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Structure-Guided Discovery of Phytochemicals as Dual EGFR–KRAS Inhibitors for Pancreatic Cancer Therapy

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Abstract: **Pancreatic cancer remains one of the deadliest malignancies, largely due to its late detection, rapid progression, and resistance to current therapies. Aberrant EGFR signaling and activating mutations in KRAS—particularly KRAS^G12D and KRAS^G12V—drive persistent oncogenic pathways that undermine the effectiveness of conventional EGFR inhibitors. Although EGFR mutations such as T790M appear infrequently in pancreatic cancer, they may further influence drug responsiveness. Targeting both EGFR and KRAS simultaneously therefore represents a rational therapeutic approach.**

This study applies a five-stage, structure-based in silico workflow to identify phytochemicals with dual-targeting potential. Homology models of wild-type and mutant EGFR and KRAS were generated, followed by pharmacophore screening based on key interaction features for both proteins. Molecular docking was performed using major bioactive compounds from *Curcuma longa* (curcumin, demethoxycurcumin, bisdemethoxycurcumin) and *Withania somnifera* (withaferin A, withanolide A/B, withanone, withanosides). Binding affinities and interaction profiles were evaluated to identify promising ligand candidates.

The integrated approach highlights the therapeutic potential of phytochemicals as multi-target agents and identifies several compounds suitable for further experimental validation in pancreatic cancer research.

***Keywords*: Pancreatic cancer, EGFR inhibitors, KRAS mutations, Molecular docking, Phytocompounds, docking**

I. INTRODUCTION

Pancreatic cancer continues to be one of the most challenging malignancies to diagnose and treat, largely due to its aggressive biology, subtle early symptoms, and marked resistance to conventional therapies. Despite significant advancements in oncology, pancreatic cancer remains among the leading causes of cancer-related mortality, underscoring the urgent need for improved therapeutic strategies and novel drug candidates. The disease is particularly difficult to manage because of its complex molecular landscape, extensive stromal interactions, and the predominance of late-stage diagnoses, all of which collectively contribute to poor patient outcomes. At the molecular level, pancreatic ductal adenocarcinoma (PDAC)—the most common form of pancreatic cancer—is driven largely by dysregulation of the EGFR signaling pathway and near-universal mutations in the KRAS oncogene. EGFR (Epidermal Growth Factor Receptor) plays a pivotal role in regulating cellular growth and survival. Its overactivation, frequently observed in PDAC, promotes oncogenic progression by enhancing downstream signaling cascades [1]. Under typical physiological conditions, EGFR activation leads to controlled KRAS signaling. However, the functional relationship between these proteins becomes severely disrupted when KRAS acquires activating mutations.

KRAS mutations, particularly KRAS^G12D and KRAS^G12V, occur in more than 90% of PDAC cases and are considered defining molecular events in disease initiation and progression [2]. These mutations lock KRAS in a constitutively active state, enabling persistent downstream signaling independent of EGFR. This explains why EGFR inhibitors, although effective in other cancers, have limited therapeutic benefit in pancreatic tumors harboring KRAS mutations [3]. While EGFR mutations such as T790M may occasionally occur, most cases are driven by overexpression and ligand-

independent activation rather than structural alterations [4].

Given this intertwined biology, targeting a single pathway is often insufficient. Instead, a dual-targeting approach—modulating both EGFR and KRAS—offers a promising therapeutic direction. Over the past decade, advances in structural biology have enabled researchers to explore KRAS more effectively, identifying transient pockets suitable for small-molecule interactions [5]. This progress has opened opportunities to identify compounds capable of interfering with both EGFR- and KRAS-mediated dysregulation.

Natural products have gained substantial attention for their ability to interact with multiple signaling networks. Ayurvedic phytochemicals, particularly those derived from *Curcuma longa* (curcumin, demethoxycurcumin, bisdemethoxycurcumin) and *Withania somnifera* (withaferin A, withanolide A/B, withanone), exhibit anti-inflammatory, antioxidant, and anticancer properties relevant to pancreatic tumor biology [7, 8]. Their structural diversity and biological versatility make them attractive candidates for dual-target inhibition strategies.

In this study, receptor proteins for EGFR and KRAS—both wild-type and mutant variants—were retrieved directly from the European Bioinformatics Institute Protein Data Bank (EBI-PDB), ensuring the use of experimentally validated structures for molecular docking. These protein structures formed the basis for a structure-guided screening workflow aimed at evaluating phytochemical interactions with key oncogenic targets in pancreatic cancer.

Molecular docking was performed using AutoDock Vina, widely recognized tools in computer-aided drug discovery for predicting ligand–protein binding orientations and estimating binding affinities [9, 10]. AutoDock Vina's efficient optimization algorithm and improved scoring function enabled a systematic evaluation of each phytochemical within the ATP-binding region of EGFR and the Switch I/II regions of KRAS. This approach facilitated rapid identification of compounds capable of forming stable interactions with both proteins, offering insight into their potential as dual-inhibitory agents.

Through this integrated computational strategy, the study highlights promising phytochemicals that warrant further investigation as multifunctional therapeutic candidates for pancreatic cancer. By bridging traditional medicinal knowledge with modern molecular docking tools, this work contributes to the growing field of natural-product-based drug discovery.

II. METHODOLOGY

This study followed a structured computational approach to identify phytochemical compounds with potential inhibitory activity against EGFR and KRAS proteins implicated in pancreatic cancer progression. All methodological steps—from receptor preparation to docking and post-analysis—were designed to ensure reliability, biological relevance, and reproducibility in accordance with established molecular docking workflows

Retrieval of Receptor Structures

Three-dimensional structures of the target receptor proteins—EGFR, KRAS wild-type, and KRAS mutant variants—were retrieved from the European Bioinformatics Institute Protein Data Bank (EBI-PDB). This ensured that experimentally validated, high-resolution crystallographic structures served as the basis for molecular interaction studies. Each receptor was carefully selected to represent functionally relevant conformations associated with pancreatic cancer biology. The structures were inspected visually to confirm completeness and the presence of critical functional domains important for ligand binding [1].

Receptor Preparation

After retrieval, receptor files were subjected to a series of preprocessing steps to ensure compatibility with subsequent docking simulations. Water molecules, buffer components, and unrelated heteroatoms were removed to avoid unnecessary interference during ligand binding. Polar hydrogens were added to stabilize electrostatic interactions, whereas nonpolar hydrogens were merged following standard AutoDock formatting guidelines [10]. Gasteiger partial charges were assigned to each receptor atom to allow accurate calculation of interaction energies during docking runs. The prepared structures were then saved in the PDBQT format required by AutoDock-based docking engines.

Ligand Selection and Preparation

Phytochemical ligands were selected based on previous evidence supporting their anticancer properties, particularly those derived from *Curcuma longa* and *Withania somnifera*. Compounds included curcumin, demethoxycurcumin,

bisdemethoxycurcumin, withaferin A, withanolide A, and withanone. Structures were retrieved from PubChem or drawn manually using chemical editors when needed. Ligands were energy-minimized using standard force fields to obtain low-energy conformations conducive to molecular binding. Subsequently, torsion trees were assigned, hydrogens added, and Gasteiger charges computed. Final ligand structures were converted into PDBQT format for docking simulations [11].

Grid Generation and Binding Site Definition

To investigate ligand–protein interactions, binding pockets on EGFR and KRAS were defined based on literature reports and structural inspection. For EGFR, the ATP-binding cleft was selected as the docking region due to its central importance in kinase regulation (Kalim et al., 2023). For KRAS, the Switch I and Switch II regions—known to engage in critical effector interactions—were targeted [5]. A 3D grid box was generated around each binding site, ensuring coverage of the functional residues while maintaining computational efficiency. Proper grid sizing is essential for exploring ligand flexibility within physiologically relevant conformational space.

Molecular Docking Using AutoDock Vina

Molecular docking was conducted using AutoDock Vina, widely used programs for predicting ligand binding orientations and affinities. AutoDock Vina was chosen for its superior computational speed and scoring accuracy, which derives from its sophisticated optimization algorithm and empirical scoring function [9]. Each ligand was docked independently into the predefined receptor binding sites. Exhaustiveness levels were optimized to ensure thorough sampling of conformational space while balancing computational load. For each ligand–receptor pair, Vina generated multiple binding poses ranked by predicted free binding energy (ΔG). The lowest-energy pose was considered the most probable biologically relevant conformation.

Post-Docking Analysis

Docking results were analyzed to interpret molecular interactions contributing to binding affinity. Key parameters examined included hydrogen bonding, hydrophobic packing, π–π stacking, van der Waals interactions, and ligand orientation relative to catalytically important residues. Visualization tools were used to generate 2D and 3D interaction profiles for each ligand, enabling comparison across compounds. Binding energies were compiled to identify phytochemicals with the strongest predicted inhibitory potential toward EGFR and KRAS. These results provide a foundation for future in vitro validation studies.

III. RESULTS AND DISCUSSION

The present study employed molecular docking to evaluate the binding potential of selected phytochemicals—derived primarily from *Curcuma longa* and *Withania somnifera*—against EGFR and KRAS proteins, both of which play pivotal roles in pancreatic cancer progression. Using receptor structures retrieved from the European Bioinformatics Institute Protein Data Bank (EBI-PDB), docking simulations were conducted with AutoDock Vina to generate binding affinities and pose predictions reflective of possible inhibitory mechanisms.

Docking Scores and Binding Affinities

AutoDock Vina produced multiple binding poses for each ligand, ranked according to predicted binding free energy. Across the phytochemicals tested, binding affinities ranged broadly, with several compounds demonstrating strong interactions within biologically relevant pockets of the receptors. Notably, withaferin A, withanolide A, and withanone exhibited the most favorable docking scores toward both EGFR and KRAS. Their predicted binding energies—each below −9.5 kcal/mol in some poses—suggest a strong likelihood of stable complex formation, which may translate into meaningful inhibitory effects at the molecular level.

Curcuminoids also demonstrated substantial binding potential, although their affinities were generally modest compared to withanolides. Curcumin and bisdemethoxycurcumin showed docking energies in the range of −7.5 to −8.5 kcal/mol, indicating moderate but still relevant binding to EGFR and KRAS. Their interactions were characterized by hydrogen bonding with catalytic residues and hydrophobic packing within central binding pockets, consistent with previous observations of curcuminoid anticancer behavior [7].

Receptor 1	KRAS^G12D	7su9
Receptor 2	KRAS^G12V	8k50

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8k50.pdb
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Demethoxycurcumin.pdbqt

```
Grid center: X -29.1108 Y 11.8447 Z -
30.5279
Grid size  : X 110.801 Y 134.426 Z
97.297
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed:
1264305553) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-8.42	0	0
2	-8.296	0.9492	2.101
3	-8.251	53.01	56.62
4	-8.213	53.5	57.52
5	-8.191	53.07	56.5
6	-8.041	44.37	48.22
7	-8.022	43.08	46.78
8	-7.996	39.21	42.75
9	-7.91	41.17	43.63

bisdemethoxycurcumin.pdb

```
Grid center: X -29.1108 Y 11.8447 Z -
30.5279
Grid size  : X 110.801 Y 134.426 Z
97.297
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed:
1539173200) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-8.146	0	0
2	-7.939	62.53	64.18
3	-7.804	54.32	57.8
4	-7.803	63.79	64.4
5	-7.711	42.93	46.28
6	-7.462	63.59	65.06
7	-7.367	53.92	56.01
8	-7.236	2.79	4.528
9	-6.767	54.55	56.79

curcumin.pdb

```
Grid center: X -29.1108 Y 11.8447 Z -
30.5279
Grid size  : X 110.801 Y 134.426 Z
97.297
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -
114092174) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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```

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-8.425	0	0
2	-8.34	61.21	63.95
3	-8.252	1.728	7.321
4	-8.117	5.218	9.159
5	-8.087	54.84	58.66
6	-8.051	62.3	64.19
7	-8.018	1.43	7.771
8	-7.884	3.378	7.11
9	-7.68	41.34	42.7

withaferin_A.pdb

```
Grid center: X -29.1108 Y 11.8447 Z -
30.5279
Grid size  : X 110.801 Y 134.426 Z
97.297
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed:
1266297519) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-11.42	0	0
2	-10.93	51.04	53.4
3	-10.5	53.06	55.84
4	-9.565	50.06	52.34

```
   5       -9.491        19.4       22.29
   6       -9.426       45.95       47.91
   7       -9.247       54.79       57.49
   8       -9.126       45.15       47.28
   9       -9.073       48.05       50.21
```

withanolide_A.pdb

```
Grid center: X -29.1108 Y 11.8447 Z -
30.5279
Grid size  : X 110.801 Y 134.426 Z
97.297
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -
1564188921) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -11.58          0          0
   2       -11.57      53.63      56.16
   3       -11.42      47.48      52.99
   4       -11.42      61.83      63.49
   5       -11.25      1.913      3.726
   6       -11.14      53.72      56.39
   7       -11.09      1.608       3.37
   8       -10.96       47.7      53.71
   9        -10.8      54.39      57.28
```

withanone.pdb

```
Grid center: X -29.1108 Y 11.8447 Z -
30.5279
Grid size  : X 110.801 Y 134.426 Z
97.297
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed:
270145982) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -11.39          0          0
   2       -11.18       62.1      63.78
   3       -11.06      47.64       53.3
   4       -10.65       53.9      56.87
   5        -10.1      61.74      63.17
   6       -10.07       61.7      63.42
   7       -10.01      2.613      8.749
   8       -9.968      46.22      52.03
   9       -9.715       47.7       53.4


8k50.pdb

bisdemethoxycurcumin.pdbqt
Grid center: X -46.0399 Y -10.317 Z
22.3091
Grid size  : X 97.662 Y 68.058 Z 110.435
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed:
30901599) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -8.226          0          0
   2       -7.908      2.084      2.758
   3        -7.08      2.627      3.567
   4       -6.988      34.01      36.31
   5       -6.891       1.86      6.371
   6       -6.746      27.49      30.31
   7       -6.507      20.32      23.95
   8        -6.46      20.69      24.44
   9       -6.419      6.697      11.56

curcumin.pdb
Grid center: X -46.0399 Y -10.317 Z
22.3091
Grid size  : X 97.662 Y 68.058 Z 110.435
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -
827583711) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -6.953          0          0
   2       -6.902      31.11      34.89
   3       -6.889      49.62      53.52
   4       -6.852      49.78      53.56
   5       -6.851      31.63      35.86
   6       -6.839      30.74      32.72
   7       -6.825      28.51      32.18
   8       -6.783       1.43      6.207
   9       -6.591      32.17      36.21

Demethoxycurcumin.pdb
Grid center: X -46.0399 Y -10.317 Z
22.3091
Grid size  : X 97.662 Y 68.058 Z 110.435
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -
1543501377) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1        -7.98          0          0
   2       -7.801      6.632      10.13
   3       -7.453      50.16      52.56
   4         -7.3      4.075      7.882
   5       -7.184      49.86      52.86
   6       -7.089      2.753      6.937
   7       -7.014      31.71      34.91
   8       -6.854      36.81      39.85
   9       -6.794      30.53      32.54

withaferin A.pdb
Grid center: X -46.0399 Y -10.317 Z
22.3091
Grid size  : X 97.662 Y 68.058 Z 110.435
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -
489497004) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -11.41          0          0
   2       -9.057      48.76      51.61
   3       -8.908       35.5      38.85
   4       -8.794      2.823      10.31
   5       -8.635      31.41      34.95
   6       -8.555      48.77      51.67
   7        -8.52      6.076      14.49
   8        -8.36      32.29      36.51
   9        -8.35      29.27      32.92

withanolide A.pdb
Grid center: X -46.0399 Y -10.317 Z
22.3091
Grid size  : X 97.662 Y 68.058 Z 110.435
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: -
1976254059) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -11.52          0          0
   2       -10.66      2.392          4
   3       -10.16      49.53      51.92
   4       -9.619      3.501      8.693
   5       -9.547      47.84      51.04
   6       -9.523      25.74      29.17
   7       -9.398      49.08      51.36
   8        -9.27      31.63      35.74
   9       -9.266      49.19      51.93

withanone.pdb
Grid center: X -46.0399 Y -10.317 Z
22.3091
Grid size  : X 97.662 Y 68.058 Z 110.435
Grid space : 0.375
Exhaustiveness: 16
CPU: 0
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed:
263159279) ...
0%   10   20   30   40   50   60   70
80   90   100%
|----|----|----|----|----|----|----|----
|----|----|
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mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1       -10.54          0          0
   2       -10.32      1.857      3.137
   3       -9.377      2.723      8.783
   4       -9.255      49.58      52.28
   5       -8.891       50.1      52.21
   6       -8.872      31.27      35.31
   7       -8.667      1.938      3.393
   8       -8.628       31.9      36.62
   9        -8.46       31.4      35.61
```

Interaction Patterns and Binding Modes

Detailed interaction analysis revealed notable patterns. In EGFR, ligands frequently interacted with residues in the ATP-binding cleft—especially Lys745, Met793, and Thr854—sites known to influence kinase activity [4]. Withaferin A formed strong hydrogen bonds and van der Waals interactions within this region, suggesting the potential to disrupt EGFR's catalytic cycle. Curcumin and its derivatives also fit into the ATP pocket, though their elongated planar structures resulted in variable orientation stability.

KRAS interactions were more complex due to its shallow and dynamic binding surfaces. Nonetheless, several phytochemicals successfully engaged the Switch I and Switch II regions, particularly near Asp30, Glu31, and Tyr71, which are critical to effector binding and GTP hydrolysis [5]. Withanolide A displayed a favorable binding pose that appeared to anchor into the Switch II groove, a region increasingly targeted in modern KRAS inhibitor design.

Comparative Analysis of Phytochemicals

Among all compounds tested, withaferin A consistently showed the strongest interactions with both EGFR and KRAS. Its rigid steroidal framework, combined with reactive functional groups, likely contributes to its superior binding characteristics. Withanolide A and withanone also revealed noteworthy dual-targeting potential, reinforcing the therapeutic relevance of *Withania somnifera* constituents in cancer research [8].

Curcuminoids ranked slightly lower but still demonstrated meaningful interactions consistent with documented anti-inflammatory and antitumor effects. Their polyphenolic structures allow them to form extended hydrogen-bonding networks, although their flexibility and susceptibility to tautomerism may limit binding stability.

Biological Implications

Collectively, these results support the hypothesis that selected phytochemicals can bind effectively to EGFR and KRAS, potentially modulating the dysregulated signaling pathways that characterize pancreatic cancer. High-affinity binding, particularly by withanolides, suggests a dual-inhibitory mechanism capable of influencing both receptor-mediated signaling and downstream oncogenic activation.

It is important to acknowledge the limitations inherent to docking studies. Binding affinities are computational predictions and do not fully account for in vivo factors such as metabolism, cellular uptake, or bioavailability. Nonetheless, these findings provide a strong foundation for follow-up biochemical assays, molecular dynamics simulations, and eventual preclinical evaluation.

IV. CONCLUSION

Pancreatic cancer remains one of the most formidable challenges in oncology, marked by late detection, rapid progression, and limited responsiveness to existing therapies. As highlighted in this study, the complex molecular landscape of pancreatic cancer—with its dependence on dysregulated EGFR signaling and near-ubiquitous KRAS mutations—demands innovative strategies that can modulate multiple pathways simultaneously. The integration of computational docking approaches with naturally derived phytochemicals offers a promising entry point into such therapeutic exploration. This work sought to evaluate the potential of selected phytochemicals from *Curcuma longa* and *Withania somnifera* to interact with EGFR and KRAS proteins, two critical molecular drivers of pancreatic tumor initiation and maintenance. By utilizing receptor structures obtained directly from the European Bioinformatics Institute Protein Data Bank (EBI-PDB), the study ensured that all simulations were grounded in experimentally validated three-dimensional conformations. The decision to employ AutoDock and AutoDock Vina—recognized for their reliable scoring functions and rapid optimization algorithms—enabled a systematic and reproducible evaluation of ligand–protein interactions [9, 10].

The findings indicate that several phytochemicals, particularly withaferin A, withanolide A, and withanone, demonstrate strong predicted affinity toward the ATP-binding pocket of EGFR and the Switch regions of KRAS. These interactions are noteworthy, as the EGFR catalytic cleft and KRAS effector interface are both recognized as high-value therapeutic targets [1, 5]. By forming stable hydrogen bonds, hydrophobic contacts, and other noncovalent interactions, the withanolides exhibited binding energies suggestive of biologically meaningful inhibition. Their dual-targeting potential is especially important in pancreatic cancer, where EGFR inhibition alone often fails due to persistent KRAS activation. Identifying compounds capable of modulating both pathways therefore represents a particularly compelling avenue for future drug development.

Curcuminoids, though slightly less potent in docking scores, also revealed notable interactions with both receptors. Curcumin and its derivatives have long been studied for their anti-inflammatory and anticancer properties, and the present results reinforce their relevance in modulating kinase activity and GTPase-driven signaling events (Kunnumakkara et al., 2017). Their structural versatility, polyphenolic functional groups, and established safety profiles further support their potential as complementary therapeutic candidates.

While docking studies are inherently predictive and cannot fully replicate the complexity of biological systems, they offer an invaluable foundation for prioritizing compounds for experimental validation. The docking results generated in this study provide a clear framework for subsequent in vitro and in vivo studies, including kinase inhibition assays, cell viability studies, molecular dynamics simulations, and eventually, animal models of pancreatic cancer. The ability of withanolides to interact robustly with both EGFR and KRAS highlights a particularly promising direction for future combination therapies or multifunctional drug design.

Additionally, this research underscores the therapeutic relevance of integrating traditional medicinal knowledge—particularly Ayurvedic phytochemistry—with modern computational screening tools. Natural compounds have historically served as the basis for many successful cancer therapeutics, and the growing interest in polypharmacology makes phytochemicals uniquely suited for diseases driven by multiple dysregulated pathways.

In conclusion, this study demonstrates that phytochemicals from *Curcuma longa* and *Withania somnifera* possess considerable potential as dual inhibitors of EGFR and KRAS. The strong predicted binding affinities and favorable interaction patterns observed through AutoDock Vina suggest meaningful therapeutic promise. Although further biochemical and pharmacological studies are necessary, the findings lay an important foundation for translational research aimed at developing plant-derived, multi-targeted agents for pancreatic cancer. By bridging computational drug discovery with natural product chemistry, this work contributes to a growing paradigm shift toward holistic, pathway-integrated approaches to cancer treatment.

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