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Significance of Bioinformatics in the Cancer Diagnosis Process

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Abstract
The improved genetic analysis increases the possibility of identifying mutations. Potentially useful prognostic or predictive biomarkers for patients with metastatic cancer to use in their fight against the disease and for enhancing their quality of life could also emerge from such an investigation. The advanced genomic analysis allows for detecting those at high risk of acquiring metastatic cancer and understanding the pathological process. Useful and making good use of the plethora of data made available by high-throughput experimental gene analysis, the methodologies for data analysis are a boon to the field. They are tasked with a wide range of classification and clustering activities, from diagnostic to mechanical, as well as survival analyses. The probable genes' relevance was hinted at using both mRNA expression analysis and existing CNA data.

1. Introduction

Gene profiles are being utilised more frequently to identify differentially expressed genes (DEG) and conduct cancer genetics research. Although there have been numerous gene profile studies on carcinoma in recent years, the outcomes of these studies do not always agree. Therefore, it is necessary to implement this methodical bioinformatics study to reintegrate public databases and collect useful hints for future cancer research. To deduce the potential biological activities and signalling pathways of DEGs and to build the Protein-Protein Interaction (PPI) network, bioinformatics studies are required. We still don't know much about how malignant cells and their surrounding normal tissues differ in gene expression. Finding DEGs between a tumour and nearby normal tissues will aid in the pathogenesis's further understanding and offer diagnostic biomarkers and therapeutic targets [1]. Breast cancer is the second factor in female fatalities. Breast cancer is a complex disease with multiple molecular subtypes, each of which may have its own unique expression profile or one that is strikingly similar to others. While there have been several advances in therapy, the definitive cure has not yet been found because of the biological variation among individuals with various subtypes of breast cancer. However, changes in the expression of genes and microRNAs, which can act as tumour suppressors or oncogenes in various disorders, including malignancies, might be a helpful cue to identify the underlying targets with therapeutic

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benefits [2]. Breast cancer can be classified into four main subtypes according to the presence or absence of the oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). These subtypes are known as triple-negative breast cancer (TNBC), HER2-positive breast cancer (HER2), Luminal A (LA), and Luminal B. (LB). However, in HER2 breast cancer, HER2 is the sole active receptor, while in triple-negative breast cancer, both HER2 and HER4 receptors are inactive (TNBC). Tumors from both LA and LB can be positive for ER and/or PR, however the hallmark of LA tumours is their consistent negative for the HER2 receptor. Each subtype possesses distinct risk factors, prognoses, prevalence, survival rates, responses to a range of treatment agents, and distinct clinical outcomes [3]. Advanced colorectal cancer has a low survival rate and is challenging to treat. Thus, biomarkers are required for detecting this malignancy at earlier, more curable stages. Several forms of cancer have shown promise for using micro-RNAs as a biomarker for early diagnosis and better treatment (miRNAs). However, because MiRNAs are non-coding, their fundamental drawback as biomarkers is that they lack a related phenotype, making it challenging to validate them using alternative methods.

To that end, any strategy that can give meaning to miRNA expression would help us better grasp the significance of miRNAs in disease. In light of this, it is difficult to deduce how miRNA contributes to the beginning and development of disease. Among all cancers, colorectal cancer is the third most frequent and the fourth leading cause of death worldwide (CRC). Endodermal cells give rise to the epithelial lining of the colon; adenocarcinoma forms when genetic and epigenetic abnormalities accumulate over time [4,5]. Using a quantitative approach, researchers have estimated that it takes another five years after the initial mutation in stem cells that changes them into malignant cells for these neoplastic cells to gain the capacity to metastasis, giving a total time frame of about 10 years. Thirty percent to forty percent of the population also suffers from chronic ailments.

The use of microarray technology lays the groundwork for identifying and assessing the traits in diseases like breast cancer. High-throughput sequencing and microarray technology advancements have revealed potential biomarkers for cancer detection and treatment and a useful tool for analysing major genetic alterations in carcinogenesis. The gene expression profiles of breast cancer and normal breast tissue were compared using data from the Gene Expression Omnibus. Data generated by microarrays and next-generation sequencing technologies are stored in this publicly accessible repository. The downloaded data set is pre-processed with the LIMMA package in R software and the resilient multi-array (RMA) function. In order to compare DEGs in breast cancer samples to those in normal samples, we first had to convert the probe IDs to gene symbols, after which we removed the background and log2 transformed the data. The final expression value was calculated by averaging all of the probe expression levels that map to the same gene symbols [6,7].

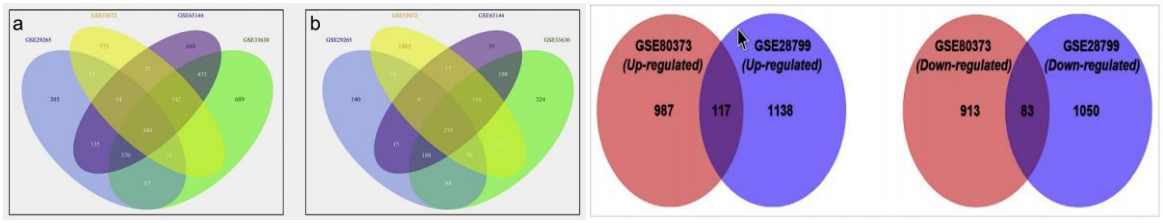

Figure 1: The Venn diagram of the DEGs in the differentially expressed gene datasets resenting DEGs up-regulated and down-regulated [1,8].

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The small non-coding RNAs known as micro-RNAs (miRNAs) have shown great promise as biomarkers for the improved management and early diagnosis of a wide variety of cancers [9]. MiRNAs range in size from 19 to 25 nucleotides, making them extremely degradable due to their short structures. Exosomes release these oncogenes into the body's physiological fluids, including serum and urine, from cancerous tissue, where they are abundantly expressed. A number of cancers, including CRC, have been associated to mir-21's function. Colorectal cancer tissue is thought to express Mir-21 at a much higher level than regular tissue. However, this phrase is linked to conflicting cancer prognosis and survival reports [5,10]. Posttranscriptional regulation is facilitated by miRNAs, which bind to the 3'-untranslated region of mRNA. MicroRNA databases like TargetScan, MiRDB, and Miranda use this data in conjunction with other characteristics to infer which genes a given microRNA regulates. In spite of this, the mathematical models and algorithms used by these databases lead to varying estimates of the genes that a given microRNA will target. For certain of these, only a small number of targets have been experimentally validated, and computational predictions, including those for highly scored targets, may be false positives. Due to the lack of evidence that any one of these microRNA databases is superior to the others, this study took the intersection of the three databases to improve gene target prediction accuracy. Afterwards, GEO2R and a second method, GSEA, were used to determine whether genes were significantly different in expression between colorectal adenomas and cancers.

GEO2R's comparison to the GSEA approach offers a basic, freely accessible tool that doesn't call for specialised knowledge, such as understanding the R programming language. Gene Expression Pathway Analysis (GEO2R) uses the limma programme to produce a completely arbitrary list of differentially expressed genes, while Gene Set Enrichment Analysis (GSEA) organises genes according to their established roles in biological pathways. It's interesting that when we intersected our GSEA list with the mir-21 gene targets, we only got a portion of the genes that the GEO2R list had uncovered. This strategy, which employs the publicly available GEO2R method to obtain a broad but comprehensive gene target, might be applied to the study of any additional microRNAs that have been implicated in a wide range of disorders. Alternatively, use our more sophisticated GSEA approach, which isolates the up and down gene regulations compared to the traditional GSEA method. This might be used to extract its chemical signature and would simplify the management of disparate data. Electromagnetic forces, as opposed to the hydrophobic effect, govern protein-protein interactions (PPIs), which are the highly specialised physical interactions between two or more protein molecules caused by biological processes. The biomolecular context of a cell or organism is the site of many of these interactions, and many of them include molecular connections and other physical interactions between molecules. Protein-protein interaction networks are fundamental to our understanding of biological processes, disease causes, and therapeutic advancements [11]. Since the network is so intricate, deciphering a PPI is a herculean task. The PPI Network provides a framework for orienting and visualising the genetic links across different animals through regulated functions and protein structures. Bioinformatics is essential for many processes, including data cleaning, sequencing, huge dataset management, storage, transfer, DNA truncation, PPI networking, and treatment planning. Modern bioinformatics tools, such as PPI Network development and drug design, significantly impact gene analysis. The current knowledge gap can be reduced by the use of computational methods to either predict protein targets for a given drug molecule or to ineract with pharmaceuticals for specific protein targets. Researchers can use Network Analyst, a robust web-based application, to conduct both basic and intricate meta-analyses of gene expression data through an intuitive web interface. The PPI network is made up of the hub protein and additional genes that are either directly or indirectly related to it.

2. Breast Cancer

In order to identify new treatment targets, researchers have traditionally focused on genetic alterations, hormone receptor status, and changes in cancer-related proteins in breast cancer. Thanks to advances in next-generation sequencing technology, scientists now know that long non-

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coding RNAs play a role in regulating normal cellular activity and are linked to a wide range of illnesses, including breast cancer. Researchers were able to explore possible therapy targets for naringenin in suppressing BCSCs by using bioinformatics analysis and 3D tumorsphere in vitro modelling in breast cancer (mammosphere). Breast cancer prognosis and diagnosis may benefit from gene and microRNA expression profiles, as has been shown. Genes annotated as part of breast cancer-specific profiles have been found to have a variety of roles in the disease, including those related to cell cycle control, invasion, metastasis, and angiogenesis. Human microRNAs (miRNAs) are short non-coding RNAs that can repress the expression of their target genes [12,13] by binding to complementary sequences in the 3′UTR region of those genes. To determine which biological processes were most relevant in the frequently down-regulated differentially expressed genes, we performed a functional enrichment analysis in Gene Ontology (DEGs). The regulation of fat accumulation and the (cellular) response to acid substances were among the processes studied. However, LEP, TESC, OSR1, and LPL stood out from the rest of these genes in terms of their involvement in GO biological processes. PTN and LPL, which are involved in glycosaminoglycan and proteoglycan binding, respectively, have the most GO molecular functions annotations in this set. Important molecular actions in this group included binding to glycosaminoglycans and proteoglycans. Bioinformatics studies isolated BCSC regulatory genes and PTTNs in addition to naringenin target proteins (NTPs) and naringenin-mediated proteins (NMPs). Gene ontology enrichment, KEGG pathways, protein-protein interaction (PPI) networks, and hub protein selection were some of the additional studies performed on the PTTNs. Mastospheres were grown in serum-free medium. The effects of naringenin were examined using several different assays, such as the MTT cell viability assay, the mammosphere forming potential (MFP) assay, the colony assay, the scratch wound-healing assay, and the flow cytometry-based cell cycle and apoptosis assays. To examine gene expression, a real-time quantitative polymerase chain reaction assay was used (q-RT PCR) [14].

No	Protein symbol	Protein name
1	ESR1	Estrogen receptor alpha
2	AKR1C1	Aldo-keto reductase family 1 member C1
3	CYP1B1	Cytochrome P450 1B1
4	KANSL3	KAT8 regulatory NSL complex subunit 3
5	SHBG	Sex hormone-binding globulin
6	CYP19A1	Cytochrome P450 19A1
7	ESR2	Estrogen receptor beta
8	RAPGEF1	Rap guanine nucleotide exchange factor 1
9	ABCB1	ATP binding cassette subfamily B1
10	CYP1A2	Cytochrome P450 1A2
11	CYP1B1	Cytochrome P450 1B1
12	LDLR	Low-density lipoprotein receptor
13	APOB	Apolipoprotein B-100
14	PPARA	Peroxisome proliferator-activated receptor alpha
15	CCL2	C-C motif chemokine 2
16	HMOX1	Heme oxygenase 1
17	BDNF	Brain-derived neurotrophic factor

Figure 2: Direct target protein of naringenin [14].

In this annotation, the genes CLIP1 and AKAP9 were particularly important due to their roles in the constructive regulation of protein complex formation [2,3]. Estradiol response, autophagy control, transcriptional activator activity, insulin-like growth factor binding, and extracellular exosome/vesicle were revealed to be the most commonly enriched GO keywords in the shared DEGs. Exosomes, or extracellular vesicles, have been linked to the development of several forms of cancer, including BC, based on the results of previous investigations. The modification of

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extracellular vesicles may also prove to be a valuable therapeutic technique in the fight against cancer. Both tumor-suppressing and tumor-promoting roles of autophagy are thought to exist; these opposing roles may be responsible for the different contexts and stages of carcinogenesis [2,15]. Relapse and metastasis, which are the end outcomes of intrinsic and acquired resistance, reduce tamoxifen's efficacy in the treatment of breast cancer; thus, more research is needed to develop a combination therapy that incorporates tamoxifen [12]. Using the TCGA data set, researchers showed that the let-7 family of miRNAs were differentially expressed in breast cancer, with let-7a, let-7d, and let-7f being elevated and let-7b, let-7c, let-7e, let-7f, and let-7i being downregulated. According to the OncomiR and dbDEMC 2.0 databases, let-7b-5p and let- 7c-5p expression levels differ amongst cancer types. Expression of let-7c-5p was found to be significantly lower in the most patient-populated tissues as compared to normal tissue. A number of cancer types, including breast, bladder, colon, cholangiocarcinoma, kidney, liver, lung, rectal, stomach, thyroid, and endometrial, were reported to have considerably lower expression of Let-7c-5p in tumour tissue compared to normal tissue. According to a GO enrichment analysis, apoptosis and intracellular signaling cascades were two biological processes PTTNs were involved. The cytosol and extracellular space are where you can find the PTTNs.

Additionally, the PTTNs have a mechanistic role in the action of transcription and growth factors. Using KEGG pathway enrichment analysis, researchers determined that the PTTNs regulate approximately 53 pathways, some of which are involved in cancer, Wnt, and TGF- beta signalling. Wnt signalling aids cancer cell growth, differentiation, invasion, migration, metastasis, and metabolism [14,16].

3. Prostate Cancer

Patients with metastatic prostate cancer frequently have somatic genetic alterations. The androgen receptor and TP53 are involved in the most common variations. Both the transcriptional regulator ETS and the tumour suppressor gene PTEN have variations to varying degrees. The prospect of capturing genetic variations is growing with advanced genomic analysis. Additionally, this can result in the identification of prognostic or predictive biomarkers. To automatically group targets into categories, principal component analysis (PCA) can be employed as a dimensionality reduction technique. It is also possible to estimate the weights of the factors used in group separation [17,18]. The biological processes of apoptosis control and nucleobase, nucleoside, nucleotide, and nucleic acid metabolism were among those elevated in the DEGs' functional enrichment analyses. Proliferation of cancer cells requires de novo nucleotide synthesis, which is directly regulated by tumour suppressors and oncogenes. P53 signalling, PI3K-AKT signalling, small cell lung cancer, MicroRNAs in cancer, and apoptosis were among the biological roles identified by KEGG analysis of the DEGs. P5 up3, a tumour suppressor gene, detects and responds to cellular stress, such as DNA damage. GC develops from normal gastric mucosa, and an increase in TP53 mutations is a key step in this process. Many different forms of cancer rely on the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signalling pathway for their development and progression. Hydroponic interactions, van der Waals forces, and salt extensions at conserved locations on each protein hold protein complexes together. The cooperative outcome for at least two proteins with a functional goal can be demonstrated in a variety of ways, including changes in the dynamic properties of chemicals like enzymes, substrate redirection via the movement of a substrate between areas or subunits, a proposed final result, the creation of a new bonding state, the activation or annihilation of a protein, and so on. The PPI Network's ability to communicate and perceive light signals through protein structures reveals the genetic connections across organs. Bioinformatics has had a significant impact on several areas, including data sequencing, enormous dataset administration, data storage, data transport, DNA shortening, PPI networking, and treatment planning. Modern bioinformatics instruments significantly impact the creation of PPI networks and drug plans in gene investment. We can also learn topological properties from this PPI network that aid in understanding the underlying biological mechanisms. For the PPI network to be constructed, Cytoscape is necessary. It's a great

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place to learn about computer science, and it's free and easy to use [19].

Genes and pathways involved in extracellular matrix organisation, extracellular exosome, extracellular matrix, extracellular space, cell adhesion, and protein binding were found to be important in the onset and progression of CRPC, as determined by an analysis of enriched GO terms. It is increasingly understood that the extracellular matrix, a crucial element of the microenvironment, is a key regulator in many different types of tumours. Given that exosome biogenesis and secretion are inhibited in CRPC C4-2B cells, this may have consequences for the biology and carcinogenesis of this disease. According to accumulating evidence, exosomes have been linked to cancer progression. Hormonal therapy led to the recurrence of the differentiated neuroendocrine phenotype in CRPC, which may be a factor in the disease's poor prognosis and therapeutic resistance. Adipocyte differentiation-relation protein found in exosomes helps prostate cancer cells develop into neuroendocrine cells. Prostate cancer is incredibly varied, as evidenced by the wide range of expected survival times for CRPC patients, from months to years. Since these samples are not required for standard clinical therapy, obtaining serial metastatic prostate cancer biopsies is particularly challenging. As a result, tracking genetic changes in CRPC patients is challenging, and reliable patient categorization and survival estimates were hindered. Focal adhesion kinase inhibitor with docetaxel is an effective strategy for combating drug resistance to the former. Proteins in the focal adhesion pathway, like BCAR1/p130Cas and paxillin, have higher concentrations after being phosphorylated by focal adhesion kinase [6,20].

4. Lung Cancer

Lung cancer is a diverse illness of two kinds. NSCLC, which accounts for 85% of lung cancer diagnoses, most often develops in the lung's neuroendocrine cells (NSCLC). Squamous-cell carcinoma (LUSC), adenocarcinoma (LUAD), and large-cell carcinoma (LUCC) are the subtypes that can be applied to these cases (LCC). The DEAD/H box RNA helicases play a role in the three phases of RNA metabolism (transcription, translation, and degradation). The helicase core, composed of two RecA-like domains, is a structural component found in all DEAD/H box proteins. The helicase function is conferred by a combination of conserved amino acid motifs dispersed throughout these areas. They work together to give the helicases their capacity to bind ATP and RNA [21]. The first member of this family to be identified was eukaryotic initiation factor 4A (eIF4A), a component of the translation initiation complex. Only a helicase core and RecA-like domains make up its structure, and its N-terminal chain is quite short. RecA domains assemble into an ATP- and RNA-binding helicase core. In contrast to ATP binding sites, the purpose of RNA binding sites is to protect the RNA strand's sugar-phosphate backbone. Helicases are not selective for certain RNA since they can interact with a target sequence without requiring complimentary base pairs. When acting as helicases, DEAD/H box proteins attach to and unwind RNA in an ATP-dependent way; however, this is only possible for very short RNA duplexes. Complex secondary structures formed by RNA duplexes regulate RNA processing. These RNA secondary structures arise from interactions between the nucleotides in the RNA molecule. Due to the stability of these structures, RNA duplexes will maintain their shape unless influenced by outside forces, such as helicases that can redesign the duplex to aid in appropriate RNA processing. The binding cleft needs to be in a very specific conformation to associate with ATP and RNA, and even little alterations to these motifs can affect how well the protein functions [22].

About 14% of all lung cancer diagnoses are small cell lung carcinomas (SCLC), which is a type of lung cancer with neuroendocrine development. The essential form of treatment is chemotherapy; the norm is platinum-based chemotherapy without ongoing care. When compared to other forms of lung cancer, small cell lung cancer (SCLC) is more amenable to treatment with chemotherapy and radiation (NSCLC). Advanced small cell lung cancer has the lowest five-year survival rate of any histological subtype of lung cancer. We have a great chance to identify new targets for drug development through the integrated analysis of high-throughput omics data and an improved understanding of the molecular drug database. Existing medications may find novel applications based on their pharmacological action mechanism.

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PCNA, or proliferating cell nuclear antigen, is a 36kDa protein that regulates numerous fundamental cellular functions, such as DNA replication, chromatin remodelling, DNA damage repair, sister chromatid interaction, and cell cycle progression [23]. Studies have shown that TP53 is the tumour suppressor gene that is altered or turned off at a higher frequency in human cancers than any other gene. Mutations in this gene can cause it to express less and speed up carcinogenesis. Previous research revealed that the various kinds of lung cancer exhibit significantly different levels of p53 and PCNA expression and that TP53 mutations are linked to SCLC.

Additionally, researchers hypothesised that TP53 could up-regulate the PCNA gene, implicating p53 in the early stages of lung carcinogenesis. A growing body of evidence points to cell growth being restricted by lowering PCNA. Additionally, nearly all human tissues express the highly conserved cyclin family proteins CCNB1, CCNB2, and CCNE2, together known as Cyclin B1, B2, and E2. CCNB1 is crucial for cell cycle regulation and maturation-promoting factor (MPF) production [9,24,25].

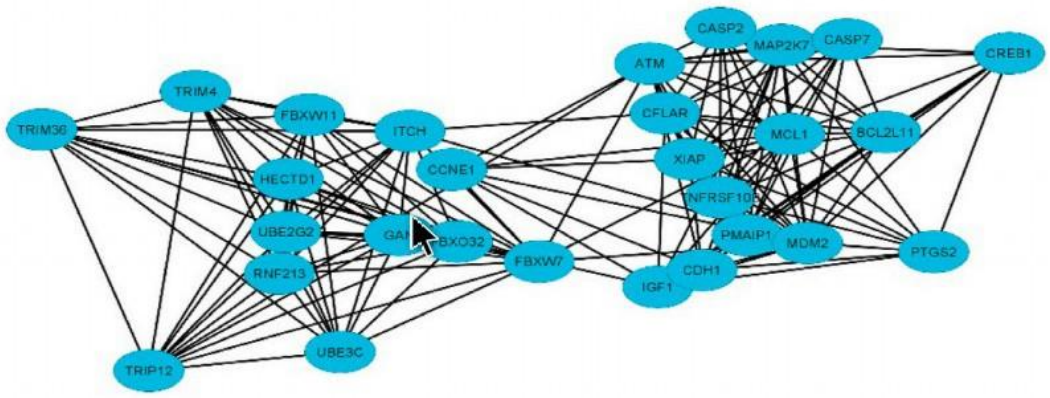

Figure 3: Protein–protein interaction (PPI) network

Autoantibodies against tumor-associated antigens were one type of promising serum biomarkers (TAAs). In the early stages of cancer, aberrantly produced TAAs could activate the immune system and cause it to create the matching antibody. TAAs can be detected using various techniques, such as 2-dimensional (2D) immune-affinity chromatography, protein microarray, western blot, serological proteome studies, and study of recombinant cDNA expression libraries. by using the sera of lung cancer patients to screen a library of lung cancer cDNA. Our bioinformatics study led us to hypothesise that the 35 lung cancer-associated antigen-encoding genes are involved in legionellosis, RNA transport, and the IL-17 signalling pathway, and that they positively influence DNA-binding transcription factor activity. Immunity, cell proliferation, cell differentiation, and cell survival are all impacted by the NF-kB transcription factors. An example of a transcription factor Important functions of NFkB include the control of immune system development, immunological response, inflammation, and cancer. The NF-B signalling network controls signals from important immune system and cancer pathways, such as the tumour necrosis factor receptor (TNFR), toll-like receptor (TLR), and interleukin-1 receptor (IL-1R), to generate a signal-specific transcriptional response (IL-1R) [7,26,27].

5. Conclusion

Using the database of already available drugs as a sort of "BioGPS," the integrated bioinformatical analysis provides a user-friendly and adaptable way to put to the test theories about genetic alterations in cancer, thereby aiding the process of moving from laboratory to bedside. The analytical method can help cut down on unnecessary tests at one or more labs, saving time and money. The integrated bioinformatical analysis, a novel research strategy built on a staggering array of polyphyletic data sources, may also link gene sets related to drugs and disease. However, there are difficulties with

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using Web-based data to study medications for cancer-related treatments. For instance, it is currently unclear whether or whether a specific biological impact of aspirin accounts for its ability to modulate its intended targets. One of the most important steps in drug development is the identification of drug-target interactions. Although high-throughput screening techniques such as microarrays and proteomics are now available, discovering drug-target interactions through experimentation is still prohibitively expensive, time-consuming, and challenging. This has led to the development of a plethora of computational models for making broad predictions on possible drug-target relationships. Computer models can be used to analyse various genes related to aspirin, providing more insight into the drug's potential use in illness prevention and therapy. The experimental viability of upcoming research examining the impact of medications on diseases can be guided by this strategy. There are now hurdles that must be overcome when using computational learning methods to forecast chemical/drug reaction. Non-coding RNAs (ncRNAs) are gaining attention as a potential new class of targets for drug discovery due to mounting data suggesting they may affect gene expression and disease progression.

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