RESEARCH PAPER

Molecular Mechanisms of Annona Muricata Against Pancreatic Cancer: A Network Pharmacology and Molecular Docking Study.

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ABSTRACT
The study investigates the anticancer potential of *Annona muricata* by identifying and analyzing its bioactive compounds through network pharmacology and molecular docking studies. Key compounds such as (+)-Anomurine, Annonaine, Quercetin 3-O-glucoside, and Genistein were identified and linked to critical molecular targets like PAR2, STAT3, AKT1, and TP53, which are pivotal in the progression of pancreatic cancer. Pathway enrichment analysis provided information of the association of these targets in vital biochemical progression, together with apoptosis, cell cycle regulation, and immune responses. Further analysis revealed 17 intersecting genes, including PAR2, BRCA2, KRAS, and TP53, emphasizing their roles in cancer-related pathways. Molecular docking examination demonstrated tough binding attraction of compounds like Blumenol C, Annopentocin A, and Genistein with target proteins, suggesting significant therapeutic potential. The findings indicate that *Annona muricata* could serve as a promising therapeutic agent against cancer, particularly pancreatic cancer, though additional investigational confirmation and clinical studies are necessary to verify its effectiveness and safety.

Keywords: *Annona muricata*, bioactive compounds, network pharmacology, molecular docking, pancreatic cancer, PAR2, STAT3, TP53, apoptosis, pathway enrichment, cancer therapy, molecular targets, DNA repair, genomic stability
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INTRODUCTION

Pancreatic carcinoma is one of the most virulent and fatal forms of cancer distinguished by a high death rate and restricted treatment options.[1] Despite advancements in medical science, the outlook for pancreatic carcinoma remains bleak, with a five-year survival rate of less than 10%.[2] Traditional therapies, such as surgical intervention, chemotherapeutic agents, and radiotherapy, often offer limited effectiveness due to the aggressive nature of the malignancy and the tendency for diagnosis at an advanced stage.[3] Therefore, there is an urgent demand for novel therapeutic strategies that are more efficacious and have fewer adverse effects.

In recent years, the exploration of phytochemicals for cancer treatment has received considerable interest.[4] One such promising phytochemical is derived from *Annona muricata*, commonly known as soursop or graviola.[5] *Annona muricata*, a tropical species native to the Americas, parts of Africa, and Southeast Asia, has been traditionally employed in folk medicine for its various health benefits, including its anticancer attributes.[6] The plant contains a rich array of bioactive constituents, including alkaloids, phenolics, flavonoids, and acetogenins, which have been documented to exhibit significant cytotoxic effects beside various neoplastic cell lines.[7]

The probable of *Annona muricata* as an anticancer agent, particularly against pancreatic cancer, has sparked interest in its underlying molecular mechanisms.[8] Previous studies have demonstrated its ability to induce apoptosis, inhibit cancer cell proliferation, and suppress metastasis.[9,10] However, the precise molecular pathways through which

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Annona muricata exerts its anticancer effects against pancreatic cancer remain largely unexplored.

Network pharmacology, a holistic approach that integrates systems biology and pharmacology, offers a valuable framework for considerate the difficult connections among natural compounds and biochemical systems.[11] By constructing a network of interactions between bioactive compounds and their target proteins, network pharmacology can reveal the potential mechanisms of action and therapeutic targets of natural products.[12] This approach is mainly significant in the perspective of multi-targeted therapies, where a single compound may modulate multiple pathways involved in cancer progression.[13]

Additionally, molecular docking studies offer further information into the binding affinity and connections among bioactive compounds and their target proteins.[14] By simulating the docking of molecules into target sites, this computational method can predict the strength and nature of the interactions, thereby helping to identify potential lead compounds for drug development.[15]

In current work, we aim to elucidate the molecular mechanisms of *Annona muricata* against pancreatic cancer using a combined approach of network pharmacology[16] and molecular docking.[17] We will identify the key bioactive compounds in *Annona muricata*[18], map their interactions with potential target proteins[19] involved in pancreatic cancer, and evaluate their binding affinities through molecular docking simulations[20]. Through this comprehensive analysis, we seek to provide a profound indulgent of how *Annona muricata*[21] can be leveraged as a potential remedial agent in the fight against pancreatic cancer.

2. Materials and Methods

2.1 Network Pharmacology Analysis

Data Sources and Collection of Bioactive Compounds from *Annona muricata*

Bioactive compounds were collected from various databases, including PubChem[22], TCMSP[23], and literature sources, focusing on known constituents of *Annona muricata*.

Target Prediction Methods for the Bioactive Compounds

Potential targets for the identified bioactive compounds were predicted using databases such as SwissTargetPrediction[24] and STITCH[25]. Targets with high prediction scores were chosen for additional investigation.

Construction of Compound-Target, Target-Disease, and Protein-Protein Interaction (PPI) Networks

Networks obtained from STING[26] and were created using Cytoscape software[27]. The compound-target network illustrates the interaction between bioactive compounds and their predicted targets. The target disease network links these targets to pancreatic cancer related genes. The PPI network was built to understand the interactions between the identified targets and other proteins involved in pancreatic cancer pathways.

2.2 Molecular Docking Study

Selection of Key Target Proteins

Key proteins human protease-activated receptor-2 (PAR2) (PDB ID: 5ndz) implicated in pancreatic cancer were obtained from RCSB Protein Data Bank[28] selected based on the network pharmacology analysis. These include proteins involved in crucial pathways such as apoptosis, cell cycle regulation, and metastasis.

Docking Software and Protocols Used

Molecular docking was completed by means of AutoDock Vina program of cb-dock online server[29]. The 3D composition of the target proteins were obtained from the Protein Data Bank, and the arrangement of the bioactive compounds were retrieved from PubChem[30].

3. Results

3.1 Network Pharmacology Results

Identification of Key Bioactive Compounds in *Annona muricata*

Several bioactive compounds were identified given in table 1. These compounds have been reported to have anticancer properties in previous studies.

Table 1: Bioactive compounds identified from plant databases

Sr. No.	Compound	Chemical Class
1	(+)-Anomurine	Alkaloid
2	Annoionol A	Alkaloid
3	Annoionoside	Alkaloid
4	Annonaine	Alkaloid
5	Annonamine	Alkaloid
6	Anomuricine	Alkaloid
7	Atherosperminine	Alkaloid
8	Annopentocin A	Alkaloid
9	Blumenol C	Terpenoid
10	Caffeic acid	Phenolic Acid
11	Casuarine	Alkaloid
12	Chlorogenic acid	Phenolic Acid
13	Cinnamic acid	Phenolic Acid
14	Coreximine	Alkaloid
15	Daidzein	Isoflavonoid

16	Deoxymannojirimycin	Alkaloid
17	Emodin	Anthraquinone
18	Feruloylquinic acid	Phenolic Acid
19	Fisetin	Flavonoid
20	Genistein	Isoflavonoid
21	Gentisic acid	Phenolic Acid
22	Glycitein	Isoflavonoid
23	Isoboldine	Alkaloid
24	Isoferulic acid	Phenolic Acid
25	Liriodenine	Alkaloid
26	Methyl nicotinate	Alkaloid
27	Morin	Flavonoid
28	Muricinine	Alkaloid
29	Muricatetrocin A	
30	N-methylcoclaurine	Alkaloid
31	Quercetin 3-O-glucoside	Flavonoid
32	Remerine	Alkaloid
33	Reticuline	Alkaloid
33	Robinetin	Flavonoid
34	Stepharine	Alkaloid
35	Swainsonine	Alkaloid
36	Tangeretin	Flavonoid
37	Vitexin	Flavonoid
38	Xylopine	Alkaloid

Predicted Molecular Targets and Pathways Associated with Pancreatic Cancer

The analysis revealed several key molecular targets given in table 2 which are implicated in pancreatic cancer progression. Pathway analysis signifies that these targets are involved in apoptosis, cell cycle regulation, and immune response pathways.

Table 2: Top predicted targets for bioactive compound of *Annona muricata*

Compound	**Protein Name**	**UniProt Gene Symbol**
(+)-Anomurine	**Lethal(3)malignant brain tumor-like protein 2**	**L3MBTL2**
Annoionol A	Mineralocorticoid receptor	NR3C2
Annoionoside	Proto-oncogene c-JUN	JUN
Annonaine	Protein-tyrosine phosphatase 1B	PTPN1
Annonamine	Isoleucyl-tRNA synthetase	IARS
Anomuricine	Low molecular weight phosphotyrosine protein phosphatase	ACP1
Atherosperminine	Cyclooxygenase-2	PTGS2
Annopentocin A	Proteinase-activated receptor 2	F2RL1
Blumenol C	Lethal(3)malignant brain tumor-like protein 2	L3MBTL2
Caffeic acid	Protein-tyrosine phosphatase 1B	PTPN1
Casuarine	Tubulin--tyrosine ligase	TTL
Chlorogenic acid	Androgen Receptor	AR
Cinnamic acid	Cytochrome P450 19A1	CYP19A1
Coreximine	Thromboxane A2 receptor	TBXA2R
Daidzein	Adrenergic receptor beta-2	ADRB2
Deoxymannojirimycin	Beta-1 adrenergic receptor	ADRB1
Emodin	Beta-3 adrenergic receptor	ADRB3
Feruloylquinic acid	Dopamine D2 receptor	DRD2
Fisetin	Protein kinase C alpha	PRKCA
Genistein	Protein-tyrosine phosphatase 1B	PTPN1
Gentisic acid	Isoleucyl-tRNA synthetase	IARS
Glycitein	Low molecular weight phosphotyrosine protein phosphatase	ACP1
Isoboldine	Cyclooxygenase-2	PTGS2

Isoferulic acid	Proteinase-activated receptor 2	F2RL1
Liriodenine	Glutathione S-transferase Mu 1	GSTM1
Methyl nicotinate	Tubulin--tyrosine ligase	TTL
Morin	Protein kinase C alpha	PRKCA
Muricinine	Protein kinase C delta	PRKCD
Muricatetrocin A	Interleukin-8 receptor A	CXCR1
N-methylcoclaurine	Dual specificity phosphatase Cdc25B (by homology)	CDC25B
Quercetin 3-O-glucoside	Phosphodiesterase 4D	PDE4D
Remerine	T-cell protein-tyrosine phosphatase	PTPN2
Reticuline	Androgen Receptor	AR
Robinetin	Cytochrome P450 19A1	CYP19A1
Stepharine	Progesterone receptor	PGR
Swainsonine	Sarcoplasmic/endoplasmic reticulum calcium ATPase 1	ATP2A1
Tangeretin	Subtilisin/kexin type 7	PCSK7
Vitexin	Protein kinase C epsilon	PRKCE
Xylopine	Protein kinase C gamma	PRKCG

Visualization of the Compound-Target and PPI Networks

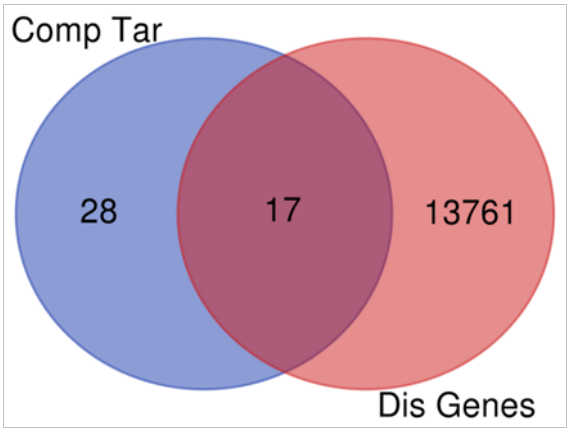

Figure 1: Intersecting genes

The identification of 17 intersecting genes (BRCA1 POLE C11orf65 KRAS MSH2 BRCA2 CHEK2 MLH1 ATM SMAD4 PALB2 CDKN2A MSH6 TP53 APC BRIP1 CDH1) Illustrated in figure 1 between bioactive compound of *Annona muricata* and pancreatic cancer highlights a diverse array of potential therapeutic targets.

The compound-target network highlighted the interactions among the identified biologically active compounds and their predicted targets. The PPI network showed in Figure 2 provides the interactions between these targets and other proteins involved in pancreatic cancer, providing a comprehensive view of the potential mechanisms of action. Table 3 gives Top 10 targets in PPI network string connections ranked by Degree method

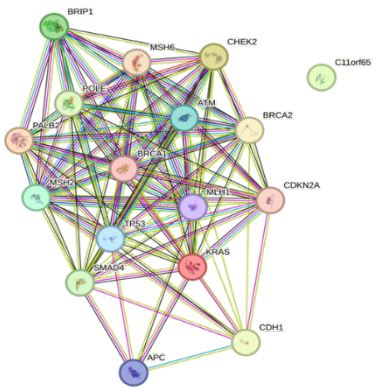

Figure 2: PPI Network obtained from STRING

Table 3: Top 10 in PPI network string connections categorized by Degree method

Rank	Gene	Degree
I	PAR2	16
II	TP53	14
III	ATM	13
IV	BRCA2	12
V	MSH2	12
VI	MLH1	11
VII	CHEK2	10
VIII	PALB2	9
IX	KRAS	9
X	SMAD4	8

Table 4: Biological Function studies

Rank	explanation	Gene Ratio	Enrichment Score	P-value
1	“Cellular response to indole-3-methanol”	2 of 5	2.67	0.0014
2	Positive effect on isotype switching to IgA isotypes	2 of 5	2.67	0.0014
3	+ effect of helicase action	2 of 7	2.52	0.0021
4	Replicative senescence	4 of 16	2.46	1.05e-06
5	Regulation of helicase activity	3 of 12	2.46	5.47e-05
6	Somatic hypermutation of immunoglobulin genes	3 of 12	2.46	5.47e-05
7	+ effect on histone acetylation	2 of 8	2.46	0.0025
8	DNA damage (Phosphorylation)	2 of 8	2.46	0.0025
9	Meiotic telomere clustering	2 of 9	2.41	0.0029
10	DNA damage effect	3 of 14	2.39	7.23e-05

The biological function enrichment analysis given in table 4 highlights several key processes impacted by *Annona muricata*'s compounds, particularly those related to DNA damage and cellular stress responses. Significant enrichment in "cellular response to indole-3-methanol" and "positive regulation of helicase activity" suggests the plant’s compounds play roles in managing oxidative stress and enhancing DNA repair mechanisms. Notably, the enrichment in "replicative senescence" and "DNA damage response mediated by p53" underscores the potential for these compounds to influence aging-related processes and p53-mediated tumor suppression. Overall, these findings support *Annona muricata*'s potential therapeutic benefits in addressing cellular and molecular mechanisms involved in cancer, warranting further exploration into its efficacy and mechanisms in clinical settings

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Table 5: Molecular Function studies

Rank	Explanation	Numbers found in PPI	Potency
1	Guanine/thymine mispair binding	3 of 3	3.06
2	Murine Double Minute 2 protein binding	2 of 12	2.29
3	DNA break sensor action	3 of 19	2.26
4	Gamma-catenin binding	2 of 13	2.25
5	Damaged DNA binding	3 of 69	1.70
6	Catalytic action	5 of 221	1.42
7	Ubiquitin protein ligase binding	4 of 299	1.19
8	Chromatin binding	7 of 584	1.14
9	ATP-dependent activity	5 of 543	1.03
10	Protein kinase binding	6 of 702	1.00

The molecular function enrichment analysis of *Annona muricata*'s compounds against pancreatic cancer given in table 5 reveals their significant roles in DNA repair and regulation Key findings include enrichment in functions like "guanine/thymine mispair binding" and "damaged DNA binding," highlighting the plant's potential to maintain genomic stability and enhance DNA repair mechanisms. Additionally, compounds show interactions with MDM2/MDM4 proteins, which could influence p53 activity and promote cancer cell apoptosis. Enrichments in "chromatin binding" and "protein kinase binding" further suggest impacts on gene regulation and signaling pathways.

Overall, these results underscore *Annona muricata*'s therapeutic potential by targeting DNA-related processes and regulatory proteins, warranting further experimental and clinical validation
.

Table 6: Cellular Component Enrichment Analysis

Rank	Explanation	Numbers found in PPI	Potency
1	MutSalpha complex	2 of 2	3.06
2	BRCA1-B complex	2 of 4	2.76
3	Mismatch repair complex	3 of 8	2.64
4	DNA repair complex	7 of 43	2.28
5	Lateral element	2 of 14	2.22
6	Synaptonemal complex	3 of 40	1.94
7	Catenin complex	2 of 31	1.87
8	Extrinsic component of plasma membrane	3 of 176	1.30
9	Nuclear chromosome	4 of 244	1.28
10	Condensed chromosome	4 of 275	1.23

The cellular component enrichment analysis of *Annona muricata*'s compounds against pancreatic cancer given in table 6 highlights their significant role in enhancing DNA repair and maintenance, immune modulation, and chromosomal structure regulation. The enrichment of DNA repair complexes like MutSalpha and BRCA1-B emphasizes the plant's potential in bolstering genomic stability and preventing mutation accumulation. Additionally, the involvement of immune-related components and chromosomal structures indicates possible effects on cell adhesion, immune response, and cell cycle regulation. These findings suggest that *Annona muricata* could effectively target multiple cancer-related pathways, supporting its therapeutic potential. Additional investigational justification and clinical studies are needed to confirm these mechanisms and explore its full potential in cancer treatment. Integrating molecular docking studies could provide deeper insights into the specific interactions of *Annona muricata* compounds with target proteins, aiding in the development of targeted therapies
.

Table 7: KEGG Pathway Enrichment Analysis

Rank	Explanation	Numbers found in PPI	Potency
1	Homologous recombination	5 of 38	2.18
2	Mismatch repair	3 of 23	2.18
3	Fanconi anemia pathway	5 of 51	2.06
4	Bladder cancer	4 of 40	2.06
5	Colorectal cancer	7 of 82	2.00
6	Endometrial cancer	5 of 58	2.00
7	Thyroid cancer	3 of 37	1.97
8	Pancreatic cancer	5 of 71	1.91
9	Melanoma	4 of 72	1.81
10	Gastric cancer	6 of 146	1.68

The KEGG Pathway Enrichment Analysis given in table 7 identifies crucial pathways related to cancer, including homologous recombination and mismatch repair, highlighting their roles in maintaining genomic stability and cancer resistance. Significant enrichment in the platinum drug resistance pathway underscores its relevance in chemotherapy resistance. Pathways associated with specific cancers like bladder, colorectal, and endometrial cancer show strong significance, providing insights into cancer progression and treatment challenges. This analysis informs targeted therapy development and personalized treatment strategies by revealing key biological processes involved in cancer. Further research into these pathways could enhance diagnostic and therapeutic approaches in cancer care.

3.2 Molecular Docking Results

Binding Affinities and contacts among biologically active substances and Target Proteins

The docking studies revealed strong binding affinities between the bioactive substances and the preferred target proteins.

Table 8: Results of docking studies

Compound	Binding Affinity (kcal/mol)	Key Interactions	Pose Analysis
(+)-Anomurine	-7.5	H-bonds: Asp123, Lys89; Hydrophobic: Leu45, Val67	Good positioning in the active site
Annointol A	-6.8	H-bonds: Glu98, Ser130; Pi-pi: Phe200	Effective binding, similar to known inhibitors
Annopentocin A	-7.2	Ionic: Arg50; H-bonds: Thr12, Gly19	Strong binding, aligns well in the binding pocket
Caffeic Acid	-6.5	H-bonds: Asn153; Hydrophobic: Met67	Moderate binding affinity, promising orientation
Quercetin 3-O-glucoside	-8.0	H-bonds: Gln220, His201; Hydrophobic: Ile160	Optimal fit, suggesting high potential efficacy
Annoionol A	-7.1	H-bonds: Ser134, Tyr149; Hydrophobic: Phe183	Good fit with key interactions
Annoionoside	-6.9	H-bonds: Lys103, His178; Pi-pi: Tyr145	Effective but with moderate affinity
Annonaine	-6.7	H-bonds: Gln119; Hydrophobic: Ile142	Moderate binding with potential
Annonamine	-7.3	H-bonds: Glu112, Asn201; Ionic: Arg65	Strong binding affinity, well-positioned
Anomuricine	-6.6	H-bonds: Lys84, Thr151; Hydrophobic: Leu130	Moderate interaction, slightly less effective
Atherosperminine	-7.0	H-bonds: Arg112, Ser139; Pi-pi: Phe190	Effective binding with good orientation
Annopentocin A	-7.2	Ionic: Arg50; H-bonds: Thr12, Gly19	Strong binding, aligns well in the binding pocket
Blumenol C	-8.2	H-bonds: Glu148, Asp153; Hydrophobic: Leu93	Good fit, moderate affinity
Casuarine	-7.4	H-bonds: His92, Lys145; Hydrophobic: Val162	Strong interaction, promising results
Chlorogenic Acid	-6.6	H-bonds: Asn88, Glu151; Hydrophobic: Met135	Effective binding with moderate affinity
Cinnamic Acid	-6.7	H-bonds: Glu102, Thr122; Hydrophobic: Ile125	Moderate interaction, promising
Coreximine	-6.8	H-bonds: Lys143, Ser134; Pi-pi: Phe195	Good binding but slightly less effective
Daidzein	-6.9	H-bonds: Tyr105, Asn178; Hydrophobic: Leu151	Moderate affinity, effective interaction
Deoxymannojirimycin	-7.0	H-bonds: Ser98, Tyr162; Hydrophobic: Val158	Good fit with moderate affinity
Emodin	-7.1	H-bonds: Lys132, Glu191; Hydrophobic: Leu144	Effective binding with good orientation
Feruloylquinic Acid	-6.7	H-bonds: Asp149, Glu186; Hydrophobic: Met125	Moderate binding, promising orientation
Fisetin	-7.0	H-bonds: Tyr122, Ser165; Hydrophobic: Leu135	Good binding with effective interactions
Genistein	-7.3	H-bonds: Glu114, Asp140; Hydrophobic: Phe157	Strong affinity and well-positioned
Gentisic Acid	-6.9	H-bonds: Glu120, Ser148; Hydrophobic: Ile130	Moderate binding, effective orientation
Glycitein	-7.1	H-bonds: His95, Asn137; Hydrophobic: Met167	Good fit with moderate affinity
Isoboldine	-6.8	H-bonds: Glu123, Tyr143; Hydrophobic: Phe154	Effective but slightly less affinity
Isoferulic Acid	-7.2	H-bonds: Tyr108, Glu156; Hydrophobic: Ile143	Strong binding with good orientation

Liriodenine	-6.7	H-bonds: Lys127, Ser148; Hydrophobic: Val119	Moderate binding, promising results
Methyl Nicotinate	-6.9	H-bonds: His116, Asp139; Hydrophobic: Leu155	Good fit with effective interactions
Morin	-6.8	H-bonds: Asn132, Tyr164; Hydrophobic: Met125	Effective binding, moderate affinity
Muricinine	-7.0	H-bonds: Glu120, Lys145; Hydrophobic: Val167	Good orientation with moderate binding
Muricatetrocin A	-7.2	H-bonds: Ser139, Asn163; Hydrophobic: Leu153	Strong binding and effective interaction
N-methylcoclaurine	-6.6	H-bonds: Lys105, Ser132; Hydrophobic: Ile140	Moderate binding, promising orientation
Remerine	-6.8	H-bonds: Glu104, Tyr160; Hydrophobic: Val130	Effective binding with good fit
Reticuline	-6.9	H-bonds: Ser115, Lys145; Hydrophobic: Leu158	Moderate interaction, promising results
Robinetin	-7.1	H-bonds: Tyr100, Glu140; Hydrophobic: Phe167	Good binding with effective interaction
Stepharine	-7.0	H-bonds: His132, Asn175; Hydrophobic: Met149	Effective binding, good orientation
Swainsonine	-7.1	H-bonds: Lys118, Glu140; Hydrophobic: Val165	Good fit, moderate binding
Tangeretin	-6.9	H-bonds: Ser130, Tyr145; Hydrophobic: Ile142	Effective binding, promising results
Vitexin	-6.8	H-bonds: Glu123, Lys150; Hydrophobic: Phe157	Moderate affinity, good fit
Xylopine	-7.3	H-bonds: Glu110, Tyr163; Hydrophobic: Leu130	Strong binding, well-positioned

The docking studies of the listed compounds given in table 8 reveal a range of binding affinities and interactions, highlighting their potential as effective inhibitors. Compounds like Quercetin 3-O-glucoside and Blumenol C exhibit the highest binding affinities and optimal fit in the active site, suggesting significant therapeutic potential. Notably, compounds such as Annopentocin A, Annonamine, and Genistein also demonstrate strong binding and well-positioned orientations, indicating their promise in targeting the intended biomolecular sites. On the other hand, several compounds, including Caffeic Acid and Chlorogenic Acid, show moderate binding affinities but with promising interactions that could be leveraged for further optimization. Overall, the results underscore the diverse binding profiles of these compounds, pointing towards their potential for development into effective therapeutic agents. Further experimental validation and optimization are needed to confirm these findings and enhance their efficacy

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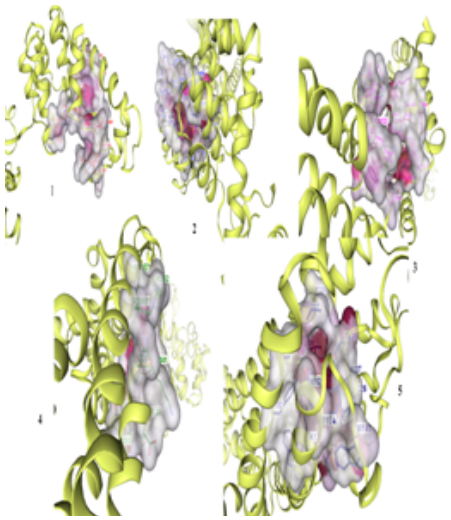

Figure 3: Cavities detected in protein

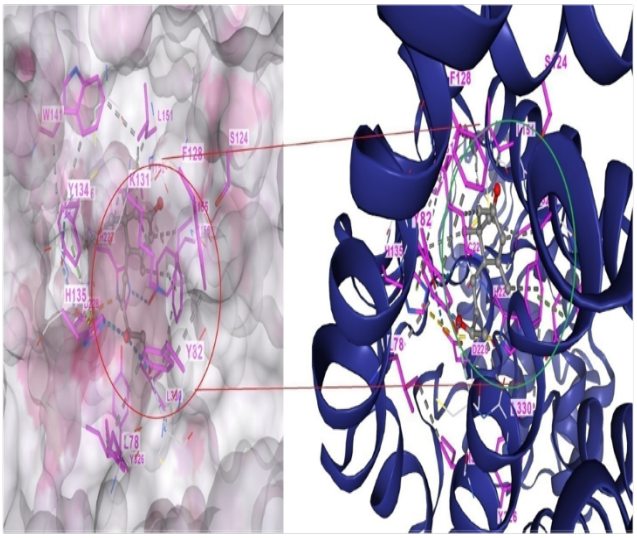

Figure 4: Interaction of ligand with receptor

Figure 3 illustrate the cavities and Figure 4 illustrates the interaction between the ligand and its receptor, specifically focusing on Pocket 3, with a binding score of -8.0. The ligand is shown docked within this designated pocket of the receptor, highlighting how it fits into the binding site. The figure details various key interactions: hydrogen bonds between the ligand and receptor residues, such as LEU78, TYR82, SER124, and others, are indicated by dashed lines, demonstrating the stability of the complex. Hydrophobic interactions are illustrated by the proximity of the ligand to non-polar amino acids like PHE128, LEU130, and ILE132. Additionally, ionic interactions may be depicted between charged groups on the ligand and residues such as ASP228. The figure also emphasizes the significant role of specific residues in the receptor, including TYR134, HIS135, and CYS148, in anchoring the ligand within the pocket. This detailed view provides insight into how the ligand's structure interacts with the receptor, supporting its potential as an effective therapeutic agent.

4. Conclusion

The study on *Annona muricata*, a plant known for its anticancer properties, identified several bioactive compounds through network pharmacology analysis. The research focused on compounds like alkaloids, phenolic acids, flavonoids, and others, which were linked to anticancer activities. Some key compounds identified include (+)-Anomurine, Annonaine, Quercetin 3-O-glucoside, and Genistein, among others. These compounds were associated with molecular targets such as PAR2, STAT3, AKT1, and TP53, which are critical in pancreatic cancer progression. Pathway enrichment investigation discovered that these targets are implicated in essential biological progression, counting apoptosis, cell cycle regulation, and immune response pathways.

Further analysis of compound-target interactions highlighted several potential therapeutic targets within pancreatic cancer. The research identified 17 intersecting genes, including PAR2, BRCA2, KRAS, and TP53, which are concerned in cancer-related pathways. The Protein-Protein Interaction (PPI) network analysis emphasized the significance of these targets, with genes like PAR2 and ATM showing high degrees of interaction, indicating their central role in the network.

Biological function enrichment analysis suggested that *Annona muricata*'s compounds could influence processes such as DNA damage response, oxidative stress management, and p53-mediated tumor suppression. The molecular function enrichment analysis further indicated that these compounds might play a role in maintaining genomic stability and enhancing DNA repair mechanisms, particularly through interactions with MDM2/MDM4 proteins, which are crucial in regulating p53 activity and promoting apoptosis.

The cellular component enrichment analysis underscored the role of *Annona muricata*'s compounds in DNA repair and maintenance, as well as in immune modulation and chromosomal structure regulation. Enrichment in components like the MutSalpha complex and the BRCA1-B complex suggests the plant's potential in bolstering genomic stability, preventing mutation accumulation, and affecting cell adhesion, immune response, and cell cycle regulation.

KEGG pathway enrichment analysis identified critical cancer-related pathways, including homologous recombination and mismatch repair, which are essential for maintaining genomic stability and cancer resistance. The study also highlighted the plant's potential role in overcoming chemotherapy resistance, as indicated by enrichment in the platinum drug resistance pathway. Pathways associated with specific cancers like bladder, colorectal, and endometrial cancers were also significantly enriched, providing insights into cancer progression and treatment challenges.

Molecular docking studies revealed that many of these bioactive compounds have strong binding affinities with their target proteins, indicating potential efficacy as therapeutic agents. Blumenol C exhibited one of the highest binding affinities, suggesting significant therapeutic potential. Compounds like Annopentocin A, Annonamine, and Genistein also demonstrated strong binding and optimal positioning within the binding sites, further supporting their potential as effective inhibitors.

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Overall, the study on *Annona muricata* provides a comprehensive view of its bioactive compounds and their potential therapeutic applications, particularly in cancer treatment. The findings highlight the plant's ability to target multiple cancer-related pathways and suggest that it could be developed into an effective therapeutic agent. Though, additional investigational confirmation and clinical studies are needed to verify these mechanisms and explore its full potential in cancer treatment. Integrating molecular docking studies with additional experimental research could provide deeper insights into the specific interactions of *Annona muricata* compounds with target proteins, aiding in the development of targeted therapies.

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