COMSATS University Islamabad Sahiwal Campus

Network Pharmacology and Molecular Docking Insights into the Therapeutic Potential of Gingko Semen for Skin Cancer Treatment

A research report submitted to Department of Biosciences, in the partial fulfillment of the requirement for the degree of BS Bioinformatics

Submitted to:

Department of Biosciences,

COMSATS University Islamabad, Sahiwal Campus

Submitted by:

Sabeen Tahir

CIIT/SP21-BSI-013/SWL

Supervisor:

Dr. Qudsia Yousafi

COMSATS University Islamabad

Sahiwal Campus, Pakistan

FALL 2024

Certificate of Approval

This report titled

"Network Pharmacology and Molecular Docking Insights into the Therapeutic Potential of Gingko Semen for Skin Cancer Treatment"

By

Sabeen Tahir CIIT/SP21-BSI-013/SWL

Has been approved

For the COMSATS University Islamabad, Sahiwal Campus

External Examiner: _____

Dr. ----------

Supervisor: _____

Dr. Qudsia Yousafi
Department of Biosciences, CUI, Sahiwal

Co-Supervisor: _____

Muhamad Saad Khan
Department of Biosciences, CUI, Sahiwal

Head of Department: _____

Dr. Muhamad Ibrahim
Department of Biosciences, CUI, Sahiwal


بسم الله الرحمن الرحيم

A research report submitted to the Department of Biosciences,

COMSATS University Islamabad,Sahiwal Campus as a partial fulfillment of the requirement for the award of the **Bachelor of Sciences in Bioinformatics (BSBI)**

DECLARATION

I Sabeen Tahir CIIT/SP21-BSI-013/SWL hereby certify that the thorough research contained in the thesis " Network Pharmacology and Molecular Docking Insights into the Therapeutic Potential of Gingko Semen for Skin Cancer Treatment" Represents my steadfast commitment to academic pursuits and dedication to my studies. I therefore declare that this research endeavor is the product of my diligent efforts, except for appropriately recognized inputs from external sources. I so attest that this academic work is unique and hasn't been submitted in part for any other academic credit.

Date: _____ _____

Sabeen Tahir
(CIIT/SP21-BSI-013/SWL)

DEDICATION

This thesis is dedicated to my family, who have been the bedrock of my academic career with their unwavering support and encouragement. Your great confidence in my ability not only made me more determined but also gave me the willpower to get past any challenges I faced. Your constant encouragement has shown me the path forward and given me the perseverance required to successfully negotiate the challenges of academia.

I owe my parents a tremendous deal because of their unselfish sacrifice and unwavering commitment, which set the groundwork for my success. Your constant faith in my ability has inspired me and helped me move forward in the face of uncertainty. Your unwavering dedication and devotion have always been a source of inspiration for me, motivating me to pursue greatness in whatever I do.

My brothers have my eternal gratitude for their steadfast support and mutual encouragement during my uncertain moments. Your presence has brought me happiness and solace, serving as a constant reminder of the value of family and the power of solidarity in the face of hardship.

I am grateful for the unwavering support and encouragement I have always received from my large and loving family. Your confidence in my skills has motivated me to strive for greater things and realize my full potential.

I dedicate this thesis to my family with immense thanks. I will always be appreciative to you for shaping me into the person I am today via your love, efforts, and support. May my thesis serve as evidence of the positive influence you have had on my life and as a tribute to the constant love and support you have given me during this entire journey.

Acknowledgments

My profound gratitude goes out to Allah Almighty, the Most "GRACIOUS" and "MERCIFUL," whose guidance and help have made it possible for me to finish this report. I want to thank my parents for their unwavering love and constant support throughout my journey. Their encouragement and belief in me have been invaluable, and I am truly thankful for their guidance in making important life decisions. Their strength has been a constant source of inspiration, enabling me to pursue my dreams wholeheartedly.

I owe a debt of gratitude to Dr. Qudsia Yousafi, my supervisor, for her wise counsel, consistent encouragement, constructive criticism, and exceptional supervision throughout this research. Her knowledge and support have been crucial in planning and carrying out the entire study endeavor. It gives me great pleasure to recognize her consistent dedication to quality and support.

It gives me great pleasure to extend my heartfelt gratitude to Muhammad Saad Khan , Co-supervisor, for his continuous support, kindness, and encouragement. His lessons and upbeat demeanor have had a profound effect on me, and I am appreciative of his motivation and direction.

My wonderful friends **Eiman Fatima**, **Ahtesham, Mahnoor, Maheen Naseer, Maham Javed and Muzammil Nazish** deserve special recognition as well for their unwavering support and encouragement. My path has been made brighter by your presence, and I treasure the special times we had together. Even though our paths have crossed, you guys are my life's bright spot.

Additionally, I am grateful to Dr. Muhammad Ibrahim, the head of the biosciences department at COMSATS University Islamabad's Sahiwal Campus, for providing the facilities I needed to complete my studies.

Sabeen Tahir CIIT/SP21-BSI-013/SWL

Summary

A thorough investigation of Ginkgo semen's therapeutic potential against skin cancer is conducted against the backdrop of a persistent worldwide health issue. Skin cancer, caused by a combination of genetic mutations and environmental factors like UV radiation, continues to pose significant challenges to effective treatment despite advancements in medical science. Conventional therapies, including chemotherapy and radiation, often show limited efficacy and adverse side effects, leading to a growing interest in natural products. Ginkgo semen, a medicinal herb with a rich profile of bioactive compounds, has demonstrated promising biological and pharmacological properties. Despite decades of research, the molecular complexities of skin cancer necessitate innovative therapeutic approaches. The rising incidence of skin cancer due to environmental exposure further emphasizes the urgent need for effective interventions. Compounding this challenge, delayed diagnosis and limited access to targeted treatments highlight the importance of exploring novel, plant-based remedies with fewer side effects. The main aim of this study is to investigate the anti-cancer potential of Ginkgo semen, focusing on its molecular mechanisms and its arsenal of anti-inflammatory, anti-proliferative, and immunomodulatory actions. Using a network pharmacology and bioinformatics framework, this research seeks to identify key molecular targets of the 10 bioactive compounds found in Ginkgo semen and elucidate their therapeutic roles. Through comprehensive network construction, Gene Ontology (GO) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis, and molecular docking simulations, the study revealed a clear picture of Ginkgo semen’s anti-cancer potential. The analysis identified 12 key molecular targets involved in skin cancer pathways, including VEGFA, PTGS2, AKT1, TP53, and CASP3, which regulate critical processes like apoptosis, angiogenesis, and immune modulation. KEGG pathway enrichment analysis further revealed 68 enriched signaling pathways, including prominent pathways such as the "PI3K-Akt signaling pathway" and "p53 signaling pathway." In conclusion, this study highlights the extraordinary potential of Ginkgo semen as a multi-target therapeutic agent against skin cancer.

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Chapter 1

Introduction

1. Introduction

Skin cancer is a global health concern, ranking among the most frequently diagnosed cancers. It results from abnormal and uncontrolled growth of skin cells, often triggered by damage to the DNA caused by ultraviolet (UV) radiation exposure from natural sunlight and artificial sources like tanning devices (Hogue & Harvey, 2019). The disease is categorized into three primary types: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. (Masood, 2016)Basal and squamous cell carcinomas are often less aggressive but can cause significant morbidity if left untreated. In contrast, melanoma, though less common, accounts for the majority of skin cancer-related deaths due to its aggressive nature and potential for metastasis.

The incidence of skin cancer is escalating globally due to factors such as increased outdoor activities, ozone layer depletion, and the popularity of artificial tanning. According to recent epidemiological data, skin cancer cases are projected to rise further, posing a growing challenge to healthcare systems. This increasing burden highlights the importance of advancing preventive measures and exploring innovative treatment modalities.

Traditional treatments for skin cancer include surgical excision, cryotherapy, radiation therapy, chemotherapy, and, more recently, targeted immunotherapies. While these methods have proven effective in many cases, they are not without limitations. Surgical removal, although curative for localized lesions, can lead to scarring and functional impairments, especially in cosmetically sensitive areas. Chemotherapy and radiation therapy, while effective in advanced or metastatic cases, often cause significant side effects such as immunosuppression, fatigue, and damage to surrounding healthy tissues. Moreover, the emergence of resistance to chemotherapeutic agents further complicates treatment outcomes. These challenges have driven interest in exploring complementary and alternative therapies, particularly from natural sources.

Herbal medicine, a cornerstone of traditional healing practices across various cultures, has emerged as a promising field of research in oncology (Eruaga et al., 2024). Plants have been a source of numerous bioactive compounds, many of which have been developed into pharmaceutical drugs. For instance, paclitaxel (Taxol) from the Pacific yew tree and vinblastine from periwinkle are notable examples of plant-derived anticancer agents. In the context of skin cancer, several herbs and their active constituents have demonstrated potential through antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, and anti-angiogenic mechanisms. Reactive oxygen species (ROS) generated by UV radiation play a crucial role in initiating skin

carcinogenesis by causing DNA damage and promoting chronic inflammation. Many herbs, such as green tea (Camellia sinensis) and grape seed (Vitis vinifera), are rich in antioxidants like catechins and proanthocyanidins that neutralize ROS, protecting skin cells from oxidative stress

Chronic inflammation is a known driver of cancer progression. Compounds like curcumin from turmeric (Curcuma longa) and oleanolic acid from olive leaves (Olea europaea) suppress inflammatory mediators such as cytokines, COX-2, and NF-κB, thereby reducing the risk of tumor development.

Several phytochemicals directly inhibit cancer cell proliferation and induce programmed cell death (apoptosis). For example, epigallocatechin gallate (EGCG) in green tea has been shown to target multiple pathways, including the MAPK and PI3K/Akt signaling cascades, to inhibit tumor growth. Similarly, aloin and emodin in Aloe vera have been reported to induce apoptosis in melanoma cells.

Tumor growth and metastasis require the formation of new blood vessels (angiogenesis). Herbal compounds like resveratrol (from grapes) and genistein (from soy) have been found to inhibit angiogenesis by downregulating VEGF and other angiogenic factors.

Certain herbs, such as Withania somnifera (Ashwagandha) and Panax ginseng, boost the immune system, enhancing the body's ability to recognize and eliminate cancer cells.

The integration of herbal medicine with conventional treatments offers a synergistic approach to cancer management. For instance, combining chemotherapy with herbal extracts may enhance therapeutic efficacy while reducing toxicity. Herbal remedies also hold promise as preventive agents, particularly for individuals at high risk of skin cancer due to genetic predisposition or occupational exposure.

However, the use of herbal medicine in oncology is not without challenges. Issues such as variability in plant composition, lack of standardization, and potential interactions with conventional drugs must be addressed through rigorous scientific research. Clinical trials and mechanistic studies are needed to validate the efficacy and safety of herbal compounds and to establish evidence-based guidelines for their use in skin cancer treatment.

Ginkgolic acids, flavonoids, and terpenoids found in Ginkgo biloba seeds have shown anticancer potential by inducing apoptosis and inhibiting proliferation in cancer cells (Yu et al., 2024). Flavonoids such as quercetin and kaempferol have demonstrated the ability to modulate signaling pathways such as PI3K/Akt and MAPK, which are critical for tumor progression.

Ginkgo semen scavenges free radicals and reduces oxidative stress, a key contributor to UV-induced skin damage and carcinogenesis. Ginkgolic acids trigger apoptosis in cancer cells by activating caspases and modulating Bcl-2 family proteins. Anti-inflammatory Effects: Inhibition of pro-inflammatory cytokines such as IL-6 and TNF-α reduces chronic inflammation, which is closely associated with tumor progression. Anti-angiogenesis: Studies suggest that Ginkgo semen compounds inhibit vascular endothelial growth factor (VEGF), preventing tumor-associated angiogenesis.

With the rise of computational biology, bioinformatics has become an indispensable tool in exploring the therapeutic potential of herbal medicines. For Ginkgo semen, bioinformatics facilitates the identification of key targets, molecular docking simulations, and pathway analyses to validate its anticancer efficacy (Li et al., 2020).

1.1 Problem Statement

Skin cancer, particularly melanoma, basal cell carcinoma, and squamous cell carcinoma, is a growing global health issue with rising incidence rates. Despite advancements in detection, early diagnosis remains a challenge, resulting in delayed treatment and increased mortality. This research aims to improve early detection methods and diagnostic accuracy for skin cancer to enhance patient outcomes and reduce the disease burden.

1.2 Proposed Solution

This research investigates the therapeutic potential of Gingko semen treating skin cancer by disease using network pharmacology and molecular docking methods. Through elucidating the molecular pathways, this study aims to discover new targets for drugs and approaches to treat skin diseases. One promising therapy option is the use of Gingko semen, a natural herb with established anti-inflammatory, and immunomodulatory characteristics. Using thorough analysis and testing, this research endeavors to overcome the shortcomings of existing treatment approaches and provide a valuable contribution towards the development of more effective and focused medicines for skin cancer disease.

Chapter 2

Materials and Methods

2. Materials and methods

This shows methadology we used in our project.

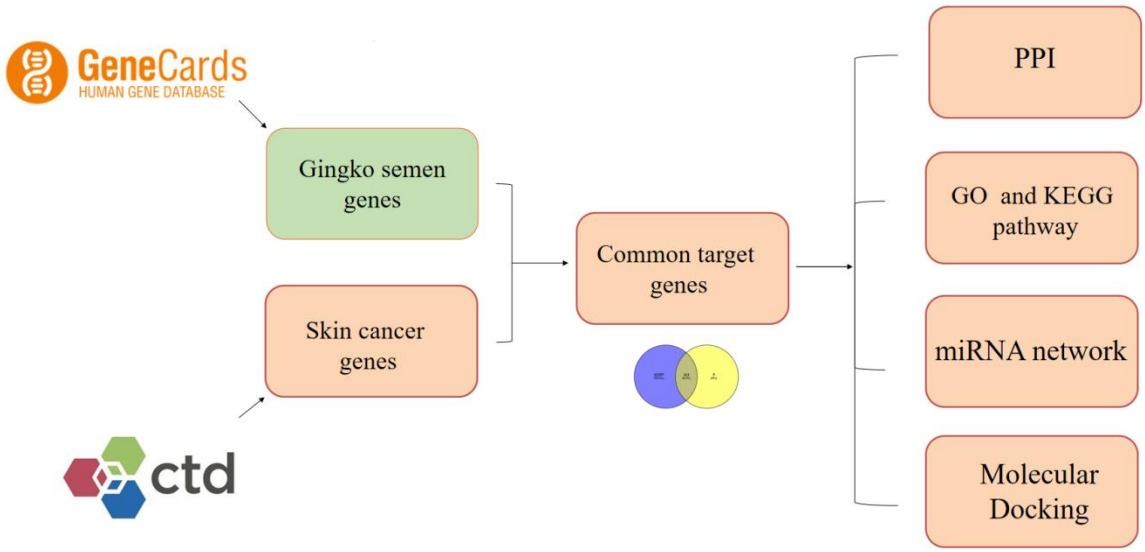

Figure 1 methods and materials

2.1 Identification of Gingko semen Targets

Gingko semen targets that could be found were identified using the GeneCard(Safran et al., 2010). The three-dimensional Gingko semen's compounds were obtained from the PubChem database(Kim et al., 2016).. Updates to the UniProt database(Consortium, 2015) were made to the assembled list of target names and IDs. (UniProt, n.d.).

2.2 Finding Skin cancer Disease Targets

Comparative Toxicogenomic Database(Davis et al., 2021) was used to get the genes of skin cancer. After utilizing the Venn Diagram tool to filter out duplicates, common targets were obtained.

2.2.1 Screening of Common Gene Targets

Venny 2.1.0 was used to find common Gingko semen and disease-related targets and a diagram was created to show the potential targets of Gingko semen in treating skin cancer disease.

2.3 Construction of Protein-Protein Interaction (PPI) Network

Database Search Tool for the Retrieval of Interacting Genes (STRING) was used to assemble information on protein-protein interactions (Szklarczyk et al., 2010). Limiting the species to "Homo sapiens" and setting the interaction confidence value to 0.7 allowed for the achievement of high confidence on the STRING platform. To build the PPI network, a network graph was created to examine the relationship between Gingko semen and targets of disease. The purpose of this action was to gather network node information.

2.4 Identification hub genes

Using Cytoscape, we examined the network's properties to find important target genes. The major targets were chosen using Plug-in Cytoscape 2.2 by calculating the mean values of betweenness, closeness, and degree (Kohl et al., 2011). The top 10 hub genes i-e TNF, IL6PTGS2, TP53, MAPK3, VEGFA, CAT, CASP3, AKT1 and JUN. were then determined using the MCC (Maximum clique centrality).

2.5 Gene Ontology and KEGG Pathway Enrichment Analysis

Using the ShinyGO platform(Ge et al., 2020), the selected important targets were examined for enrichment in KEGG metabolic pathways and GO functions. "Homo Sapiens" was selected as the species background for ShinyGo, translating to "human source". The biological process (BP), cellular component (CC), and molecular function (MF) were all annotated for GO using the Enrichr database.

2.6 miRNA formation

The top 10 hub genes were used to make miRNA through MIRNET platform (Chang et al., 2020). The GRAPHML file is downloaded and adjusted by Cytoscape 2.2.

2.7 Molecular Docking

Below diagram shows the process of docking.

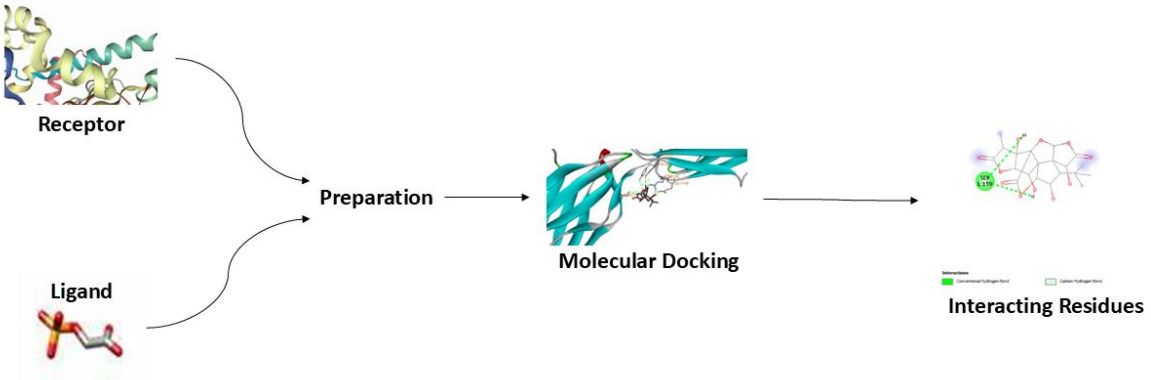

Figure 2 molecular docking method

2.7.1 Protein Preparation for Docking

The Protein Data Bank of the RCSB released the target proteins' 3D crystal structures in PDB format. The Autodock tools (1.5.6) were used to apportion charges and remove water from the protein molecule to successfully convert proteins to the PDBQT format(El-Hachem et al., 2017).

2.7.2 Ligand Preparation for Docking

Open Babel Tool was used to convert the 3D SDF structure of Gingko semen from the PubChem database into the PDB format. Autodock was used to create a PDBQT file of Gingko semen.

2.7.3 Grid Generation

Create a grid around the active site of the target protein where the ligand is expected to bind. This grid defines the search space for docking calculations. Save the grid file in text format. Create a new Txt file named Config and add information in it according to the grid file calculations value.

2.7.4 Docking and Visualization

Autodock was used to find the target protein's docking with the compound Gingko semen and its binding affinity. The binding pose and binding interactions were found using Discovery Studio (Pawar & Rohane, 2021).

Chapter 3

Results

3 Results

3.1 Gingko Semen Target Network

The genecard database yielded 118 Gingko semen targets. By importing an Excel file of Gingko semen targets in Cytoscape 3.10.2, the Gingko semen target network was made creating node connections.

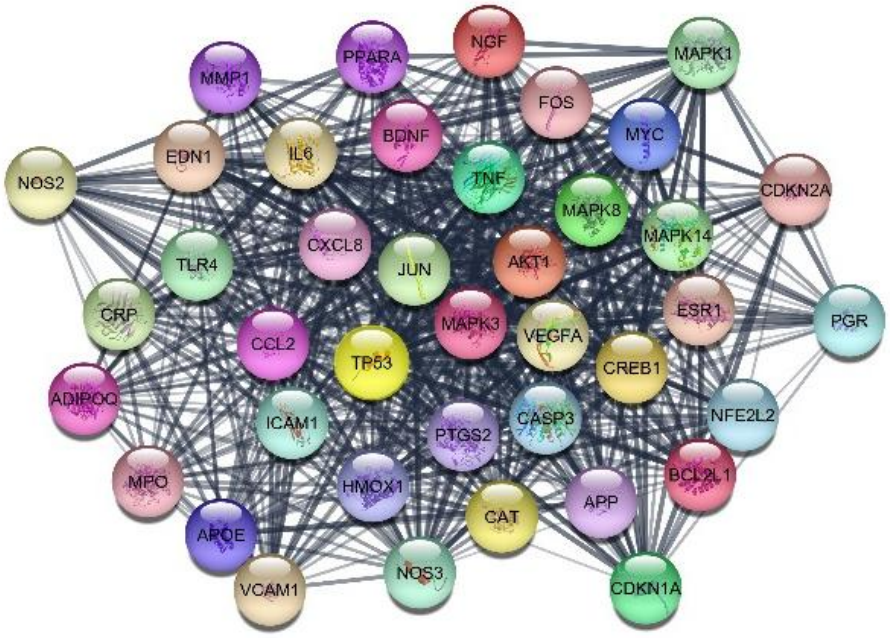

Figure 3 gingko semen genes PPI network

Following are the compounds of Gingko Semen, Bilobalide, Ginkgolic acid, Ginkgolide A, Ginkgolide B, Ginkgolide C, Isorhamnetin, Kaempferol, Myricetin, Quercetin, Shikimic acid. (Biernacka et al., 2023).

3.2 Skin Cancer Target Network

The targets of Skin cancer disease were retrieved from CTD. Then a network of disease-related targets was constructed using Cytoscape 3.10.2. by importing the network from the STRING Database.

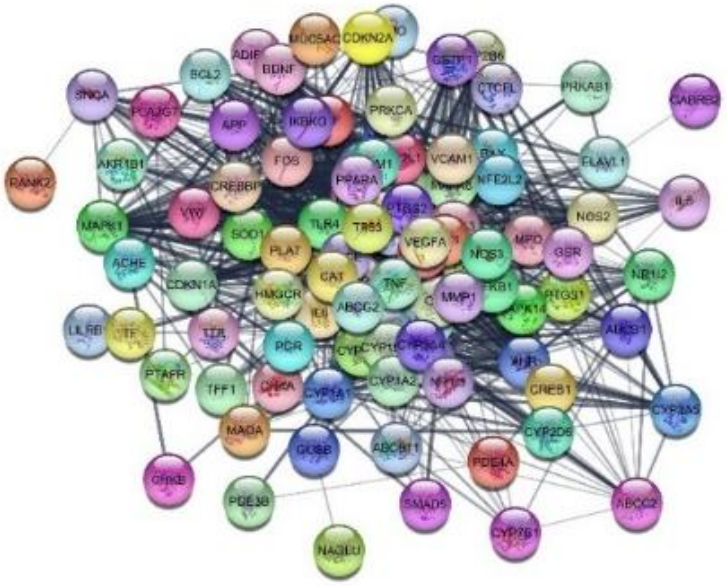

Figure 4 skin cancer genes PPI network

3.3 Common Target Genes

113 shared targets for Gingko Semen and Skin cancer disease were identified using the Venn Diagram tool based on the aforementioned data. Using these shared targets, the Protein-Protein Interactions Network was constructed by importing these common targets into the STRING database.

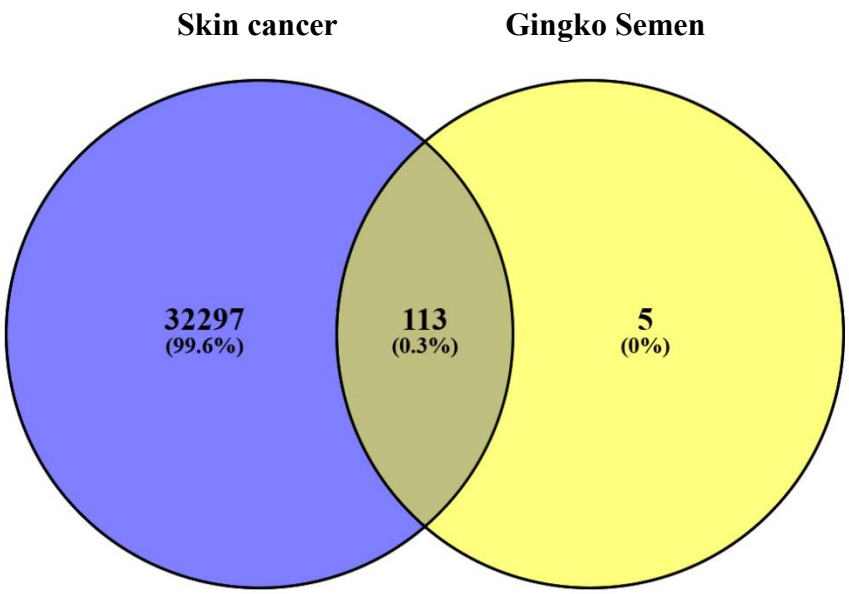

Figure 5 venn diagram showing common target genes of skin cancer related genes and gingko semen genes

3.4 Hub Gene Identification

Then 10 core targets were selected by using the MCC method (maximum Calique Centrality). TNF, IL6PTGS2, TP53, MAPK3, VEGFA, CAT, CASP3, AKT1 and JUN were the hub genes. Thus, these hub targets were critical to the molecular docking study and could be important in the treatment of skin cancer disease with Gingko semen.

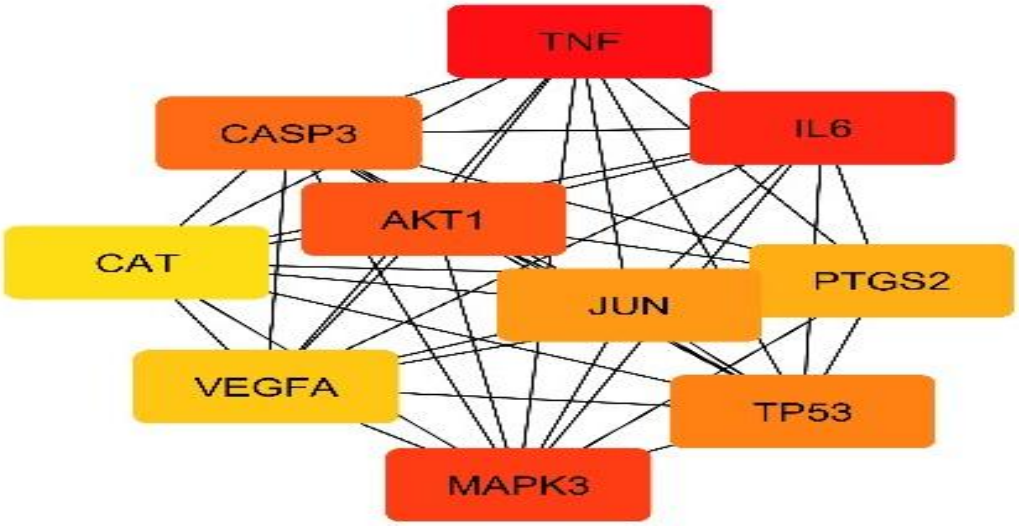

Figure 6 hub genes from our common target genes extracted by using cytoscape

3.5 MIRNA formation

We had made MIRNA from our selected hub genes. AKT1 has largest number (36) of miRNA.

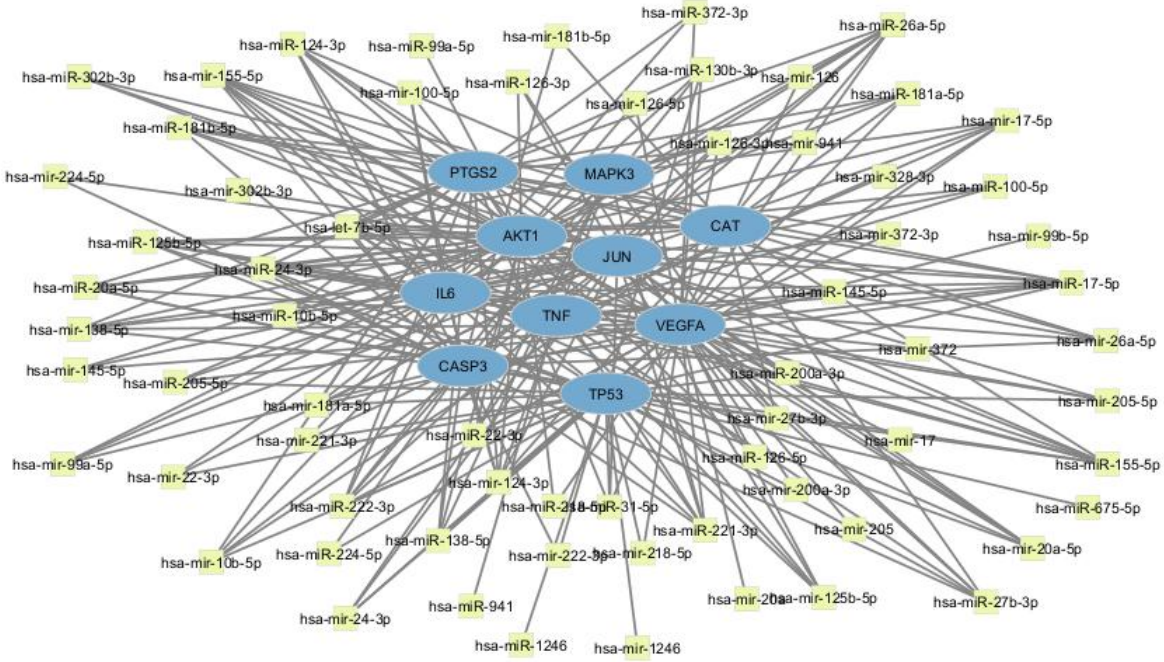

Figure 7 miRNA network

Table 1 no. of miRNAs in each hub gene and their names

miRNA

genes	No. of miRNA	miRNA		
AKT1	36	hsa-mir-22-3p hsa-mir-99a-5p hsa-mir-100-5p hsa-mir-10b-5p hsa-mir-125b-5p hsa-mir-138-5p hsa-mir-126-3p hsa-mir-155-5p hsa-mir-302b-3p hsa-let-7b-5p hsa-mir-126-5p hsa-mir-145-5p	hsa-mir-205-5p hsa-mir-20a-5p hsa-mir-124-3p hsa-miR-100-5p hsa-miR-10b-5p hsa-miR-124-3p hsa-miR-125b-5p hsa-miR-126-3p hsa-miR-126-5p hsa-miR-130b-3p hsa-miR-138-5p hsa-miR-155-5p	hsa-miR-17-5p hsa-miR-181a-5p hsa-miR-181b-5p hsa-miR-205-5p hsa-miR-20a-5p hsa-miR-218-5p hsa-miR-22-3p hsa-miR-24-3p hsa-miR-26a-5p hsa-miR-302b-3p hsa-miR-99a-5p hsa-mir-17-5p
JUN	6	hsa-miR-302b-3p hsa-miR-224-5p	hsa-mir-145-5p hsa-mir-99a-5p	hsa-mir-155-5p hsa-miR-138-5p
PTGS2	19	hsa-miR-302b-3p hsa-miR-20a-5p hsa-miR-138-5p hsa-mir-155-5p hsa-miR-181b-5p hsa-mir-205-5p hsa-mir-20a-5p	hsa-mir-124-3p hsa-miR-100-5p hsa-miR-10b-5p hsa-miR-124-3p hsa-miR-125b-5p hsa-miR-126-3p	hsa-miR-130b-3p hsa-miR-138-5p hsa-miR-155-5p hsa-miR-17-5p hsa-miR-181a-5p hsa-miR-126-5p
CASP3	21	hsa-miR-224-5p hsa-miR-20a-5p hsa-miR-138-5p hsa-mir-99a-5p hsa-mir-155-5p hsa-miR-181b-5p hsa-mir-205-5p hsa-mir-20a-5p	hsa-mir-124-3p hsa-miR-100-5p hsa-miR-10b-5p hsa-miR-124-3p hsa-miR-125b-5p hsa-miR-126-3p hsa-miR-126-5p	hsa-miR-130b-3p hsa-miR-138-5p hsa-miR-155-5p hsa-miR-17-5p hsa-miR-181a-5p hsa-miR-181b-5p
TP53	18	hsa-miR-20a-5p hsa-mir-155-5p hsa-mir-205-5p hsa-mir-20a-5p hsa-mir-124-3p hsa-miR-100-5p	hsa-miR-124-3p hsa-miR-155-5p hsa-miR-17-5p hsa-miR-181a-5p hsa-miR-181b-5p hsa-miR-205-5p	hsa-miR-20a-5p hsa-miR-218-5p hsa-miR-22-3p hsa-miR-24-3p hsa-miR-26a-5p hsa-miR-10b-5p
VEGFA	22	hsa-miR-20a-5p hsa-miR-138-5p hsa-mir-145-5p hsa-mir-155-5p hsa-miR-181b-5p hsa-mir-205-5p hsa-mir-20a-5p hsa-mir-124-3p	hsa-miR-100-5p hsa-miR-10b-5p hsa-miR-124-3p hsa-miR-125b-5p hsa-miR-155-5p hsa-miR-17-5p hsa-miR-181a-5p	hsa-miR-205-5p hsa-miR-20a-5p hsa-miR-218-5p hsa-miR-22-3p hsa-miR-24-3p hsa-miR-26a-5p hsa-miR-181b-5p
CAT	24	hsa-miR-20a-5p hsa-mir-155-5p	hsa-miR-125b-5p hsa-miR-126-3p	hsa-miR-181b-5p hsa-miR-205-5p

		hsa-miR-181b-5p hsa-mir-205-5p hsa-mir-20a-5p hsa-mir-124-3p hsa-miR-100-5p hsa-miR-10b-5p	hsa-miR-126-5p hsa-miR-130b-3p hsa-miR-138-5p hsa-miR-155-5p hsa-miR-17-5p hsa-miR-181a-5p	hsa-miR-20a-5p hsa-miR-218-5p hsa-miR-22-3p hsa-miR-24-3p hsa-miR-26a-5p hsa-miR-124-3p
IL6	13	hsa-miR-138-5p hsa-mir-99a-5p hsa-mir-155-5p hsa-mir-205-5p hsa-mir-20a-5p	hsa-mir-124-3p hsa-miR-100-5p hsa-miR-10b-5p hsa-miR-20a-5p	hsa-miR-22-3p hsa-miR-24-3p hsa-miR-26a-5p hsa-miR-218-5p
TNF	22	hsa-mir-155-5p hsa-mir-205-5p hsa-mir-20a-5p hsa-mir-124-3p hsa-miR-100-5p hsa-miR-10b-5p hsa-miR-124-3p hsa-miR-125b-5p	hsa-miR-126-3p hsa-miR-126-5p hsa-miR-130b-3p hsa-miR-138-5p hsa-miR-155-5p hsa-miR-17-5p hsa-miR-181a-5p	hsa-miR-205-5p hsa-miR-20a-5p hsa-miR-218-5p hsa-miR-22-3p hsa-miR-24-3p hsa-miR-26a-5p hsa-miR-181b-5p
MAPK3	22	hsa-miR-181b-5p hsa-mir-205-5p hsa-mir-20a-5p hsa-mir-124-3p hsa-miR-100-5p hsa-miR-10b-5p hsa-miR-124-3p hsa-miR-125b-5p	hsa-miR-126-3p hsa-miR-126-5p hsa-miR-130b-3p hsa-miR-138-5p hsa-miR-155-5p hsa-miR-17-5p hsa-miR-181a-5p	hsa-miR-205-5p hsa-miR-20a-5p hsa-miR-218-5p hsa-miR-22-3p hsa-miR-24-3p hsa-miR-26a-5p hsa-miR-181b-5p

3.6 GO Enrichment Analysis

The top ten shared targets were analyzed using Enrichr. The top 10 BP, CC, and MF categories were selected based on the p-value and number of counts. The top 3 biological processes were the regulation of apoptotic process, Positive regulation of smooth muscle cell proliferation, and Positive regulation of Protein Proliferation. These targets were enriched in many molecular functions including Cytokine activity, general transcription initiation factor binding, transcription regulatory region nucleic acid binding and DNA binding transcription factor binding. Enrichment in Cellular compartments includes Endoplasmic reticulum lumen, intracellular organelle lumen and nuclear outer membrane.

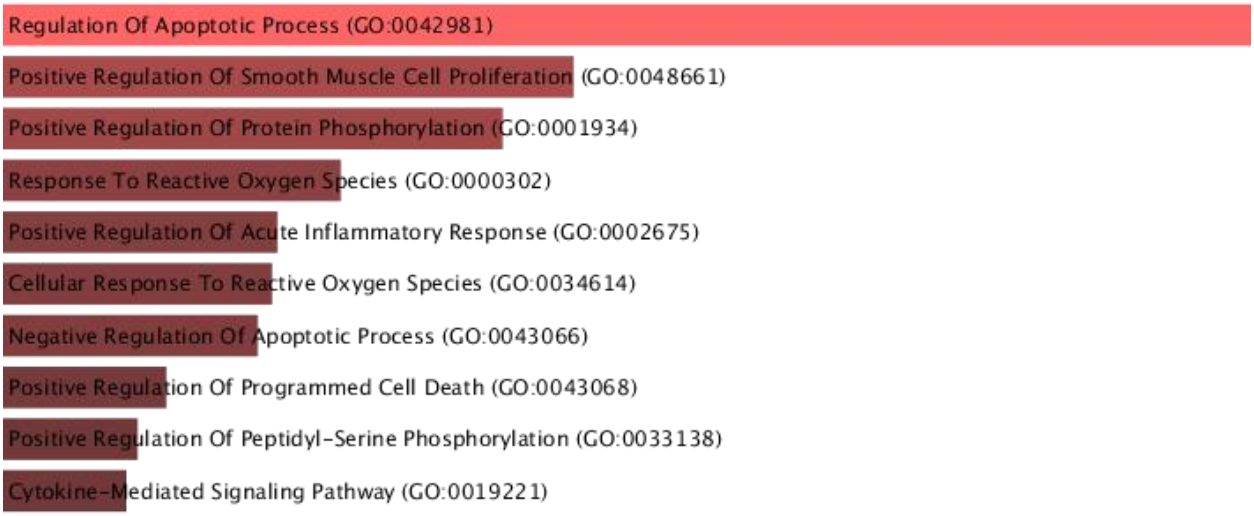

Figure 8 GO biological process: biological processes in which hub genes are involved

Table 2 GO biological process: no.of genes involved in specific biological processes alongwith their bames

Term	Biological process(direct)	Count	P Value	Genes
GO:0006805	xenobiotic metabolic process	15	2.18E-15	ABCB1, ABCC2, UGT1A1, GSTP1, NR1I2, AHR, ABCB11, CYP3A4, CYP3A5, CYP2B6, CYP2D6, CYP1A2, CYP1A1, CYP1B1, CYP2E1
GO:0032496	response to lipopolysaccharide	14	3.70E-13	EDN1, VCAM1, UGT1A1, NOS2, NOS3, FOS, PTGS2, SOD2, MPO, NAGLU, CASP3, CYP1A1, TLR4, SNCA
GO:0010628	positive regulation of gene expression	21	1.67E-12	CRP, APP, CXCL8, TFRC, CDKN2A, NOS3, NR1I2, NGF, MAPK14, TNF, PRKAB1, VEGFA, IL6, MAPK8, SP1, MYC, AKT1, PGR, TP53, TLR4, NFE2L2
GO:0043066	negative regulation of apoptotic process	20	1.46E-11	CDKN1A, TFRC, GSTP1, AKR1B1, SOD2, MPO, TNF, SMAD5, NFKB1, VEGFA, IL6, MAPK8, CREB1, MYC, CAT, BCL2, AKT1, TP53, BCL2L1, SNCA
GO:0009410	response to xenobiotic stimulus	15	5.95E-11	CDKN1A, ABCB1, AHR, FOS, PTGS2, SOD2, TNF, SOD1, CREB1, MYC, CASP3, CAT, BCL2, TP53, SNCA
GO:0071356	cellular response to tumor necrosis factor	12	1.29E-10	EDN1, VCAM1, CXCL8, CYP1B1, MAPK1, CCL2, AKT1, FOS, MAPK14, NFKB1, MAPK3, NFE2L2
GO:0001666	response to hypoxia	13	1.40E-10	CREBBP, VCAM1, NOS2, TFRC, ADIPOQ, PLAT, SOD2, TNF, VEGFA, CASP3, CAT, CYP1A1, PPARA

GO:0033138	positive regulation of peptidyl-serine phosphorylation	10	1.48E-10	APP, IL6, TFRC, BDNF, BCL2, AKT1, NGF, PTGS2, TNF, SNCA
GO:0008202	steroid metabolic process	9	1.87E-10	CYP2B6, UGT1A1, CYP2D6, NR1I2, CYP1A1, CYP1B1, CYP2E1, CYP3A4, CYP3A5
GO:0048661	positive regulation of smooth muscle cell proliferation	9	3.57E-10	PDGFRB, IL6, EDN1, PTAFR, HMOX1, AKT1, PTGS2, TNF, TLR4
GO:0071276	cellular response to cadmium ion	8	5.12E-10	JUN, MAPK8, CYP1A2, HMOX1, MAPK1, AKT1, FOS, MAPK3
GO:0045893	positive regulation of DNA-templated transcription	21	6.81E-10	CREBBP, JUN, CDKN2A, NR1I2, AHR, FOS, ESR1, TNF, SMAD5, NFKB1, TF, IL6, CREB1, IL5, SP1, MYC, AKT1, APOE, PPARA, TP53, NFE2L2
GO:0006979	response to oxidative stress	11	8.84E-10	APP, MAPK8, HMOX1, AKT1, APOE, ABCB11, PTGS2, MPO, TP53, NFE2L2, PTGS1
GO:0045944	positive regulation of transcription by RNA polymerase II	27	8.95E-10	APP, NR1I3, NR1I2, AHR, TNF, MYC, AKT1, IKBKG, MAPK3, JUN, CREBBP, EDN1, CDKN2A, FOS, MAPK14, ESR1, SMAD5, NFKB1, VEGFA, IL6, CREB1, SP1, PGR, PPARA, TP53, TLR4, NFE2L2
GO:0045429	positive regulation of nitric oxide biosynthetic process	8	2.81E-09	EDN1, AKT1, APOE, SOD2, PTGS2, ESR1, TNF, TLR4
GO:0006954	inflammatory response	16	5.13E-09	CRP, VCAM1, CXCL8, NOS2, PLA2G2A, PTAFR, FOS, TNF, NFKB1, IL6, IL5, CCL2, AKT1, IKBKG, TLR4, NFE2L2
GO:0010629	negative regulation of gene expression	14	8.33E-09	APP, CDKN1A, EDN1, CXCL8, ABCC2, NOS2, ESR1, TNF, SMAD5, NFKB1, VEGFA, AKT1, PGR, APOE
GO:0008210	estrogen metabolic process	7	1.42E-08	UGT1A1, CYP2D6, CYP1A2, CYP1A1, CYP1B1, CYP3A4, CYP3A5
GO:0031663	lipopolysaccharide-mediated signaling pathway	7	2.08E-08	NOS3, PTAFR, MAPK1, AKT1, MAPK14, TLR4, MAPK3
GO:0071466	cellular response to xenobiotic stimulus	8	6.41E-08	EDN1, NOS2, TFRC, MYC, ADIPOQ, PDE4A, TP53, NFE2L2
GO:0045471	response to ethanol	9	9.57E-08	G6PD, VCAM1, ADIPOQ, CAT, FOS, ABCB11, PPARA, TNF, SOD1
GO:0043524	negative regulation of neuron apoptotic process	10	9.63E-08	BDNF, BCL2, BAX, CCL2, APOE, NGF, SOD2, BCL2L1, SOD1, SNCA
GO:0001525	angiogenesis	12	1.02E-07	PDGFRB, PANK2, CXCL8, NOS3, PDE3B, CYP1B1, HMOX1, CCL2, PRKCA, MAPK14, PTGS2, VEGFA
GO:0042178	xenobiotic catabolic	6	1.10E-07	CYP2B6, CYP2D6, CYP1A2, NR1I2,

	process			CYP3A4, CYP3A5
GO:0014823	response to activity	7	2.30E-07	IL6, EDN1, ADIPOQ, CAT, FOS, SOD2, TNF
GO:0070374	positive regulation of ERK1 and ERK2 cascade	11	3.21E-07	PDGFRB, APP, PLA2G2A, CCL2, PRKCA, APOE, TNF, TLR4, ICAM1, MAPK3, VEGFA
GO:0007165	signal transduction	23	3.39E-07	PDGFRB, GABRB2, CREBBP, CXCL8, NR1I3, PDE3B, NR1I2, ADIPOQ, MAPK14, ESR1, SMAD5, PRKAB1, NFKB1, MAPK8, CREB1, TTR, SP1, CCL2, AKT1, PDE4A, MAPK1, TFF1, PGR
GO:0042572	retinol metabolic process	7	3.68E-07	CYP2D6, CYP1A2, CYP1A1, AKR1B1, CYP1B1, CYP3A4, CYP3A5
GO:0071222	cellular response to lipopolysaccharide	10	7.08E-07	IL6, MAPK8, CXCL8, NOS2, GSTP1, CCL2, MAPK14, TNF, TLR4, NFKB1
GO:0051881	regulation of mitochondrial membrane potential	6	7.42E-07	PANK2, BCL2, BAX, SOD2, BCL2L1, SOD1
GO:0071456	cellular response to hypoxia	9	7.88E-07	EDN1, MYC, BCL2, HMOX1, FOS, PTGS2, TP53, NFE2L2, VEGFA
GO:2000379	positive regulation of reactive oxygen species metabolic process	6	8.67E-07	PDGFRB, CDKN1A, CYP1B1, MAPK14, TP53, NFE2L2
GO:0043065	positive regulation of apoptotic process	12	9.66E-07	IL6, JUN, MAPK8, CDKN2A, BCL2, BAX, CYP1B1, PTGS2, TNF, TP53, SOD1, SNCA
GO:0042542	response to hydrogen peroxide	6	1.34E-06	CASP3, CAT, BCL2, HMOX1, SOD2, SOD1
GO:0006915	apoptotic process	15	2.47E-06	APP, CDKN2A, AHR, MAPK14, NFKB1, SOD1, VEGFA, CASP3, BCL2, BAX, MAPK1, IKBKG, TP53, BCL2L1, MAPK3
GO:0035094	response to nicotine	6	2.56E-06	EDN1, VCAM1, CASP3, BCL2, HMOX1, MAPK1
GO:0030316	osteoclast differentiation	6	3.64E-06	TF, CREB1, TFRC, FOS, MAPK14, TNF
GO:0019373	epoxygenase P450 pathway	5	3.91E-06	CYP2B6, CYP1A2, CYP1A1, CYP1B1, CYP2E1
GO:0042759	long-chain fatty acid biosynthetic process	5	3.91E-06	CYP2D6, CYP1A2, CYP1A1, CYP2E1, CYP3A4
GO:0016098	monoterpenoid metabolic process	4	4.76E-06	CYP2D6, CYP1A2, CYP2E1, CYP3A4
GO:0002933	lipid hydroxylation	4	4.76E-06	CYP1A1, CYP2E1, CYP3A4, CYP3A5
GO:0033554	cellular response to stress	5	4.76E-06	MAPK8, MAPK1, MAPK14, NFKB1, MAPK3
GO:0043536	positive regulation of blood vessel endothelial cell	6	6.18E-06	SP1, NOS3, AKT1, PRKCA, NFE2L2, VEGFA

	migration			
GO:0051384	response to glucocorticoid	6	6.18E-06	IL6, CASP3, ADIPOQ, BCL2, PTGS2, TNF
GO:0008203	cholesterol metabolic process	7	6.26E-06	APP, CYP2D6, CYP1A2, CAT, APOE, CYP3A4, CYP7B1
GO:0051403	stress-activated MAPK cascade	5	6.86E-06	MAPK8, MAPK1, MAPK14, TLR4, MAPK3
GO:0006809	nitric oxide biosynthetic process	5	6.86E-06	NOS2, NOS3, CYP1B1, AKT1, TLR4
GO:0070371	ERK1 and ERK2 cascade	6	7.51E-06	EDN1, TF, MYC, MAPK1, TLR4, MAPK3
GO:0001836	release of cytochrome c from mitochondria	5	8.14E-06	BCL2, BAX, SOD2, TP53, BCL2L1
GO:0034614	cellular response to reactive oxygen species	6	8.26E-06	JUN, MAPK8, MAPK1, AKT1, FOS, MAPK3
GO:0010332	response to gamma radiation	5	1.12E-05	MYC, BCL2, BAX, SOD2, TP53
GO:0045776	negative regulation of blood pressure	5	1.50E-05	NOS2, NOS3, ADIPOQ, PTAFR, PPARA
GO:0007584	response to nutrient	6	1.53E-05	VCAM1, UGT1A1, TFRC, ADIPOQ, CYP1B1, PPARA
GO:0070989	oxidative demethylation	4	1.61E-05	CYP2D6, CYP1A2, CYP3A4, CYP3A5
GO:0008285	negative regulation of cell population proliferation	12	1.66E-05	APP, IL6, CDKN1A, CXCL8, CDKN2A, NOS3, CYP1B1, TFF1, NGF, SOD2, PTGS2, TP53
GO:0034599	cellular response to oxidative stress	7	1.75E-05	G6PD, MAPK8, NAGLU, GSR, SOD2, NFE2L2, SNCA
GO:0050665	hydrogen peroxide biosynthetic process	4	2.21E-05	CYP1A2, CYP1A1, SOD2, SOD1
GO:0045766	positive regulation of angiogenesis	8	2.35E-05	CXCL8, SP1, NOS3, CYP1B1, HMOX1, PRKCA, NFE2L2, VEGFA
GO:0048147	negative regulation of fibroblast proliferation	5	4.05E-05	MYC, GSTP1, BAX, SOD2, TP53
GO:0001541	ovarian follicle development	5	5.00E-05	BCL2, BAX, BCL2L1, SOD1, VEGFA
GO:1900182	positive regulation of protein localization to nucleus	5	5.54E-05	EDN1, CREBBP, TFRC, CDKN2A, AKT1
GO:0006919	activation of cysteine-type endopeptidase activity involved in apoptotic process	6	5.83E-05	CDKN2A, BCL2, BAX, TNF, BCL2L1, SNCA
GO:0051402	neuron apoptotic process	6	6.97E-05	APP, CASP3, BCL2, TP53, BCL2L1, SNCA
GO:0019430	removal of superoxide radicals	4	7.36E-05	NOS3, SOD2, MPO, SOD1
GO:0006749	glutathione metabolic process	5	7.39E-05	G6PD, GSTP1, GSR, SOD2, SOD1

GO:0032722	positive regulation of chemokine production	5	7.39E-05	APP, IL6, HMOX1, TNF, TLR4
GO:0031281	positive regulation of cyclase activity	3	8.07E-05	MAPK8, MAPK14, MAPK3
GO:0032355	response to estradiol	6	8.75E-05	CASP3, CAT, CYP1B1, PTGS2, ESR1, CYP19A1
GO:1904646	cellular response to amyloid-beta	5	8.85E-05	APP, VCAM1, TNF, TLR4, ICAM1
GO:0042448	progesterone metabolic process	4	8.90E-05	CYP2D6, CYP1A2, CYP1A1, CYP1B1
GO:2000573	positive regulation of DNA biosynthetic process	4	8.90E-05	PDGFRB, CYP1B1, TNF, VEGFA
GO:0055093	response to hyperoxia	4	8.90E-05	CDKN1A, CAT, CYP1A1, SOD2
GO:0030890	positive regulation of B cell proliferation	5	9.65E-05	CDKN1A, IL5, TFRC, BCL2, TLR4
GO:0034374	low-density lipoprotein particle remodeling	4	1.06E-04	PLA2G2A, APOE, MPO, PLA2G7
GO:0008637	apoptotic mitochondrial changes	4	1.06E-04	CDKN2A, BAX, AKT1, BCL2L1
GO:0032930	positive regulation of superoxide anion generation	4	1.06E-04	CRP, GSTP1, ELAVL1, SOD1
GO:0042446	hormone biosynthetic process	4	1.06E-04	CYP2D6, CYP1A2, CYP1A1, CYP1B1
GO:0016310	phosphorylation	13	1.14E-04	PDGFRB, CDKN1A, PANK2, CHKB, CHKA, PRKCA, MAPK14, PRKAB1, MAPK8, AKT1, MAPK1, IKBKG, MAPK3
GO:0035994	response to muscle stretch	4	1.26E-04	EDN1, FOS, MAPK14, NFKB1
GO:0046889	positive regulation of lipid biosynthetic process	4	1.26E-04	CREB1, AKT1, APOE, PPARA
GO:0008630	intrinsic apoptotic signaling pathway in response to DNA damage	5	1.45E-04	BCL2, BAX, SOD2, TNF, BCL2L1
GO:0006801	superoxide metabolic process	4	1.48E-04	NOS2, NAGLU, SOD2, SOD1
GO:0031334	positive regulation of protein-containing complex assembly	5	1.56E-04	TFRC, MMP1, BAX, TNF, VEGFA
GO:0009822	alkaloid catabolic process	3	1.61E-04	CYP2D6, CYP3A4, CYP3A5
GO:1904019	epithelial cell apoptotic process	4	1.72E-04	CASP3, BCL2, BAX, HMOX1
GO:0014911	positive regulation of smooth muscle cell	4	1.72E-04	PDGFRB, BCL2, CYP1B1, TLR4

	migration			
GO:0043123	positive regulation of canonical NF-kappaB signal transduction	8	1.89E-04	EDN1, TFRC, ADIPOQ, HMOX1, IKBKG, TNF, TLR4, VEGFA
GO:0032755	positive regulation of interleukin-6 production	6	2.05E-04	APP, IL6, NOS2, PTAFR, TNF, TLR4
GO:0090398	cellular senescence	5	2.24E-04	CDKN1A, MAPK8, CDKN2A, MAPK14, TP53
GO:0045599	negative regulation of fat cell differentiation	5	2.39E-04	IL6, ADIPOQ, SOD2, TNF, VEGFA
GO:1902895	positive regulation of miRNA transcription	5	2.73E-04	JUN, MYC, FOS, TNF, TP53
GO:0050729	positive regulation of inflammatory response	6	2.79E-04	APP, PLA2G2A, TNF, PLA2G7, TLR4, SNCA
GO:0032094	response to food	4	2.92E-04	G6PD, CYP1A1, AKT1, MPO
GO:0032757	positive regulation of interleukin-8 production	5	3.50E-04	IL6, NOS2, ADIPOQ, TNF, TLR4
GO:0035902	response to immobilization stress	4	3.69E-04	CYP1A1, TFF1, FOS, SOD2
GO:0006006	glucose metabolic process	5	3.71E-04	G6PD, ADIPOQ, AKT1, MAPK14, TNF
GO:0046222	aflatoxin metabolic process	3	3.99E-04	CYP1A2, CYP3A4, CYP3A5
GO:1990962	xenobiotic transport across blood-brain barrier	3	3.99E-04	ABCB1, ABCC2, ABCG2
GO:1902894	negative regulation of miRNA transcription	4	4.11E-04	PPARA, ESR1, TNF, VEGFA
GO:0006879	intracellular iron ion homeostasis	5	4.17E-04	TF, TFRC, MYC, HMOX1, SOD1
GO:0001774	microglial cell activation	4	4.57E-04	APP, NAGLU, TNF, SNCA
GO:1902042	negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	4	5.06E-04	NOS3, HMOX1, BCL2L1, ICAM1
GO:0098869	cellular oxidant detoxification	5	6.08E-04	GSTP1, GSR, APOE, PTGS2, PTGS1
GO:2001234	negative regulation of apoptotic signaling pathway	4	6.14E-04	BDNF, BCL2, BAX, TNF
GO:0035924	cellular response to vascular endothelial growth factor stimulus	4	6.72E-04	VCAM1, AKT1, MAPK14, VEGFA
GO:0008217	regulation of blood pressure	5	7.07E-04	NOS3, SOD2, PTGS2, SOD1, PTGS1
GO:0071260	cellular response to	5	7.07E-04	MAPK8, PTGS2, TLR4, NFKB1,

	mechanical stimulus			MAPK3
GO:0030522	intracellular receptor signaling pathway	4	7.35E-04	NR1I3, NR1I2, AHR, PPARA
GO:0048873	homeostasis of number of cells within a tissue	4	7.35E-04	NOS3, BCL2, BAX, VEGFA
GO:0001934	positive regulation of protein phosphorylation	7	7.42E-04	APP, CDKN1A, TFRC, ADIPOQ, AKT1, TNF, VEGFA
GO:0009636	response to toxic substance	5	7.42E-04	CDKN1A, BCL2, BAX, FOS, AHR
GO:0048511	rhythmic process	5	7.79E-04	CREBBP, MAPK8, SP1, AHR, TP53
GO:0006468	protein phosphorylation	9	7.95E-04	APP, MAPK8, CREB1, MAPK1, CCL2, AKT1, PRKCA, PRKAB1, MAPK3
GO:0045727	positive regulation of translation	5	8.56E-04	IL6, MYC, PTAFR, CYP1B1, ELAVL1
GO:0010467	gene expression	6	8.66E-04	ADIPOQ, RHO, AKT1, APOE, TLR4, SOD1
GO:0071407	cellular response to organic cyclic compound	4	8.70E-04	NAGLU, CYP1A1, CYP1B1, SMAD5
GO:0046326	positive regulation of glucose import	4	9.43E-04	ADIPOQ, AKT1, MAPK14, NFE2L2
GO:0097193	intrinsic apoptotic signaling pathway	4	9.43E-04	CDKN1A, CASP3, BAX, TP53
GO:2001240	negative regulation of extrinsic apoptotic signaling pathway in absence of ligand	4	9.43E-04	BCL2, AKT1, TNF, BCL2L1
GO:0009651	response to salt stress	3	9.48E-04	BAX, TNF, TP53
GO:0010042	response to manganese ion	3	9.48E-04	TFRC, SOD2, PTGS2
GO:0050731	positive regulation of peptidyl-tyrosine phosphorylation	5	9.81E-04	IL6, IL5, ADIPOQ, TP53, VEGFA
GO:0050728	negative regulation of inflammatory response	6	0.001044	ADIPOQ, AHR, APOE, PPARA, NFKB1, SOD1
GO:0006974	DNA damage response	8	0.001141	CDKN1A, MYC, CASP3, BCL2, MAPK1, IKBKG, TP53, MAPK3
GO:0032872	regulation of stress-activated MAPK cascade	3	0.001181	GSTP1, MAPK1, MAPK3
GO:0010888	negative regulation of lipid storage	3	0.001181	CRP, IL6, TNF
GO:0070633	transepithelial transport	3	0.001181	ABCB1, ABCC2, ABCG2
GO:0051248	negative regulation of protein metabolic process	3	0.001181	EDN1, APOE, NFKB1
GO:0006953	acute-phase response	4	0.001186	CRP, IL6, UGT1A1, TFRC

GO:0008625	extrinsic apoptotic signaling pathway via death domain receptors	4	0.001186	BCL2, BAX, NGF, TNF
GO:0031647	regulation of protein stability	5	0.001216	TF, CDKN2A, CASP3, BCL2, MAPK1
GO:0043154	negative regulation of cysteine-type endopeptidase activity involved in apoptotic process	4	0.001367	AKT1, TNF, SNCA, VEGFA
GO:0071479	cellular response to ionizing radiation	4	0.001367	CDKN1A, MAPK14, TNF, TP53
GO:0019933	cAMP-mediated signaling	4	0.001367	CREB1, PDE3B, PDE4A, AHR
GO:0046427	positive regulation of receptor signaling pathway via JAK-STAT	4	0.001464	IL6, IL5, CYP1B1, TNF
GO:0051091	positive regulation of DNA-binding transcription factor activity	5	0.001489	IL6, EDN1, AKT1, ESR1, TNF
GO:0000122	negative regulation of transcription by RNA polymerase II	14	0.0015	CREBBP, JUN, EDN1, NR1I3, NR1I2, ESR1, TNF, SMAD5, NFKB1, VEGFA, MYC, PPARA, TP53, SNCA
GO:0006631	fatty acid metabolic process	5	0.001549	CYP1A1, CYP2E1, ABCB11, PPARA, SNCA
GO:0045454	cell redox homeostasis	4	0.001566	NOS2, NOS3, GSR, NFE2L2
GO:0042311	vasodilation	4	0.001671	NOS3, APOE, TNF, VEGFA
GO:0097267	omega-hydroxylase P450 pathway	3	0.001721	CYP1A2, CYP1A1, CYP1B1
GO:0042982	amyloid precursor protein metabolic process	3	0.001721	ACHE, NAGLU, APOE
GO:0048538	thymus development	4	0.002014	BCL2, MAPK1, SOD1, MAPK3
GO:0042149	cellular response to glucose starvation	4	0.002014	CHKA, BCL2, TP53, NFE2L2
GO:0046685	response to arsenic-containing substance	3	0.002027	CDKN1A, CYP1A1, CYP1B1
GO:0071346	cellular response to type II interferon	5	0.002083	EDN1, NOS2, CCL2, TNF, TLR4
GO:0034198	cellular response to amino acid starvation	4	0.002265	CDKN1A, MAPK8, MAPK1, MAPK3
GO:0010745	negative regulation of macrophage derived foam cell differentiation	3	0.002357	CRP, ADIPOQ, PPARA
GO:0031623	receptor internalization	4	0.002535	ACHE, CXCL8, TFRC, SNCA

GO:0007249	canonical NF-kappaB signal transduction	4	0.002677	CREBBP, AKT1, IKBKG, NFKB1
GO:0010039	response to iron ion	3	0.00271	TFRC, BCL2, TFF1
GO:0030278	regulation of ossification	3	0.00271	MAPK1, MAPK14, MAPK3
GO:0000302	response to reactive oxygen species	3	0.00271	GSTP1, CAT, APOE
GO:0071320	cellular response to cAMP	4	0.002824	ADIPOQ, PTAFR, CYP1B1, AHR
GO:0032091	negative regulation of protein binding	4	0.002824	CDKN1A, MAPK8, BAX, AKT1
GO:0018107	peptidyl-threonine phosphorylation	4	0.002975	MAPK8, MAPK1, AKT1, PRKCA
GO:0043406	positive regulation of MAP kinase activity	4	0.002975	PDGFRB, EDN1, TNF, TLR4
GO:0051146	striated muscle cell differentiation	3	0.003087	CASP3, AKT1, MAPK14
GO:0090399	replicative senescence	3	0.003087	CDKN1A, CDKN2A, TP53
GO:0006469	negative regulation of protein kinase activity	4	0.003132	CDKN2A, GSTP1, AKT1, SNCA
GO:0034644	cellular response to UV	4	0.003294	CREBBP, MYC, BAX, TP53
GO:0006935	chemotaxis	5	0.003727	CXCL8, PTAFR, MAPK1, CCL2, MAPK14
GO:0006357	regulation of transcription by RNA polymerase II	18	0.003848	JUN, PTAFR, AHR, FOS, MAPK14, SOD2, ESR1, SMAD5, NFKB1, VEGFA, CREB1, SP1, MYC, HMOX1, MAPK1, PGR, TP53, NFE2L2
GO:0048143	astrocyte activation	3	0.003909	APP, NAGLU, TNF
GO:0010165	response to X-ray	3	0.003909	CDKN1A, CASP3, TP53
GO:0042326	negative regulation of phosphorylation	3	0.003909	CDKN1A, CDKN2A, PGR
GO:0035234	ectopic germ cell programmed cell death	3	0.003909	BAX, BCL2L1, SOD1
GO:0071548	response to dexamethasone	3	0.003909	EDN1, PTAFR, CYP1B1
GO:0008631	intrinsic apoptotic signaling pathway in response to oxidative stress	3	0.003909	BCL2, CYP1B1, SOD2
GO:0030335	positive regulation of cell migration	7	0.003955	PDGFRB, EDN1, CCL2, AKT1, PRKCA, SOD2, VEGFA
GO:0007254	JNK cascade	4	0.003991	MAPK8, TNF, TLR4, NFKB1
GO:1902176	negative regulation of oxidative stress-induced intrinsic apoptotic signaling pathway	3	0.004354	AKT1, SOD2, NFE2L2
GO:0006959	humoral immune response	4	0.00437	IL6, BCL2, CCL2, TNF

GO:0043525	positive regulation of neuron apoptotic process	4	0.004771	CASP3, BAX, TNF, TP53
GO:0032731	positive regulation of interleukin-1 beta production	4	0.004771	APP, IL6, TNF, TLR4
GO:0001649	osteoblast differentiation	5	0.004809	NR1I3, CAT, AKT1, MAPK14, SMAD5
GO:0001516	prostaglandin biosynthetic process	3	0.004821	EDN1, PTGS2, PTGS1
GO:0043401	steroid hormone receptor signaling pathway	3	0.004821	MAPK1, PPARA, ESR1
GO:0045780	positive regulation of bone resorption	3	0.004821	TF, TFRC, PRKCA
GO:0021675	nerve development	3	0.004821	NAGLU, BDNF, NGF
GO:0010595	positive regulation of endothelial cell migration	4	0.004979	EDN1, AKT1, PRKCA, VEGFA

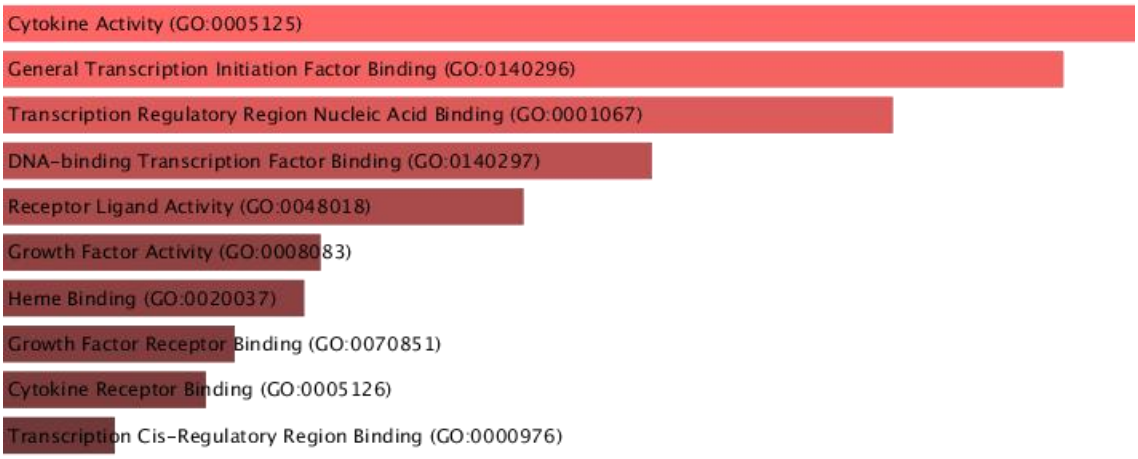

Figure 9 GO molecular function: role of hub genes in various processes at molecular level

Table 3 GO molecular function: no. of genes invovled in various processes at molecular level along with their names

Term	Molecular-component(direct)	Count	P Value	Genes
GO:0020037	heme binding	17	1.37E-16	NOS2, NOS3, CYP3A4, CYP7B1, PTGS2, MPO, CYP3A5, CYP19A1, PTGS1, CYP2B6, CYP2D6, CYP1A2, CAT, CYP1A1, CYP1B1, HMOX1, CYP2E1
GO:0019899	enzyme binding	21	5.92E-15	PDGFRB, APP, JUN, UGT1A1, PRKCA, CYP3A4, PTGS2, MAPK14, SOD2, ESR1, MAPK8, CREB1, CYP1A2, CAT,

				CYP1A1, AKT1, HMOX1, PGR, CYP2E1, APOE, TP53
GO:0070330	aromatase activity	9	3.28E-12	CYP2B6, CYP2D6, CYP1A2, CYP1A1, CYP1B1, CYP2E1, CYP3A4, CYP19A1, CYP3A5
GO:0042802	identical protein binding	34	3.11E-11	CRP, APP, TFRC, TNF, TTR, MYC, AKT1, HMOX1, MAPK1, IKBKG, APOE, MAPK3, SNCA, JUN, G6PD, VWF, ADIPOQ, FOS, SOD2, ESR1, NFKB1, SOD1, VEGFA, CREB1, TMX2, SP1, CAT, BCL2, BAX, PGR, TP53, TLR4, ABCG2, BCL2L1
GO:0016712	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen	8	1.72E-10	CYP2B6, CYP2D6, CYP1A2, CYP1B1, CYP2E1, CYP3A4, CYP19A1, CYP3A5
GO:0004497	monooxygenase activity	9	8.16E-10	CYP2B6, CYP2D6, CYP1A2, CYP1A1, CYP1B1, CYP2E1, CYP3A4, CYP19A1, CYP3A5
GO:0042803	protein homodimerization activity	21	1.98E-09	ACHE, G6PD, UGT1A1, NOS2, TFRC, CHKA, ADIPOQ, AHR, PTGS2, ELAVL1, VEGFA, SP1, CAT, BCL2, BAX, AKT1, HMOX1, IKBKG, APOE, ABCG2, BCL2L1
GO:0101020	estrogen 16-alpha-hydroxylase activity	5	5.06E-08	CYP1A2, CYP1A1, CYP1B1, CYP3A4, CYP3A5
GO:0005506	iron ion binding	10	5.54E-08	CYP2B6, CYP2D6, CYP1A2, CYP1A1, CYP1B1, CYP2E1, CYP3A4, CYP7B1, CYP19A1, CYP3A5
GO:0016491	oxidoreductase activity	9	2.87E-07	MAOA, CYP2D6, CYP1A2, CYP1A1, CYP2E1, CYP3A4, COX5A, CYP3A5, SNCA
GO:0061629	RNA polymerase II-specific DNA-binding transcription factor binding	10	5.71E-07	CREBBP, JUN, CREB1, CDKN2A, SP1, FOS, AHR, PPARA, TP53, NFE2L2
GO:0016705	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	6	1.23E-06	CYP2D6, CYP1B1, CYP2E1, CYP3A4, CYP19A1, CYP3A5
GO:0101021	estrogen 2-hydroxylase activity	4	1.42E-06	CYP2B6, CYP1A2, CYP1A1, CYP3A4

GO:0019825	oxygen binding	6	1.42E-06	CYP1A1, CYP2E1, CYP3A4, SOD2, CYP19A1, CYP3A5
GO:0050661	NADP binding	6	3.06E-06	G6PD, NOS2, NOS3, GSR, CAT, HMGCR
GO:0004508	steroid 17-alpha-monooxygenase activity	4	4.94E-06	CYP2D6, CYP1A2, CYP1A1, CYP1B1
GO:0004879	nuclear receptor activity	6	9.61E-06	NR1I3, NR1I2, PGR, AHR, PPARA, ESR1
GO:0001228	DNA-binding transcription activator activity, RNA polymerase II-specific	13	1.13E-05	JUN, NR1I3, NR1I2, FOS, ESR1, NFKB1, CREB1, SP1, MYC, PGR, PPARA, TP53, NFE2L2
GO:0000976	transcription cis-regulatory region binding	9	4.58E-05	JUN, SP1, FOS, AHR, TNF, TP53, NFKB1, NFE2L2, SNCA
GO:0001221	transcription coregulator binding	5	4.72E-05	SP1, MYC, FOS, ESR1, NFE2L2
GO:0008559	ABC-type xenobiotic transporter activity	4	5.00E-05	ABCB1, ABCC2, ABCB11, ABCG2
GO:0001223	transcription coactivator binding	5	1.20E-04	CREBBP, PGR, AHR, PPARA, ESR1
GO:0003700	DNA-binding transcription factor activity	12	1.24E-04	JUN, CREB1, SP1, NR1I3, FOS, AHR, PPARA, ESR1, TP53, SMAD5, NFKB1, NFE2L2
GO:0062187	anandamide 8,9 epoxidase activity	3	1.65E-04	CYP2B6, CYP2D6, CYP3A4
GO:0062188	anandamide 11,12 epoxidase activity	3	1.65E-04	CYP2B6, CYP2D6, CYP3A4
GO:0030544	Hsp70 protein binding	5	1.90E-04	TFRC, CYP1A1, BAX, CYP2E1, SNCA
GO:0062189	anandamide 14,15 epoxidase activity	3	2.74E-04	CYP2B6, CYP2D6, CYP3A4
GO:0009055	electron transfer activity	5	3.04E-04	CYP1A2, GSR, AKR1B1, COX5A, CYP19A1
GO:0051434	BH3 domain binding	3	4.09E-04	BCL2, BAX, BCL2L1
GO:0005515	protein binding	84	4.66E-04	ACHE, APP, CDKN1A, CXCL8, TFRC, PDE3B, AKR1B1, PLAT, AHR, MPO, ELAVL1, TNF, ICAM1, MYC, CASP3, CYP1B1, PDE4A, AKT1, IKBKG, PDGFRB, G6PD, EDN1, ABCC2, VWF, ADIPOQ, PRKCA, FOS, NGF, PRKAB1, CREB1, TMX2, TFF1, PGR, PPIG, PPARA, TLR4, TP53, ABCG2, CRP, ABCB1, MAOA, GSTP1, NR1I3, NR1I2, PTAFR, HMGCR, CYP3A4, ABCB11, PTGS2, COX5A, CYP3A5, PTGS1, MAPK8, TTR, RHO, CCL2, HMOX1, MAPK1, APOE, MAPK3, SNCA, JUN, CREBBP, NOS2, CDKN2A, NOS3, BDNF, MAPK14, SOD2, ESR1, SMAD5,

				NFKB1, SOD1, VEGFA, TF, IL6, IL5, SP1, CYP1A2, CYP1A1, BCL2, BAX, NFE2L2, BCL2L1
GO:0106256	hydroperoxy icosatetraenoate dehydratase activity	3	5.71E-04	CYP1A2, CYP1A1, CYP1B1
GO:0005496	steroid binding	4	5.78E-04	UGT1A1, PGR, CYP3A4, ESR1
GO:0005102	signaling receptor binding	9	7.60E-04	PDGFRB, APP, ADIPOQ, CCL2, PGR, PLAT, APOE, GUSB, TLR4
GO:0051400	BH domain binding	3	9.72E-04	BCL2, BAX, BCL2L1
GO:0042626	ATPase-coupled transmembrane transporter activity	4	0.001056	ABCB1, ABCC2, ABCB11, ABCG2
GO:0031625	ubiquitin protein ligase binding	8	0.001317	CDKN1A, JUN, ABCB1, BCL2, IKBKG, TP53, SMAD5, NFE2L2
GO:0097371	MDM2/MDM4 family protein binding	3	0.001763	CDKN2A, PPARA, TP53
GO:0034056	estrogen response element binding	3	0.001763	NR1I3, PGR, ESR1
GO:0004861	cyclin-dependent protein serine/threonine kinase inhibitor activity	3	0.001763	CDKN1A, CDKN2A, CASP3
GO:0008083	growth factor activity	6	0.001835	IL6, IL5, BDNF, TFF1, NGF, VEGFA
GO:0004707	MAP kinase activity	3	0.002076	MAPK1, MAPK14, MAPK3
GO:0002020	protease binding	5	0.003557	VWF, CASP3, BCL2, TNF, TP53
GO:0005125	cytokine activity	6	0.003773	IL6, EDN1, IL5, ADIPOQ, TNF, VEGFA
GO:0046982	protein heterodimerization activity	8	0.003926	UGT1A1, BCL2, BAX, AHR, IKBKG, TP53, TLR4, BCL2L1
GO:0005543	phospholipid binding	5	0.004494	PLA2G2A, PTAFR, APOE, PLA2G7, SNCA

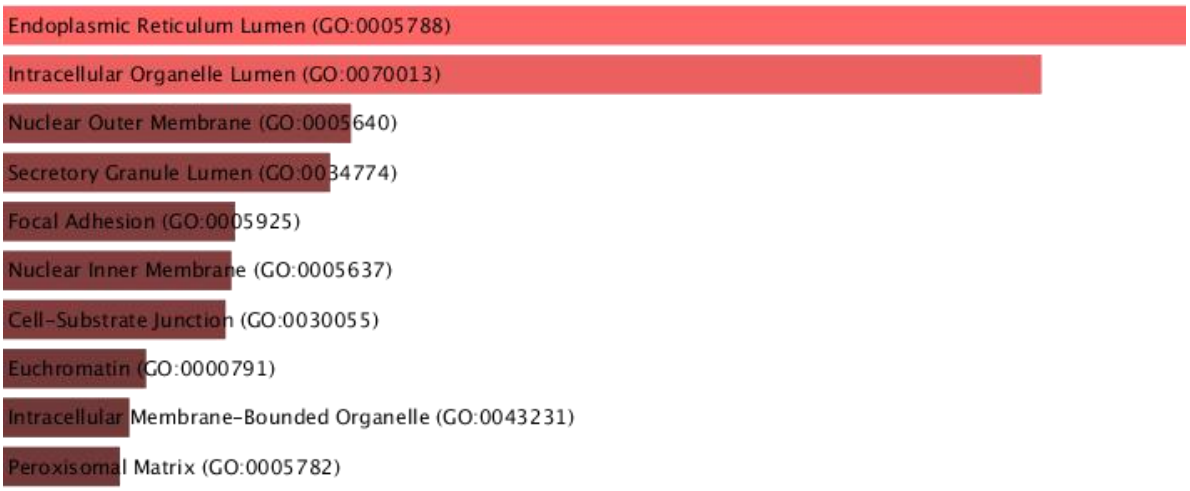

Figure 10 GO cellular component of hub genes: location where hub genes are located in a cell

Table 4 GO cellular component: no. Of genes at specific location along with their names

Term	Cellular-component(direct)	Count	P Value	Genes
GO:0005615	extracellular space	34	4.45E-10	CRP, APP, ACHE, CXCL8, TFRC, GSTP1, AKR1B1, PLAT, MPO, TNF, ICAM1, TTR, CCL2, HMOX1, APOE, GUSB, SNCA, EDN1, VCAM1, VWF, MMP1, BDNF, PLA2G2A, ADIPOQ, NGF, MUC5AC, SOD1, VEGFA, TF, IL6, IL5, CAT, TFF1, TLR4
GO:0005576	extracellular region	33	4.36E-09	CRP, APP, ACHE, CXCL8, TFRC, GSTP1, PLAT, MPO, PLA2G7, TNF, TTR, CCL2, MAPK1, APOE, GUSB, SNCA, EDN1, VWF, MMP1, BDNF, PLA2G2A, ADIPOQ, NGF, MAPK14, MUC5AC, NFKB1, SOD1, VEGFA, TF, IL6, IL5, CAT, TFF1
GO:0005739	mitochondrion	25	2.11E-07	PANK2, MAOA, GSTP1, MAPK8, CYP2D6, CYP1B1, AKT1, MAPK1, MAPK3, SNCA, CDKN2A, GSR, PRKCA, MAPK14, SOD2, SMAD5, NFKB1, SOD1, TMX2, CAT, BCL2, BAX, PPIG, TP53, BCL2L1
GO:0005783	endoplasmic reticulum	21	1.36E-06	APP, VCAM1, UGT1A1, VWF, PLA2G2A, PDE3B, ADIPOQ, PRKCA, FOS, HMGCR, PTGS2, ELAVL1, CYP19A1, VEGFA, CYP2D6, BCL2, BAX, HMOX1, APOE, TP53, BCL2L1
GO:0009986	cell surface	15	4.73E-06	ACHE, APP, VCAM1, ABCB1, ABCC2, TFRC, ADIPOQ, PLAT, ABCB11, TNF, ICAM1, VEGFA, TF, SP1, TLR4
GO:0005737	cytoplasm	50	1.58E-05	APP, PLAT, AHR, ELAVL1, CYP2D6, MYC, CASP3, AKT1, IKBKG, PDGFRB, G6PD,

				EDN1, PRKCA, PRKAB1, CAT, PGR, PPIG, CYP2E1, TLR4, TP53, ABCB1, GSTP1, NR1I3, CYP3A4, PTGS2, PTGS1, MAPK8, CYP2B6, MAPK1, APOE, MAPK3, SNCA, CREBBP, CHKB, CHKA, NOS2, CDKN2A, NOS3, BDNF, MAPK14, ESR1, SMAD5, NFKB1, SOD1, VEGFA, SP1, BCL2, BAX, NFE2L2, BCL2L1
GO:0005789	endoplasmic reticulum membrane	19	1.81E-05	UGT1A1, PLA2G2A, HMGCR, CYP3A4, CYP7B1, PTGS2, CYP3A5, CYP19A1, PTGS1, CYP2B6, TMX2, CYP2D6, CYP1A2, CYP1A1, BCL2, BAX, CYP1B1, HMOX1, CYP2E1
GO:0070062	extracellular exosome	27	3.28E-05	GABRB2, APP, ABCB1, TFRC, GSTP1, AKR1B1, PLAT, ABCB11, MPO, PTGS1, ICAM1, TTR, NAGLU, APOE, GUSB, G6PD, VCAM1, VWF, PLA2G2A, GSR, PRKCA, SOD2, MUC5AC, SOD1, TF, CAT, BAX
GO:0032991	protein-containing complex	14	3.52E-05	CDKN1A, CDKN2A, AHR, PTGS2, ESR1, SMAD5, SOD1, MYC, CAT, BCL2, AKT1, IKBKG, TP53, SNCA
GO:0043231	intracellular membrane-bounded organelle	16	4.67E-05	PDGFRB, G6PD, TFRC, CYP3A4, MPO, CYP3A5, PTGS1, CYP2B6, CYP2D6, CYP1A2, CAT, CYP1A1, CYP1B1, CYP2E1, PPIG, GUSB
GO:0048471	perinuclear region of cytoplasm	14	1.04E-04	ACHE, APP, CDKN1A, UGT1A1, NOS2, TFRC, BDNF, PLA2G2A, PRKCA, TF, PDE4A, HMOX1, TLR4, SNCA
GO:0005654	nucleoplasm	36	3.73E-04	CDKN1A, NR1I3, NR1I2, AKR1B1, AHR, MPO, ELAVL1, MAPK8, MYC, CASP3, AKT1, PDE4A, HMOX1, MAPK1, IKBKG, MAPK3, JUN, CREBBP, NOS2, CDKN2A, PRKCA, FOS, MAPK14, ESR1, SMAD5, PRKAB1, NFKB1, SOD1, CREB1, SP1, PGR, PPIG, PPARA, TP53, ABCG2, NFE2L2
GO:0000785	chromatin	16	5.93E-04	CREBBP, JUN, NR1I3, NR1I2, AHR, FOS, ESR1, SMAD5, NFKB1, CREB1, SP1, MYC, PGR, PPARA, TP53, NFE2L2
GO:0016020	membrane	41	8.13E-04	GABRB2, APP, ACHE, PANK2, ABCB1, TFRC, MAOA, PDE3B, PTAFR, HMGCR, ABCB11, CYP3A4, ELAVL1, CYP3A5, CYP19A1, ICAM1, CYP2D6, MYC, RHO, CYP1B1, AKT1, PDE4A, HMOX1, APOE, GUSB, SNCA, PDGFRB, G6PD, ABCC2, VCAM1, UGT1A1, BDNF, CYP7B1, ESR1, VEGFA, TMX2, CAT, BCL2, BAX, TP53, TLR4
GO:0097136	Bcl-2 family protein complex	3	8.64E-04	BCL2, BAX, BCL2L1
GO:0005741	mitochondrial outer	7	8.80E-04	MAOA, PLA2G2A, BCL2, BAX, HMOX1,

	membrane			PGR, BCL2L1
GO:0005788	endoplasmic reticulum lumen	8	9.39E-04	APP, IL6, TF, BDNF, MAPK1, APOE, PTGS2, MAPK3
GO:0005769	early endosome	8	0.001012	APP, TF, VCAM1, TFRC, MAPK1, APOE, TLR4, MAPK3
GO:0005829	cytosol	44	0.001093	APP, CDKN1A, PANK2, MAOA, GSTP1, NR1I3, PDE3B, AKR1B1, AHR, ELAVL1, MAPK8, CASP3, AKT1, PDE4A, HMOX1, MAPK1, IKBKG, MAPK3, SNCA, CREBBP, G6PD, CHKB, CHKA, NOS2, CDKN2A, NOS3, GSR, PRKCA, FOS, NGF, MAPK14, ESR1, SMAD5, PRKAB1, NFKB1, SOD1, CAT, BCL2, BAX, PGR, PPIG, TP53, BCL2L1, NFE2L2
GO:0005667	transcription regulator complex	7	0.001457	CREBBP, JUN, NR1I2, AHR, ESR1, TP53, NFKB1
GO:0034774	secretory granule lumen	5	0.00271	TF, GSTP1, CAT, MAPK14, NFKB1
GO:0005794	Golgi apparatus	14	0.00319	PDGFRB, ACHE, APP, VCAM1, NOS3, PDE3B, ESR1, PTGS1, VEGFA, RHO, MAPK1, APOE, NFE2L2, MAPK3
GO:1904813	ficolin-1-rich granule lumen	5	0.003545	GSTP1, CAT, MAPK1, MAPK14, GUSB
GO:0005634	nucleus	45	0.00376	APP, ACHE, CDKN1A, PANK2, GSTP1, NR1I3, NR1I2, AHR, MPO, ELAVL1, MAPK8, MYC, CASP3, AKT1, PDE4A, HMOX1, MAPK1, IKBKG, APOE, MAPK3, SNCA, PDGFRB, JUN, CREBBP, NOS2, CDKN2A, NOS3, PRKCA, FOS, MAPK14, ESR1, SMAD5, PRKAB1, NFKB1, SOD1, VEGFA, CREB1, SP1, BCL2, BAX, PGR, PPIG, PPARA, TP53, NFE2L2
GO:0000791	euchromatin	4	0.004009	JUN, CREB1, SP1, ESR1

3.6.1 KEGG Enrichment Analysis

We looked at the 10 therapeutic targets for KEGG pathway enrichment using ShinyGO, and we discovered pathways with a p-value < 0.05. Ten main pathways were identified following the screening of the data. Three pathways were considerably enriched in the network:(TNF signaling pathway), (kegg of colorectal cancer), and (kegg of hepatitis B).

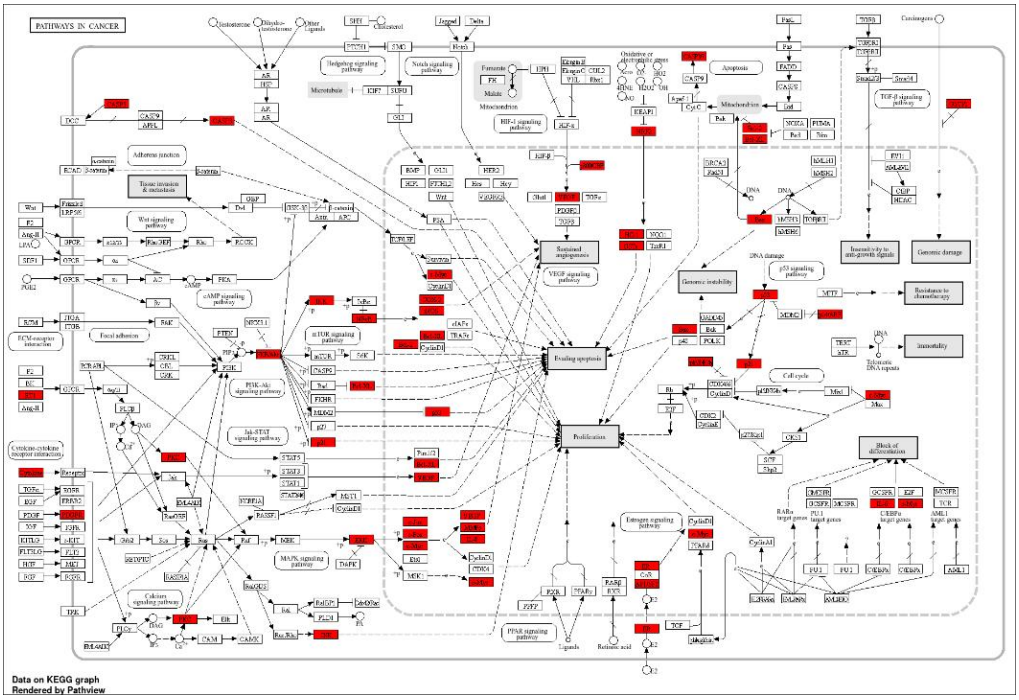

Figure 11 kegg pathway in cancer

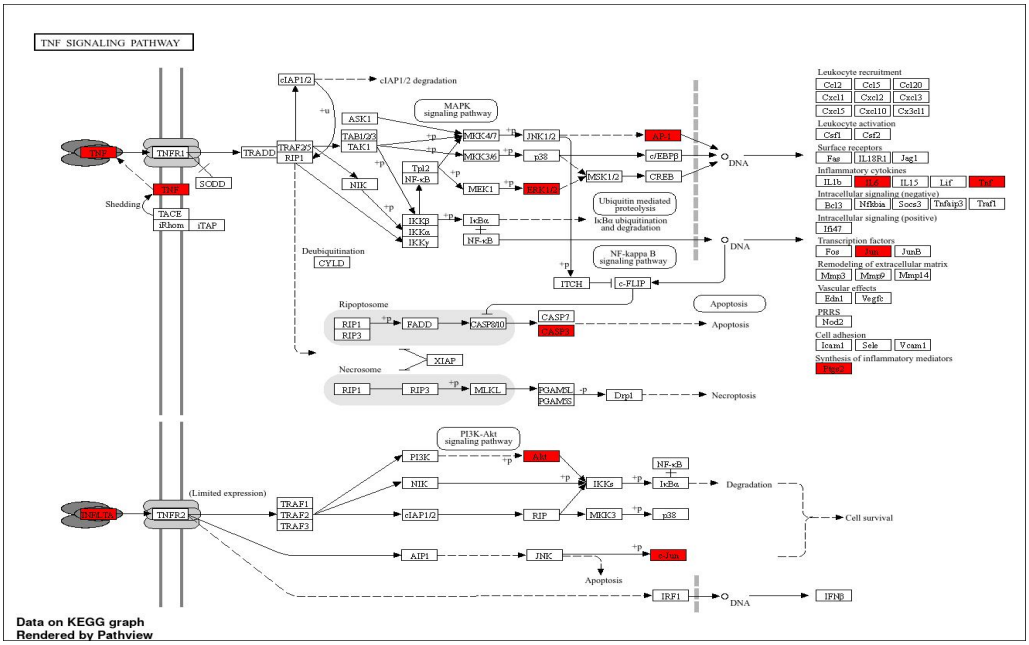

Figure 12 TNF signaling pathway

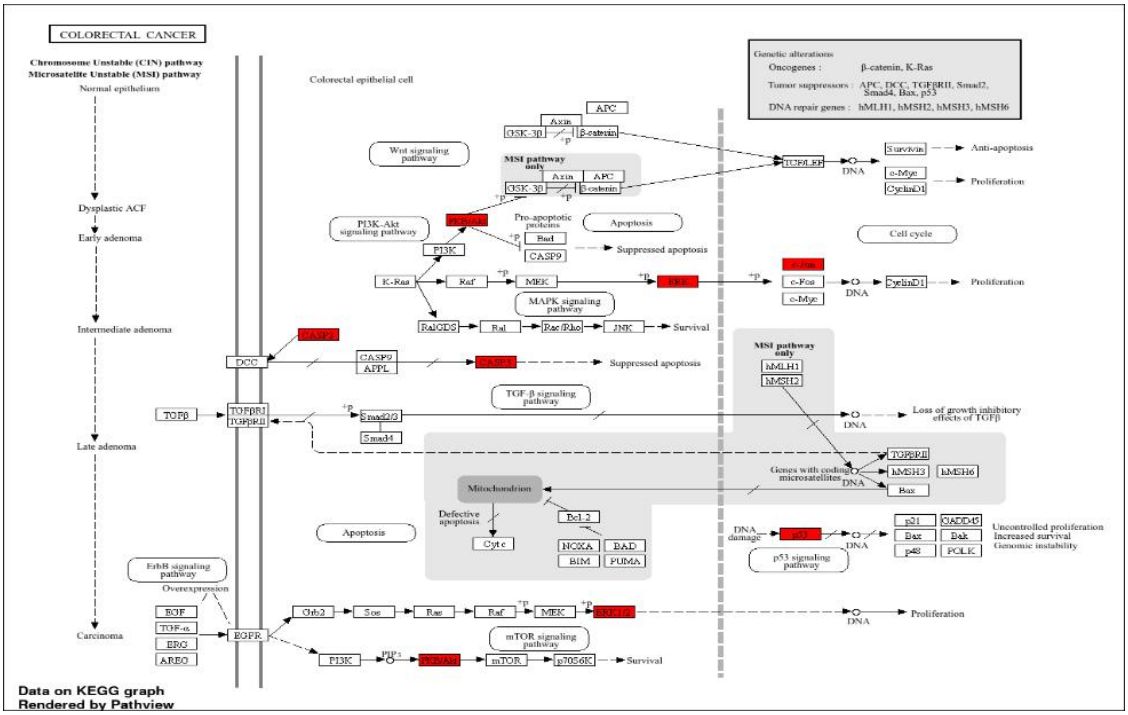

Figure 13 kegg pathway of colorectal cancer

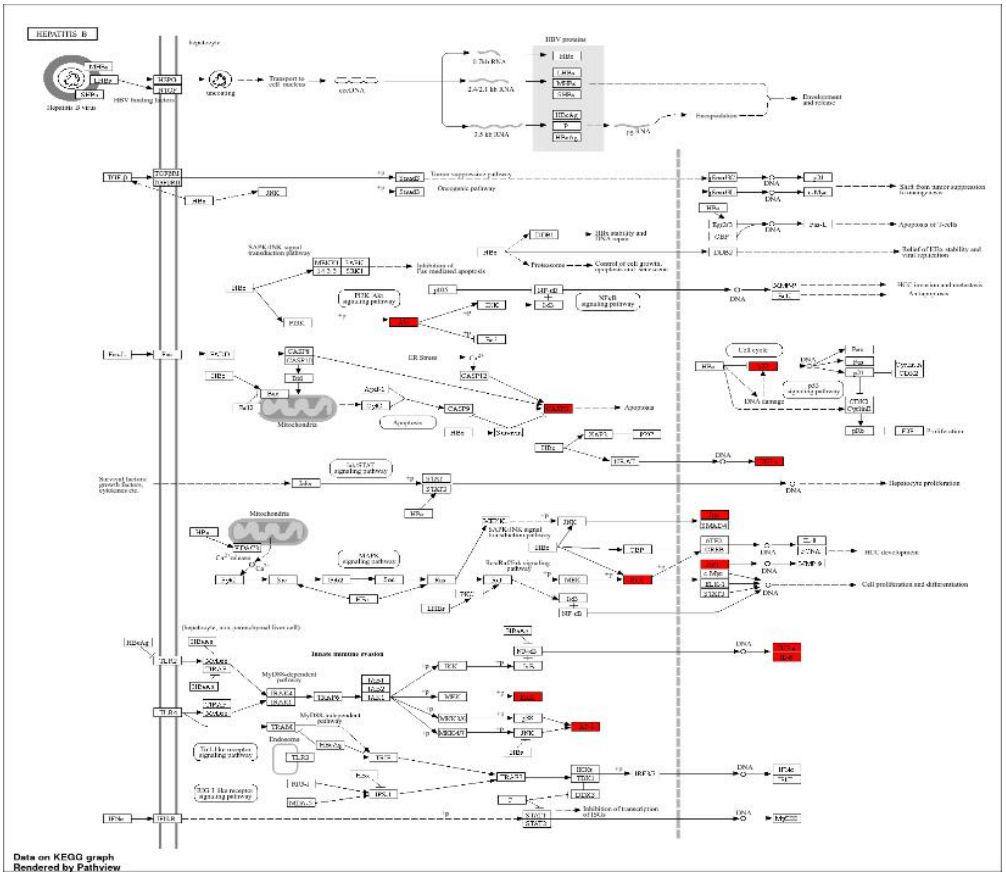

Figure 14 kegg pathway of hepatitis B

3.7 Molecular Docking Results

To precisely predict conformational changes of small molecules in the pertinent target binding region and to assess binding affinity, the drug development process commonly uses the molecular docking technique. Target protein candidates for molecular docking analysis in this study were chosen based on their high frequency in the core PPI network among human species. Using a new scoring function and effective optimization, the docking process merged the AutoDock 1.5.6 tools with Vina, or AutoDock Vina, a novel and popular molecular docking technique. It was confirmed to increase molecular docking speed and accuracy. as well as multitasking.

The potential bioactive compound was molecularly docked with ten possible target proteins, including TNF, IL6PTGS2, TP53, MAPK3, VEGFA, CAT, CASP3, AKT1 and JUN. Vina carried out the docking process, while the AutoDock 1.5.6 tools provided the docking box settings. Because the PDBQT files include information about the ligands and proteins for docking, they were employed during the process in addition to the configuration file for the protein and ligand.

After Vina completed the run, the results were output as. Pdbqt and log.txt files and evaluated by docking binding free energy to determine the lowest binding affinity were binding affinity score between target protein receptors and small molecule ligands.

Discovery Studio (2D), which are both frequently used to visualize docking results, including the docking site and hydrogen bond interaction patterns between the ligand and main or side chain elements protein, were used to display docking models with visualization and hydrogen bonds.

3.7.1 1bj1 and ligand Interactions

1bj1 is Vascular Endothelial Growth Factor (VEGF) in complex with neutralizing antibody. Protein interaction with Bilobalide compound.

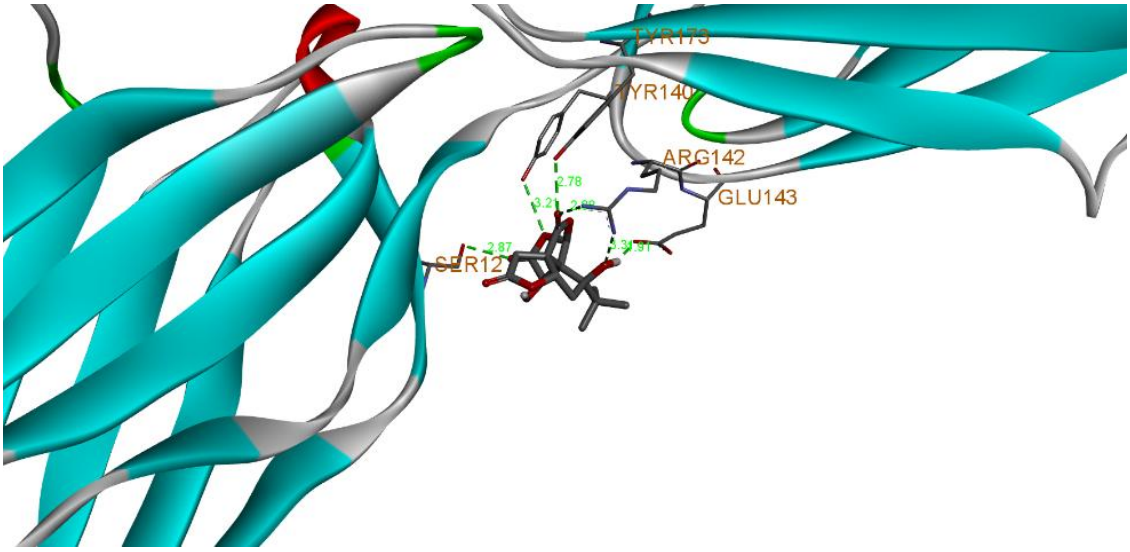

Figure 15 1bj1 and Bilobalide interaction

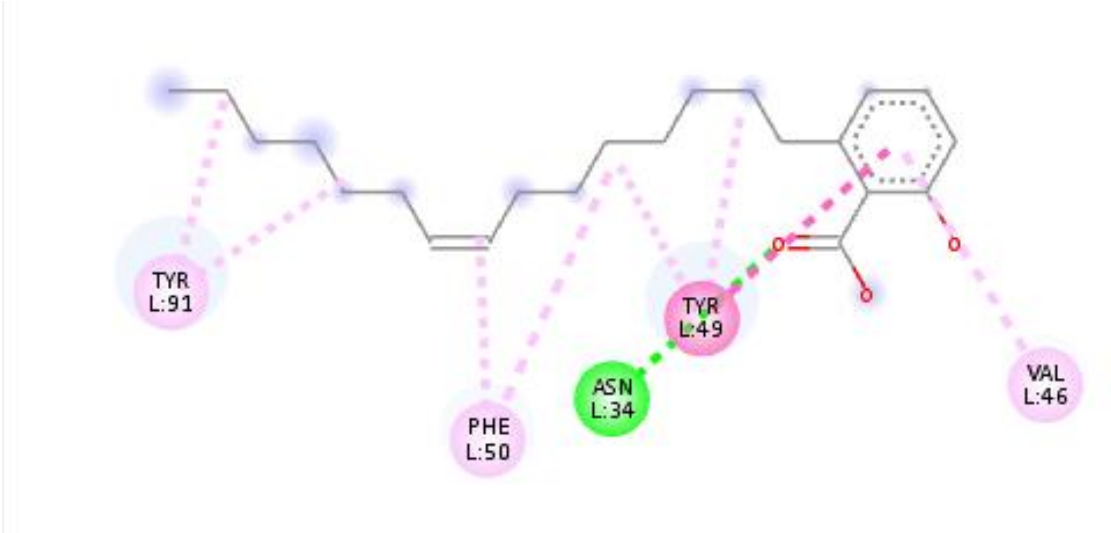

Figure 16 2D structure of 1bj1 and Bilobalide interaction

Protein interaction with Ginkgolide A.

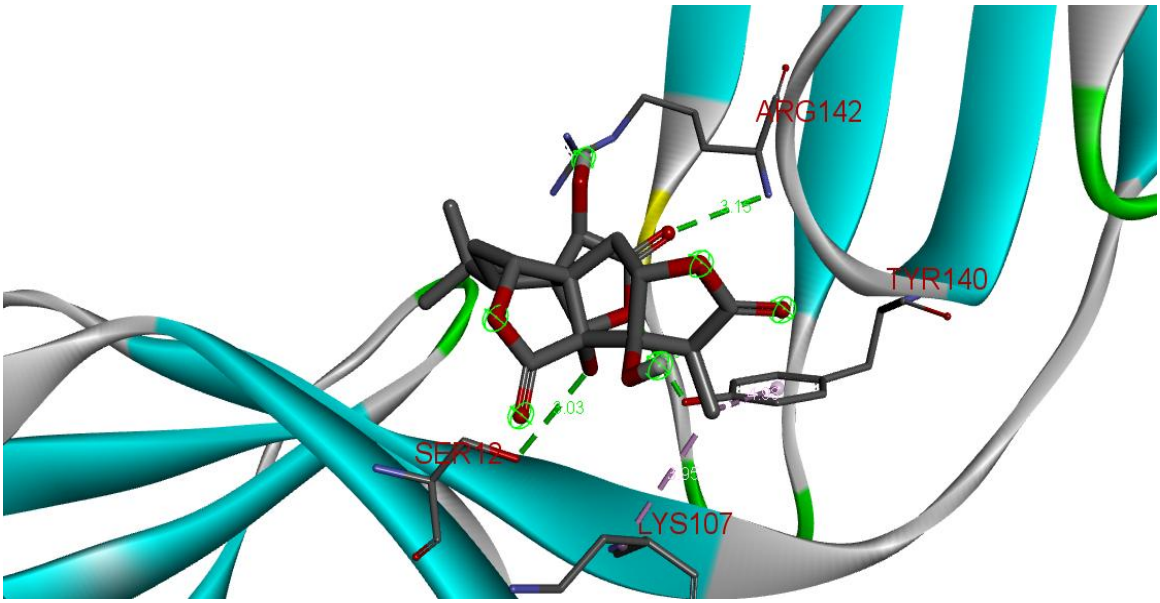

Figure 17 1bj1 and Ginkgolide A interaction

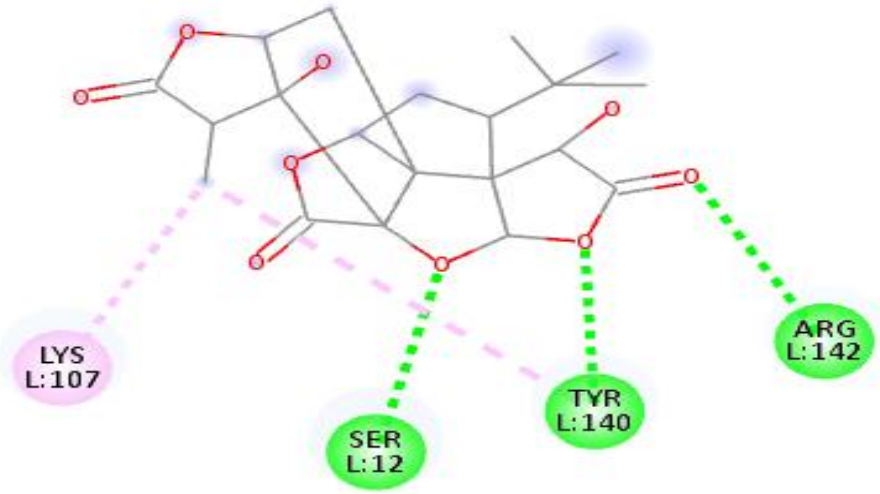

Figure 18 2D structure of 1bj1 and Ginkgolide A interaction

Protein interaction with Ginkgolide B.

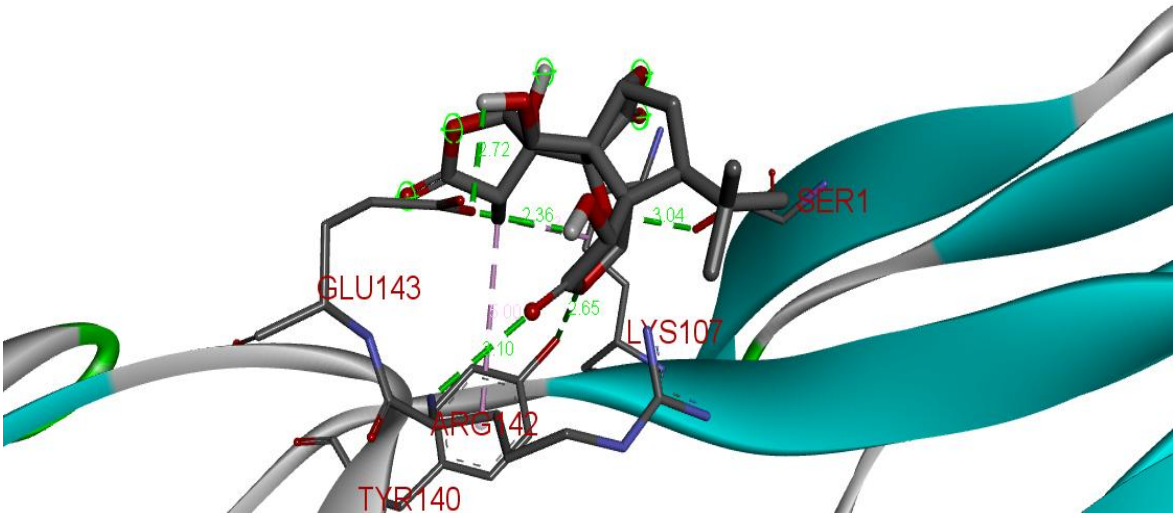

Figure 19 1bj1 and Ginkgolide B interaction

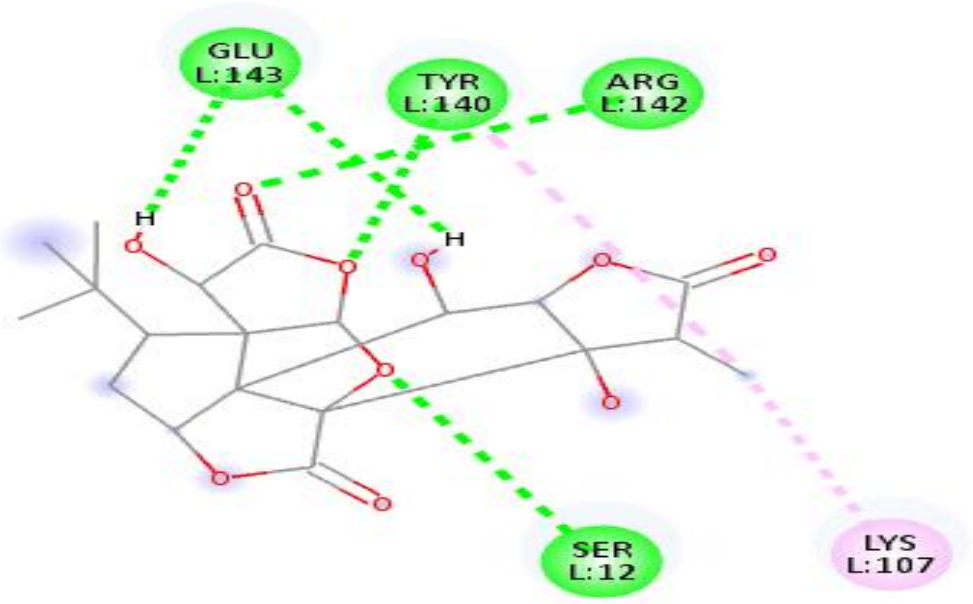

Figure 20 2D Structure of 1bj1 and Ginkgolide B interaction

Protein interaction with Ginkgolide C.

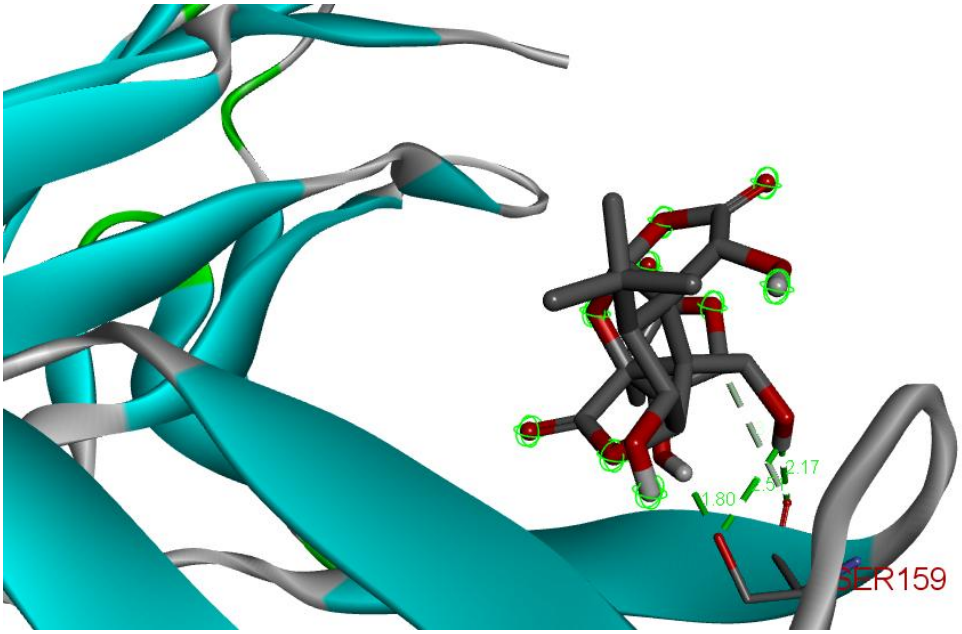

Figure 21 1bj1 and Ginkgolide C interaction

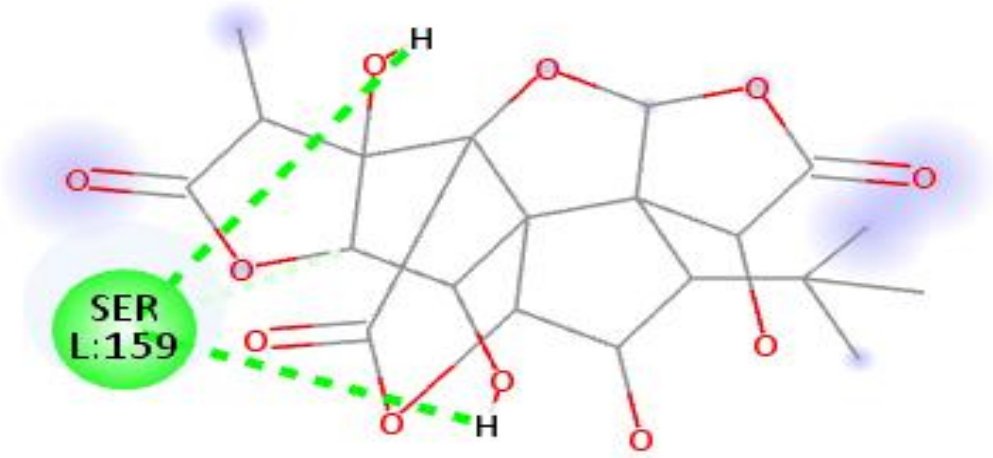

Figure 22 2D structure of 1bj1 and Ginkgolide C interaction

Protein interaction with Isorhamnetin.

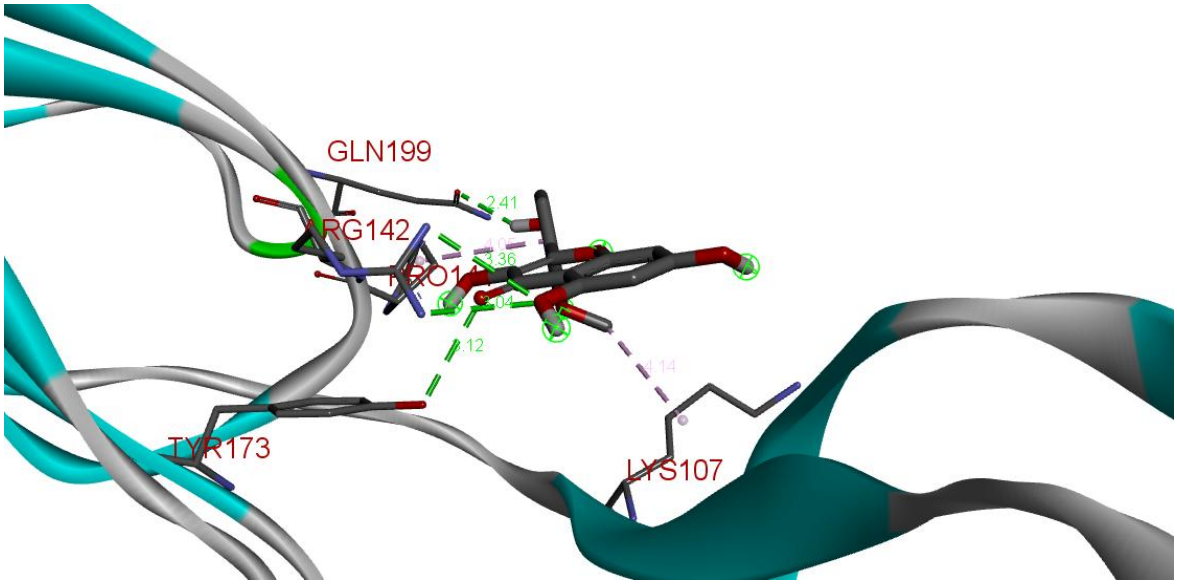

Figure 23 1bj1 and Isorhamnetin interaction

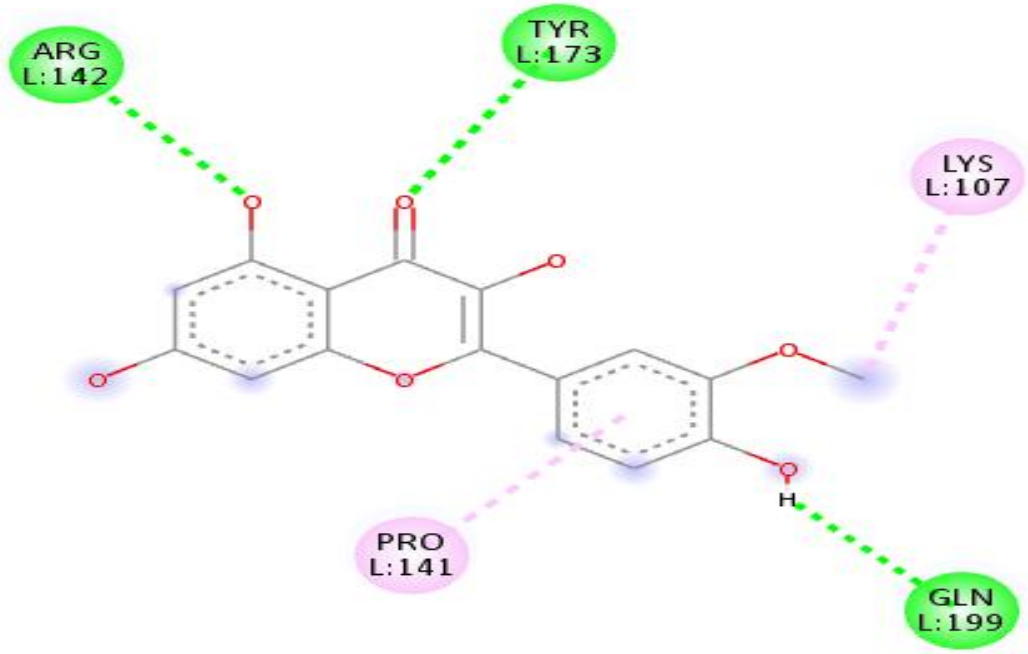

Figure 24 2D structure of 1bj1 and Isorhamnetin interaction

Protein interaction with Kaempferol.

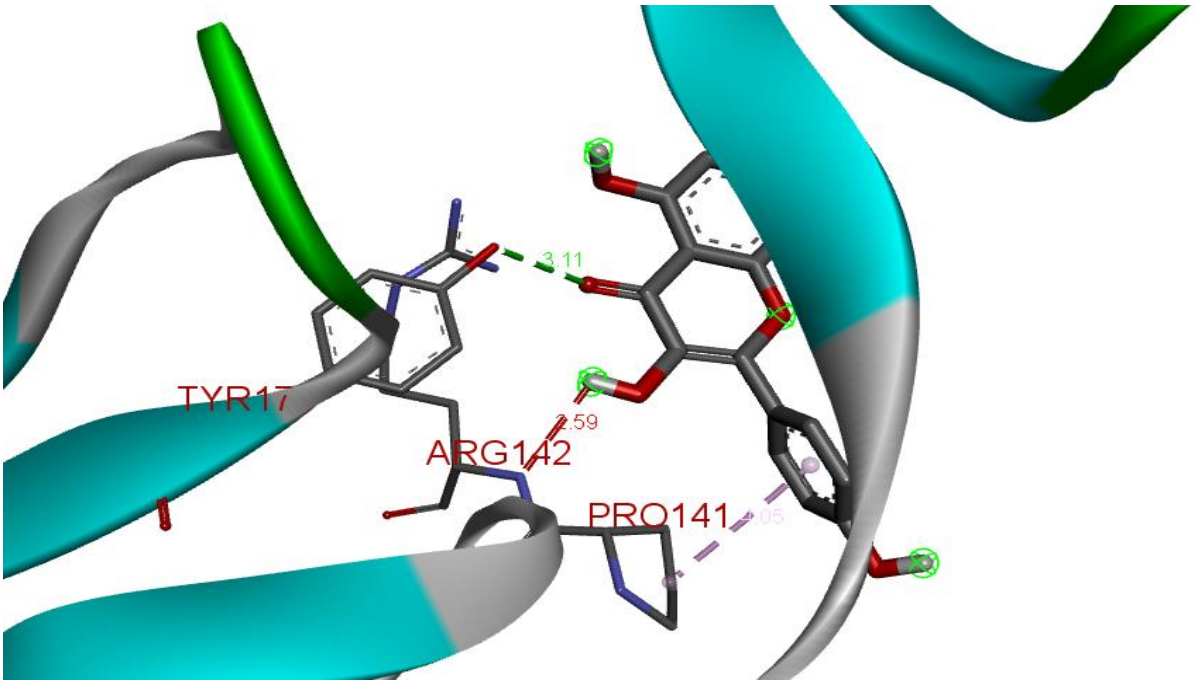

Figure 25 1bj1 and Kaempferol interaction

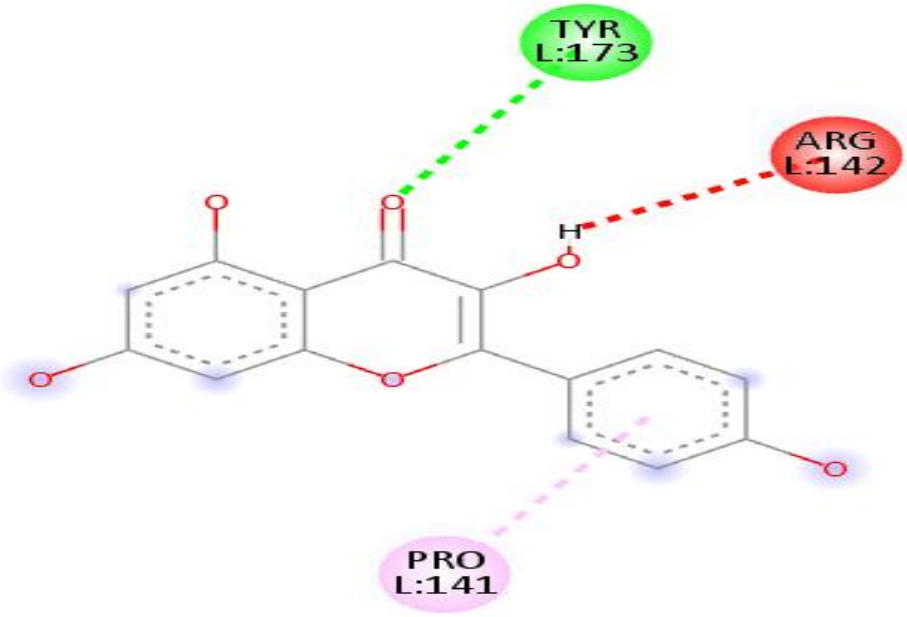

Figure 26 2D structure of 1bj1 and Kaempferol interaction

Protein interaction with Myricetin.

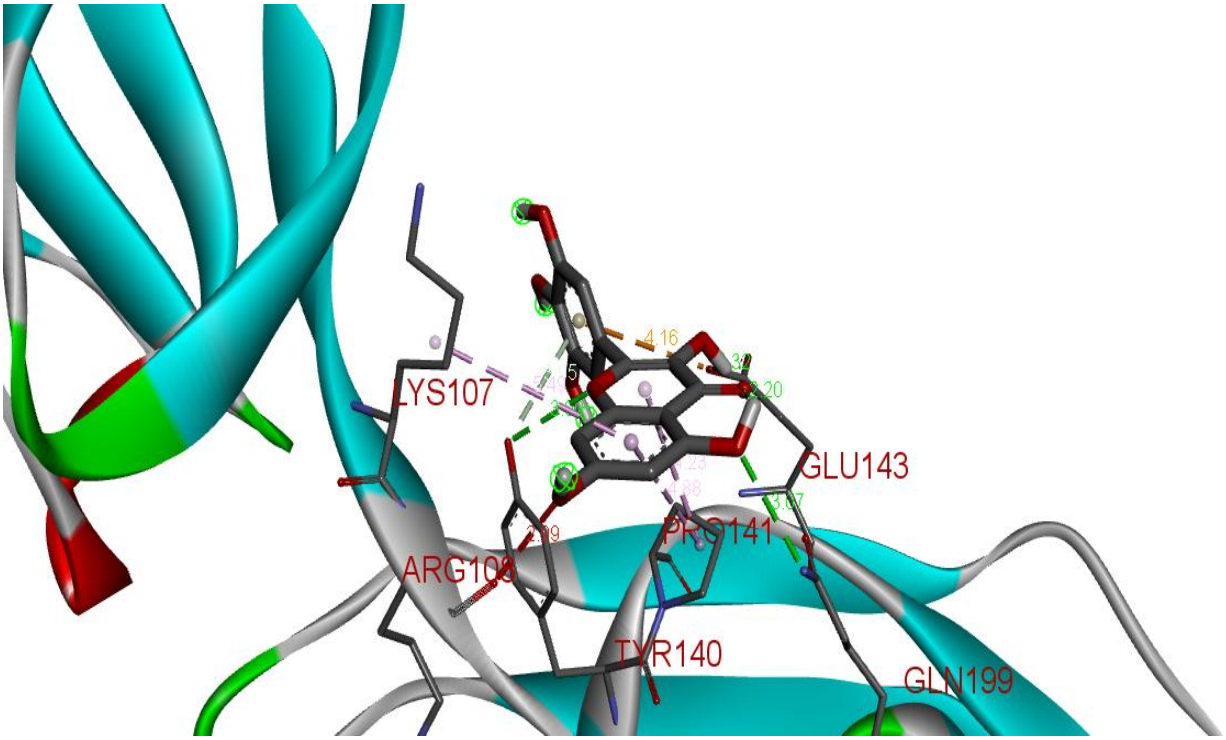

Figure 27 1bj1 and Myricetin interaction

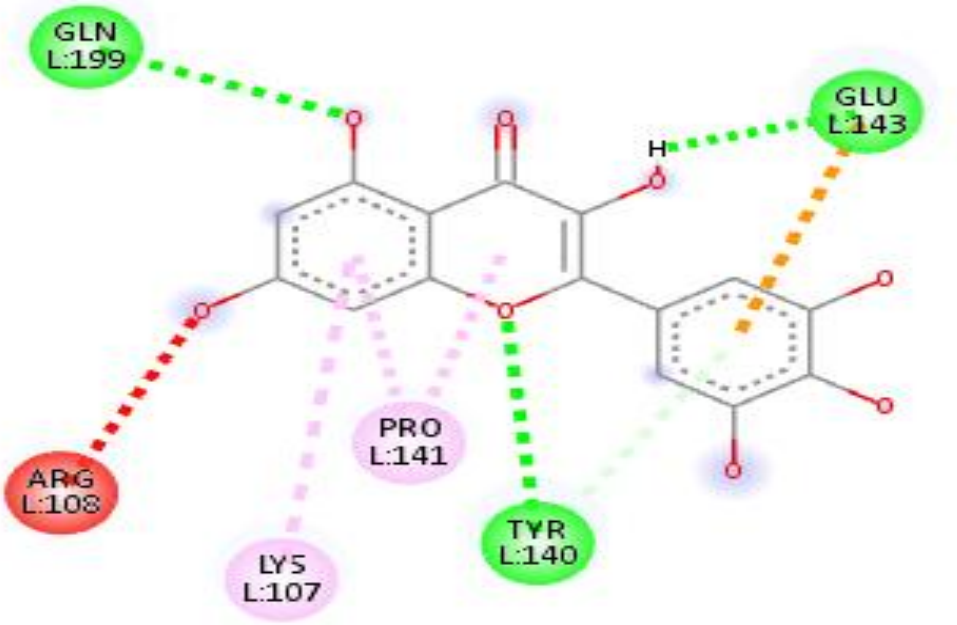

Figure 28 2D structure of 1bj1 and Myricetin interaction

Protein interaction with Quercetin.

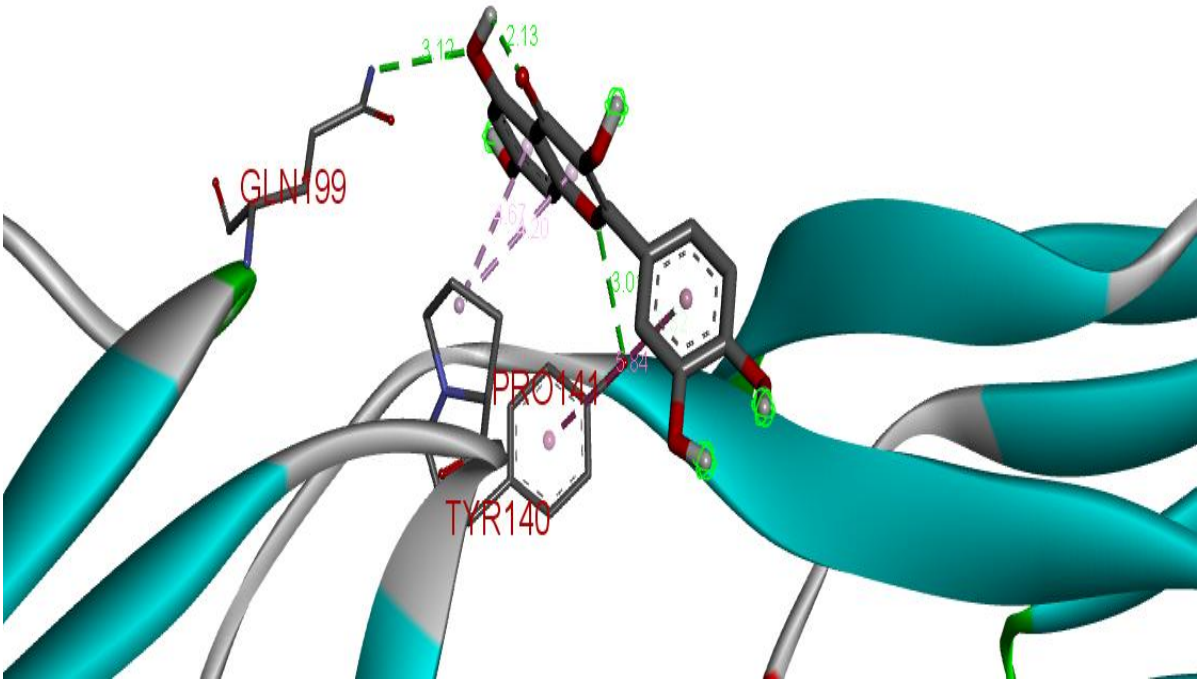

Figure 29 1bj1 and Quercetin interaction

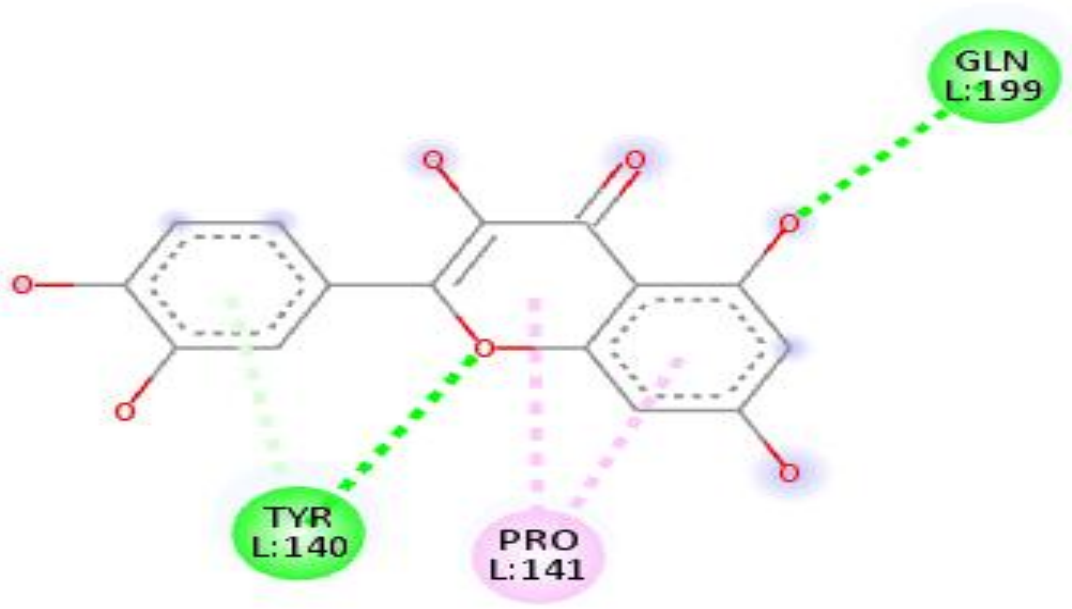

Figure 30 2D structure of 1bj1 and Quercetin interaction

Protein interaction with Shikimic acid.

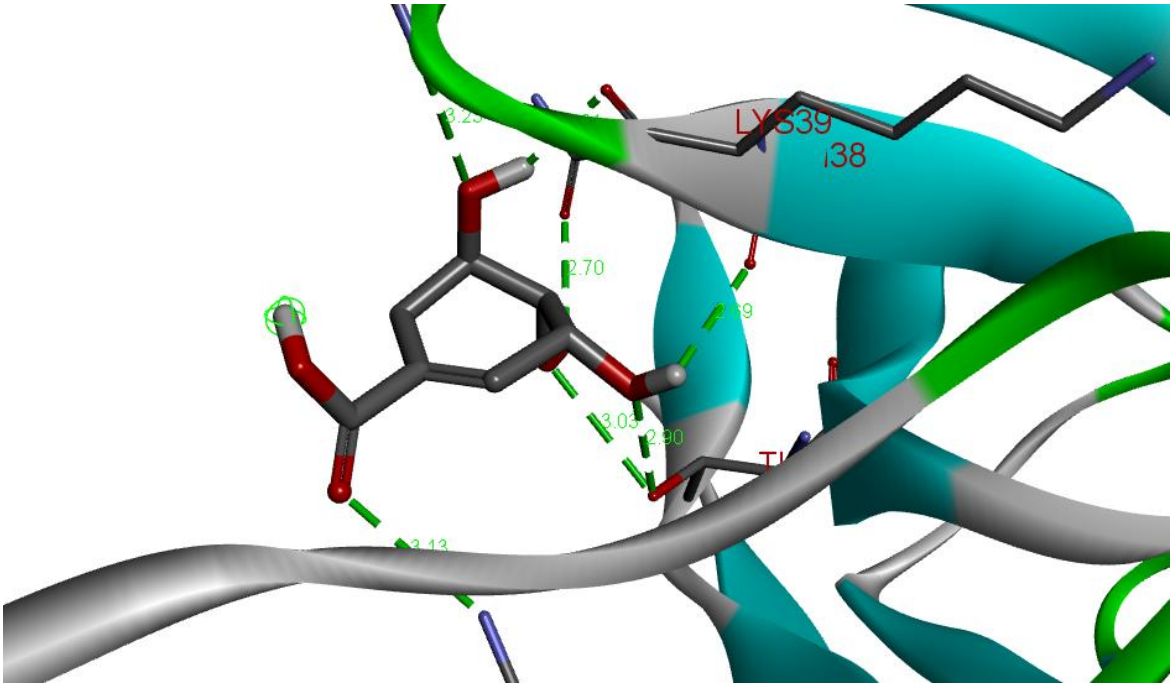

Figure 31 1bj1 and Shikimic acid interaction

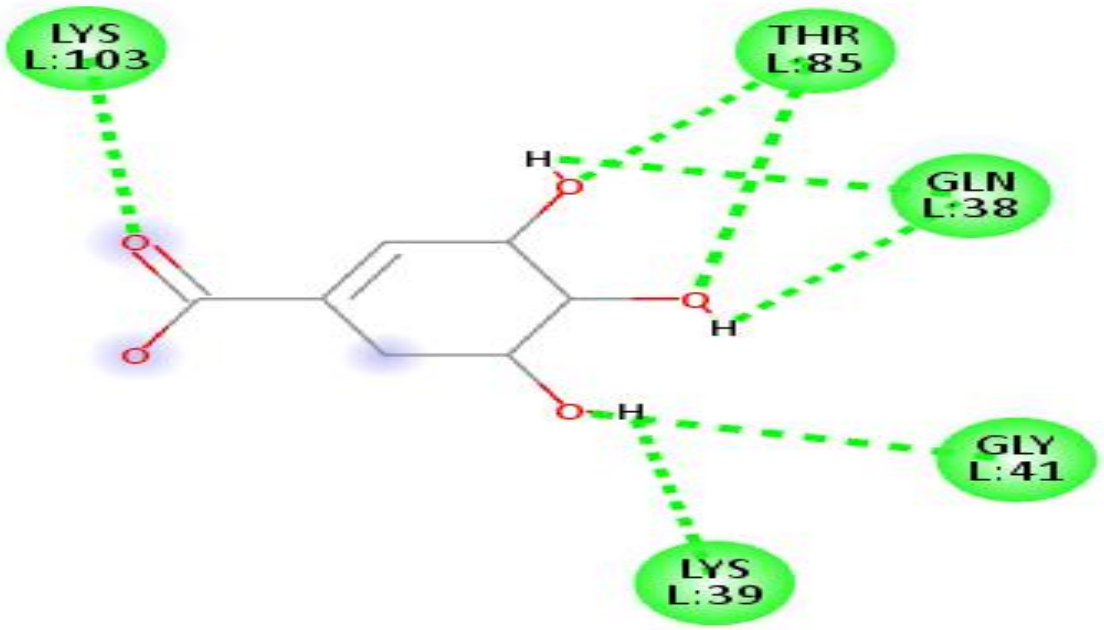

Figure 32 2D structure 1bj1 and Shikimic acid interaction

Table 5 Protein 1 docking (VEGF)

Protein 1 docking (1bj1)			
Compound name	**C.I.D**	**Binding energy**	**No. of H bond**
Bilobalide	73581	-6.1	5
Ginkgolic acid	5281858	-5.1	4
Ginkgolide A	115221	-7.1	2
Ginkgolide B	65243	-7.2	5
Ginkgolide C	24721502	-7.2	3
Isorhamnetin	5281654	-6.4	4
Kaempferol	5280863	-6.3	1
Myricetin	5281672	-6.5	4
Quercetin	5280343	-6.5	3
Shikimic acid	8742	-4.8	6

3.7.2 1gfw and ligand interaction

1gfw is Caspase-3 protein in complex with Isatin Sulfonamide inhabitor.. Protein interaction with Bilobalide compound.

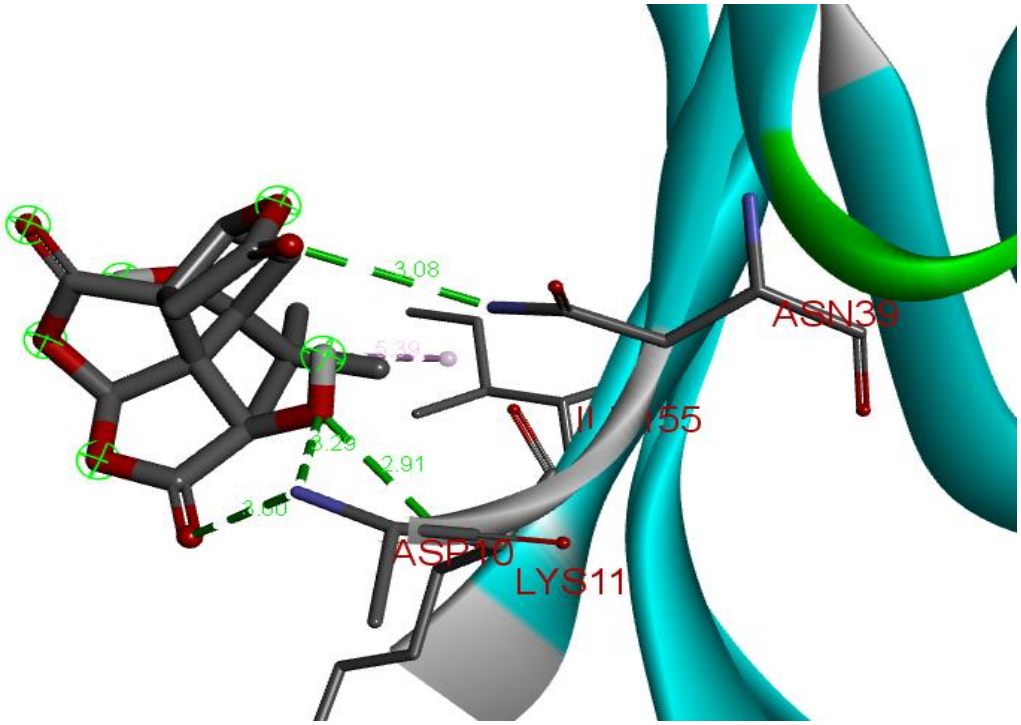

Figure 33 1gfw and Bilobalide interaction

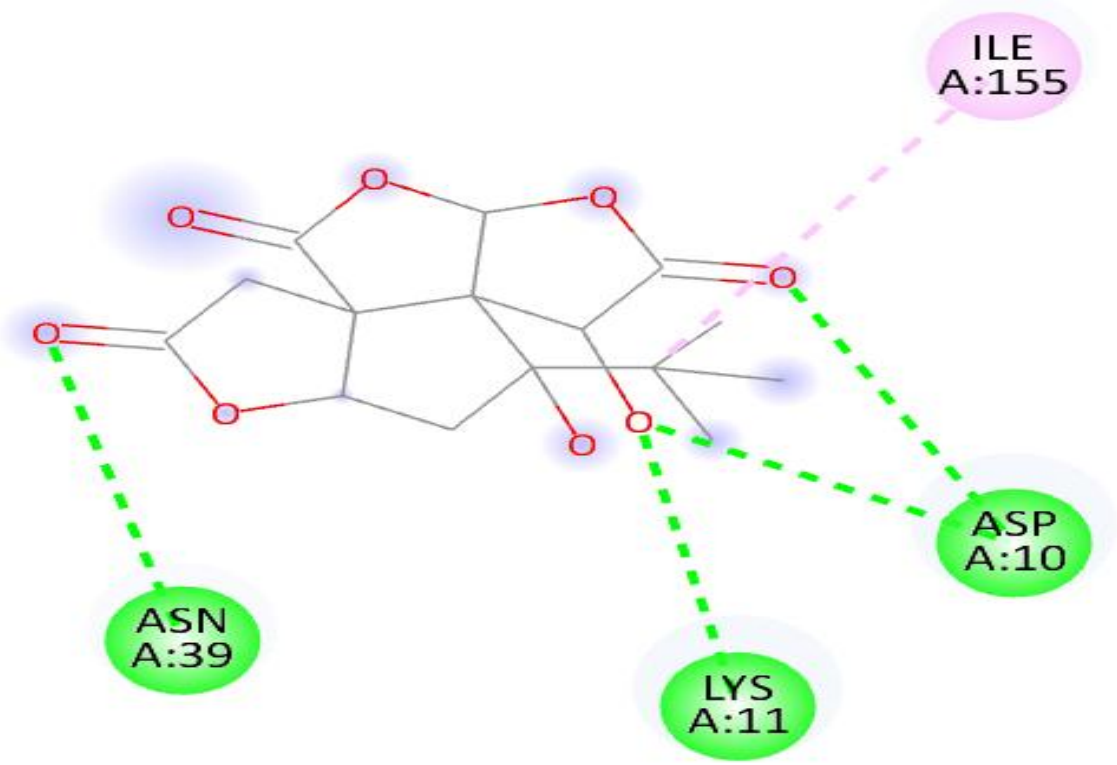

Figure 34 2D structure of 1gfw and Bilobalide interaction

Protein interaction with Ginkgolide A.

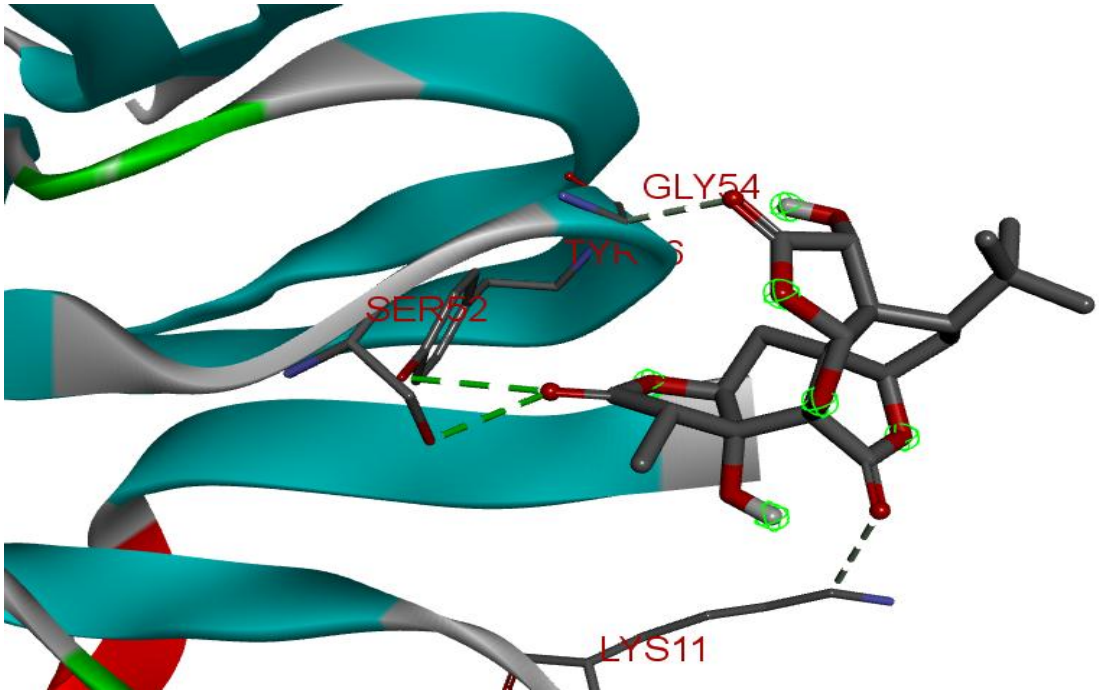

Figure 35 1gfw and Ginkgolide A interaction

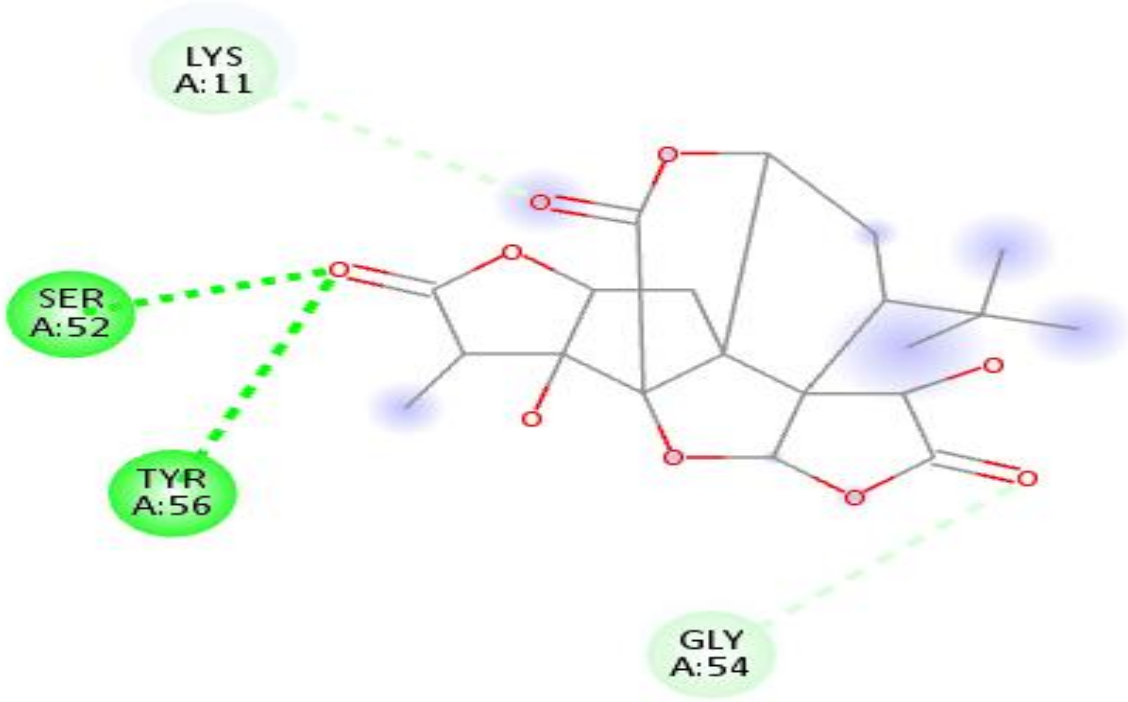

Figure 36 2D structure of 1gfw and Ginkgolide A interaction

Protein interaction with Ginkgolide C.

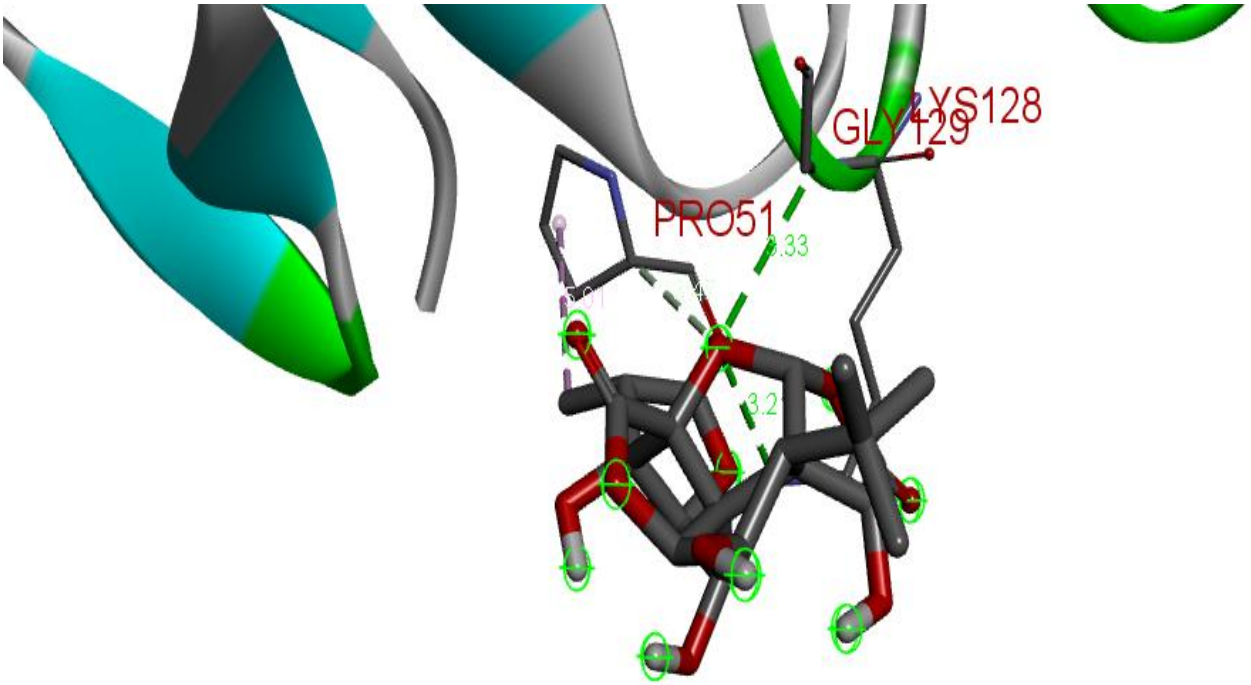

Figure 37 1bj1 and Ginkgolide C interaction

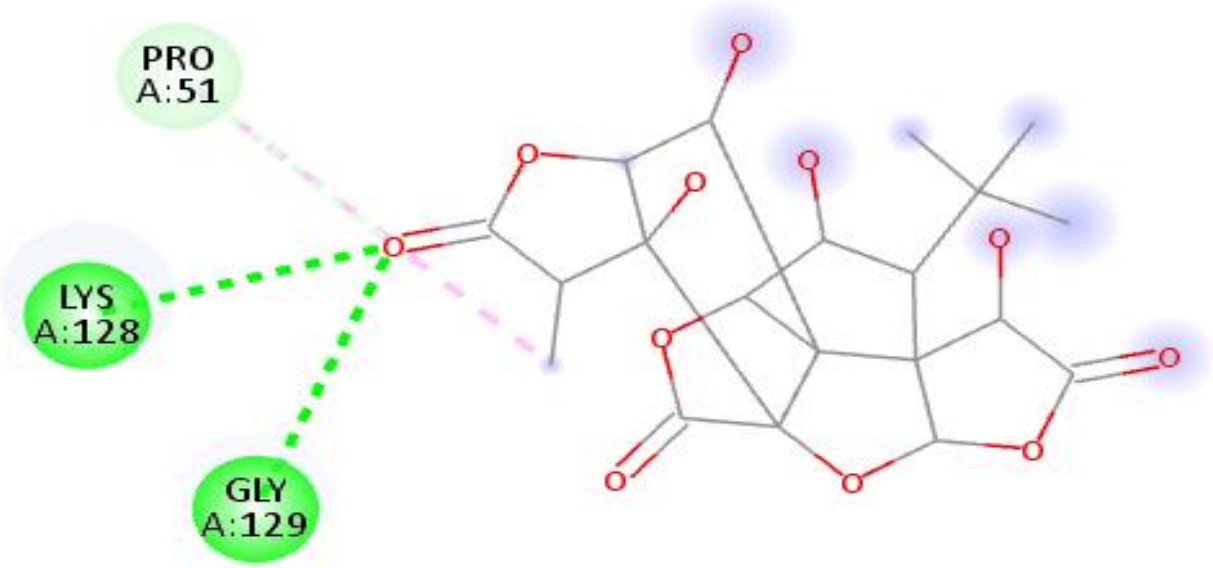

Figure 38 2D structure of 1bj1 and Ginkgolide C interaction

Protein interaction with Isorhamnetin.

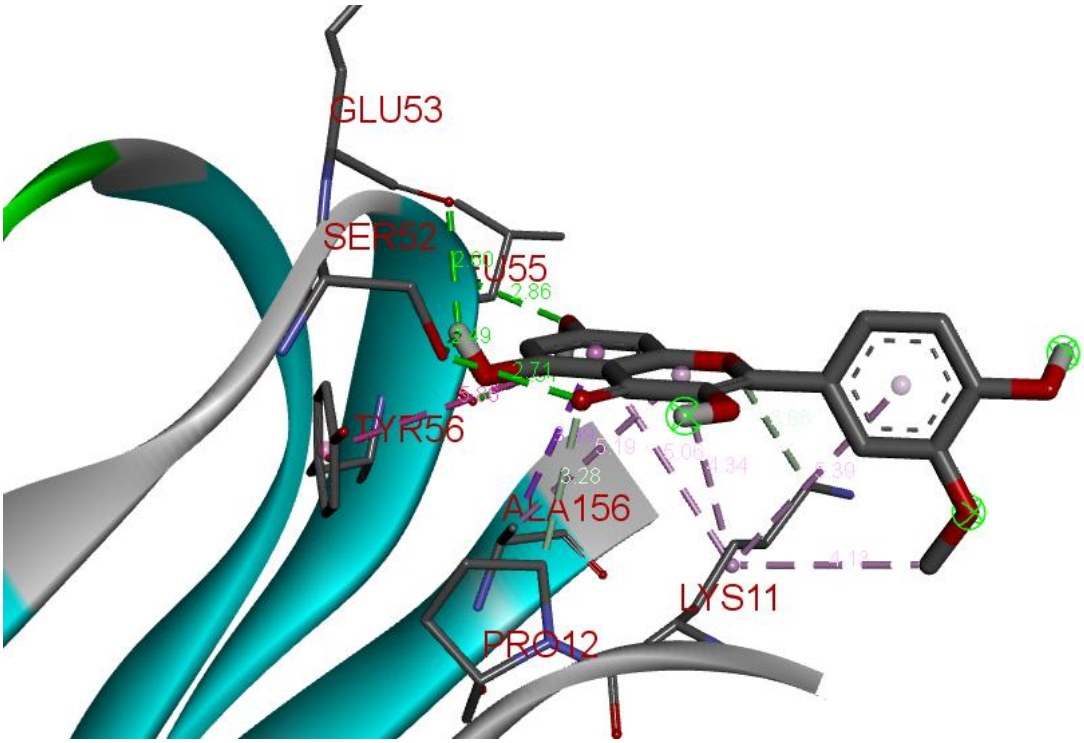

Figure 39 1gfw and Isorhamnetin interaction

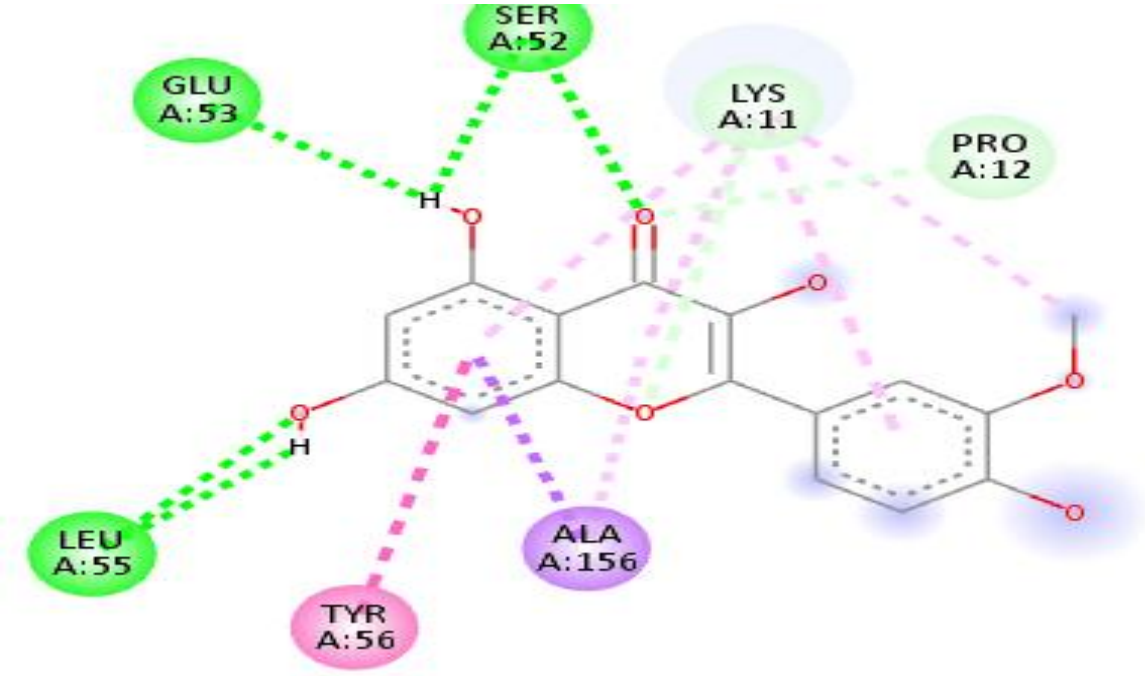

Figure 40 2D structure of 1gfw and Isorhamnetin interaction

Protein interaction with Kaempferol.

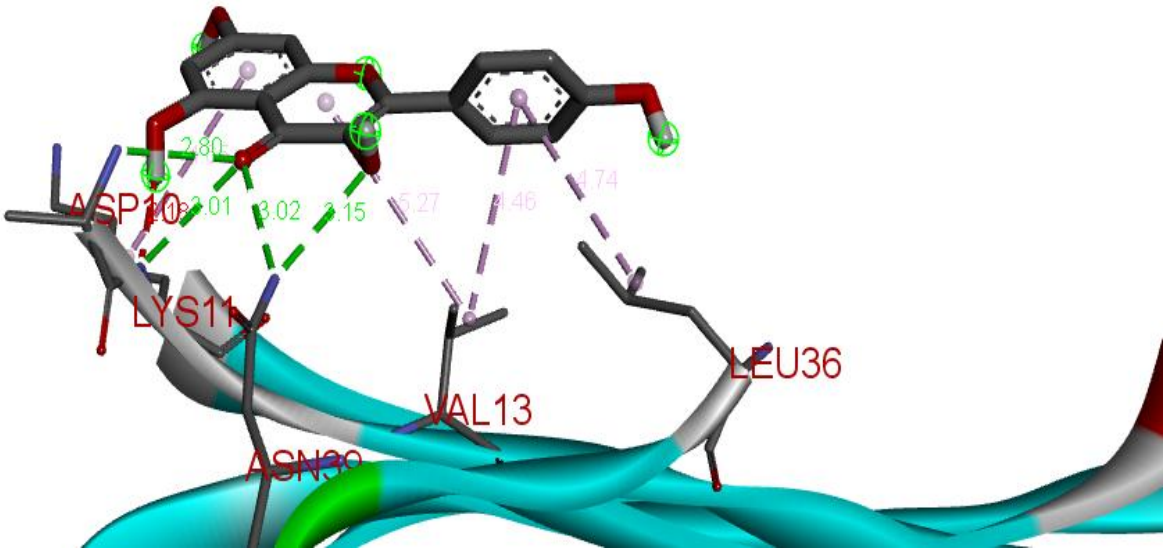

Figure 41 1gfw and Kaempferol interaction

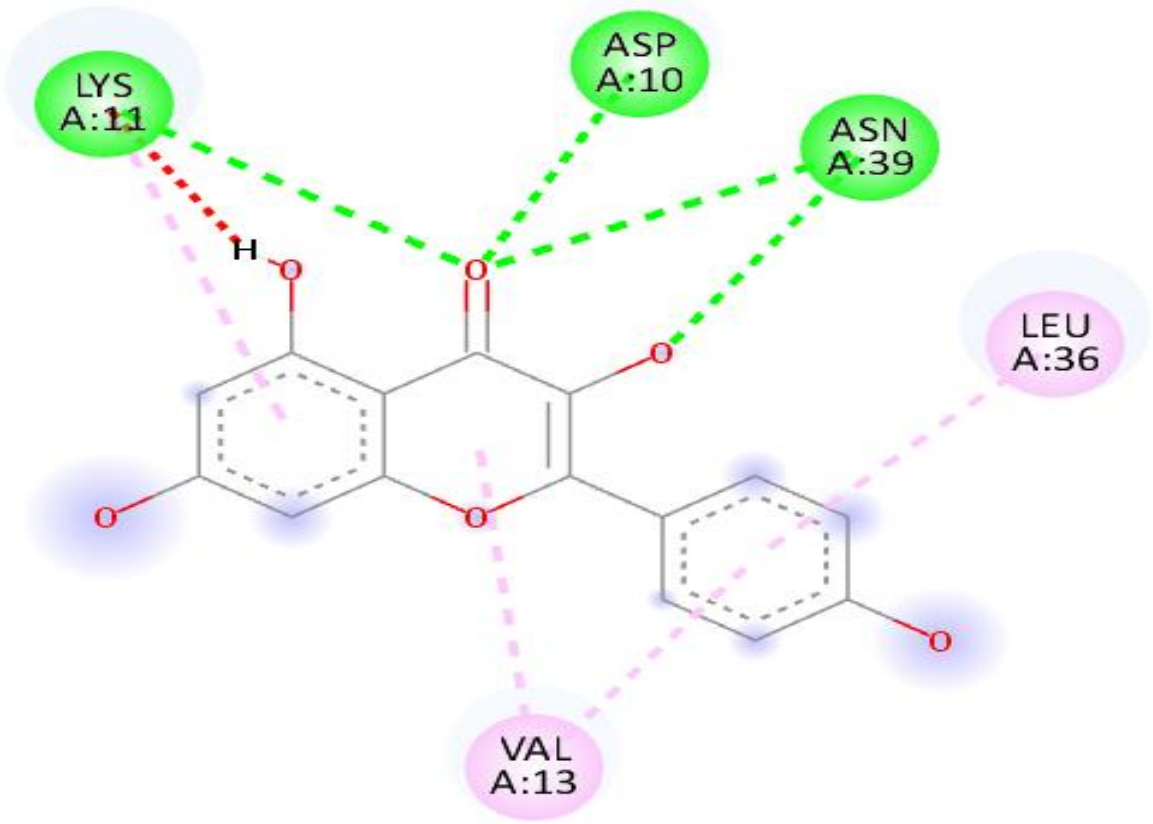

Figure 42 2D structure of 1gfw and Kaempferol interaction

Protein interaction with Myricetin.

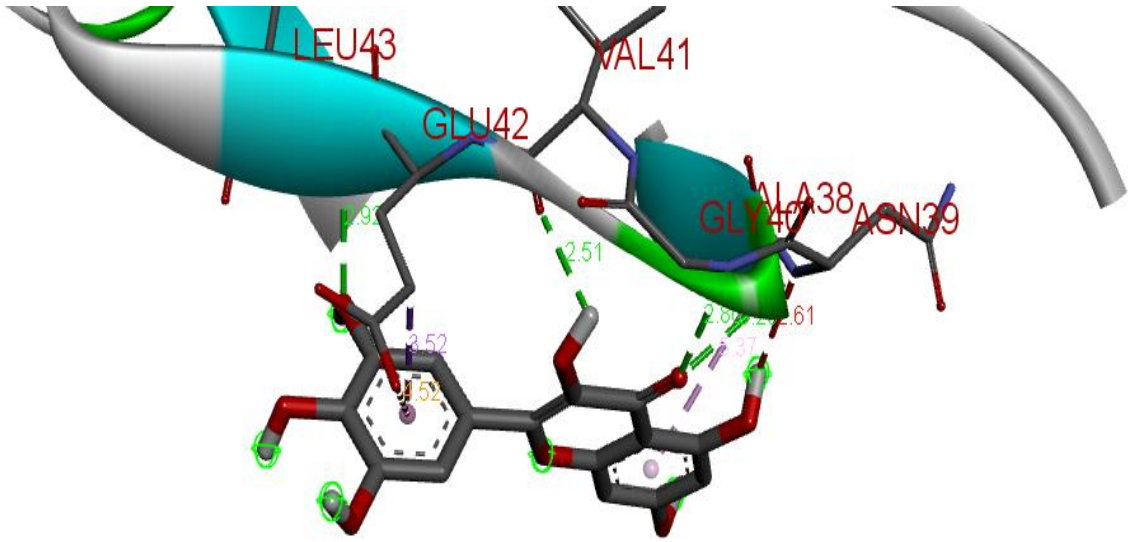

Figure 43 1gfw and Myricetin interaction

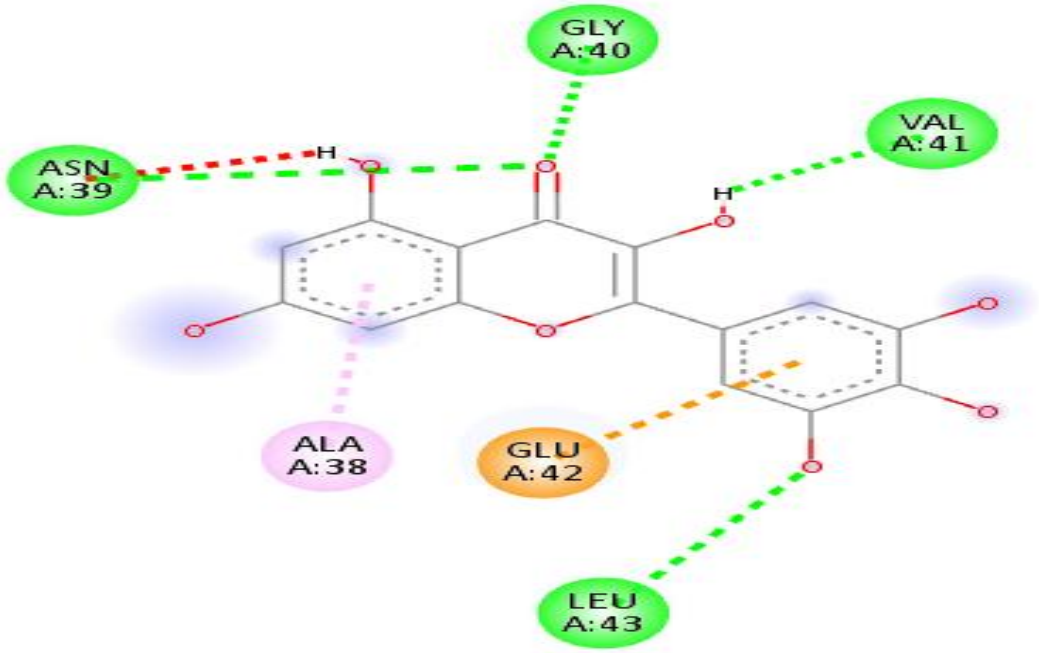

Figure 44 2D structure of 1gfw and Myricetin interaction

Protein interaction with Quercetin.

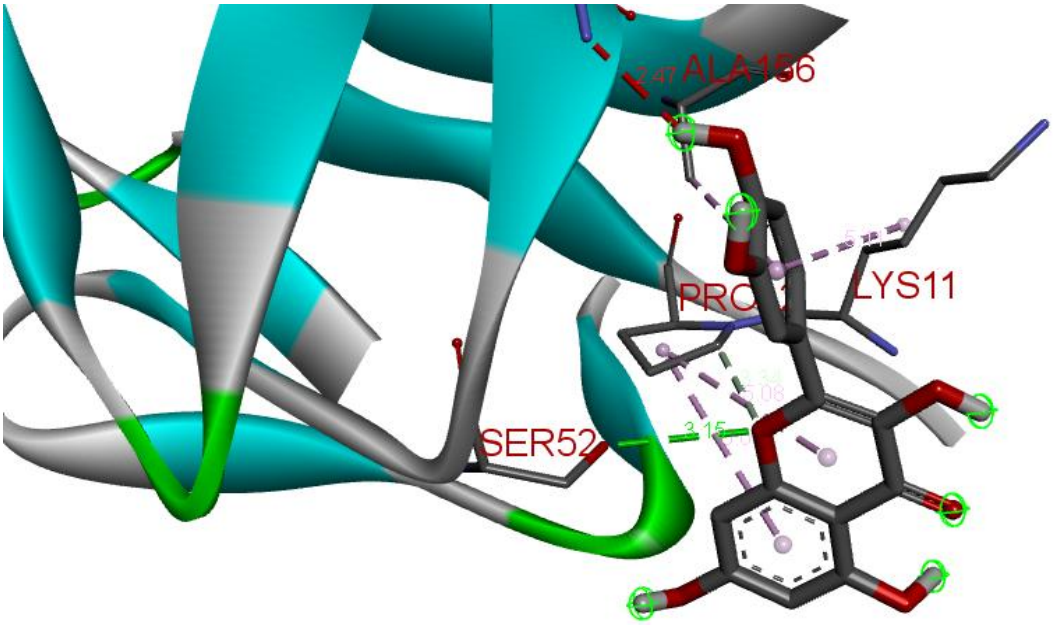

Figure 45 1gfw and Quercetin interaction

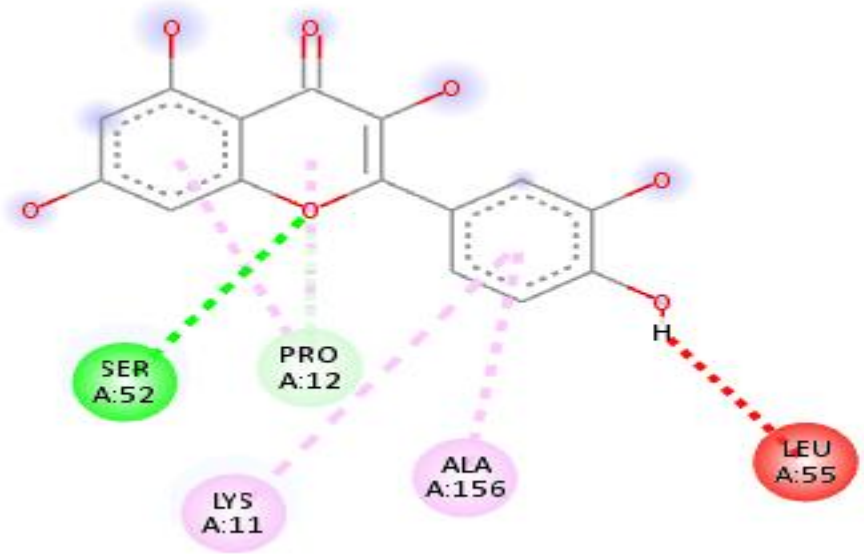

Figure 46 2D structure of 1gfw and Quercetin interaction

Protein interaction with Shikimic acid.

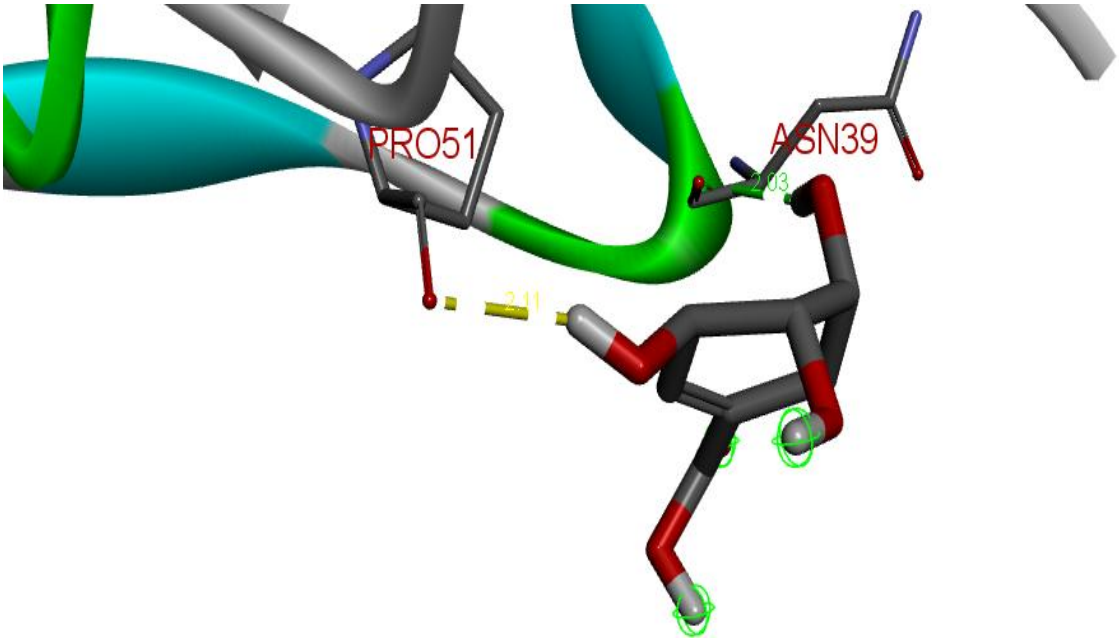

Figure 47 1gfw and Shikimic acid interaction

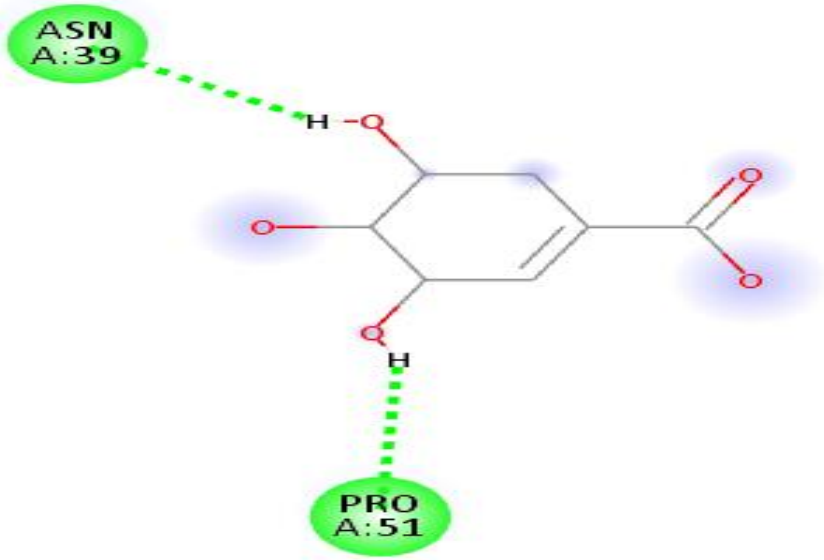

Figure 48 2D structure of 1gfw and Shikimic acid interaction

Table 6 Protein 2 docking (Caspase-3 complexed wth Isaton Sulphonamide inhabitor)

Protein 2 docking (1gfw)			
Compound name	**C.I.D**	**Binding energy**	**No. of H bond**
Bilobalide	73581	-4.6	4
Ginkgolic acid	5281858	-3.6	2
Ginkgolide A	115221	-5.0	2
Ginkgolide B	65243	-5.1	0
Ginkgolide C	24721502	-5.3	2

Isorhamnetin	5281654	-5.3	4
Kaempferol	5280863	-4.7	4
Myricetin	5281672	-4.9	4
Quercetin	5280343	-5.2	1
Shikimic acid	8742	-3.1	1

3.7.3 2az5 and ligand interaction

2az5 is Tumour Necrosis Factor-aplha (TNF-alpha). Protein interaction with Bilobalide compound.

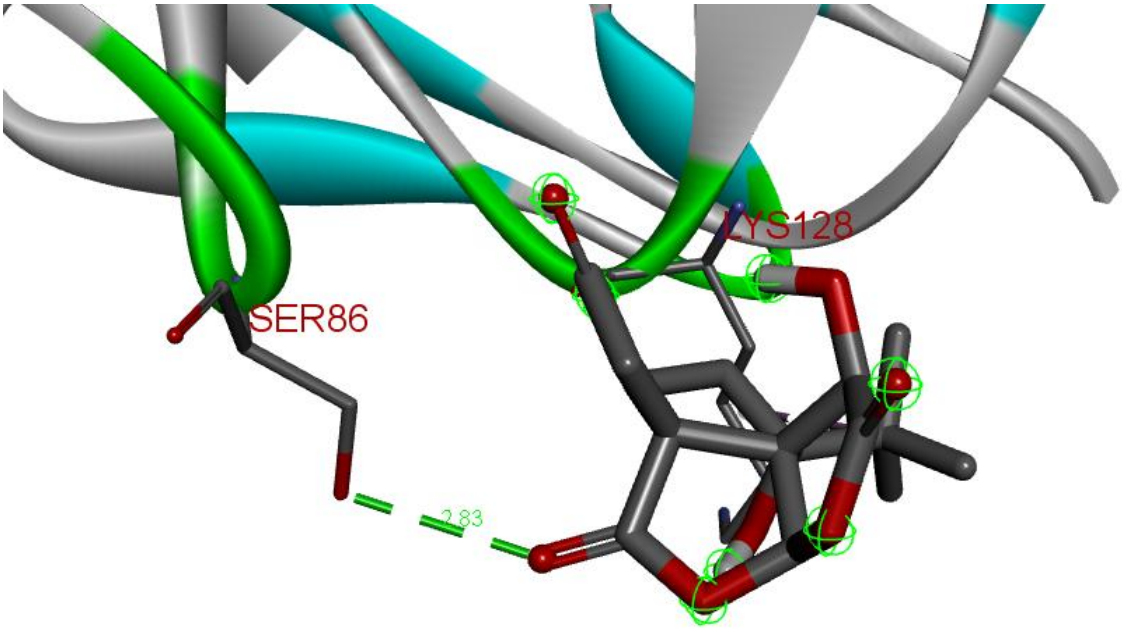

Figure 49 2az5 and Bilobalide interaction

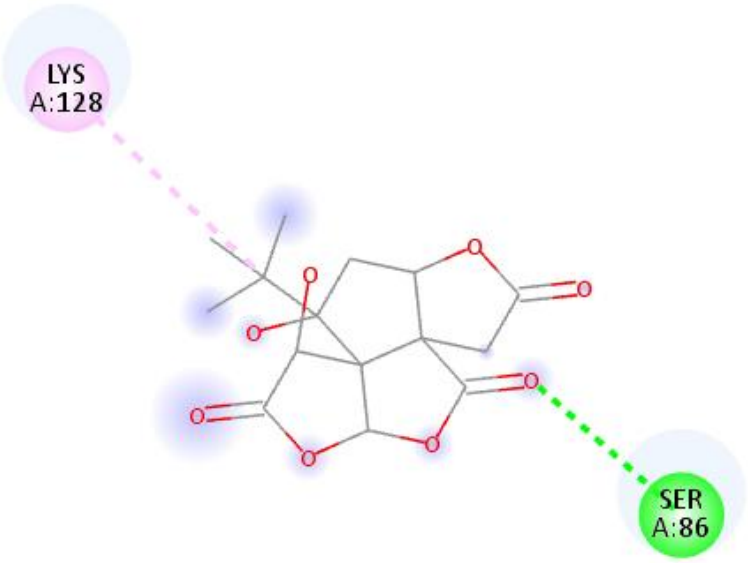

Figure 50 2D structure of 2az5 and Bilobalide interaction

Protein interaction with Ginkgolide A.

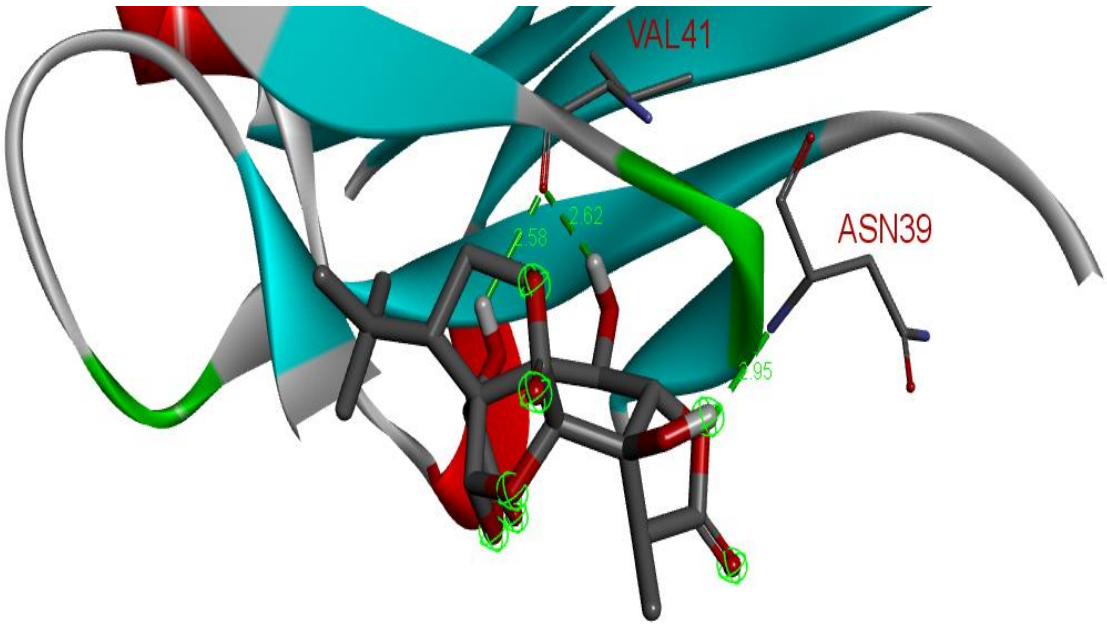

Figure 51 2az5 and Ginkgolide B interaction

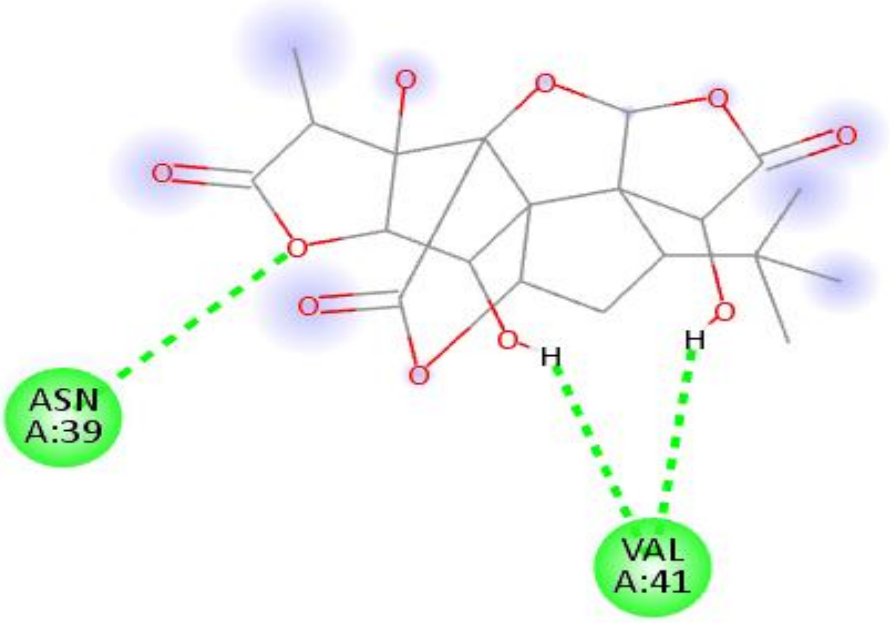

Figure 52 2D Structure of 2az5 and Ginkgolide B interaction

Protein interaction with Ginkgolide C.

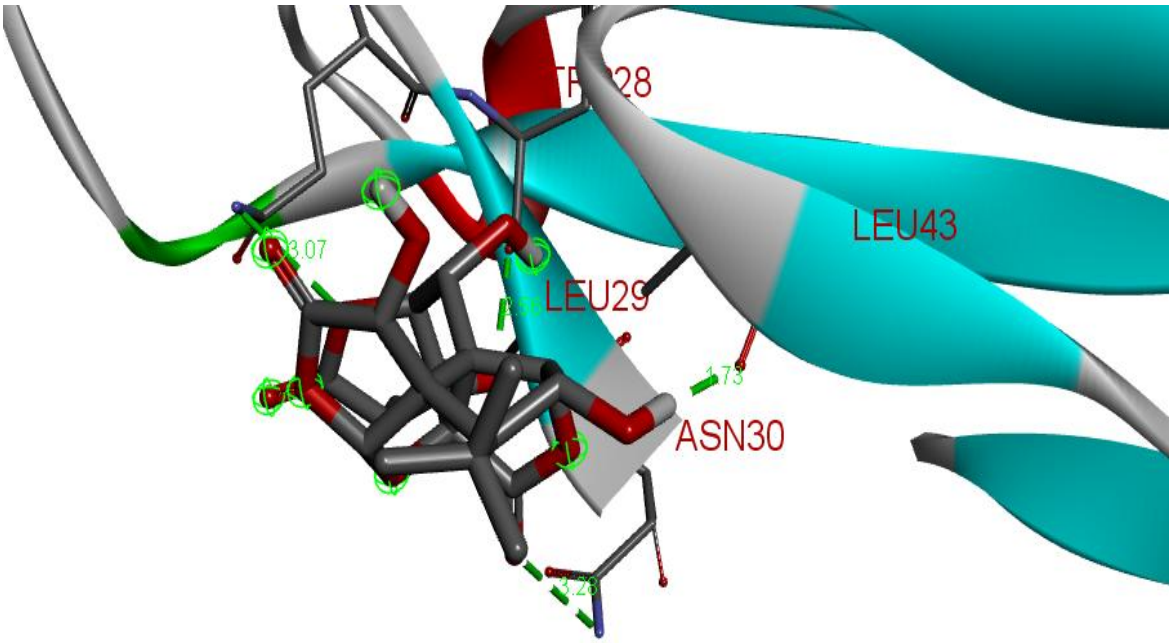

Figure 53 2az5 and Ginkgolide C interaction

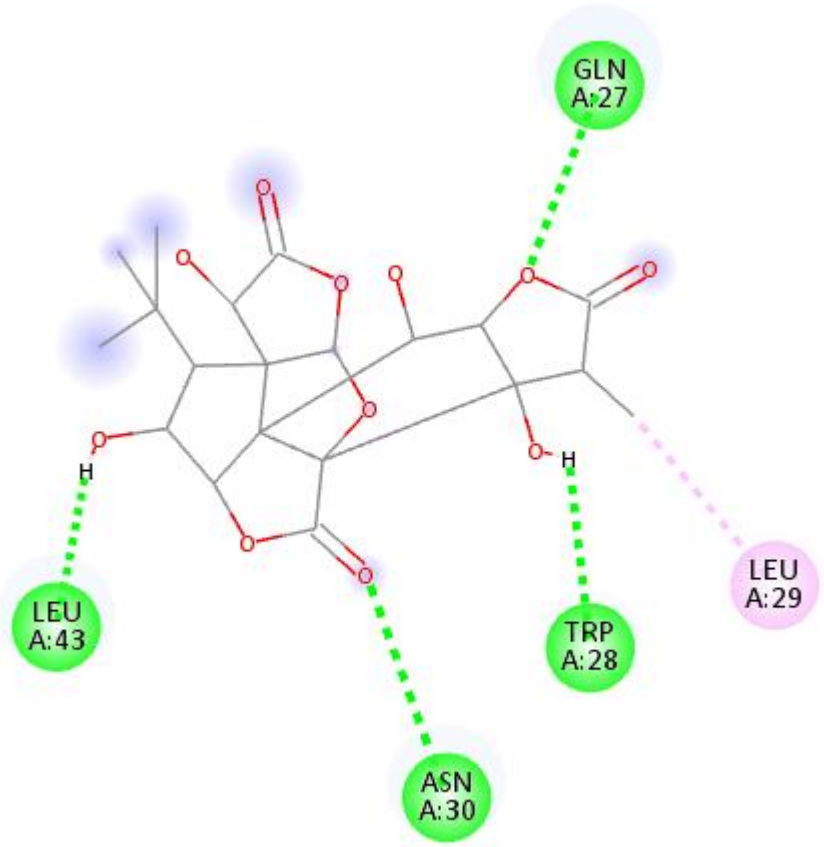

Figure 54 2D Structure of 2az5 and Ginkgolide C interaction

Protein interaction with Isorhamnetin.

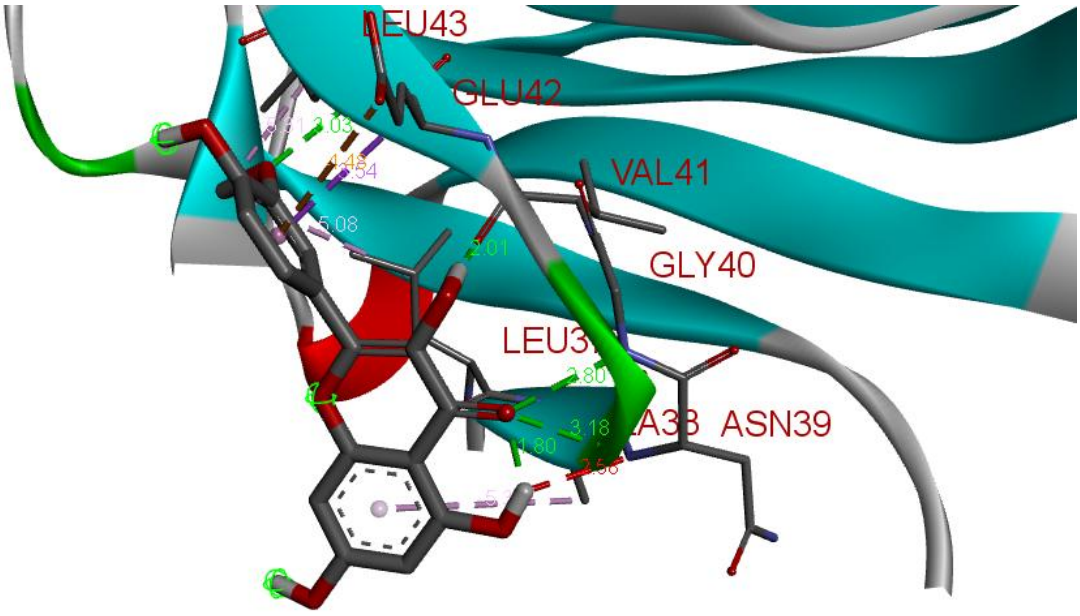

Figure 55 2az5 and Isorhamnetin interaction

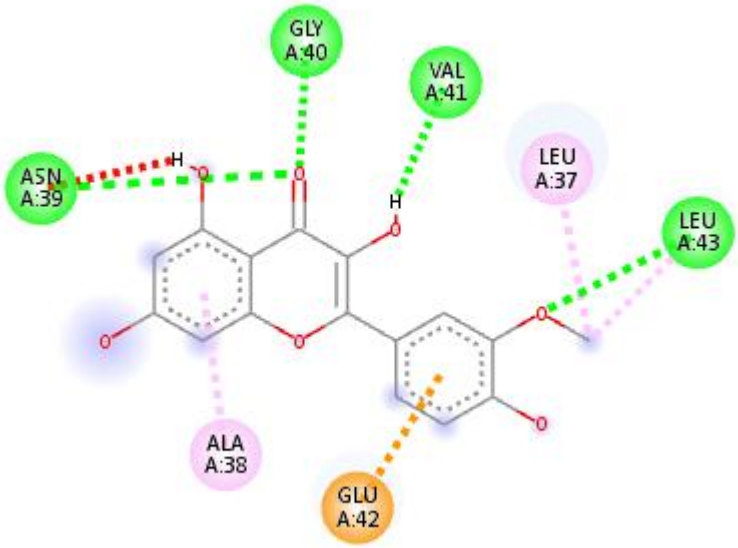

Figure 56 2D structure of 2az5 and Isorhamnetin interaction

Protein interaction with Kaempferol.

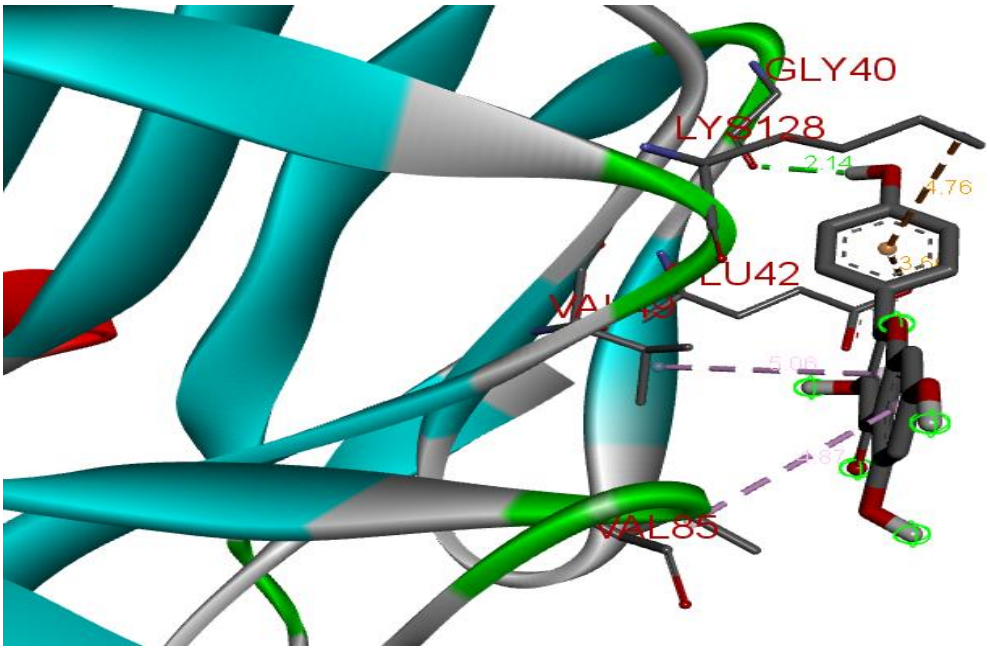

Figure 57 2az5 and Kaempferol interaction

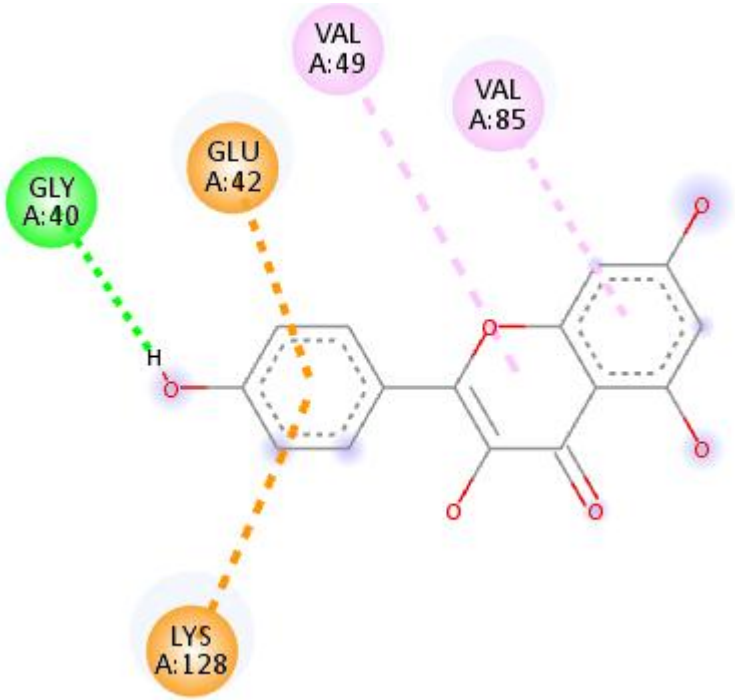

Figure 58 2D structure of 2az5 and Kaempferol interaction

Protein interaction with Myricetin.

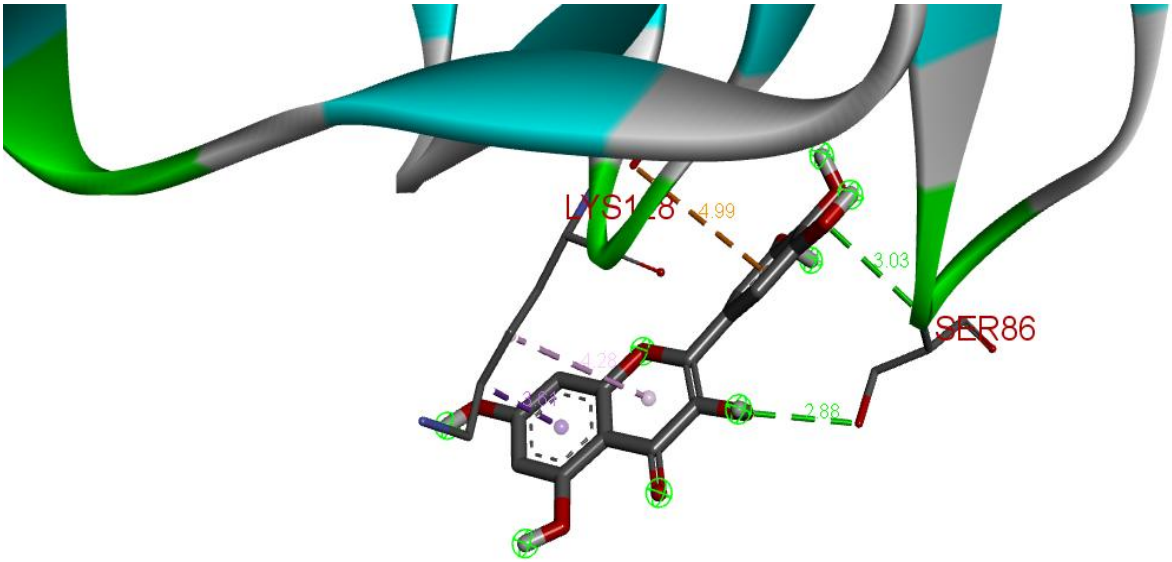

Figure 59 2az5 and Myricetin interaction

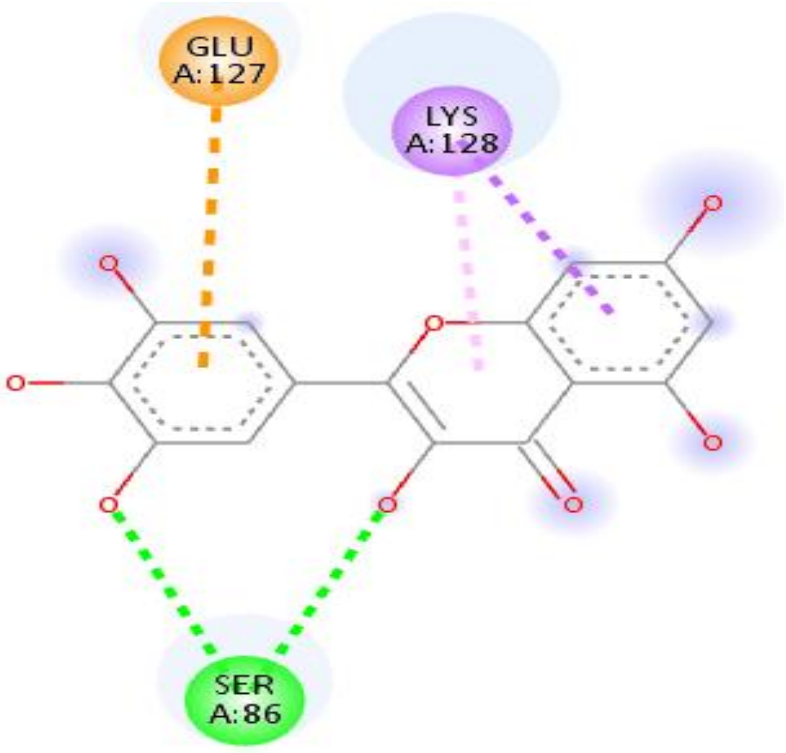

Figure 60 2D structure of 2az5 and Myricetin interaction

Table 7 Protein 3 docking (TNF-alpha)

Protein 3 docking (2az5)			
Compound name	**C.I.D**	**Binding energy**	**No. of H bond**
Bilobalide	73581	-4.1	1
Ginkgolic acid	5281858	-3.1	1
Ginkgolide B	65243	-5.3	3
Ginkgolide C	24721502	-6.1	3
Isorhamnetin	5281654	-5.1	5
Kaempferol	5280863	-4.9	1
Myricetin	5281672	-4.8	2

3.7.4 3dcy and ligand interaction

3dcy is TP53- induced glycolysis and apoptosis regulator (TIGAR). Protein interaction with Bilobalide compound.

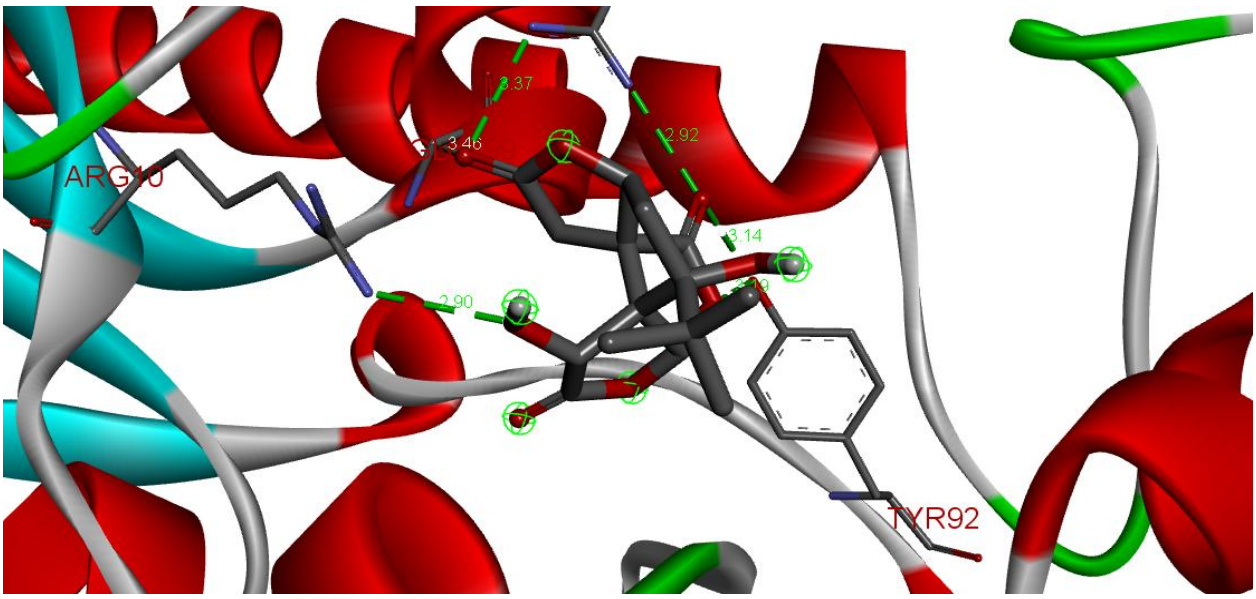

Figure 61 3dcy and Bilobalide interaction

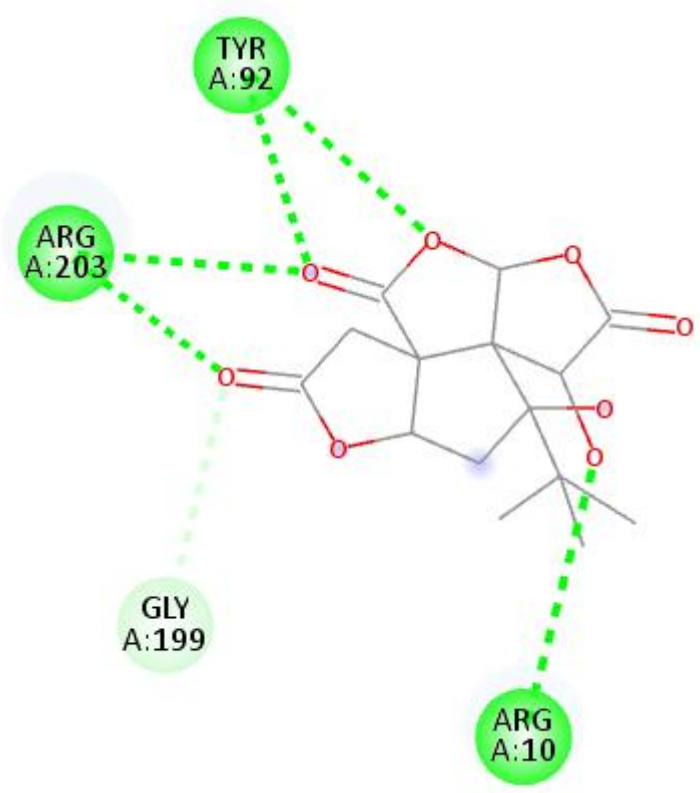

Figure 62 2D structure of 3dcy and Bilobalide interaction

Protein interaction with Ginkgolide A.

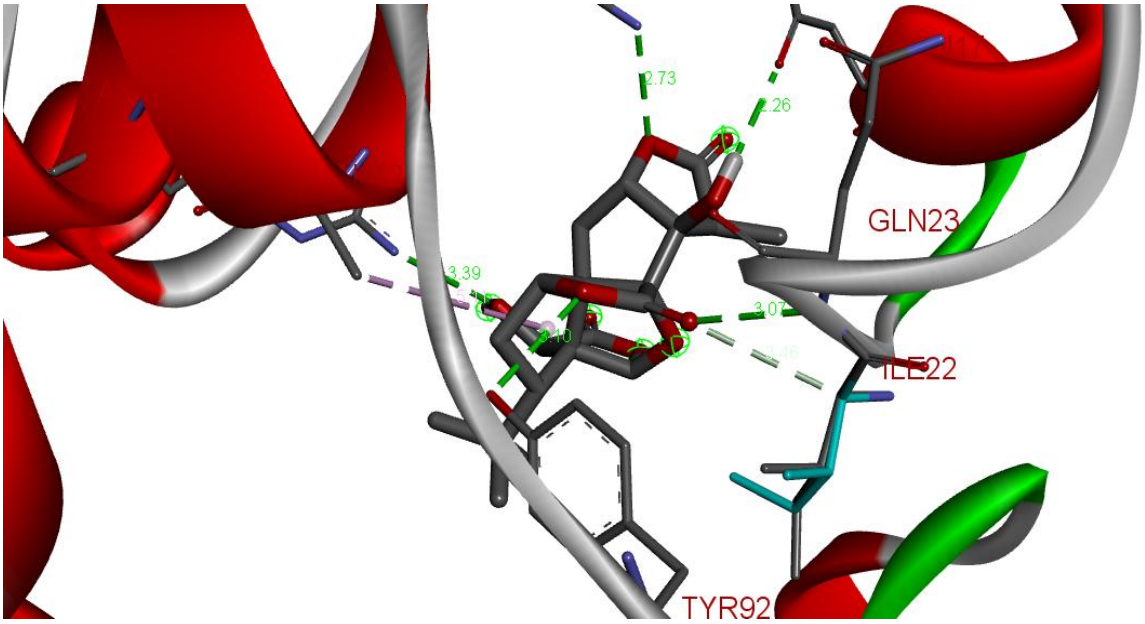

Figure 63 3dcy and Ginkgolide A interaction

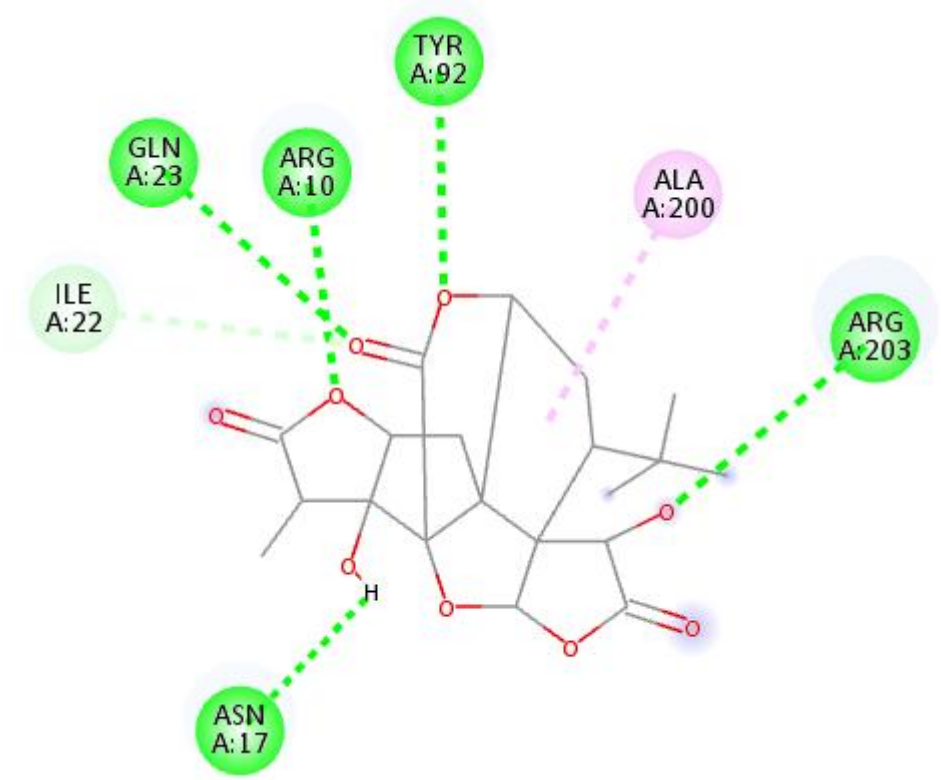

Figure 64 2D structure of 3dcy and Ginkgolide A interaction

Protein interaction with Ginkgolide B.

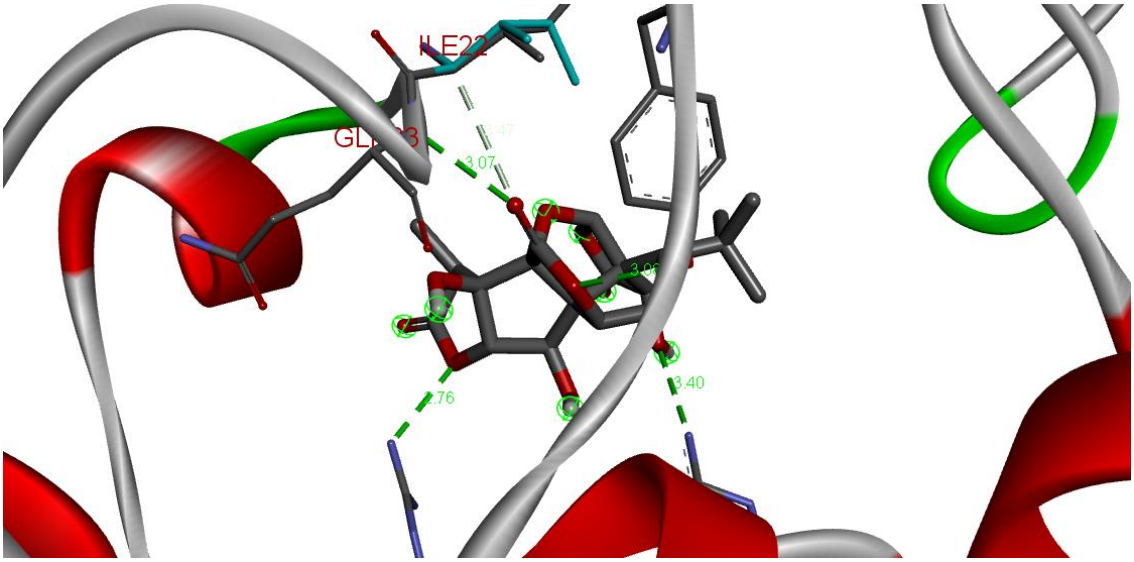

Figure 65 3dcy and Ginkgolide B interaction

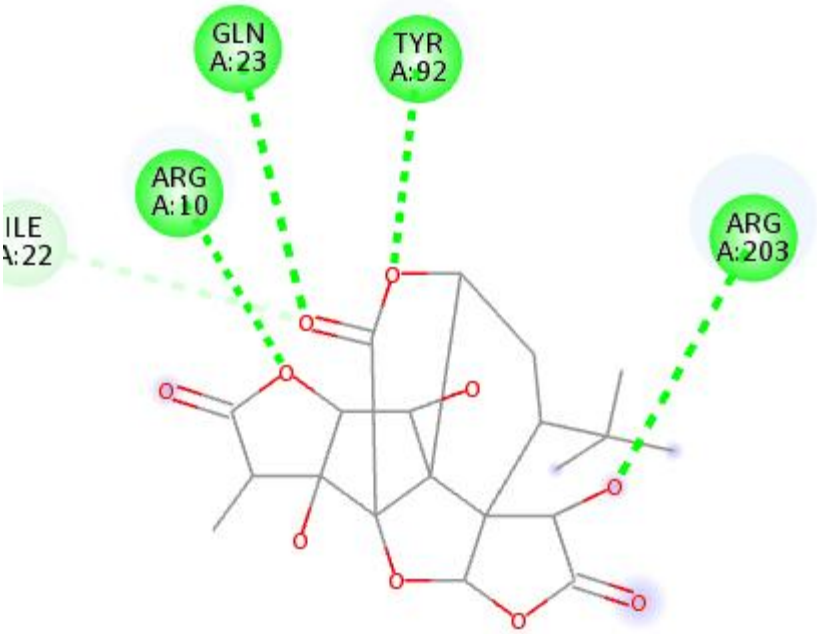

Figure 66 2D structure of 3dcy and Ginkgolide B interaction

Protein interaction with Ginkgolide C.

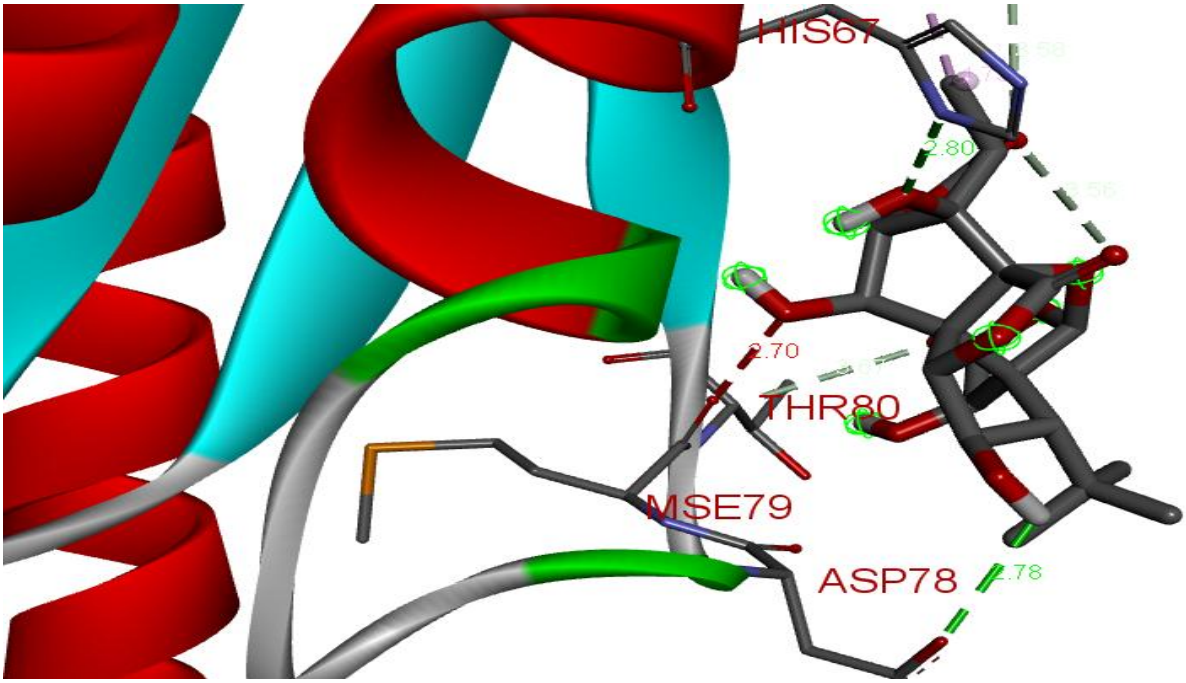

Figure 67 3dcy and Ginkgolide C interaction

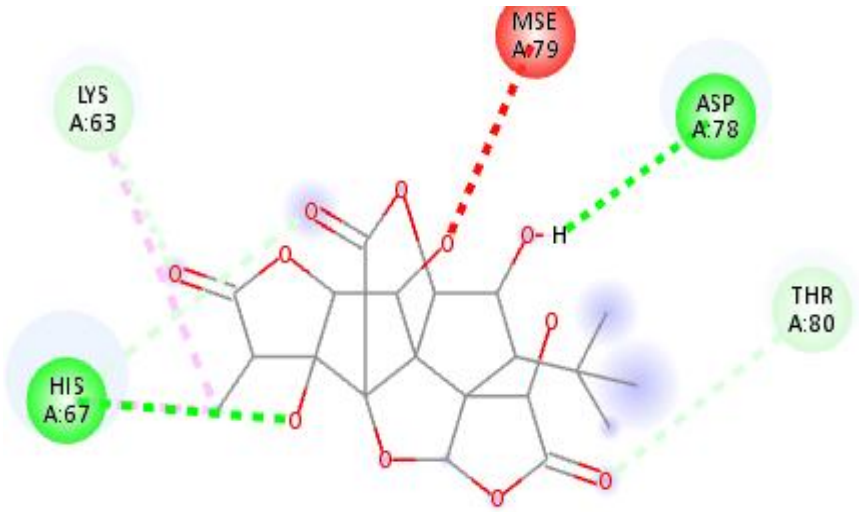

Figure 68 2D structure of 3dcy and Ginkgolide C interaction

Protein interaction with Isorhamnetin.

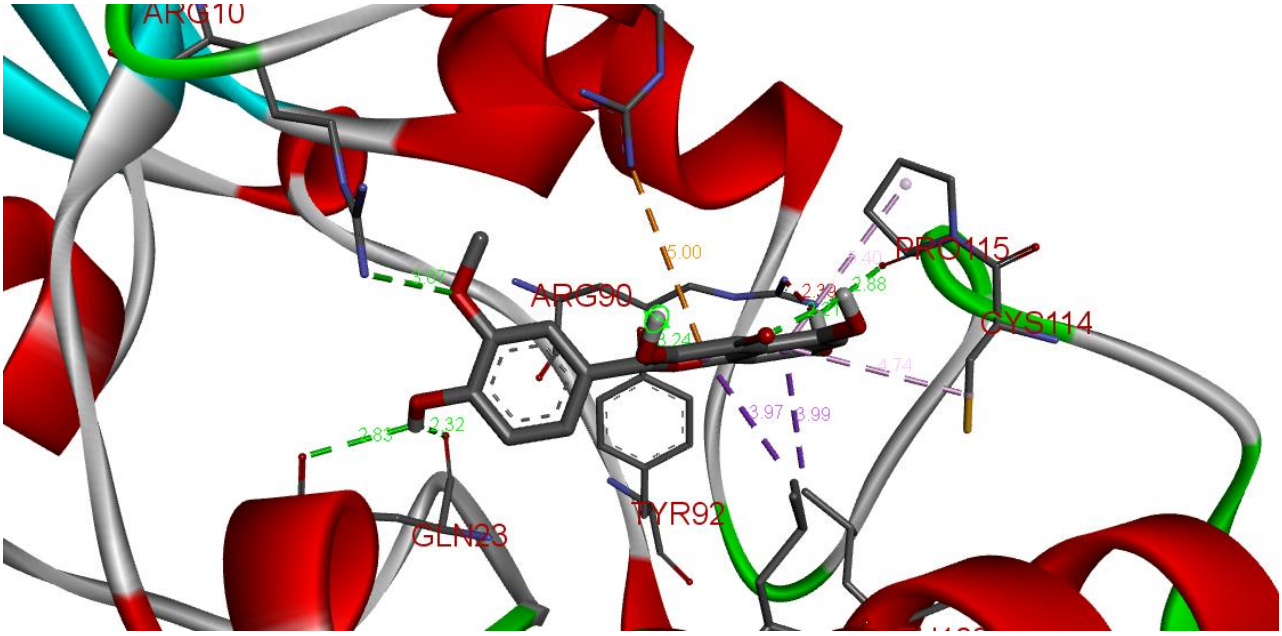

Figure 69 3dcy and Isorhamnetin interaction

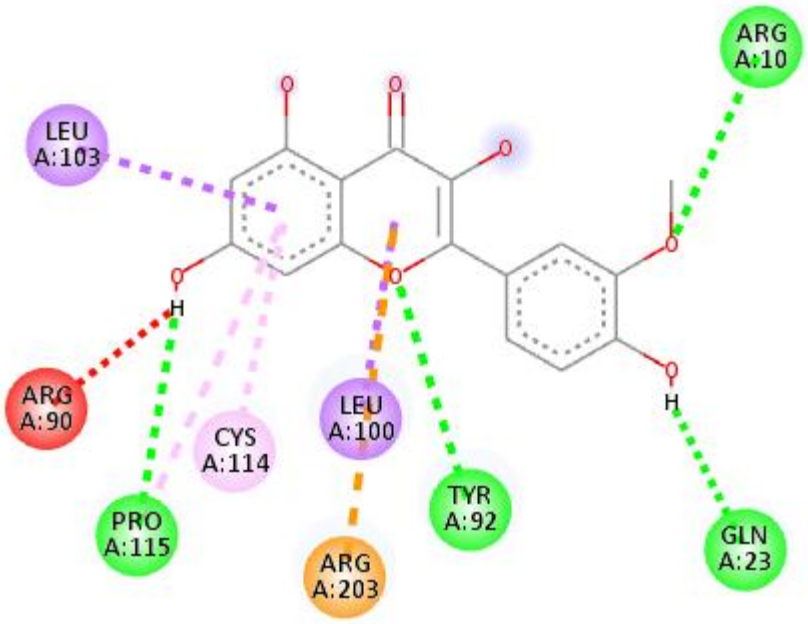

Figure 70 2D structure of 3dcy and Isorhamnetin interaction

Protein interaction with Kaempferol.

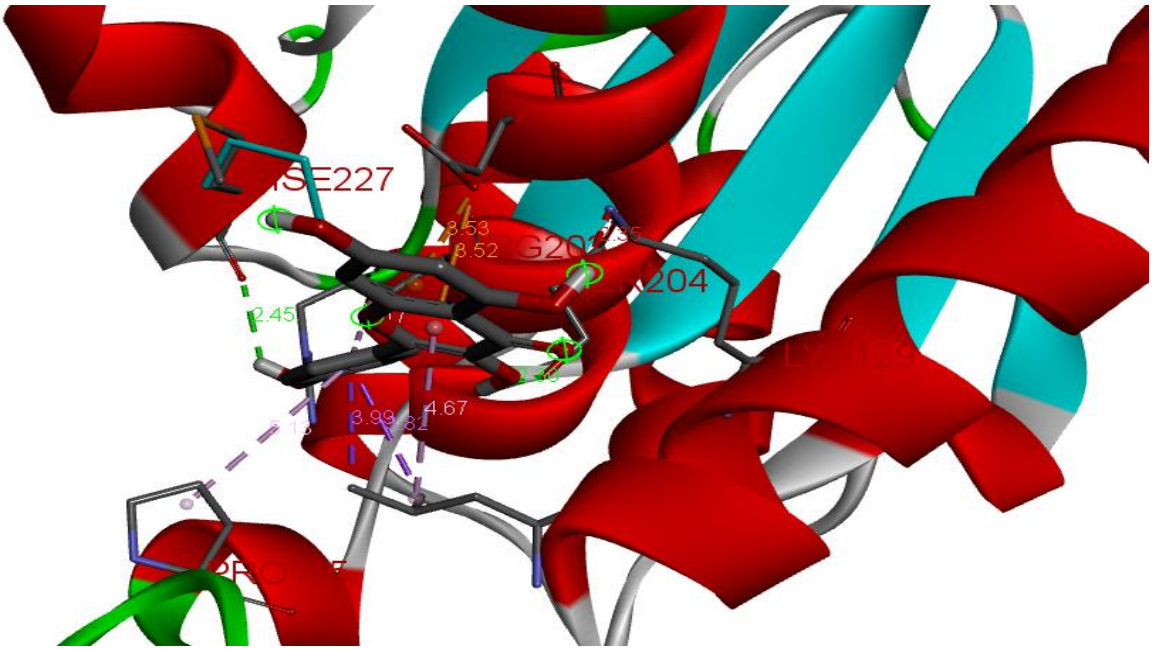

Figure 71 3dcy and Kaempferol interaction

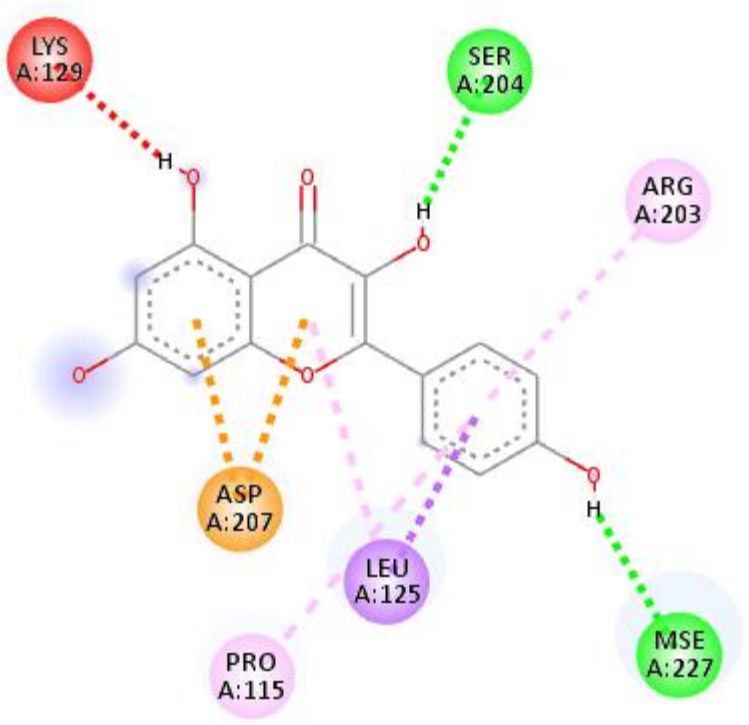

Figure 72 2D structure of 3dcy and Kaempferol interaction

Protein interaction with Myricetin.

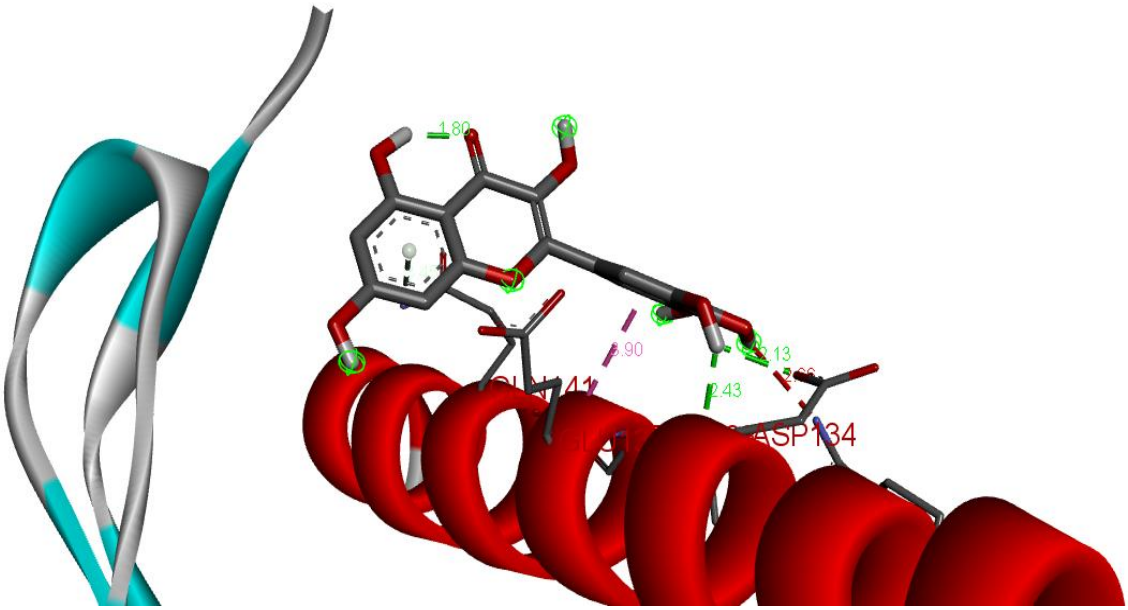

Figure 73 3dcy and Myricetin interaction

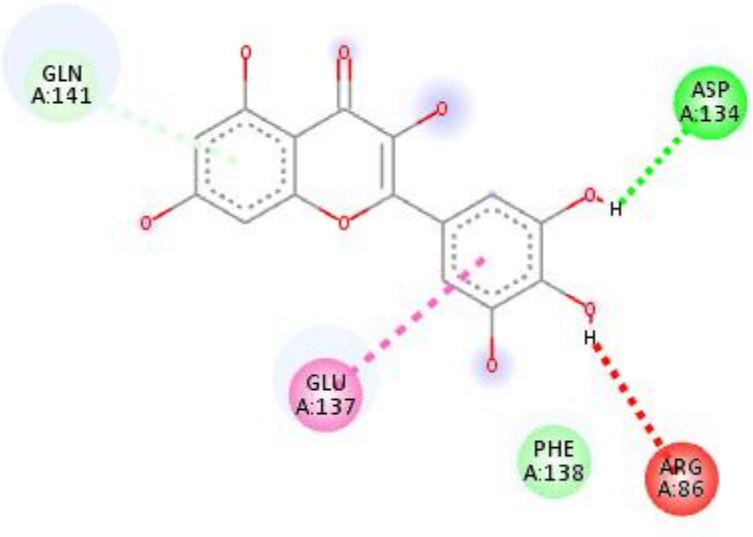

Figure 74 2D structure of 3dcy and Myricetin interaction

Protein interaction with Quercetin.

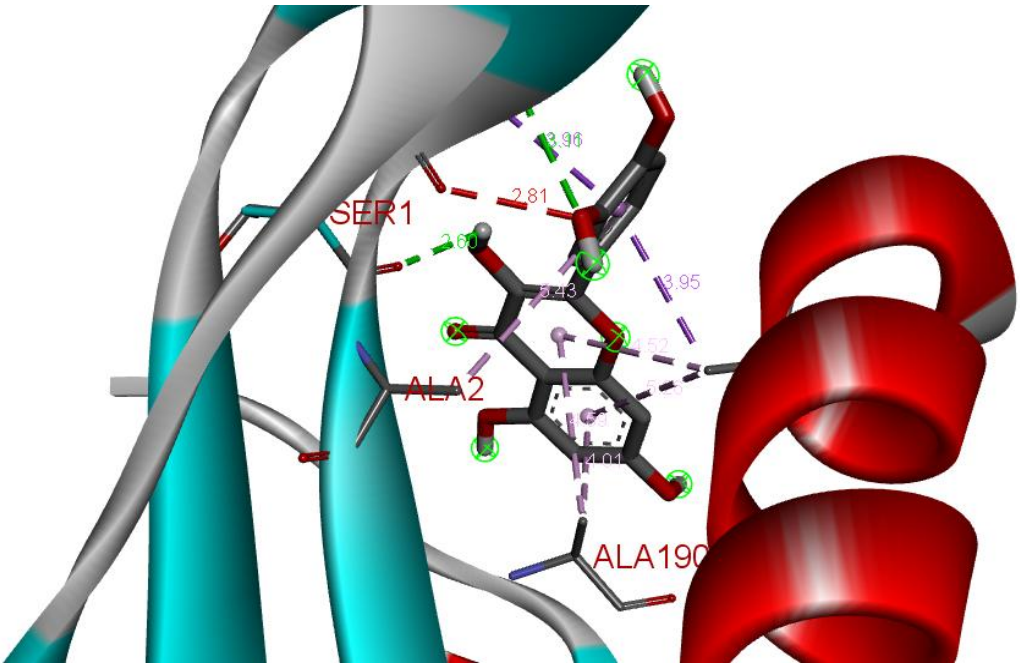

Figure 75 3dcy and Quercetin interaction

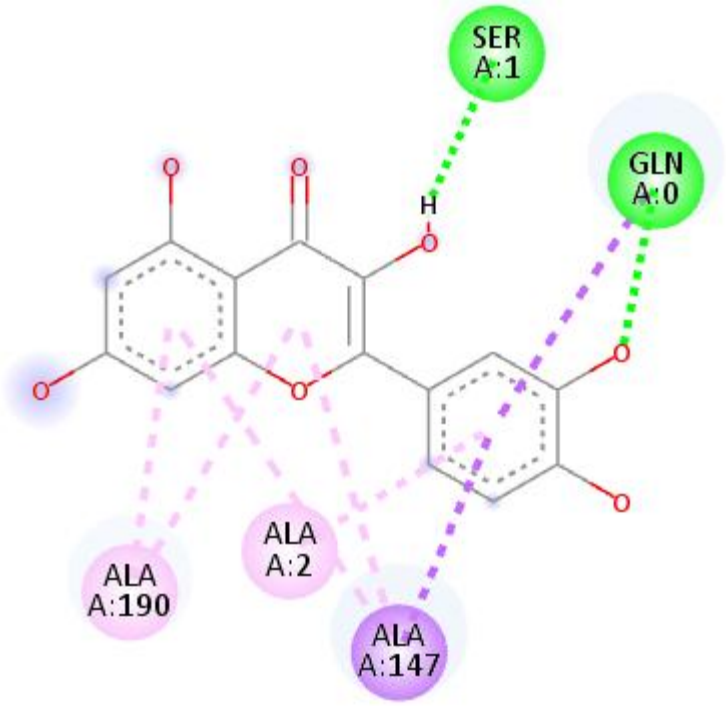

Figure 762D structure of 3dcy and Quercetin interaction

Protein interaction with Shikimic acid.

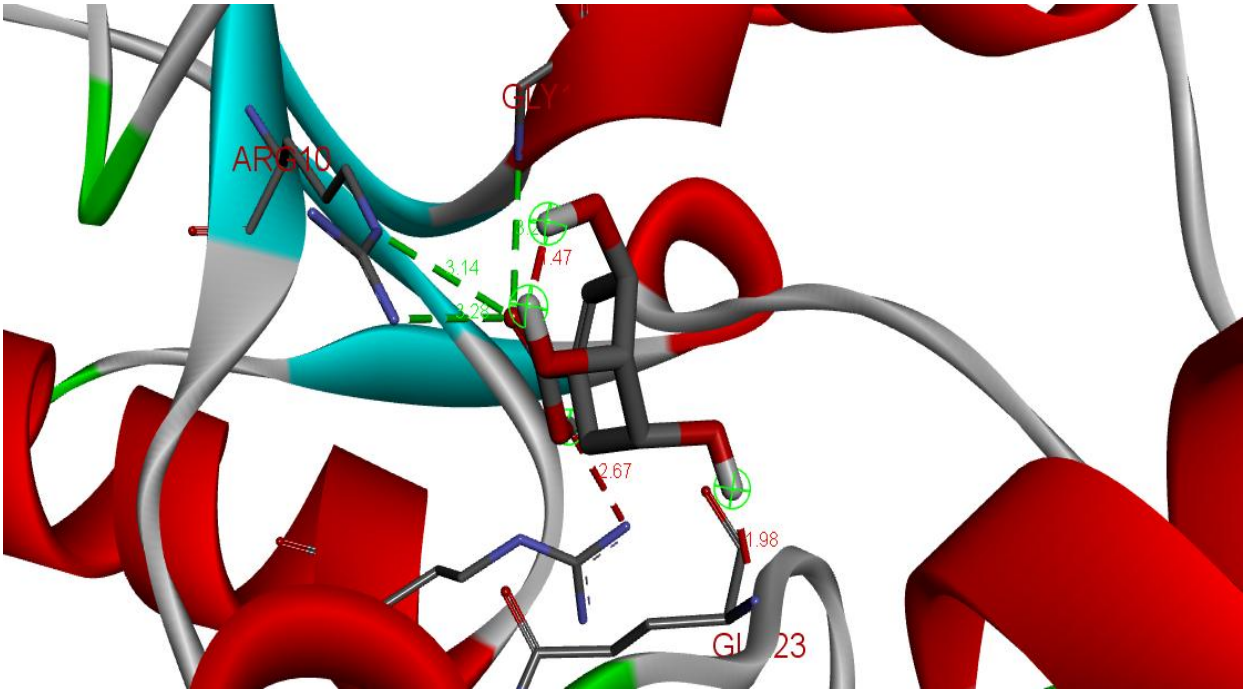

Figure 77 3dcy and Shikimic acid interaction

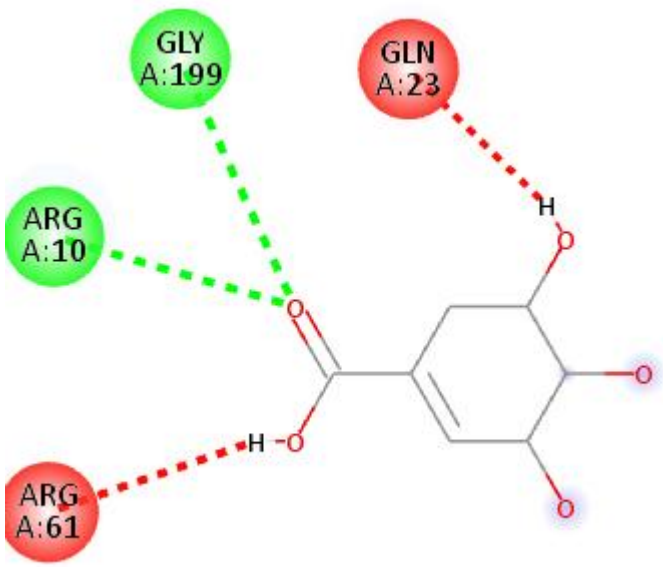

Figure 78 2D structure of 3dcy and Shikimic acid interaction

Table 8 Protein 4 docking (TIGAR)

Protein 4 docking (3dcy)			
Compound name	**C.I.D**	**Binding energy**	**No. of H bond**
Bilobalide	73581	-9.4	5
Ginkgolic acid	5281858	-6.2	1
Ginkgolide A	115221	-9.5	5
Ginkgolide B	65243	-9.7	4
Ginkgolide C	24721502	-6.5	2
Isorhamnetin	5281654	-7.7	5
Kaempferol	5280863	-6.7	2
Myricetin	5281672	-6.1	3
Quercetin	5280343	-6.9	2
Shikimic acid	8742	-6.4	3

Chapter 4

Discussion

4 Discussion

Skin cancer incidence is rising significantly due to increased UV exposure, genetic predisposition, and environmental factors. Current treatments, including surgical excision, chemotherapy, and targeted therapies, often face limitations like side effects, resistance, and recurrence. This study highlights the potential of Ginkgo Semen as an alternative therapy, leveraging its bioactive compounds for their anti-inflammatory, antioxidant, and anti-carcinogenic properties.While Ginkgo Semen has been studied for its therapeutic effects in various cancers, its application in skin cancer remains underexplored. The findings of this study provide a novel perspective on Ginkgo Semen's role in modulating molecular pathways associated with skin cancer, such as p53 signaling, PI3K-Akt signaling, and MAPK signaling, which are critical in cancer cell survival and proliferation (Wang et al., 2024).

Network pharmacology revealed key targets like TP53, VEGFA, AKT1, and MAPK, central to the biological processes of inflammation, apoptosis, and angiogenesis. These findings suggest that Ginkgo Semen not only addresses skin cancer progression but also offers potential in mitigating drug resistance and synergizing with existing therapies (Marques et al., 2024). The study successfully integrates bioinformatics and network pharmacology to identify multi-target mechanisms of Ginkgo Semen. This holistic approach enhances the understanding of its therapeutic potential, paving the way for more effective and safer treatment strategies.This research is computational and theoretical, lacking experimental validation. While network pharmacology provides valuable insights, in vivo studies are necessary to confirm the predicted interactions and therapeutic effects of Ginkgo Semen compounds.

Future research should focus on validating these findings through experimental studies and exploring Ginkgo Semen's synergistic effects with conventional therapies. Additionally, personalized medicine approaches informed by network pharmacology should be investigated to optimize treatment regimens for individual patients.

Chapter 5

Conclusion

5 Conclusion

This study highlights the therapeutic potential of Ginkgo Semen in addressing the complex molecular landscape of skin cancer. Through the application of network pharmacology, key targets such as TP53, VEGFA, AKT1, IL6, and MAPK were identified, along with their involvement in critical pathways like p53 signaling, PI3K-Akt signaling, and MAPK signaling. According to our docking results,it can be used on TIGAR protein to treat skin cancer. These findings emphasize Ginkgo Semen's capacity to modulate essential processes such as inflammation, apoptosis, and angiogenesis, which are central to skin cancer progression and treatment.

The integrative analysis demonstrated that Ginkgo Semen's bioactive compounds possess a multi-target therapeutic profile, making it a promising candidate for addressing challenges in skin cancer treatment, such as drug resistance and tumor recurrence. Additionally, network pharmacology provided a framework for understanding Ginkgo Semen's interactions within the broader biological system, paving the way for the development of personalized and safer therapeutic strategies. Ginkgo Semen represents a valuable resource for advancing skin cancer therapy by targeting multiple pathways simultaneously. Future research should focus on experimental validation of these targets, exploring the synergistic effects of Ginkgo Semen with conventional treatments, and assessing its clinical efficacy. These efforts will further solidify its role as a novel and complementary approach in skin cancer management.

Chapter 6

References

6 References

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