preclinical [47]
45	Aloe vera	Aloin, emodin	Cytotoxicity; topoisomerase effects (emodin)	Preclinical [48]
46	Hypericum perforatum (St John's wort)	Hypericin	Photodynamic cytotoxicity; apoptosis	Preclinical/Clinical (PDT) [49]
47	Betula spp. (Birch)	Betulinic acid	Mitochondrial apoptosis; melanoma models	Preclinical [50]
48	Citrus spp. (Lemon, orange)	Limonene, naringenin	Chemoprevention; apoptosis; phase-I enzymes	Clinical/Preclinical [51]
49	Prunella vulgaris (Self-heal)	Rosmarinic/ursolic acids	Anti-angiogenesis; NF-κB inhibition	Preclinical [52]
50	Origanum vulgare (Oregano)	Carvacrol, thymol	Apoptosis; cell-cycle arrest	Preclinical [53]

Table no 2. Binding energy of docked protein molecule (5XLT) with ligand (Podophyllotoxin)

Ligand	**Binding Energy**	**rmsd/ub**	**rmsd/lb**

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5XLT_10607_uff_E=825.29	**-7.2**	**0**	**0**
5XLT_10607_uff_E=825.29	-7.2	2.252	0.462
5XLT_10607_uff_E=825.29	-6.8	32.037	28.874
5XLT_10607_uff_E=825.29	-6.7	31.907	28.738
5XLT_10607_uff_E=825.29	-6.6	32.272	28.933
5XLT_10607_uff_E=825.29	-6.6	32.281	29.081
5XLT_10607_uff_E=825.29	-6.3	28.463	25.297
5XLT_10607_uff_E=825.29	-6.3	5.609	2.306
5XLT_10607_uff_E=825.29	-6.2	31.735	28.583

Table no 3. Binding energy of docked protein molecule (9FPX) with ligand (Curcumin)

Ligand	Binding Energy	rmsd/ub	rmsd/lb
9FPX_969516_uff_E=272.07	**-8.7**	**0**	**0**
9FPX_969516_uff_E=272.07	-7.8	5.424	1.727
9FPX_969516_uff_E=272.07	-7.7	7.052	1.987
9FPX_969516_uff_E=272.07	-7.6	5.629	2.038
9FPX_969516_uff_E=272.07	-7.6	6.675	1.783
9FPX_969516_uff_E=272.07	-7.5	5.776	1.866
9FPX_969516_uff_E=272.07	-7.2	5.653	2.056
9FPX_969516_uff_E=272.07	-6.9	3.166	2.146
9FPX_969516_uff_E=272.07	-6.9	5.694	2.394

Discussion

The exploration of medicinal plants as potential anticancer agents has gained considerable attention due to their bioactive phytochemicals, structural diversity, and relatively lower toxicity compared to conventional chemotherapeutics. Numerous plant-derived compounds such as alkaloids, flavonoids, terpenoids, phenolics, and glycosides have demonstrated anticancer activities through mechanisms including induction of apoptosis, inhibition of angiogenesis, modulation of signaling pathways, and interference with cell cycle progression. *Catharanthus roseus* produces vincristine and vinblastine that play a vital role in the treatment of lymphomas and leukemias by disrupting microtubule of the cancer cells. Similarly, paclitaxel, the chemical constituent of *Taxus brevifolia*, activates the caspase 3 and 9 and causes programe cell death of the cancer cells [54].

Curcumin a derivative of *Curcuma longa* has shown the ability to sensitize tumor cells and enhancing treatment efficacy. Additionally, compounds such as epigallocatechin gallate, berberine and quercetin have been reported the broad-spectrum anticancer effects via tumor suppressor genes, regulation of oxidative stress and mitochondrial pathways [55]. It is interesting phenomenon in the plant metabolites that they often act on multiple molecular targets concurrently, which is one of the advantages of the medicinal plants to managing heterogeneous cancers.

Molecular docking study and structural analysis exhibit that ligand “podophyllotoxin”

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have the conventional hydrogen bonds with GLU (A:22) and ASN (A:228) amino acids. Moreover, the ligand (podophyllotoxin) and amino acids (GLY A:81 and GLU A:77) bind with each other through the carbon hydrogen bonds.

Podophyllotoxin are well-established ligands of tubulin. Podophyllotoxin binds at a tubulin pocket and causes depolymerization; the crystal structure of tubulin in complex with a demethyl-epipodophyllotoxin (PDB ID: **5XLT**) confirms that podophyllotoxin compound support the tubulin targeting mechanism [56].

Molecular docking and structural analysis indicate that ligand "Curcumin" have the conventional hydrogen bonds with amino acids (GLU A:203, LEU A:241 and ASN A:292); non covalent interaction (Pi-Pi stacked) of benzene ring with PHE A:283 amino acid; carbon hydrogen bond with amino acid ASP A:307; LYS A:167 form Pi-donor hydrogen bond and Pi-alkyl bonds with PHE A:170, VAL A:306, LYS A:188 and VAL A:222 amino acids.

Curcumin docking against kinase targets frequently reveals a pattern of H-bonding to hinge-region residues and hydrophobic occupation of adjacent pockets; this is exemplified by the recently deposited structure of **DYRK1A (**Dual-specificity Tyrosine-(Y)-phosphorylation Regulated Kinase 1A) in complex with curcumin (PDB ID: **9FPX**), which shows curcumin occupying the ATP-competitive site and forming stabilizing interactions consistent with kinase inhibition (https://doi.org/10.2210/pdb9FPX/pdb).

Docking of curcumin to kinase active sites (DYRK1A) or other kinases typically yields moderate-to-good predicted binding affinities and confirms that the flexible, polyphenolic curcumin scaffold can assume conformations that maximize π–π stacking and hydrogen bonds with conserved active-site residues, an observation supported by multiple computational studies of curcumin binding [57].

Binding energy in molecular docking studies represents the **predicted free energy change in kcal/mol** when a ligand and target proteins are bind with each other's. The highest negative binding energy suggest that the ligand fit better and is more stable with the binding site of protein.

Molecular docking study

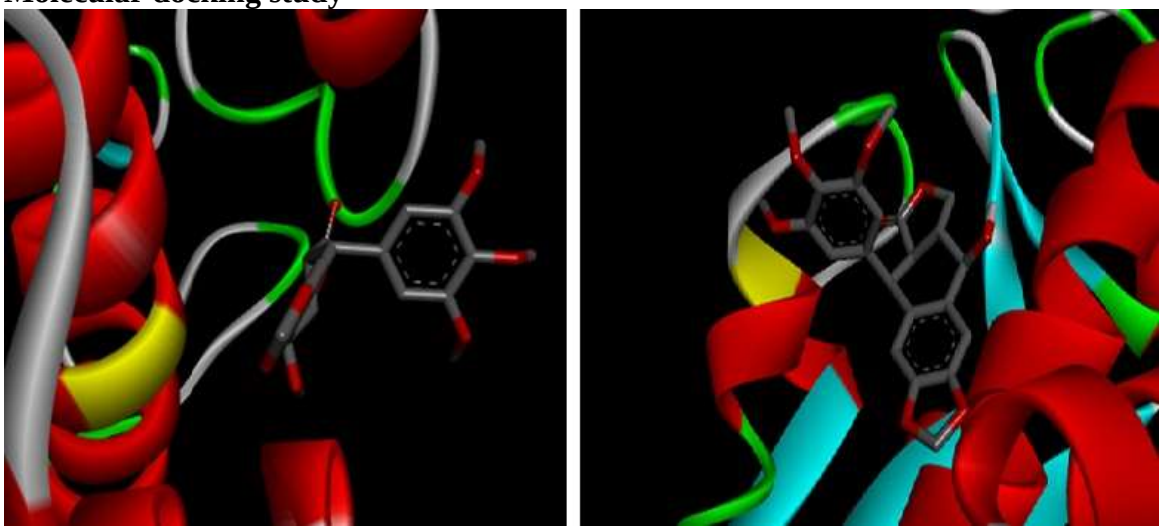


Figure 1. 3D structure of podophyllotoxin and protein (5XLT) interaction

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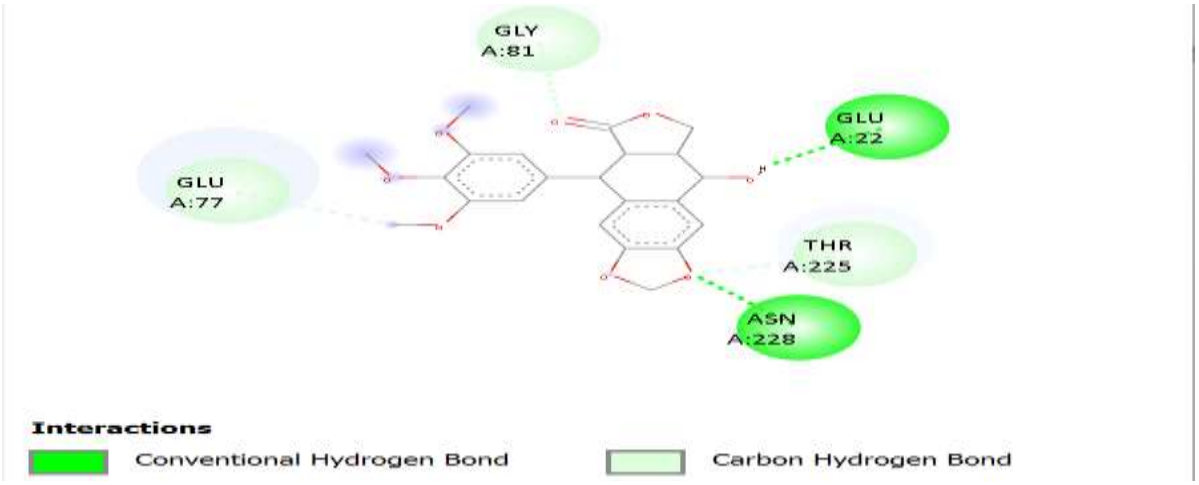


Figure 2. 2D structure of podophyllotoxin and protein (5XLT) interaction

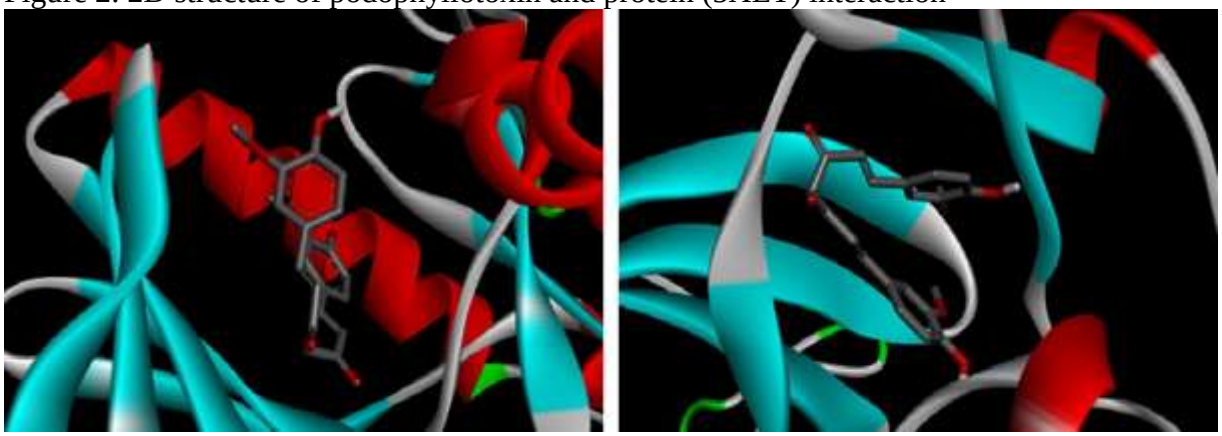


Figure 3. 3D structure of curcumin and protein (9FPX) interaction

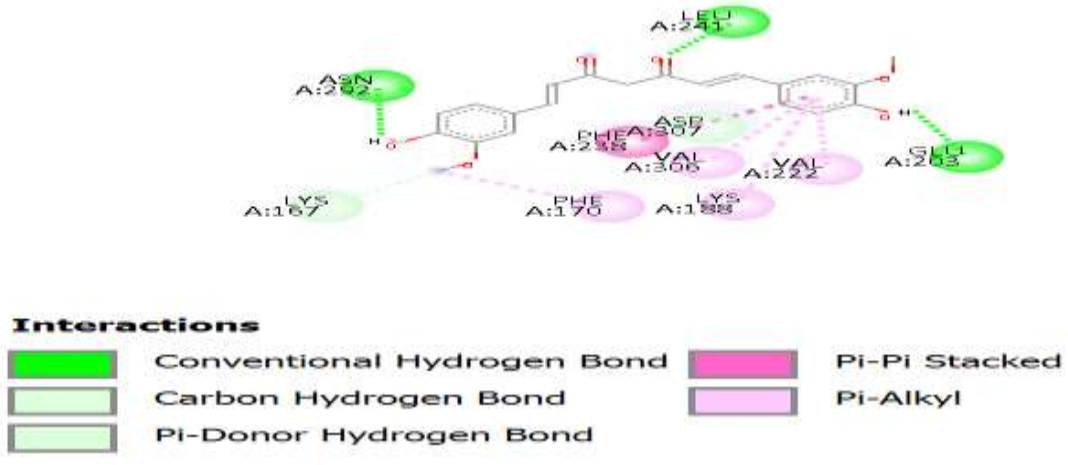


Figure 4. 2D structure of curcumin and protein (9FPX) interaction

Conclusion

Medicinal plants represent a valuable reservoir of anticancer agents, with both established drugs and novel leads. The results of docking study explained that how **podophyllotoxin and curcumin** interacts with its protein target **tubulin** and

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DYRK1A binding ligand respectively. The podophyllotoxin **and curcumin docked with** tubulin and DYRK1A with binding energy **-7.2 kcal/mol and -8.7 kcal/mol respectively.** These results predict that podophyllotoxin as a potential tubulin-binding ligand and curcumin as a DYRK1A-binding ligand.

Future research should integrate phytochemistry, molecular biology, and advanced drug delivery systems to unlock the full therapeutic potential of plant-derived compounds in oncology.

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