MSc Thesis Khushi

by Asmita Das

Submission date: 24-May-2026 07:29PM (UTC+0530)
Submission ID: 2968252332
File name: thesis_checking_draft.docx (378.75K)
Word count: 8066
Character count: 49564

ABSTRACT

Breast cancer becomes the most frequent and widespread cancer impacting women globally. Frequently, it is monitored that females diagnosed with the condition PCOS display a greater inclination towards the expansion of breast cancer. Many studies demonstrate an increased risk of breast cancer in females diagnosed with PCOS, and the interrelation shared by both disorders remains unsolved to date. Available studies data depict an essential role of chronic unopposed estrogen exposure, hyperandrogenism, and hyperinsulinemia in modulating the growth of cells and their proliferation, and also serve a potent role acting as a tumor suppressor in numerous cancers, which also involve breast cancer.

For a better transparency of this interconnection, we used an advanced bioinformatics approach in which the collection of disease-related genes takes place with the help of the Comparative Toxicogenomics Database (CTD). Quantitative and qualitative comparison analysis takes place between both disorders, breast cancer and PCOS, and identification of 17 shared common genes takes place. Furthermore, the construction of the three regulatory networks model takes place with the help of the online platform NetworkAnalyst. Networks named as gene–miRNA interaction networks, gene–transcription factor networks, and tissue-specific co-expression networks

The regulatory analysis of all three networks led to the identification of NAMPT (Nicotinamide Phosphoribosyltransferase) as the critical key hub gene, which correlates with all three regulatory networks of disorders, breast cancer, and PCOS. NAMPT plays a vital role in the formation of the NAD+ biosynthetic pathway, cellular metabolism, repair of DNA, and balance energy, and the extracellular form of NAMPT serves as an inflammatory interconnector adipokine and triggers resistance to insulin, formation of new blood vessels, and survival of cancerous cells. NAMPT plays a double role as it bridges the link between metabolic dysregulation of PCOS and the growth and survival of breast cancer cells.

The current research broadcasts an overlapping link between PCOS and breast cancer, shared molecular and genetic pathways, and how they may be disrupted due to PCOS. In addition, we postulate a novel mechanism and predict the outcomes of drugs for cancer linked with PCOS, which potentially contribute to the emergence of a novel therapeutic strategy.

Keywords—Breast Cancer, epigenetic modification, miRNA interaction, PCOS, Transcription Factor

Chapter.1

Introduction: Polycystic Ovary Syndrome, Breast Cancer, and the Rationale for Network-Based Molecular Analysis

1.1 Worldwide Prevalence and Etiological Association of Breast Cancer and PCOS

Breast cancer (BC) has become the most frequent and widespread cancer impacting women globally1, which is rightfully determined as a critical and rapidly increasing global health crisis.2 The prevalence of female health is supported by the reporting of approximately 2.3 million newly diagnosed cases globally in 2022 3, which depicts it as the most widely disseminated cancer among women. Globally, breast cancer holds the second place as the most common cancer overall, after lung cancer. In contrast, it holds the third most frequent type of cancer position in India, according to World Cancer Research Fund findings. A recent issue by the International Agency for Research on Cancer (IARC-WHO) analysis forecasts a 38% rise in breast cancer cases worldwide by 2050, and about 1 in 20 females will be affected with breast cancer in their lifespan.4

The epidemiology scenario of breast cancer in India represents itself varied complications. The number of cancer cases in India for 2022 observed was around 14,61,427 (non-standardized rate: 100.4 per 100,000), with a non-standardized incidence rate of 100.4 per 100,0005. Compared to other Western countries, India tends to diagnose breast cancer about 9-10 years earlier8. The rate of patients' survival diagnosed with breast cancer is low in India with the comparison to Western countries because of their earlier age, later stages of disease presentation, the initiation of definitive management being delayed, and inadequate/fragmented treatment 9. The incidence of cancer cases is estimated to increase by 12.8 per cent in 2025 as compared to 2020(ICMR 2023), which indicates that this situation needs urgent intervention to identify new mechanisms of cancer development and new forms of treatment for cancer.

Coinciding with the expanding cancer stress, Polycystic Ovary Syndrome (PCOS) tends to be a recurrently encountered endocrinal disease in females of fertile age. PCOS also features a combination of symptoms that include menstrual irregularities, chronic anovulation, hyperandrogenism, hirsutism, acne, and metabolic complications such as obesity and insulin resistance 15 16. An epidemiological analysis evaluation of roughly 11-13% of females globally afflicted by PCOS, and its frequency crossed double number from the past three decades 17.

Despite its universal prevalence, its significance depicts long-term viable variety in the public, with remarkably fluctuating estimation across Asian publics 18. In India, PCOS makes an appearance as a considerable health issue for the general population; however, region-specific epidemiological resources remain bounded, particularly in urban livelihoods where lifestyle, diets, and environmental surroundings may play a significant role in contributing to higher ubiquity and various clinical profiles 19

A significant association was found between PCOS symptoms and breast cancer. Some PCOS characteristics represent a powerful interconnection 21. Epidemiological analysis, including a recent case-control study comparing 246 breast cancer patients with exact number of control matches, describes that women corresponding to symptoms of PCOS, involving irregularities in the menstrual cycle, acne, hirsutism, and obesity, had a profoundly strong probability of evolving

breast cancer. especially, the occurrence of hirsutism was autonomously linked to higher risks, advising that hyperandrogenism had played a vital role in breast carcinogenesis. After adjusting for potential confounders, the overall odds ratio indicated that women with PCOS were more than three times more likely to develop breast cancer in the comparison with those without PCOS. The presence of hirsutism acts as a molecular marker of hyperandrogenism, identified as an independent risk factor for developing breast cancer. This supports the concept that excess androgen levels are instrumental in the development of breast cancer. The finding of hirsutism and associations with breast cancer may also explain some of the shared hormonal and metabolic abnormalities as a possible mechanism by which they may be related.

1.2 Molecular Pathogenesis: The PCOS-Breast Cancer Interaction

The macromolecular association that links PCOS to breast cancer is sophisticated and influenced by multiple parameters, overlaps with several shared hormonal cascades, metabolic systems, and epigenetic routes. The foundational convergence of abnormal biological and molecular intermediaries is a persistent increase in estrogen exposure, hyperandrogenism, and hyperinsulinemia, all of which play a vital role in shaping cellular proliferation, growth signalling, and oncogenesis.

Excess in the level of estrogen, which becomes a characteristic feature of PCOS arising from a lack of ovulation and non-central aromatization of androgens, becomes a critical mitogenic prompt for breast epithelial cells. Sustained large increase in the level of estrogen hormone leads to irregular cellular proliferation by affecting the activation of estrogen receptor-dependent transcriptional responses, as a result leads to increase in the tendency of cancer.

Hyperandrogenism also becomes an important contributor to PCOS by stimulating a direct increase in breast epithelial cell proliferation, promoting DNA replication errors, and commencing tumor-inducing processes. These effects operate together and contribute to the increased level of insulin termed as hyperinsulinemia, which corresponding activates important growth and signalling pathways, including the mTOR, PI3K, and AKT pathways, along with cyclin-dependent regulatory programs. Altogether, these interconnecting paths lead to a conditional environment condition which tends to increase the occurrence of breast cancer.

Another important connection, post-transcriptional modulatory interaction, significantly contributes to the functional imbalance of microRNAs (miRNAs), which act as a novel and understudied molecular layer connecting PCOS and breast cancer. miRNAs are small, non-coding RNA molecules that help to regulate gene expression by association with complementary sequences in the 3'-untranslated regions of target messenger RNAs, resulting in their translational downregulation and disintegration. Some specific miRNAs have been associated with influencing the expression of genes of both PCOS and breast cancer. Similarly, transcription factors (TFs) synchronize critical transcriptional regulation that regulates cellular differentiation, proliferation, and hormonal stimulus response, subsequently demonstrating them as critical interaction elements of merging unification between the two circumstances.

Although after many increasing epidemiology studies and findings, a holistic systems-level comprehension of the shared network of gene-regulatory pathways inducing the association of PCOS-breast cancer prevails, it is notable that it is not fully understood and is incomplete. Specifically, a substantial gap of knowledge remains while recognising and characterizing key hub genes that simulate and coordinate aberrant molecular function in both diseases, and in the mapping of the miRNA and controlling cascade of transcription factors, which mediates the resulting expression.

1.3 Recent Therapeutic Challenges and the Foundation of Network-Based Analysis

Despite remarkable new and advanced technologies in the treatment of cancer and reproductive medication, the treatment framework for both breast cancer and PCOS remains incomplete and fails to recognize their existence. Breast cancer is treatable with the help of plenty of advanced techniques and therapies, which include surgery, chemotherapy, targeted therapies, and immunotherapy. Such advanced technologies enhance the survival rate of patients and particularly focus on patients with an early stage of cancer. Despite having advanced technologies, several patients, especially those with hormone-receptor-positive cancer and metabolic concurrent disorders such as PCOS, often experience poor prognosis, resistance to the treatment, and recurrence of the disorder. The reasonable mode of action which influence complexity of resistance and is deeply linked to dysregulation of metabolic and hormonal features of PCOS.

Comparedly, the regulation of PCOS specifically focuses on its controlled symptoms, which targets and concentrates conditions such as menstrual irregularity, hirsutism, and infertility, without completely recognising and treating the dysfunction that regulates and increases the risk of cancer for a long period of time. This creates a void in therapeutic strategies that need to meet its critical unmet clinical approaches, which leads to the development of integrated, mechanism-informed approaches that can simultaneously target the common molecular mechanisms shared between PCOS and breast cancer.

The analysis of gene-regulatory networks provides a superior and powerful spectrum for recognising and solving problems and challenges. With the help of systematic profiling of the shared molecular pathways between PCOS and breast cancer, which involves the identification of key hub genes, key miRNA regulators, and mediating transcription factors, this approach enables the finding of multi-pathway target therapies that the single-pathway therapies are unable to detect. The discovery of NAMPT as a central hub gene helps to regulate multiple interconnecting network types in this study, exemplifying the potential to establish a molecular target to detect the intervening bridge between therapeutic strategies in the disorders. By using an established network-centric approach as an analytical tool, but a fundamental strategy to treat and understand the complexity of the diseases, is proposed altogether.

Chapter 2

Materials and Methods

2.1 Data Collection and Gene Identification

The methodological landscape of this investigation was built using a systematic and unambiguous bioinformatics workflow, curated to ensure method reproducibility and scientific robustness in the detection of molecular linkage between PCOS and breast cancer. The experimental process proceeded in a series of well-defined sequential steps, starting with disease-gene data collection, followed by comparative gene analysis, and culminating in the generation and topological scrutiny of multiple gene regulatory networks for analysis.

2.1.1 Use of Comparative Toxicogenomics Database (CTD) for disease-gene collection

The datasets for both disease genes were taken from the Comparative Toxicogenomics Database (CTD), which is a well-organized, free, and publicly available online repository that curates data on the interactions between gene-disease derived from published and experimental research studies and evidence. CTD is predominantly suitable for this type of study because it provides an extensive and methodologically verified dataset of gene-disease association induced from human samples with properly documented, controlled case composition.

Two separate database search performed using the standardized search terms 'Breast Cancer' and 'Polycystic Ovary Syndrome (PCOS)'. For a particular disease, the top 200 genes associated with each condition were selected on the basis of their gene score and clinical relevance to the respective disease, as given within CTD. The list of initial genes was completely conserved for its succeeding comparative analysis, which ensured that no potent and relevant molecular genes were missing or excluded from analysis.

2.1.2 Identification of Common Genes Through Comparative Analysis

To identify shared genes between disease-associated gene lists specifically, a Python-based comparative analysis was performed using Google Colab, an accessible and generative computational conditions. The list of two gene lists was first imported and subjected to a system for standard nomenclature, which ensures proper identification across both datasets, thereby removing any Possible inconsistencies that arise while naming systems and synonyms for the same gene names. After this, an intersection methodology was applied to identify common genes present in both the disorder gene list and to recognize its overlapping genes as well. This study identifies a set of 17 genes common to both disorders, named breast cancer and PCOS, which were selected for all further regulatory and network-based analyses. The use of an accountable computational approach at this step increases its reproducibility and verified selection process.

2.2 Regulatory and Interaction Network Construction

For an extensive study of the regulatory framework mediating the 17 common shared genes, which defined as multi-network analytical approach was conducted. Three different complementary network type construction and evaluation take place and name networks as a gene-miRNA interaction network, a gene-transcription factor (TF) interaction network, and a tissue-specific gene co-expression network. All these networks were created and visualized using NetworkAnalyst (https://www.networkanalyst.ca/), an advanced web-based platform which generated for holistic network analysis and gene regulatory interactions for visual exploration. NetworkAnalyst uses multi-network comparison through the addition of multiple combined databases to make more reliable and predicted interactions and biologically relevant.

2.2.1 Construction of Gene-miRNA Regulatory Network

To analyze post-transcriptional regulation of the 17 shared genes, a gene-miRNA interaction network was also generated using NetworkAnalyst. The list of common genes was shared with the platform, and miRNA-gene interaction data were collected from multiple curated databases, especially miRTarBase, which helps to provide miRNA-target interactions that are experimentally identified and validated from a wide array of methodological approaches, including reporter gene assays, western blotting, microarray profiling, and next-generation sequencing (NGS). Both validating and computationally predicting the interaction data from different sources, which increases the extent and reliability of the network, helps to understand the post-transcriptional regulatory network that influences the expression of shared genes in both PCOS and breast cancer.

2.2.2 Construction of Gene-Transcription Factor (TF) Interaction Network

To identify transcriptional regulatory systems influenced by the shared genes, a gene-transcription factor (TF) interaction network was constructed, especially using TRRUST (Transcriptional Regulatory Relationships Unraveled by Sentence-based Text Mining), a collective database of both human and mouse transcriptional regulatory network which retrieve through a platform called NetworkAnalyst. This database detects TF-gene regulatory relationships that are experimentally reliable and derived from extensive text-based analysis of the biomedical literature, which provides advanced data on the direct influence of transcriptional regulatory relationships. Transcription factors are recognised as regulators of the common genes with the help of nodes within the network, which enable the identification of upstream regulatory factors that may derive the same shared gene expression patterns in both PCOS and breast cancer.

2.2.3 Analysis of Tissue-Specific Gene Co-expression Network

To study the coordinated pattern expression of the commonly shared genes within biological tissues, a network of tissue-specific gene co-expression was generated, especially using NetworkAnalyst, with the help of the iNetModels database. The database provides data based on tissue-specific gene co-expression networks that span a range of human tissues, with particular analytical focus on tissues directly relevant to the pathophysiology of PCOS and breast cancer, namely, breast and ovarian tissues. Genes show a strong pattern of co-expression within these tissues and are considered functionally related or involved in similar or overlapping biological pathways, and thereby such genes are considered as potential therapeutic targets.

2.2.4 Network Visualization and Hub Gene Identification

In each of the constructed networks, genes, miRNAs, and transcription factors are depicted as 'nodes', while the regulatory relationships between them are represented as 'edges' that connect the respective nodes. Network analysis was performed and helped to identify key regulatory nodes based on two major centrality measures: degree centrality, which measures and quantifies the number of direct interaction routes of each node and helps to identify highly important connected regulatory molecules with their widespread biological role; and betweenness centrality, which measures and identifies nodes that act as major intermediates for the transfer of regulatory information across the network.

For better understanding and highlighting significant biological interactions, the generation and visualization of minimal networks were used to focus on key hub genes and their direct interacting elements. For their better visualization, node color encodes different connectivity levels: genes displayed in red and orange indicate a higher connectivity degree and strong regulatory influence, while yellow and blue nodes represent genes with relatively lower connectivity degree. Genes or regulatory molecules that show high connectivity across multiple network types consistently, specifically across the multiple networks like gene-miRNA, gene-TF, and tissue-specific co-expression networks, are termed as hub genes and help to identify remarkable candidates for future biological study and investigation, and used for targeted therapies.

2.3 Identification and Compatibility Analysis of Potential Therapeutic Drugs

The main goal of studying the derangement of gene-miRNA networks in BC and PCOS is to use their molecular information to discover possible therapeutic strategies. The study identifies potential drug candidates and to analyzes their incompatibility by majorly focusing on their efficiency to remodulate the identified molecular changes.

2.3.1 Drug Identification Strategy

Identification of existing therapeutic drugs with the prospective interference in the abnormal networks of gene-miRNA of BC and PCOS, the DrugBank database (https://go.drugbank.com/) was systematically used.

DrugBank is a deeply and fully annotated online resource that combines knowledge on targets of pharmacology and their mechanisms of action with detailed data on drugs. Its include information not only on FDA-approved and biotech drugs but also experimental, withdrawn, and other compounds as well, which provides a wide range of data on pharmacology, pharmacokinetics, and molecular biology. Because of this, DrugBank is a useful resource for in silico identification of drug targets, drug design, and its metabolism and interaction prediction studies.

The primary goal of the process of drug identification is to correct the dysregulated activity or expression of abnormal genes and identify miRNA in the experimental studies, and ensure that selected drug candidates are relevant to the observed molecular spectrum of BC and PCOS. For example, if we found a gene overexpressed, we search and prioritize drugs that inhibit that gene's activity or reduce its expression, and if we found an underexpressed gene, we search r and prioritize drugs that upregulate its expression or mimic its function as well.

An important aspect of the search strategy was to study the expression of miRNAs, which aim to study and identify drugs that influence both overexpression (acting as oncogenes) and underexpression (acting as tumor suppressors) in the generated gene-miRNA network. This strategy moves beyond the traditional single-target drug discovery as it regulates multiple molecular routes at a fixed time.

The goal is to find potent drugs that suppress the detrimental effects of harmful miRNAs while restoring the beneficial functional miRNAs, which offer more comprehensive and potentially more effective therapeutic strategies for BC and PCOS. This network-based selection of drugs enhances the translational and therapeutic potential of the study.

2.3.2 Drug Compatibility Analysis

To assess the clinical usefulness and safety of the identified drug targets for potential therapeutic applications, an extensive compatibility analysis was performed. This critical step involved information from both the DrugBank and PubMed databases. The purpose is to identify possible drug-drug interactions, to study their synergistic or antagonistic effects, and to consider any known adverse effects and safety challenges.

DrugBank provides exclusive data on drug-drug interactions (listing over 13,000 such interactions) and food-drug interactions. A wide variety of datasets help to identify their potential adverse events or altered efficiency of drug efficacy in the case of multiple medication combinations. The information within DrugBank, compiled from various web and textbook resources and pharmacists, offers a rigorous initial screening for comparative studies.

Further investigation and analysis of potency, we prefer PubMed (https://pubmed.ncbi.nlm.nih.gov/), an in-depth and publicly available database that contains over 38 million records from biomedical and life sciences literature, was used. Requirement of performing focused literature searches to obtain extensive data on:

- Established interactions between the selected drug target and other commonly used medications.
- Antagonistic or Synergistic effects of different combinations of drugs.
- Clinical trial and Preclinical study data related to the safety and efficacy of drug combinations, patient tolerance.

PubMed is also an important resource which evaluate and accesses detailed biomedical and scientific research and evidence. The overall aim is to identify drug combinations to be used safely and effectively in a clinical environment, and also to recognise possible risks that require proper monitoring, dose adjustments, or alternative therapeutic approaches. This detailed evaluation of the pharmacological scenario is to fill the void between in silico findings and real-world clinical application, providing a new approach for the development of new therapeutic strategies for BC and PCOS.

Chapter 3
Results

The extensive bioinformatics study, which includes disease-gene data collection, identification of comparative genes, construction of a multi-network, and network analysis. The series of results depicts a crucial molecular association between PCOS and breast cancer. and the biological knowledge of two diseases

3.1 Identification of Common Genes Between PCOS and Breast Cancer

By using the top 200 associated genes with PCOS and the same for BC, with the help of the CTD database and comparative analysis identifies 17 genes that are common in both. These shared genes are essential as their malfunction is involved in both disease and act as molecular associations with imbalance in hormonal changes, metabolic derangement, as well as oncogenic dysregulation

Gene Symbol	Functions	Role in PCOS and Breast Cancer
NAMPT	Biosynthesis of NAD+, enzyme metabolism, adipokine	Inflammation, resistance to insulin, and tumor survival
TP53	Tumor suppression, regulation of the cell cycle	Repair of DNA and prevention of cancer
BRCA1	Repair of DNA	Susceptibility to breast cancer; PCOS oxidative stress
VEGFA	VGF, Angiogenesis	Angiogenesis of the tumor and follicular development in PCOS
TNF	Pro-inflammatory cytokine	PCOS and BC chronic inflammation
IL6	Signaling of Cytokine, JAK/STAT signals	Provides insulin resistance in case of PCOS; oncogenic in case of breast cancer
MYC	transcription factor, Oncogene	Tumor growth in BC and signaling of insulin/androgen
ESR1	Alpha Estrogen receptor	Includes in Hormone receptor-positive breast cancer

Table 1: Representative Common Genes Identified Between PCOS and Breast Cancer

The top three genes act as downregulated genes in BC and PCOS

1. NAMPT (Nicotinamide Phosphoribosyltransferase)

Gene Symbol: NAMPT

Function: The conversion of nicotinamide into nicotinamide mononucleotide (NMN) leads to the production of NAD+, which acts as visfatin, an inflammatory adipokine

Expression: Normal expression in metabolically activated tissues, including adipose, liver, muscle, and ovarian tissues. In PCOS patients, circulating levels of NAMPT, but intracellular protective isoforms are reduced in several breast cancer subtypes.

Prognosis Correlation: Low intracellular activity of NAMPT is linked to poor DNA repair, increased genomic instability, and inflammation level also increases.

Role: Acts as a dual regulator —inside the cell balances metabolism activity and supports tumor suppression through sirtuin proteins, whereas the extracellular form promotes pro-inflammatory adipokine signalling, insulin resistance, and angiogenesis. NAMPT downregulation disrupts the activity of NAD+-dependent sirtuin, leading to easy breakdown of epigenetic and metabolic checkpoints and leading to the formation of cancer.

Mechanism of Action: Intracellular NAMPT maintains the NAD+ level required for repair of DNA, phosphorylation of mitochondrial oxidation, and sirtuin activity, whereas extracellular eNAMPT triggers Toll-like receptor 4 (TLR4 to activate NF-kB-driven inflammatory gene transcription.

Impact of Downregulation: Reduced level of NAMPT activity weakens DNA repair and suppresses pathways of tumor formation, boosts metabolic rearrangement, and also leads to inflammation, and in PCOS, increases the risk of breast cancer.

2. BRCA1 (Breast Cancer Gene 1)

Gene Symbol: BRCA1

Function: Repairs damaged DNA and leads to genomic stablility especial participation in double-strand DNA break repair via the homologous recombination pathway.

Expression: The expression level of BRCA1 is elevated in normal activating dividing cells, but reduced in breast cancer, and in the case of PCOS, get suppress because of oxidative stress.

Prognosis Correlation: Low expression level of BRCA1 or absent expression aggressive breast cancer metastasis, and ppo level of survival. In PCOS patients, low level of BRCA1 associates with lifetime breast cancer risk.

Role: Serves as a tumor suppressor that controls DNA repair, cell cycle checkpoints and apoptosis to avoid the accumulation of harmful mutations.

Mechanism of Action: BRCA1 leads to the formation of functional complexes with BARD1 and RAD51 proteins, which repair DNA by homologous recombination pathways and activate repair genes like p21 and GADD45.

Impact of Downregulation: Abnormal functioning of DNA repair because of the loss of BRCA1 activity increases genomic instability and increases the risk of cancer-causing mutations, particularly in the hormonal environment of PCOS, where oxidative stress increases rapidly.

3. TP53 (Tumor Protein p53)

Gene Symbol: TP53

Function: Helps in the encoding of the p53 transcription factor. In the condition of DNA damage, the cell cycle arrests. It also controls apoptosis and DNA repair.

Expression: Extreme low level of expression in p53, as it continuously degraded by MDM2, and in conditions of DNA damage and stress, p53 is rapidly activated. Mutations rapidly occur in the TP53 genes, particularly in triple-negative cancer and in PCOS, leading to suppression by oxidative stress.

Prognosis Correlation: TP53 mutation is associated with cancer resistance to chemotherapy, metastasis, and is strongly associated with poor survival.

Role: Identification of damaged p53 cells and arresting their cell cycle, and in case no repair is possible, then leads to apoptosis to prevent the development of cancer.

Mechanism of Action: p53 activates the phosphorylation of ATM, ATR, and CHK kinases in response to DNA damage through p53 and p21, and pro-apoptotic genes like BAX, NOXA, and PUMA are also activated.

Impact of Downregulation: Loss of p53 activity by mutation affects the survival rate of cells and loss of activity to divide and increases the risk of cancer and PCOS.

The top three genes act as upregulated genes in BC and PCOS

1. NAMPT (extracellular role in oncogenes)

Gene Symbol: NAMPT (eNAMPT/visfatin isoform)

Function: The NAMPT (eNAMPT) extracellular form is upregulated in nature in PCOS and breast cancer, which serves as an inflammatory adipokine that triggers Toll-like receptor 4 to stimulate NF-kB-dependent transcription signaling, angiogenesis, and metabolic reprogramming.

Expression: The high level of expression of eNAMPT, especially in women diagnosed with PCOS, is also positively linked to resistance to insulin, obesity, and androgen levels. By analysis, we predicted overexpression in cancer tissues.

Prognosis Correlation: High expression of NAMPT in the tissue of breast cancer is associated with advanced tumor stage, therapy resistance, poor survival, and in PCOS, elevated metabolic syndrome severity and risk of breast cancer association predicts

Role: eNAMPT tumor cell survival, proliferation, migration, and angiogenesis are promoted through its NF-kB-signaling and adipokine functioning induced by VEGF and chronic inflammation, and insulin resistance is maintained in PCOS

Mechanism of Action: eNAMPT induces TLR4 on tumor cells, stromal fibroblasts, and endothelial cells to activate NF-kB inflammatory pathways by which inflammatory genes VEGF, IL-6 and TNF-alpha expression increases while intracellular NAMPT suppresses p53 activity.

Impact of Upregulation: increased level of eNAMPT induces chronic inflammation, angiogenesis, insulin resistance, and enhances the level of anti-apoptotic signaling, leading to establishing a strong pro-cancer environment in both PCOS and breast cancer.

2. MYC (Myelocytomatosis Proto-Oncogene)

Gene Symbol: MYC

Function: c-Myc transcription factor is encoded by myc, stimulates cell growth, ribosome biogenesis, reprogramming of metabolism, and entry into the cell cycle.

Expression: In normal cells tightly regulated, but overexpression in breast cancer is common, especially in triple-negative and HER2-positive cancer, and insulin and IGF-1 signaling increases expression of MYC in the case of PCOS.

Prognosis Correlation: Amplified levels of MYC amplification, a combative nature to tumor cells, resistance to endocrine therapy, metastasis, and association with poor survival.

Role: Cell proliferation in cyclin, activates CDK4 and metabolic enzymes, and increases nucleotide synthesis.

Mechanism of Action: The MYC-MAX heterodimer binds to canonical 5'-CACGTG-3' E-box sequences for activation and MYC stability and activity controlled by PI3K-AKT signalling.

Impact of Upregulation: Increase in c-Myc activity to increase development of breast cancer in PCOS.

3. VEGFA (Vascular Endothelial Growth Factor A)

Gene Symbol: VEGFA

Function: VEGFA is a major angiogenesis regulator that leads to the formation of new blood vessels, growth of endothelial cells, and control of vascular permeability.

Expression: In normal cells expressed at low levels, but in conditions like hypoxia, wound healing, and stimulation of growth factoer get increases. VEGFA is overexpressed in both diseases.

Prognosis Correlation: Elevated VEGFA expression in breast cancer is related to increased tumor growth, metastasis, resistance to chemotherapy, and poor survival, and acts as a marker of disease severity in PCOS.

Role: For supplying oxygen and nutrients for the formation of new blood vessels and supports immune evasion and tumor survival**.**

Mechanism of Action: By the influence of hypoxia, HIF-1alpha VEGFA expression level increases and binds to VEGFR2 for activation of P13K-AT, MAPK, and PKC signalling, which promotes endothelial cell proliferation and angiogenesis.

Impact of Upregulation: Excessive VEGFA activity in breast cancer leads to abnormal blood vessel formation , growth of tumor, metastasis, and promotes ovarian vascular abnormalities to create a pro-cancer microenvironment in PCOS and BC.

3.2 Network Topological Analysis

For every network constructed for regulatory network analysis, the construction of three coregulatory networks takes place, and node tables were created in a detailed form and used for topological analysis as well. With the help of degree centrality, we can identify the genes that share a direct correlation. The network of genes influences the regulatory cascade. In addition to this, Betweenness centrality is used to identify genes that connect different regions of the regulatory network and control the flow of regulatory signals across the molecular framework.

Genes that exhibit high degree values are considered the most highly influential regulatory genes, as molecular interactions take place on a higher level. Genes of high betweenness centrality act as critical gene connectors, and any kind of disturbance in such a network causes downstream effects.

For better transparency, the construction of minimal networks takes place, and network images were visualized as in PNG format, and different color nodes depict better and clearer visualization as red and orange nodes represent genes with high level of connectivity, while yellow and blue nodes represent genes with low level of connectivity, by appropriate color depiction makes smooth identification of most important biologically important components present in the regulatory networks.

3.3 Identification of Hub Genes Across Multiple Network Types

The primary purpose of network analysis is the recognition of key hub genes. Hub genes are defined as genes that show a high degree and betweenness centrality across multi-regulatory network subtypes.

As these hub genes appear as central regulators in gene-miRNA, gene-TF, and tissue-specific co-expression networks and play a role of critical molecular regulators, and include in the shared pathway of both PCOS and breast cancer.

3.3.1 Hub Genes in the Gene-miRNA Interaction Network

Comparative analysis of gene miRNA interaction with other networks shows the presence of four 4 red colored node hub genes common, which depict a high connectivity level and importance of regulation within the network, and 4 orange colored node hub genes common with gene-TF interaction, which depict a moderate level of connectivity and a significant level of regulation.

By this analysis, NAMPT, along with other highly connected genes, serves as a major post-transcriptional suppressor in the miRNA family. The miRNAs which pretent to interact with these hub genes involve tumor suppressor and oncogenic miRNA families, which supports the biological significance and reproducibility of the estimated interaction in between of regulatory networks

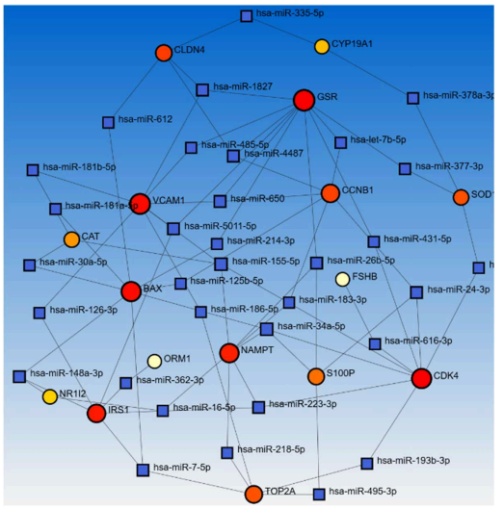

Fig1. Gene–miRNA interaction network illustrating key miRNAs and hub genes involved in PCOS and breast cancer

miRNA ID	Type / Function
hsa-miR-21-5p	OncomiR – enhances cell proliferation and apoptosis inhibition
hsa-miR-34a-5p	Tumor suppressor – signaling of p53 to lead to apoptosis
hsa-let-7a-5p	Tumor suppressor – target oncogenes like MYC and RAS
hsa-miR-155-5p	OncomiR – leads to inflammation and proliferation of cells
hsa-miR-126-3p	Tumor suppressor – VEGF regulation and promotion of angiogenesis
hsa-miR-146a-5p	Anti-inflammatory – Regulates the signalling of NF-kB and insulin cascade

Table 2: Tabular representation of miRNAs association with key hub gene involved in PCOS and Breast Cancer

3.3.2 Hub Genes in the Gene-Transcription Factor Interaction Network

Comparative topological analysis of gene-TF interaction with other networks show presence of four 4 red colored node hub genes is common, and the 4 orange-colored node hub gene common with gene-miRNAthe presence of four 4 red colored node hub genes common, which depict a high connectivity level and importance of regulation within the network, and 4 orange colored node hub genes common with gene-TF interaction, which depict a moderate level of connectivity and a significant level of regulation. This cross-network significance and identification of hub gene make a strong remark of reliability and biological importance.

In addition, NAMPT was identified as a consistently present and important hub gene in the TF interaction network. These factors of transcription, recognized as upstream regulators of the shared genes, include major regulators that are involved in inflammation, homeostasis, metabolism, and cancer development, which explains the common transcriptional derangement seen in both conditions BC and PCOS.

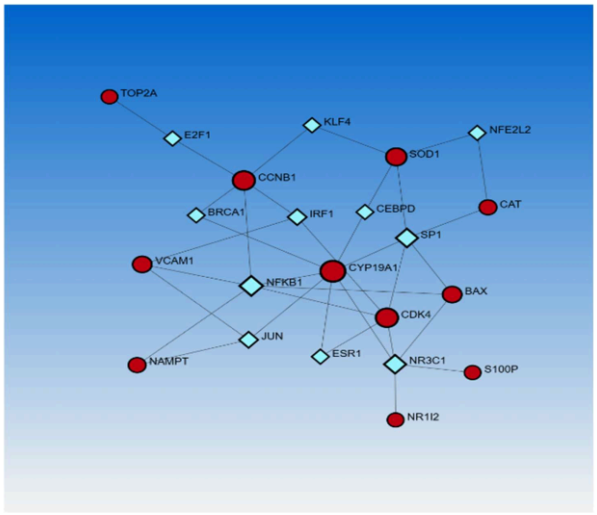

Fig. 2. Transcription factor–gene interaction network highlighting key regulatory transcription factors involved in PCOS and breast cancer

Transcription Factor	Known Role	Relevance to PCOS/Breast Cancer
TP53	Act as a major tumor suppressor and helps in apoptosis regulation	Mutation in breast cancer; oxidative stress in PCOS
NF-kB	Major regulator of inflammatory signaling	Chronic inflammation in BC and PCOS
STAT3	Play a vital role in JAK/STAT and cytokine signalling	Oncogenic in BC; causes resistance to insulin in PCOS
SP1	Help in cell proliferation and gene regulation in metabolism	Controlled by the signaling of estrogen and androgen
HIF1A	Response to hypoxia and regulation of VEGF	Creates a microenvironment for the tumor

Table 3: Tabular representation of Transcription Factors Regulates Shared Hub Genes

3.3.3 Hub Genes in the Tissue-Specific Gene Co-expression Network

Comparative analysis of tissue-specific gene co-expression with other networks shows the presence of two genes represented by red-colored nodes, which exhibit a high level of co-expression connectivity in which one red colored node hub gene and another 1 red colored node hub gene are common with gene-miRNA interaction. More specifically, one red colored node gene was also consistently present in the gene-TF interaction network. NAMPT is recognized as a major molecular hub gene consistently present in all three regulatory networks, which confirms the positioning of the main molecular node to link the framework of both BC and PCOS.

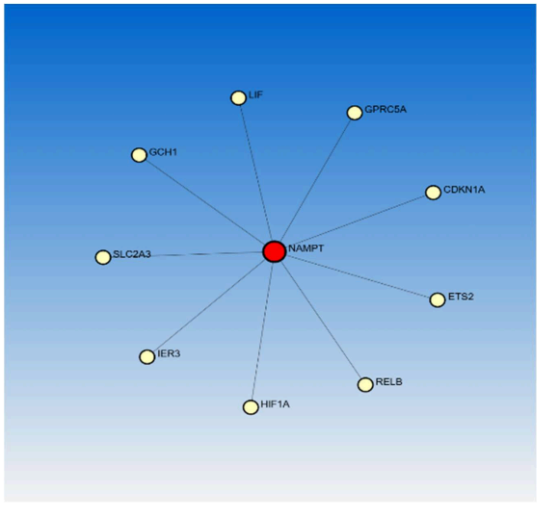

Fig. 3. Tissue-specific co-expression network demonstrating gene clusters expression (OVARY-PCOS) involved in PCOS and breast cancer

NAMPT as the Central and Convergent Hub Gene

The sustained and constant recurrence of NAMPT (Nicotinamide Phosphoribosyltransferase) identified as a hub gene in the three given regulatory networks named as gene-miRNA network, the gene-TF network, and the tissue-specific co-expression network, contributes to being the most vital factor of the analysis. NAMPT is defined best as a rate-limiting enzyme involved in the pathway of NAD+ salvage biosynthetic, and plays a dual biological role, first as a critical intracellular metabolic enzyme and second as an extracellularly secreted pro-inflammatory adipokine.

Within the cell, the key gene, NAMPT, helps to maintain NAD levels, which are necessary for the production of energy, DNA repair, and the enzymatic activity of enzymes like sirtuins and PARPs.In the extracellular secretory form, NAMPT (also called visfatin/eNAMPT) enhances inflammation, resistance to insulin, angiogenesis, and leads to the activation of cancer-causing signalling pathways. By the persistence of these characterizations, NAMPT is strongly associated with inflammation, metabolic dysfunction, and tumor-related signaling visualization in both the disorders PCOS and BC, and proves and confirms as a common hub gene in all three respective regulatory networks.

The finding consider as vital therapeutic applicability. For the inhibition of NAMPT, small molecule of NAMPT inhibitors like FK866 (also known as APO866) and CHS-828 depicts the possibility to destroy and eliminate cancer cells in the pre-clinical studies of the disorder, and by the reduction in the intracellular form of NAD levels, and weaken the survival effect of cancer cells.

In addition to PCOS, NAMPT mediates gene targets inflammation and pathways involved in resistance to insulin, which may contribute to its functioning in the hormonal and metabolic imbalance, which directly or indirect increase the risk of cancer in females. In favor of the study, NAMPT acts as a viable and advantageous therapeutic target in both disorders, breast cancer and PCOS.

Identification and Compatibility Analysis of Potential Therapeutic Drugs

For the recognisation of abnormal genes and miRNas present regulatory networks of both BC and PCOS elevates the chance of occurance of breast cancer and this scenerio led to the search effective and possible therapeutic measures. In the analysis we concentrate on common 17 genes which identified by mechanism of regulatory networks as these genes serves as vital overlapping molecular molecules play its role in both diseases. The existing drugs in the market formulates or pay special focuys to such genes which we studied to favour and understand their capability and to regulate signalling routes and also balce and restore molecular balance in both disorders.

Amajor discovery of this analysis is to identify molecular drugs which contribute a significant role in regulatory cascade of miRNA with the common 17 genes. These cascades involves oncogenic miRNAs and tumor suppressor miRNAs , as oncogenic miRNAs are upregulated miRNAs which leads cancer and tumor-suppressor miRNAs which downregulates miRNAs which perform normal activity to prevent cancer.This explains the multiple level targeting of derangement of sharedmiRNa by molecular hubs which are common in nature and provide complex and more efficient strategies for treatment of BC and PCOS.

In this finding, Drug compatibility refer to the effective level of identified compounds which targets in the shared molecular and regulatory network which includes their ability to communicate and interact with common protein present in the network as for regulation dysfunctioning of signaling pathways and modulate the associated process of miRNAregulatory genes. The drugs which depict strong and high interaction scores and more complex connectivity of network referred to be more important in therapeutical domain

In all analyzed and identified compounds, Compounds like Genistein and Amsacrine shows more significant presence depending on their interaction score which is higher in the within the network regulation. Genistein shows the highest interaction frequencies which demonstrates strong role in the regulating cascade whichshows correlation with proliferation of cell, signalling of hormones, oxidative stress, and inflammatory reactions because of its features like phytoestrogenic and anticancer. Genistein contribute in the modulating of hormonal imbalance in both PCOS and BC-related tumor progression

Table 4: Potential Therapeutic Drugs and their Compatibility

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Drug	Classes of drug	Primary Mechanism	Therapeutic Application	Compatibility
Genistein	Phytoestrogen / Isoflavone	Inhibition in Topoisomerase	Inflammation, bone loss (Osteoporosis)	High
Amsacrine	Derivative of Acridine / Topoisomerase II Inhibitor	Intercalation in DNA strand and Topoisomerase II poisoning	Leukemia, Lymphoma	**High**
Doxorubicin	Anthracycline antibiotic	ROS induction	Broad-spectrum cancer treatment	**High**
Paclitaxel	Taxane	Microtubule stabilization leads to mitotic arrest	Ovary cancer, Breast cancer, Lung cancer	**High**
Erlotinib	EGFR-TKI	competitive inhibition in EGFR ATP-site	\ Pancreatic cancer	**High**
Tamoxifen	SERM (Selective oestrogen receptor modulator)	Estrogen Receptor antagonism in tissue of breast	Breast cancer (Hormone receptor-positive breast cancer)	**High**

Drug	Classes of drug	Primary Mechanism	Therapeutic Application	Compatibility
Resveratrol	Stilbenoid Polyphenol	SIRT1 pathway activation	Cancer prevention	**Moderate**
Quercetin	Flavonoid	PI3K inhibition	Cancer and chronic Inflammation	**Moderate**
Mifepristone	Antiprogestogen	Antagonism of progesterone and glucocorticoid receptor	Breast cancer, Cushing's syndrome Endometriosis	**Moderate**
Ritonavir	HIV Protease Inhibitor	CYP3A4 enzyme inhibition	HIV and cancer drugs	**Moderate**
Warfarin	Anticoagulant	VKORC1 inhibition and affectsVitamin K pathway	Thrombosis (cancer-related)	**Moderate**
Dexamethasone	Corticosteroid	Agonism of Glucocorticoid receptor	Haematological malignancies	**Moderate**

Compatibility Key:

High means Clinically validated or strong network centrality

Moderate means investigational or indirect evidence;

Low means Limited network connectivity or primarily non-oncological use.

Detailed Analysis of Key Drug Modulators and Their Mechanisms

The two major drugs with degree ≥ 2 are represented as the most highly connected nodes in the DPI drug protein interaction network. The high betweenness centrality shows their regulation as critical mediators, as it connects multiple protein interaction cascades.

Detailed Information provided below:

Genistein — Primary Network Hub

Genistein (DB00077)

Drug Class: Phytoestrogen and Isoflavone

Degree: 2

Betweenness Centrality:4030

Closeness :0

Main Targets:

- Topoisomerase II
- Estrogen Receptors (ERα/ERβ)
- EGFR
- HER2
- VEGFR
- Protein Tyrosine Kinases

Mechanisms

- Geinstein serves as a competitive inhibitor of protein tyrosine kinases at the ATP-binding site
- Geinstein blocks topoisomerase II alpha and leads to poisoning of topoisomerase II alpha to stabilise the enzyme-DNA cleavage complex
- Modulation of the estrogen receptor by acting as a partial agonist/antagonist
- Suppress the cascade signalling of I3K/Akt/mTOR and MAPK signallings
- Genistein triggers the process of apoptosis by the downregulation of Bcl-2 protein and activation of caspase-3/9 enzymes.
- Genisein initiates and suppresses the secretion of VEGF and blocks VEGFR signalling, which leads to anti-angiogenicity.

Therapeutic Use:

- Anti-cancer (prostate, breast, colon)
- Osteoporosis
- Cardiovascular protection

Compatibility → High

Amsacrine — Secondary Network Hub

Amsacrine (DB00276)

Drug Class → Topoisomerase II Inhibitor and Acridine Derivative

Degree → 2

Betweenness Centrality → 726

Closeness → 0

Targets

- Topoisomerase II alpha
- Topoisomerase II beta
- DNA

Mechanisms

- Amsacrine planar acridine ring adds between base pairs of DNA, leading to DNA intercalation
- Prevention of re-ligation of ds breaks leads to Topoisomerase II poisoning
- Permanent accumulation of the enzyme-DNA complex triggers the signalling of the double-strand break
- Cell arrest in G2/M stage and activation of ATM/ATR -Chk1/Chk2 checkpoint protein
- Induction of apoptosis via a cascade of p53-dependent and p53-independent pathways
- By high expression of topoisomerase II, induce selective cytotoxicity to the rapidly dividing cells

Therapeutic Use

- Acute myeloid leukemia (AML)
- Refractory lymphomas ·
- Paediatric ALL

Compatibility → High

Likewise, Amsacrine depicts a strong interconnection with regulatory networks and its anticancer activity through DNA intercalation and inhibition of topoisomerase II. Its significance in the shared network shows a high chance of targeting abnormal cell proliferation and pathways linked to the common genes of BC and PCOS.

Along with these top-rated drugs, there are several other drugs with low interaction affects the pathway signalling by cell proliferation, apoptosis, hormonal signalling, and lead to oxidative stress, but support the signalling complex and share a multi-molecular relationship between PCOS and BC

These drugs include anticancer drugs, hormonal modulators, antibiotics, flavonoids, and anti-inflammatory compounds.

Table of Additional Identified Drugs

Functional Category	**Representative Drugs Identified**	**Potential Relevance**
Anticancer agents	Doxorubicin, Epirubicin, Paclitaxel, Docetaxel, Etoposide	Regulates tumor proliferation and apoptosis as well
Hormonal modulators	Tamoxifen, Progesterone, Estradiol, Mifepristone	Dual Hormonal signalling routes in PCOS and BC
Natural bioactive compounds	Resveratrol, Quercetin, Piperine, Lupeol	Antioxidant effects, anti-inflammatory effects, and antiproliferative properties
Endocrine/metabolic regulators	Spironolactone, Fenofibrate, Dexamethasone	Modulation in Metabolic and inflammatory cascade

Antimicrobial/other agents	Ciprofloxacin, Ketoconazole, Ritonavir	Indirect modulation of the signalling and cell proliferation system

The outcome of the interaction between drug–protein analysis determines some molecular compounds' relevance with their therapeutic potency in the spite of shared molecular scenario of both disorders BC and PCOS. The discovery and determination of multifunctional drugs, especially Genistein and Amsacrine, which initiate targeting of every possible outcome in common regulatory pathways and mechanisms, are associated with the help of network- related therapeutic strategies.

Chapter 4

Discussion

This study applies a comprehensive and structural approach to determine the molecular relationship between polycystic ovary syndrome (PCOS) and Breast cancer (BC). The main goal is to recognise common shared regulatory genes and identify their possible therapeutic strategies that share both disorders. The results obtained show transparency and biological importance og the interconnection between PCOS and BC by the shared molecular routes.

The recognition of 17 common genes appears between PCOS and breast cancer by a bioinformatics approach named the Comparative Toxicogenomics Database (CTD). The identified common genes play a major role in biological processes spanning hormonal signalling, inflammation regulation, metabolic homeostasis, and DNA repair, and their functioning clearly demonstrates that females diagnosed with PCOS may have a higher chance of breast cancer development.

To check the accuracy of gene interaction and for analysis, regulatory networks are used. Three types of regulatory networks, named gene–miRNA networks, gene–transcription factor networks, and tissue-specific co-expression networks, are constructed. With the help of such multifunctional network analysis, the identification of NAMPT as a central hub gene in all three networks is proven. The persistent result confirms the role of NAMPT in the association of the molecular mode of action between PCOS and BC.

The regulatory analysis of all three networks led to the identification of NAMPT (Nicotinamide Phosphoribosyltransferase) as the critical key hub gene, not random but an accurate identification, which correlates with all three regulatory networks of disorders, breast cancer, and PCOS. NAMPT plays a vital role in the formation of the NAD+ biosynthetic pathway as cancer cells grow and divide repeatedly. A large amount of NAD maintains the cellular metabolism and plays a vital role in biological association in both disorders by repairing DNA, and balances energy.

The extracellular form of NAMPT serves as an inflammatory interconnector adipokine and triggers resistance to insulin, formation of new blood vessels, and survival of cancerous cells. Females diagnosed with PCOS show higher levels of NAMPT in circulation and are linked to hyperandrogenism and higher resistance to insulin, which is triggered by NAMPT, and shows a better example of disease occurrence.NAMPT plays a double role as it bridges the link between metabolic dysregulation of PCOS and the growth and survival of breast cancer cells.

The network-level significance of NAMPT is controlled by multiple miRNAs and transcription factors, involved in pro-inflammatory and metabolic interconnectors, which perfectly depicts its double role in the linkage of PCOS and breast cancer regulatory networks. Several miRNAs that trigger Napt are dysregulated in the BC and PCOS, which suggests regulatory routes of NAMPT disturbed in multifunctional approaches. Restoring the regulatory energy balance can lead to advanced therapeutic approaches.

The analysis supports the modern approach of complex diseases like PCOS and BC, enabling the finding of multi-pathway target therapies that the single-pathway therapies are unable to detect. The discovery of NAMPT as a central hub gene helps to regulate multiple interconnecting network types in this study, exemplifying the potential to establish a molecular target to detect the intervening bridge between therapeutic strategies in the disorders. By using an established network-centric approach as an analytical tool, a fundamental strategy to treat and understand the complexity of the diseases is proposed. The analysis of this study led to the discovery and recognition of the cancer drug Sorafenib, which plays a critical role in multiple interconnected pathways rather than a single pathway.

Despite these findings, the study has some limitations as the whole analysis is supported by in silico findings (computational-based), the estimated gene interconnections and regulatory mode of the mechanism need experimental authentication. Future research findings confirm the expression of the NAMPT gene and its linkage to regulatory miRNAs in the tissue of patients by using several clinical approaches, such as qPCR-based validation, and for further evaluation and investigation of inhibitors of NAMPT in cell culture and animal models, which emulate the BC and PCOS overlap.

Chapter 5

Conclusion

This research introduces a structured bioinformatics approach designed to examine the molecular connections between polycystic ovary syndrome (PCOS) and breast cancer. Employing node table analysis, topological parameters, and network visualizations, the study furnishes robust computational support for the recognition of shared molecular pathways associated with PCOS and breast cancer from the Comparative Toxicogenomics Database (CTD) with network analysis through the NetworkAnalyst platform.

The identification of shared genes, notably those serving as hub genes within gene–miRNA, gene–TF, and co-expression networks, signifies a coordinated regulatory disruption rather than a spontaneous occurrence. The visual representation shows the central significance of hub genes in the regulatory network, and also demonstrates their function as vital regulatory components that link PCOS- and breast cancer-related pathways.

Consequently, the results depict validation and significant knowledge of both disease mechanisms, which provide potential future experimental validation and therapeutic analysis of NAMPT as a target and can regulate NAD-dependent pathways involved with cell survival and inflammatory processes. The Pharmacological inhibition of NAMPT reveals a reduction in tumor size and metabolic stress, and NAMPT-related pathways may reduce resistance to insulin and inflammation in females suffering from Polycystic Ovary Syndrome (PCOS).

Therefore, the co-utilization of NAMPT as a target could help manage the probability of susceptibility to breast cancer due to PCOS. This led to the possibility of a single target treatment approach rather than a multiple approach for consideration.

Overall, this study leads us to a strong computational foundation for future approaches in clinical labs and studies, as it focused on NAMPT major hub genes targeted therapies. IT demonstrates the bioinformatics-based network approachesfor the identification of common molecular cascades and potential for superior therapeutic targets in complex disorders.

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