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Repurposing the Anti-Fungal Drug Itraconazole for the Treatment of Skin Cutaneous Melanoma: An in-Silico Study

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Abstract:

- ***Context:***
  Itraconazole, a triazole antifungal drug, is being explored for its anti-cancer properties through in-silico approaches.

- ***Aims:***
  To investigate the repurposing potential of itraconazole against Skin Cutaneous Melanoma (SKCM) using network pharmacology and molecular docking.

- ***Methods and Material:***
  Target genes were identified using SwissTargetPrediction and TargetNet. SKCM-associated genes were collected from GeneCards, DisGeNET, and OMIM. Protein-protein interaction (PPI) network, GO and KEGG enrichment analyses, gene expression profiling, and docking studies were performed.

- ***Statistical analysis used:***
  Survival analysis and stage-wise expression were assessed using GEPIA2.

- ***Results:***
  Key genes identified included TNF, CASP8, EGFR, MAPK14, MMP9. Docking studies confirmed strong binding with several targets including MMP9 and CASP3.

- ***Conclusions:***
  Itraconazole shows promise as a therapeutic candidate in SKCM via modulation of apoptosis and immune pathways. Further experimental validation is warranted.

Keywords: *Itraconazole, Skin Cutaneous Melanoma, Network Pharmacology, in-Silico, Molecular Docking, Gene Expression.*

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I. INTRODUCTION

Network pharmacology is a systems-level approach integrating bioinformatics, pharmacology, and systems biology to examine drug actions holistically. Unlike traditional one-drug-one-target paradigms, this methodology focuses on the interaction of multiple compounds with multiple targets. This is particularly relevant in complex diseases, such as cancer, where compensatory biological mechanisms often diminish single-target efficacy [15]. biological networks—such as gene, protein, and pathway maps—form the core of this analysis. With the help of computational tools and biological databases, researchers can identify critical targets and pathways, facilitating drug repurposing and the development of multi-target therapies [16]. Traditional medicine also benefits from network pharmacology, as many herbal formulations consist of numerous bioactive compounds. By mapping compound-target-pathway interactions, this method provides scientific

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insights into the poly-pharmacological nature of such remedies [17].

Network pharmacology also plays a vital role in evaluating off-target effects and toxicity. Understanding the broader interaction profile of a drug helps anticipate adverse reactions and guides safer drug development [18]. While data complexity and integration remain challenges, advances in AI and data science continue to enhance this field's capabilities. As medicine moves toward multitarget therapeutics, network pharmacology is pivotal in shaping modern drug discovery [19]. itraconazole is a broad-spectrum triazole antifungal initially developed in the 1980s as an improvement over ketoconazole [9]. It inhibits fungal cytochrome P450-dependent 14α-demethylase, disrupting ergosterol synthesis, a key fungal cell membrane component [10]. Its pharmacokinetic flexibility (oral and IV forms) and ability to treat both superficial and systemic infections make it widely used [11].

The drug is used in treating infections such as onychomycosis, histoplasmosis, blastomycosis, aspergillosis, and as prophylaxis in immunocompromised patients [11]. Case studies support its effectiveness: a leukaemia patient with invasive pulmonary aspergillosis recovered completely after switching to itraconazole from amphotericin B [2]. Another patient with sporotrichosis saw full resolution in three months [5]. A third case with histoplasmosis also showed marked improvement after six months of therapy [4]. Preclinical evidence confirms its antifungal potency against Aspergillus, Candida, and Cryptococcus spp. [12]. Importantly, itraconazole has shown anti-angiogenic and anti-inflammatory activity through Hedgehog pathway inhibition, suggesting potential for repurposing in cancer, particularly lung and basal cell carcinoma [6]. Recent data also indicate anti-neuroinflammatory effects, broadening its scope in neurodegenerative diseases [1]. fungal infections pose a serious global health burden, especially in immunocompromised individuals. Invasive aspergillosis affects over 200,000 people annually, while histoplasmosis remains endemic in parts of the U.S. and Latin America [8,14]. Candida infections are a major cause of hospital-acquired illness [7], and superficial infections like tinea and onychomycosis impact millions globally [3]. given its broad efficacy and potential for repurposing, itraconazole continues to play a central role in antifungal therapy and beyond.

II. MATERIALS AND METHODS

A. Network Pharmacology:

- *Identification of the Intersection Genes Between SKCM (Skin Cutaneous Melanoma) and Itraconazole Compound:*

Potential targets linked to the compounds were taken from two prediction databases, TargetNet (http://targetnet.scbdd.com/) [20] and Swiss Target Prediction (http://www.swisstargetprediction.ch/) [21]. Three extensive databases were used to gather targets relevant to skin cancer: GeneCards (https://www.genecards.org/) [22], DisGeNet (https://www.disgenet.org/search), and Online Mendelian Inheritance in Man (OMIM, https://www.omim.org/) [23]. Using particular search terms like "SKCM," "Skin Cancer," "Melanoma," and "Skin Cutaneous Melanoma," the search for targets associated to skin cancer was carried out independently for each form of malignancy. UniProt IDs and gene symbols were acquired from the UniProt database (https://www.uniprot.org/) [24] after target identification. Duplicate targets were removed from the dataset in order to preserve data integrity. A Venn diagram was created using an online bioinformatics tool (https://bioinformatics.psb.ugent.be/webtools/Venn/), in order to visualize and examine the intersection between cancer targets connected to the itraconazole targets.

- *Constructing the Protein–Protein Interaction (PPI) Network:*

The obtained target genes were submitted to the interaction gene search tool STRING (https://cn.string-db.org/) [25] to construct protein–protein interaction (PPI) networks. The PPI network data were imported into Cytoscape 3.7.2 software to construct the “components-target-disease” network of “SKCM” and “Itraconazole”. Essential active genes of "SKCM" and "Itraconazole" were found by filtering them according to their degree value using the CytoHubba plugin in Cytoscape, underscoring their importance in possible cancer treatment. Additionally, by choosing the components with a higher degree value, the essential elements were identified. Key modules of the PPI network were then identified using Cytoscape version 3.7.2 software's molecular complex identification (MCODE) tool, with default settings [26], [27], [28].

- *Gene Ontology (GO) Functional and Kyoto Encyclopaedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis:*

The STRING platform was utilized to conduct Gene Ontology (GO) and KEGG pathway analysis on the hub genes and the genes retrieved from MCODE tool. The analysis results were then visualized using the same platform [25]. We were better able to comprehend the functional enrichment and pathway affiliations of the genes through meticulous analysis and interpretation of the data, which gave us important information for investigating possible treatment targets for SKCM.

B. Computational Analysis of Gene Expression in SKCM:

The expression patterns and clinical importance of the identified core target genes were examined using publicly accessible databases in order to learn more about their possible involvement in different types of cancer. The seven key target genes' expression levels were examined using the GEPIA2 resource (http://gepia.cancer-pku.cn/ [29]. The SKCM cancer type was the main focus of this analysis. Furthermore, the Genotype-Tissue Expression (GTEx) project's expression levels in comparable normal tissues were assessed. With an emphasis on the pathological stage of the skin cancer, GEPIA2 was used to evaluate the relationship between gene expression and clinicopathological characteristics. Additionally, Kaplan–Meier survival analysis was used in GEPIA2 to examine the possible relationship between gene expression and OS. Based on the median

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expression level for each gene, patients were divided into groups with high and low expression. Hazard ratios (HRs) with 95% confidence intervals were computed and survival curves were compared using the log-rank test. The HR value shows how much more likely the high expression group is to die than the low expression group. An HR < 1 indicates that higher gene expression is linked to lower risk, whereas an HR > 1 indicates that lower risk is linked to higher gene expression. For the log-rank test, statistical significance was established at $p < 0.05$.

C. Docking Studies Protocol:

This study used computational docking analysis to look at the molecular interactions between core target proteins and ten Itraconazole. Target proteins three-dimensional crystal structures acquired from the Protein Data Bank [31] **(table 1)**. Using OpenBabel 2.4.1, the Itraconazole compound were transformed into dockable formats after being extracted from the PubChem database [32], [33]. Grid coordinates for each protein's active site were determined using the AutoDock Vina suite, and molecular docking was carried out using AutoDock Vina 1.1.2. Docking scores (kcal/mol) were used to evaluate binding affinities; higher scores denoted stronger interactions [34]. For every ligand, the pose with the lowest root mean square deviation (RMSD) value was chosen as the best scorer.

III. RESULTS

➢ *Investigation of the Network of Protein-Protein Interactions:*

This STRING network's edges, or connections, are coloured to represent several forms of interaction evidence. Green edges show database-curated interactions, while blue and purple edges show interactions that have been confirmed through experimentation. Red edges indicate co-occurrence within established pathways, while yellow edges come from text-mining. Stronger functional correlations are shown by thicker margins, which are correlated with the interaction confidence score's strength. The inferred protein roles in cancer-related pathways are more reliable because to this multi-layered technique. The Protein-Protein Interaction (PPI) network has 76 nodes and 132 edges, much higher than the expected 40 edges, showing it is highly enriched. Each protein connects with about 3.47 others, forming a biologically important system (fig 1). The clustering coefficient is 0.497, indicating proteins moderately group together. With a p-value of less than 1.0e-16, these interactions are very likely meaningful and not random, playing key roles in cellular processes, signalling, or disease mechanisms. This indicates that there are more interactions between your proteins than would be predicted from a random sample of proteins selected from the genome that are the same size and degree of distribution. An enrichment of this kind suggests that the proteins are at least somewhat related to one another physiologically.

➢ *Identification of Hub Genes from the Protein-Protein Interaction Network:*

Hub genes are important nodes in a network of protein-protein interactions (PPIs) that control a number of carcinogenic processes, including immune evasion, invasion, tumour growth, and metastasis. Finding these genes aids in the development of targeted treatments and better understanding of the progression of melanoma. A popular bioinformatics tool for ranking hub genes according to topological analysis is CytoHubba, a Cytoscape plugin (fig 2). The most linked and functionally important genes in melanoma were found by using degree centrality. HSP90AA1, EGFR, TNF, CASP3, and MMP2 were the top five (table 2) hub genes among them ; each is essential to the pathophysiology of melanoma. The gene with the highest connectivity, HSP90AA1 (Score: 17), is probably crucial to the development of melanoma. One important gene frequently linked to cancer cell signalling is EGFR (Score: 16). Participating in apoptosis, CASP3 (Score: 15) may be essential for the survival and resistance of melanoma. A significant inflammatory cytokine that suggests immunological involvement is TNF (Score: 14). Matrix Metalloproteinase 9 (MMP9) (Score: 12) is an essential enzyme that breaks down the extracellular matrix (ECM) and is implicated in tumor invasion, metastasis, and angiogenesis in a number of malignancies, including cutaneous melanoma of the skin.

➢ *Identification of Highly Interconnected Gene Cluster by MCODE Tool:*

The gene cluster found in the network image by the MCODE tool is a collection of closely related genes that are part of pathways linked to melanoma (fig 3). With an MCODE score of 5.2, the top-scoring cluster comprises six important genes: TNF, MMP9, MAPK8, EGFR, MAPK14, and CASP8. The progression of melanoma depends on these genes' strong involvement in apoptosis, cell proliferation, extracellular matrix remodelling, and inflammatory response.

➢ *Pathway Enrichment Analysis:*

To find out how itraconazole affects the treatment of skin cutaneous melanoma, gene ontology (GO) enrichment studies were performed on eight hub and MCODE genes. This led to the discovery of 45 terms in all GO categories, including 3 MFs and 42 BPs. The top ten enriched GO phrases were graphically displayed after these terms were chosen based on an adjusted p-value of less than 0.05. The enrichment results highlight several processes (fig 4) that are crucial in melanoma development, including responses to environmental stressors, immune modulation, and signalling pathways affecting tumour progression. SKCM is a very aggressive cancer with intricate molecular interactions that promote tumour growth and proliferation. A number of important molecular processes (fig 5) that play a major role in the biology of melanoma are highlighted by the enrichment analysis. Enzyme binding is one of the most enriched processes found (GO:0019899), and important genes including MAPK14, EGFR, CASP3, HSP90AA1, CASP8, MAPK8, and TNF are strongly implicated (FDR: 0.0018). These genes have a key role in controlling signalling pathways that affect the survival, proliferation, and death of cancer cells. The KEGG enrichment analysis identifies key biological pathways enriched in the given dataset (fig 6). The most significant pathways, ranked by false discovery rate (FDR), include: the IL-17 signalling pathway, TNF signalling

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pathway, PI3K-Akt signalling pathway, and p53 signalling pathway, which are highly relevant to melanoma progression and immune evasion.

- *In Silico Analysis of Hub Gene and MCODE genes Expression:*

The Gene Expression Profiling Interactive Analysis website (GEPIA2) was used to perform in silico analysis of hub gene expression and prognostic relevance using publicly accessible datasets. The seven primary target genes in SKCM and their corresponding normal tissues were analysed using box plots, which showed notable differences in expression patterns (fig 7). Hub genes significance in tumour growth, immune evasion, apoptosis resistance, and metastasis are highlighted by the examination of their variable expression patterns. MAPK14 and MAPK8, two important regulators of the MAPK signalling system, are increased in SKCM, which encourages uncontrolled melanoma cell proliferation and resistance to treatment. Melanoma is characterized by an overexpression of the extracellular matrix remodelling enzyme MMP9, which promotes tumour invasion and metastasis. Immune evasion and inflammation are encouraged by tumour necrosis factor (TNF), and elevated TNF expression may indicate that persistent inflammation plays a role in the development of melanoma. The main apoptosis regulators, caspase-3 and caspase-8, are downregulated in SKCM, which may indicate that mechanisms of programmed cell death are being suppressed. Elevated EGFR, a key oncogene linked to tumour growth and cell proliferation, is associated with SKCM and uncontrolled PI3K-AKT and MAPK signalling cascades. Additionally increased is the important chaperone HSP90AA1, which may be involved in drug resistance and tumour adaptation to stress. To improve the results of melanoma treatment, it is still essential to target these pathways with immune checkpoint inhibitors, apoptosis-inducing drugs, MMP inhibitors, and MAPK inhibitors.

According to the stage plot analysis (fig 8), CASP3, CASP8, MAPK14, and MMP9 exhibit a considerable increase in expression as melanoma progresses, suggesting their roles in stress adaption, metastasis, and apoptotic control. Later stages see a significant upregulation of MMP9, which promotes tumour invasion and extracellular matrix breakdown. MAPK14 activation is a crucial therapeutic target because it promotes melanoma survival under stress.TNF and EGFR, on the other hand, do not change with the stages, indicating that they play a part in early carcinogenesis as opposed to progression. Later stages show an increased trend in HSP90AA1, which is associated with resistance to therapy. These results point to MAPK inhibitors, medications that target MMP9, and HSP90 inhibitors as possible treatment approaches for metastatic melanoma. The prognosis of cancer is frequently impacted by gene expression patterns that affect immune response, apoptosis, and cell proliferation. In this survival analysis, hazard ratios (HRs), log-rank tests, and Kaplan-Meier survival curves are used to assess the prognostic value of CASP3, CASP8, EGFR, HSP90AA1, MAPK8, MAPK14, MMP9, and TNF. The hazard ratio (HR) shows whether increased gene expression raises or lowers survival risk, whereas the log-rank p-value evaluates statistical significance. According to this survival studies (fig 9), TNF and CASP8 are protective biomarkers that have a strong correlation with higher survival. As survival declines, EGFR's carcinogenic function is further supported. In this dataset, no significant survival relationships are found for other genes, such as CASP3, HSP90AA1, MAPK8, MAPK14, and MMP9.

- *Molecular Docking Study:*

Molecular docking was performed on seven key proteins using AutoDock Vina to evaluate ligand-binding affinities (fig 10). The strongest binding was observed with MMP9 (-8.1 kcal/mol), followed by CASP3 (-7.6 kcal/mol), and TNF (-7.2 kcal/mol). These proteins are classified as hub and/or MCODE genes, making them biologically significant and promising therapeutic targets. EGFR (-6.8 kcal/mol) and MAPK14 (-6.6 kcal/mol) also showed strong to moderate binding, further supporting their potential involvement in disease modulation. In contrast, CASP8 and HSP90AA1 exhibited poor docking scores (+7.2 and +1.6 kcal/mol, respectively), indicating weak or no binding under the current conditions.

IV. DISCUSSION

The melanoma architecture profoundly deviates from normal epidermal structure and function. In healthy skin, the stratified layers of the epidermis (stratum corneum, lucidum, granulosum, spinosum, basale), along with basal melanocytes and the dermis composed of vasculature, fibroblasts, and immune cells, maintain tissue homeostasis. In melanoma, this architectural integrity is lost, resulting in invasive growth, immune cell infiltration, and increased vascularization supporting tumor progression—a hallmark of malignant transformation [30, 31, 32]. Key hub genes identified—MMP9, EGFR, HSP90AA1, CASP3, CASP8, MAPK14, and MAPK8—play pivotal roles in these shifts. EGFR, a receptor tyrosine kinase, activates the MAPK/ERK and PI3K/AKT pathways, promoting proliferation, migration, and therapeutic resistance. EGFR overexpression in melanoma is associated with poor prognosis and is considered a promising therapeutic target [33, 34]. MMP9 mediates extracellular matrix degradation, tumor invasion, and metastasis. Elevated MMP9 levels in melanoma correlate with advanced disease and poor survival. It is regulated by inflammatory cytokines in the tumor microenvironment and cooperates with EGFR signaling to enhance invasion and angiogenesis [31, 35]. HSP90AA1, which encodes heat shock protein 90 alpha, functions as a molecular chaperone stabilizing numerous oncogenic client proteins—including BRAF, EGFR, and AKT. Its overexpression in melanoma promotes tumor growth, stress resilience, and angiogenesis. Extracellular HSP90 has been shown to enhance invasiveness by activating MMP2/MMP9 and interacting with cell-surface receptors [36, 37]. MAPKs, specifically MAPK14 (p38α) and MAPK8 (JNK1), regulate cellular responses to stress, inflammation, apoptosis, and proliferation. Within melanoma, p38 MAPK supports survival under oxidative stress, while JNK can have either pro-apoptotic or pro-survival roles depending on context [38].

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CASP3 and CASP8 are essential mediators of apoptosis, executing intrinsic and extrinsic cell death pathways. Their downregulation contributes to apoptosis resistance in melanoma. Interestingly, expression of these caspases may increase under therapeutic stress in advanced tumors, suggesting opportunities for pro-apoptotic interventions [31, 39]. Protein-protein interaction (PPI) analysis revealed a high clustering coefficient and significant PPI enrichment ($p < 1.0 \times 10^{-16}$), indicating these hub genes form a tightly interconnected network driving melanoma progression. Among these, HSP90 emerges as a compelling therapeutic target. HSP90 inhibition with agents such as ganetespib has demonstrated potent anti-melanoma activity in both preclinical models and resistant melanoma cell lines, inducing cell-cycle arrest and apoptosis [10]. Dual inhibitors like DHP1808 (targeting HSP90 and PI3K) further disrupt the HSP90–EGFR complex, attenuating downstream MAPK and AKT signaling with synergistic antitumor effects [40]. MMP9 inhibition remains under investigation for impairing tumor invasion and metastasis, though translation into clinical therapies faces challenges due to off-target toxicity and compensatory mechanisms. EGFR-targeted therapies, successfully employed in other cancers, may enhance outcomes in melanoma when used in combination with inhibitors targeting HSP90 or MAPK pathways. Similarly, therapeutic activation of CASP3 and CASP8, potentially through epigenetic or transcriptional modulation, may restore apoptosis sensitivity—particularly in combination with immune checkpoint inhibitors. The tumor immune microenvironment plays a critical role in melanoma progression. Interactions between tumor-secreted HSP90/MMP9 and immune cells, coupled with upregulation of PD-L1 and CTLA-4, facilitate immune evasion. Integrative therapeutic strategies combining targeted molecular inhibitors with immune checkpoint blockade could overcome resistance and yield more durable responses.

V. CONCLUSION

This study highlights the critical role of hub genes—EGFR, MMP9, HSP90AA1, MAPK14, MAPK8, CASP3, and CASP8—in driving melanoma progression through interconnected signaling networks that regulate proliferation, invasion, angiogenesis, stress adaptation, and apoptosis resistance. Among these, HSP90 and EGFR emerge as promising therapeutic targets due to their central roles in stabilizing oncogenic signaling and promoting tumor aggressiveness. Targeted inhibition of these pathways, particularly in combination with pro-apoptotic strategies and immune checkpoint blockade, holds potential to overcome therapeutic resistance and improve clinical outcomes. Overall, the integration of molecular targeting with immunotherapy represents a rational strategy for developing more effective and durable treatments against melanom.

- *Data Availability Statement:*

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

- *Funding Statement:*

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TABLES

Table 1 Protein Details to be used for Docking Analysis

S.NO	PROTEIN NAME	PDB ID
1	HSP90AA1	4BQG / 1.90 Å
2	EGFR	8SC7 / 1.98 Å
3	CASP3	1RE1 / 2.50 Å
4	TNF	5MU8 / 3.00 Å
5	MMP9	6ESM / 1.10 Å
6	MAPK14	7BDO / 2.70 Å
7	CASP8	3KJQ / 1.80 Å

Table 2 Top 5 Hub Genes

Rank	Name	Score
1	HSP90AA1	17
2	EGFR	16
3	CASP3	15
4	TNF	14
5	MMP9	12

FIGURES

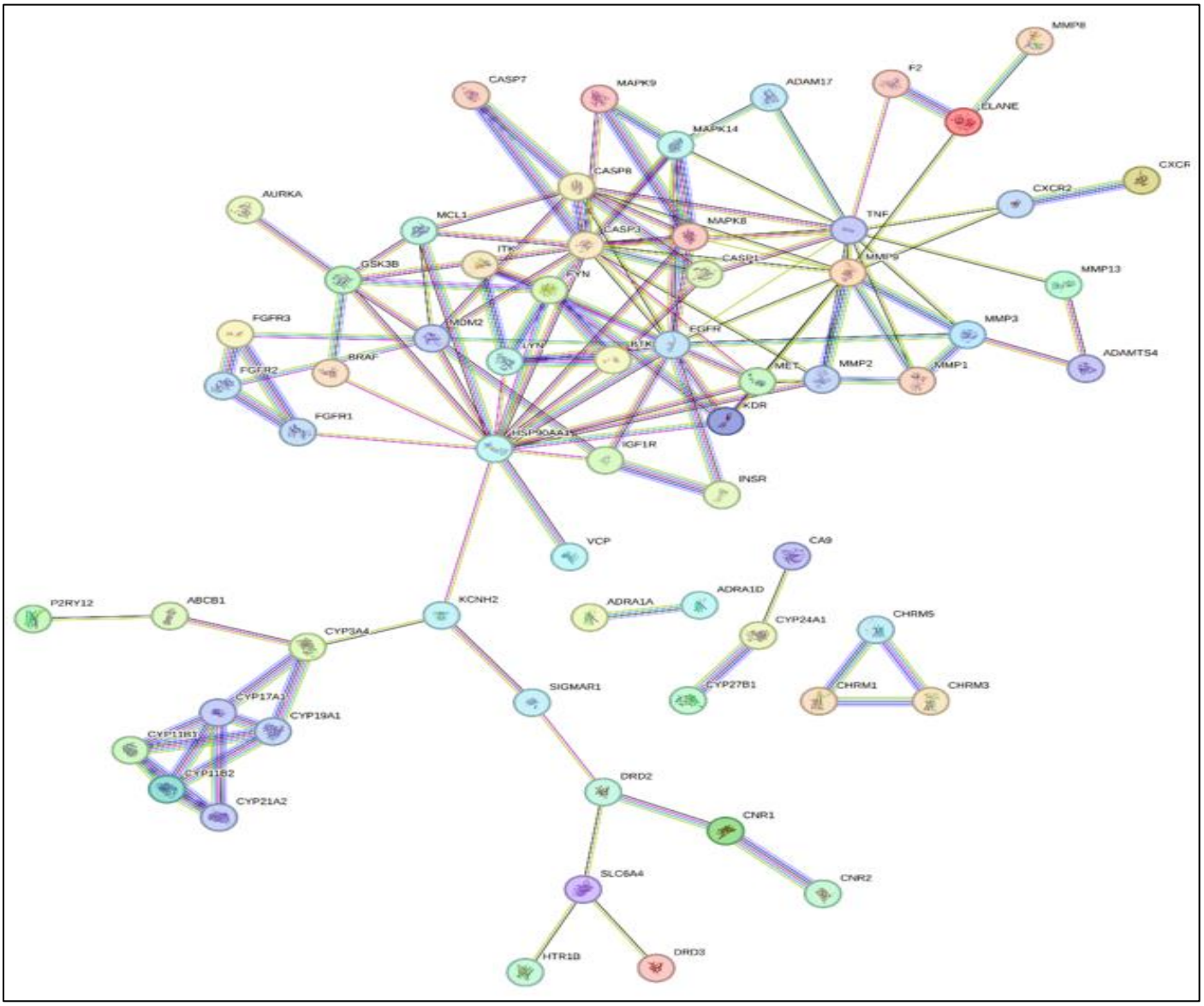

Fig 1 Protein–Protein Interaction (PPI) Network Generated using STRING Database.

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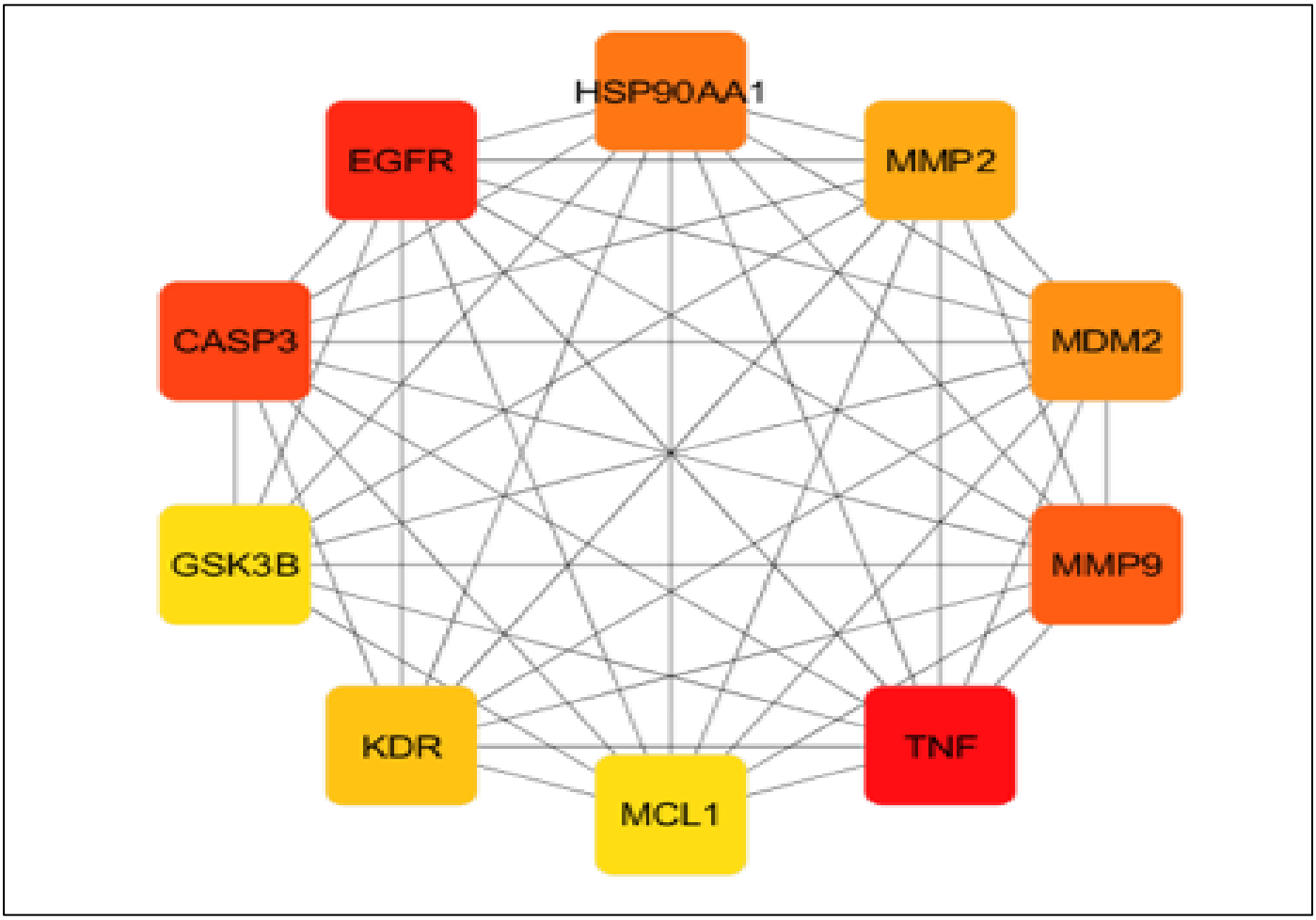

Fig 2 Identification of Hub Genes using CytoHubba

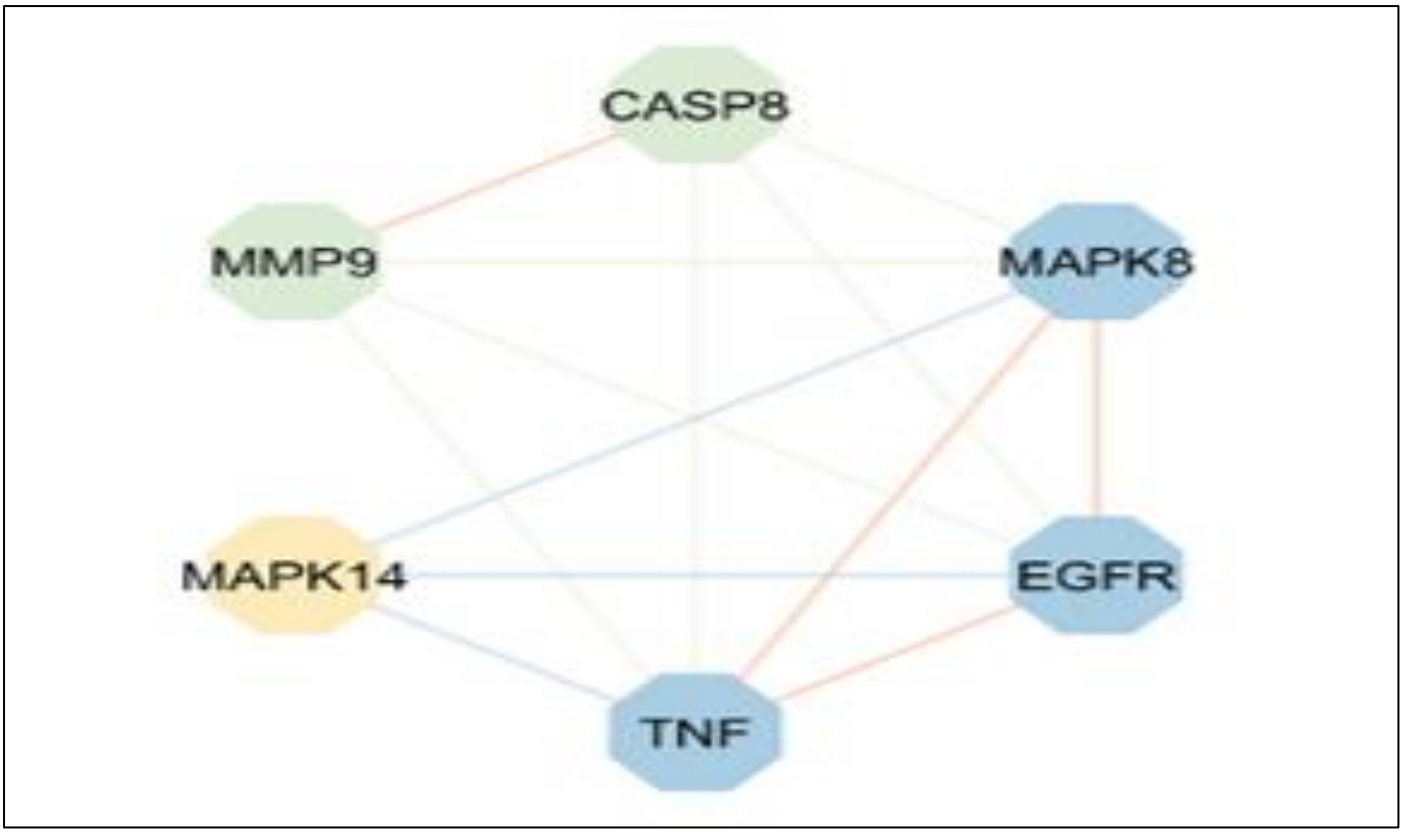

Fig 3 Visualization of Significant Gene Cluster using MCODE in Cytoscape

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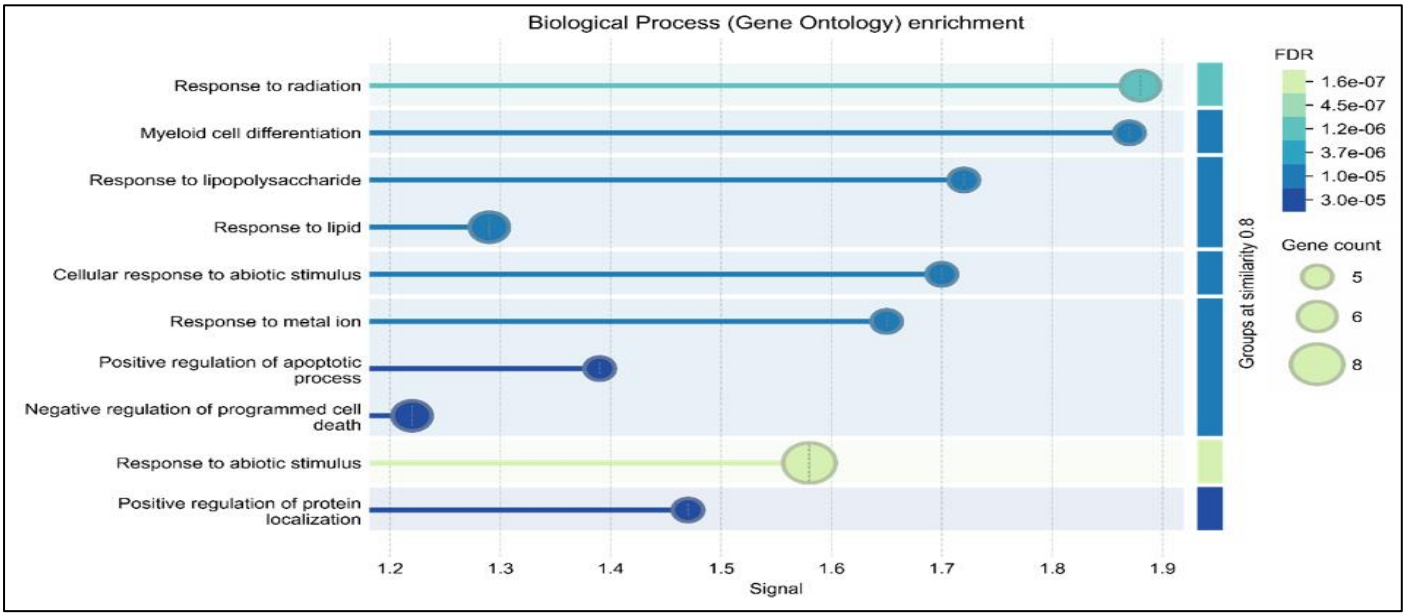

Fig 4 Gene Ontology (GO) Enrichment Analysis of Hub and MCODE-Clustered Genes (Biological Process)

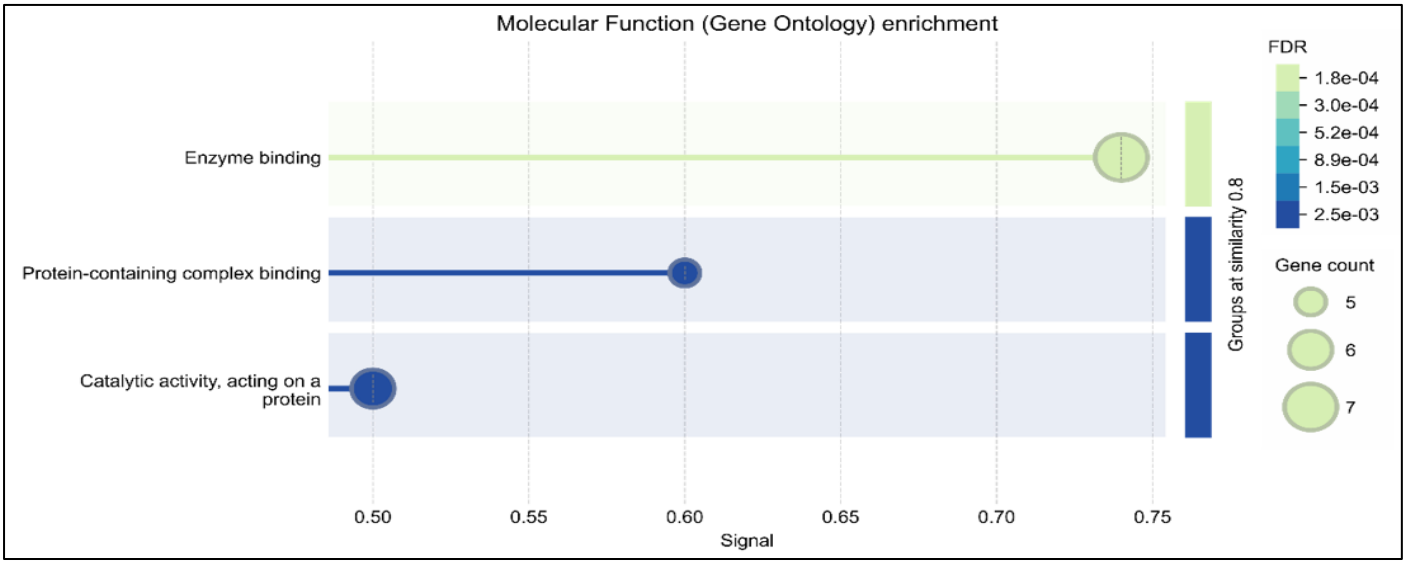

Fig 5 Gene Ontology (GO) Enrichment Analysis of Hub and MCODE-Clustered Genes (Molecular Function)

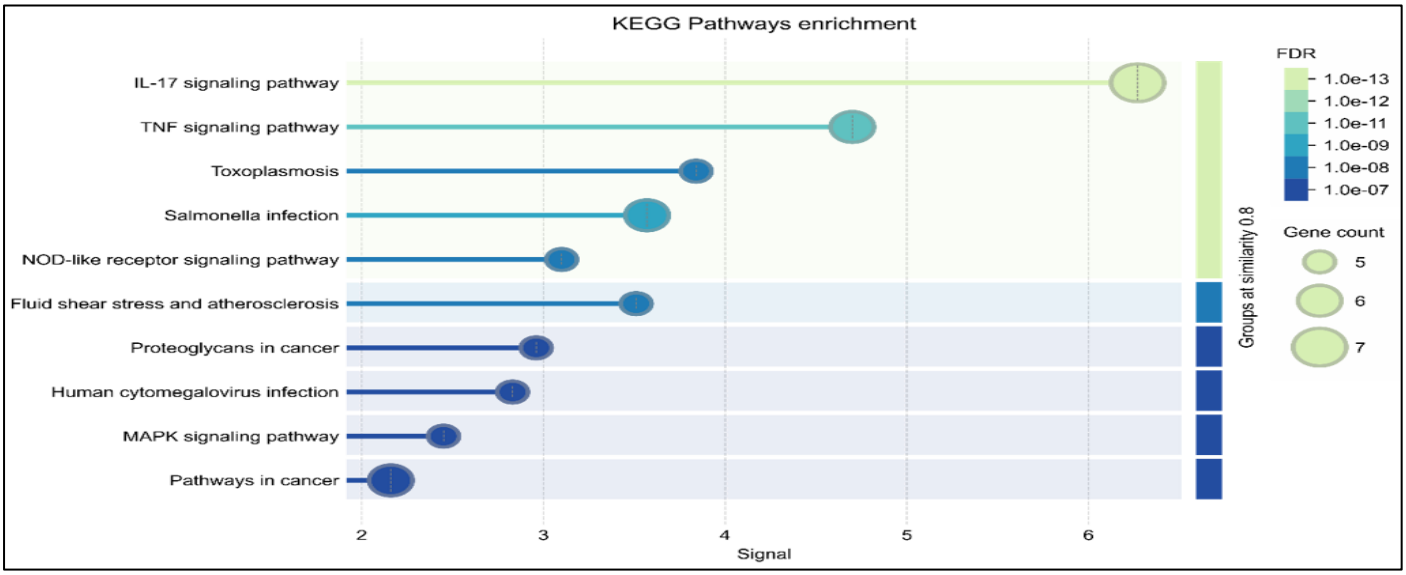

Fig 6 KEGG Pathway Enrichment Analysis of Hub and MCODE-Clustered Genes

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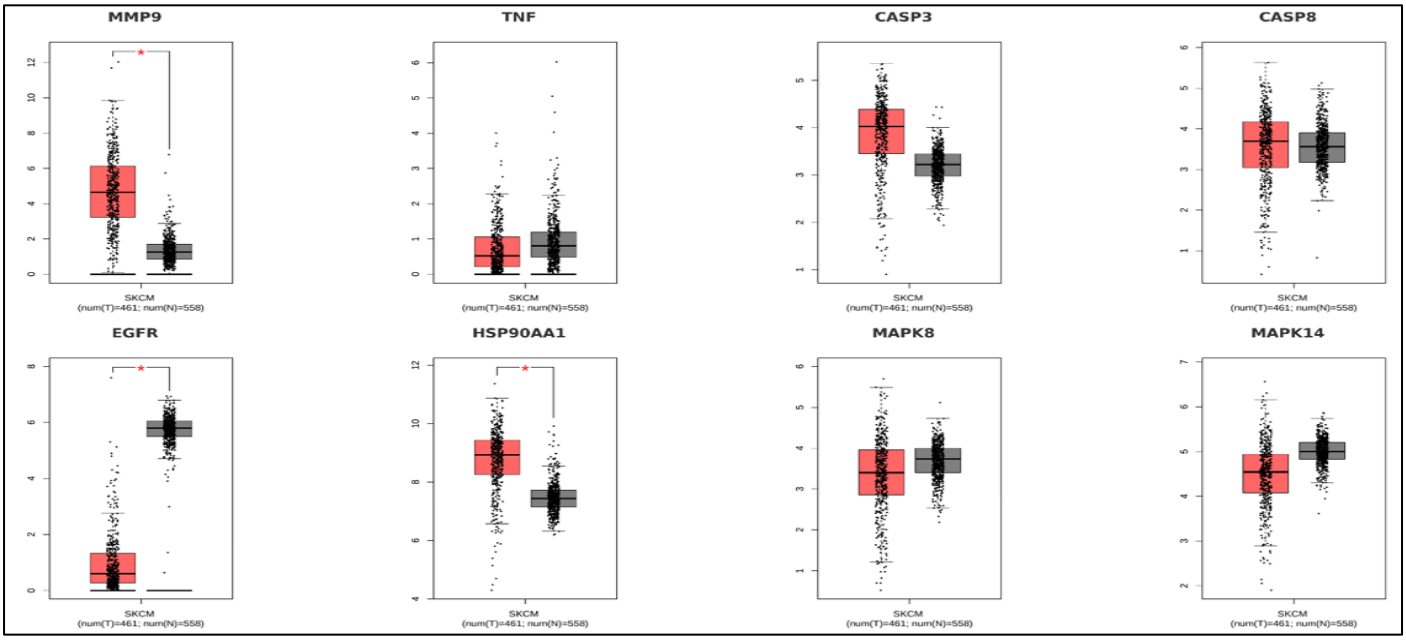

Fig 7 Differential Gene Expression Analysis using GEPIA2 (Boxplot)

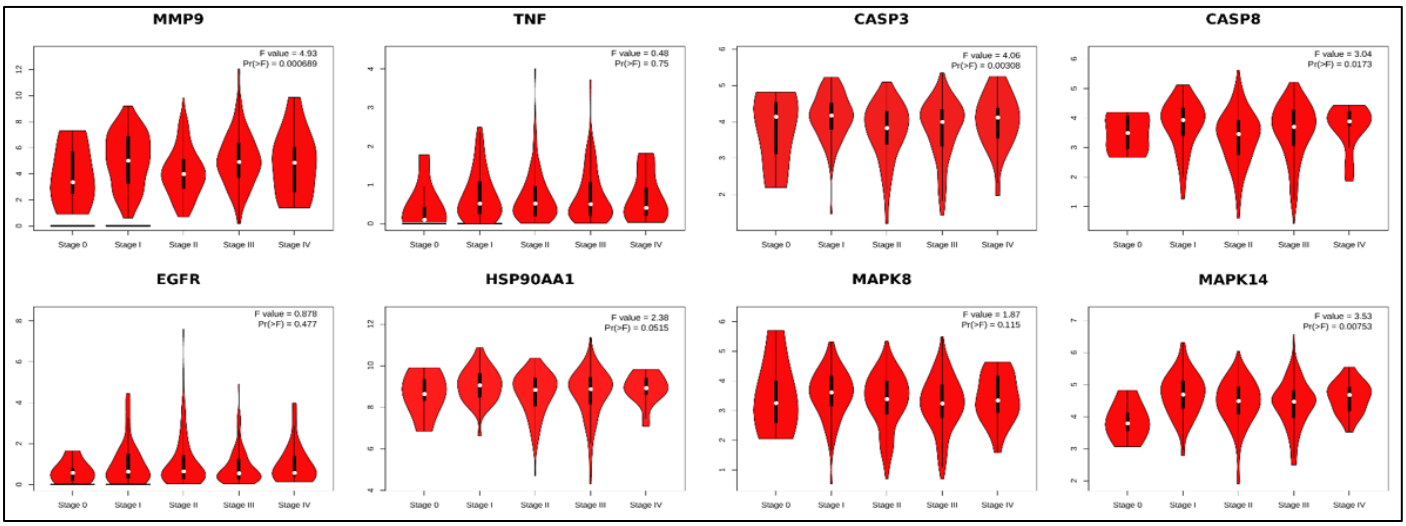

Fig 8 Stage-Specific Expression Analysis of Hub Genes using GEPIA2 (Stage Plot)

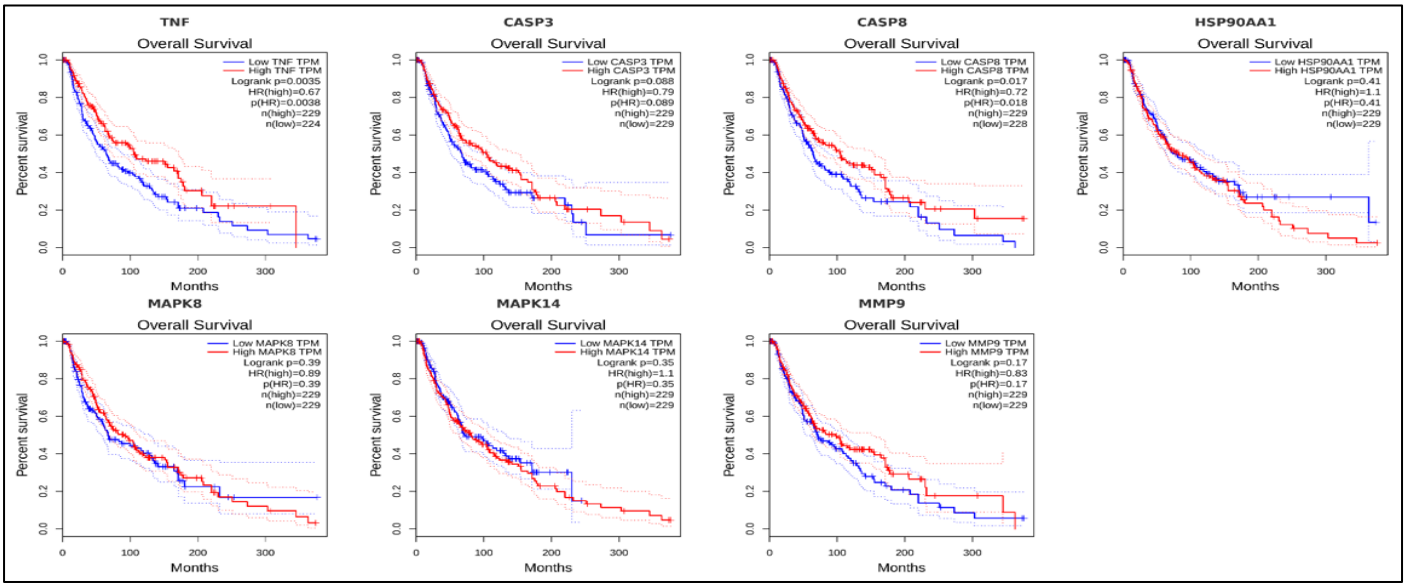

Fig 9 Kaplan–Meier Survival Analysis

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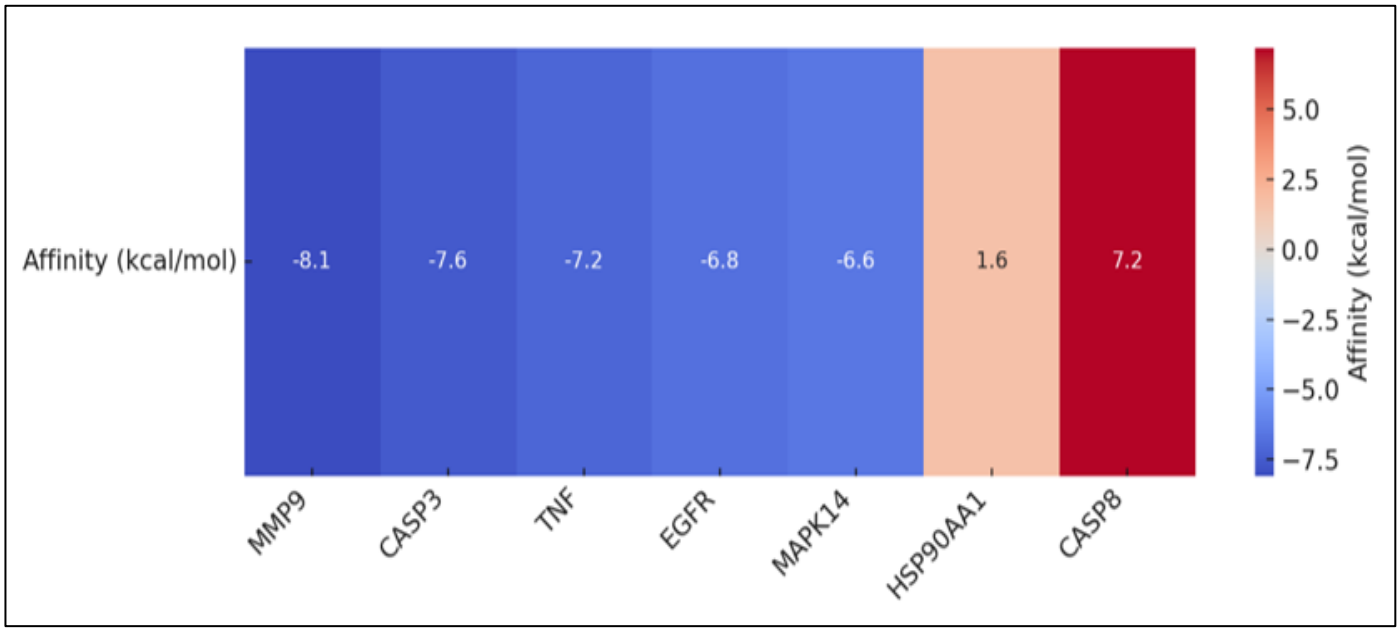

Fig 10 Heat Map of Docking Scores Generated using AutoDock.