CURRENT TRENDS IN COMPUTATIONAL CHEMISTRY FOR BREAST CANCER

Project Report submitted in partial fulfillment for the award of the degree of

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Submitted by

UTSAV GUPTA

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BRANCH OF STUDY

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Under the Supervision of

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SCHOOL OF MEDICAL& ALLIED SCIENCE

BONAFIDE CERTIFICATE

Certified that this project report **"CURRENT TRENDS IN COMPUTATIONAL CHEMISTRY FOR BREAST CANCER"** is the bonafide work of "**UTSAV GUPTA (17SMAS102018)**" who carried out the project work under my supervision.

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Examiners

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Supervisor (s)

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Statement of Project Report Preparation

1. Thesis title: CURRENT TRENDS IN COMPUTATIONAL CHEMISTRY FOR BREAST CANCER

2. Degree for which the report is submitted: BACHELOR OF PHARMACY

3. Project Supervisor was referred to for preparing the report.

4. Specifications regarding thesis format have been closely followed.

5. The contents of the thesis have been organized based on the guidelines.

6. The report has been prepared without resorting to plagiarism.

7. All sources used have been cited appropriately.

8. The report has not been submitted elsewhere for a degree.

(Signature of the student)

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ABSTRACT

Breast cancer is the second commonly diagnosed cancer and one of the prime reasons for cancer death in the world among females. The threat for breast cancer occurrences increases with increasing age and with that increases the non-success in treatment. Therefore, over a period of time the desire to analyze the factor facilitating the succession of breast cancer, prediction, reduction in the time taken for diagnostics, treatment, and drug discovery for breast cancer increased. However, with traditional methods it's hard to study all those things therefore computational approaches like artificial intelligence, bioinformatics, QSAR studies, molecular docking are used to analyze those things. In this project, current trends of computational chemistry are discussed for different fields.

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List of Abbreviations

Breast cancer	BC
Human Breast Cancer	HBC
Tumor Suppressor Gene Deactivation	TSG
Positron emission tomography	PET
Magnetic resonance imaging	MRI
Artificial intelligence	AI
Support Vector Machine	SVM
k-Nearest Neighbors	KNN
Next-generation sequencing	NGS
Extracellular-Signal-Regulated Kinase	ERK
Quantitative Structure-Activity Relationship	QSAR

CHAPTER-1

1. Introduction

Breast cancer is second commonly diagnosed and prime reason of cancer death in the world among females (Bray et al., 2018; *GLOBOCAN 2020: New Global Cancer Data*, n.d.). However, with increasing age the breast cancer threat and its non-success in treatment also rising (DeSantis et al., 2014). However, In addition to succession of external factors that facilitate the development, several genetic settings (internal factors) greatly direct the commencement and advancement of breast cancer. Oncogene activation and tumor suppressor gene deactivation (TSG) have a significant effect on the preservation and on cells integrity that contribute to tumorigenesis (X. Xu et al., 2001). Other genetic factors interrupt TSGs tumorigenesis-related expressions and functions indirectly because not all TSGs are susceptible to mutations,.(Osborne et al., 2004) Many genes, like PTEN, ATM, TP53, BRCA1, , RAD51, p27, Skp2, BRCA2, etc., are familier TSGs in humans that are associated in DNA repair and cellular mechanisms.(Burke et al., 1997; Kerangueven F, Essioux L, Dib A, Noguchi T, Allione F, Geneix J, Longy M, Lidereau R, Eisinger F, Pébusque MJ, Jacquemeir J, Bonaiti-Pellie C, Sobol H, 1995)As a result in all stages of life the strategies for prevention and self-assessment of breast become critically important. Normally diagnostic techniques involve positron emission tomography (PET) and elastography, mammography, ultrasonography, magnetic resonance imaging (MRI), , however, all of these techniques have notable efficacy-related Limitations exist, and false-positive or false-negative results may occur(Abreu et al., 2005; Athanasiou et al., 2010; Avril & Adler, 2007; Bird et al., 1992; Le-Petross & Shetty, 2011; Mienkina et al., 2010; Obi et al., 2011; Paci, 2002; Rosenberg, 1998; Schulz et al., 2006; Takei et al., 2009; Tromberg et al., 2008; Wendie A. Berg , MD et al., 2012). Since, these tools are the basic one, the tissue biopsy specimens analysis need to be verified for the diagnosis(Adamietz et al., 2011; C.D. Morrison, 2000; Massoud &

Gambhir, 2003; Naumann, 2001; Ramaz et al., 2004; WINFRIED DENK,* JAMES H. STRICKLER, 1990). However, even after this much progress the mortality rate is high which suggests that new methods such as computational approaches are the need of hour.

For lead design and optimization, databases, broad genome data mining, network analysis, systems biology, , similarity analysis, structure-activity relationship, docking, and pharmacophore methods are all benefited from computational methods(Kortagere et al., 2012). The aim of computational approaches are to overcome the problems of traditional methods like late prediction and diagnosis, time taken to find possible drug for treatment, and understanding the genetic cause for breast cancer. By using traditional method understanding the above mention things were the biggest issues as it will take lots of resources and time to find them.

This project aims to summarize the current knowledge of computational approaches we have regarding the treatment, diagnosis, early detection identification, screening and other use of like finding lead compound for the breast cancer.

CHAPTER-2

2. COMPUTATIONAL APPROACHES

The word "in silico" or computational approaches is a modern term that refers to computer-assisted experimentation and is related to the words "in vivo" and "in vitro." (Ekins et al., 2007).

2.1. Artificial Intelligence

New generation of technology that can communicate with their surroundings and attempt to mimic human intelligence are known as Artificial intelligence (AI) (Glikson & Woolley, 2020). AI technologies are developing into fields that were traditionally considered solely the domain of human mastery, thanks to recent advances in digitised data acquisition, machine learning, and computing infrastructure (K. H. Yu et al., 2018). The different fields were AI used in breast cancer has been shown in fig.1.

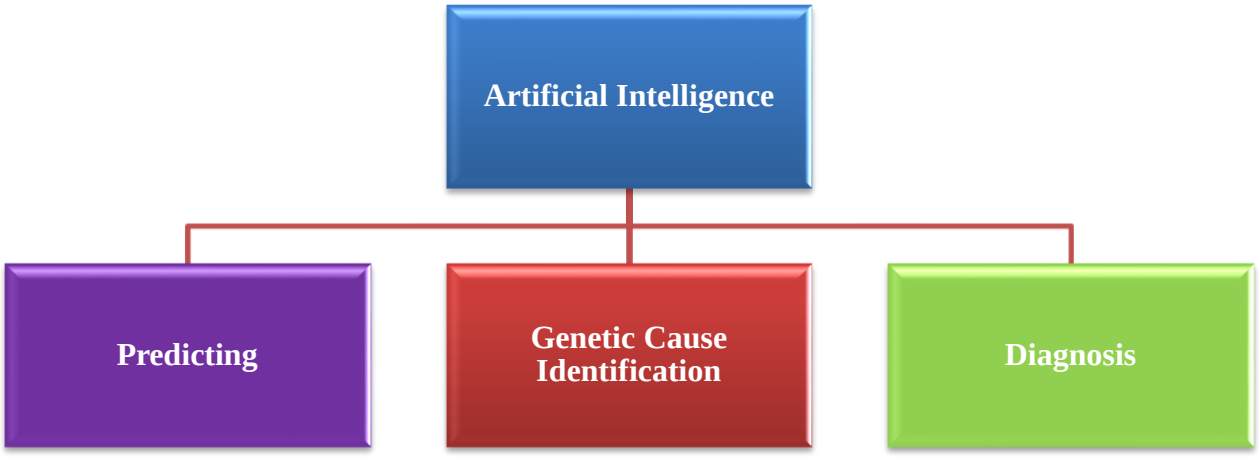


Fig.1- different field where AI used(Burke et al., 1997; Rosenberg, 1998).

2.1.1. AI in Genetic Cause For Breast Cancer

It is a cumbersome job to predict the breast cancer driver gene, since it creates a bunch of false positive data and it is most difficult to corroborate those findings. In this research, the researcher used a dozen approaches to the identification of computational driver genes, to discover highest possible genes causing breast cancer to prevent restriction of every proposal; those approaches include online resources, offline and online tools. These include National Cancer Database, The Cancer Genome Atlas, cBioportal , International Cancer Genome Consortium, Human Cancer Database, 1000 Genomes, Catalogue of Somatic Mutations in Cancer, OASIS and countless other valuable tools for cancer. Highly systematic methods that furnish examined cancer result, comprising mutation profiles, variations in copy number, information on gene expression, microRNA, etc is Pan-Cancer, which is produced by the TCGA database, (Abel Gonzalez-Perez, Christian Perez-Llamas, Jordi Deu-Pons, David Tamborero, Michael P Schroeder, Alba Jene-Sanz, 2013; Altshuler et al., 2010; Forbes et al., 2009; Gao et al., 2013). Gene pathway, statistical modeling, and network analysis are other achievable approach suggested to classify the most likely driver genes(Torkamani & Schork, 2009). The different tools which were used in predicting or in analyzing the driver genes are discussed in table.1.

Tools name	Function	Reference
DrGap	instrument that uses statistical analysis to predict driver genes and their signaling pathways	(Lawrence et al., 2013)
FunCoup	Genes and their roles have a functional relationship.	(Hou & Ma, 2014)
Genemania web server	Is the genetic network, which forecast gene functions by combining many functionally related networks	(Jia et al., 2014)

MUFFINN	The resulting degree of network analysis is performed. It defines major familiar driver genes by mutation frequency and the major related neighbors of the pathway	(Ryslik et al., 2014; Zhang et al., 2014)
FunRich	(functional enrichment) software to build the network	(Benito-Martin & Peinado, 2015)
PolyPhen2	This model forecasts the likelihood of amino acid substitutions, as well as their combined effects on structural and functional patterns. To evaluate the functional collision of known driver genes and to validate their validity the SIFT algorithm is also used.	(Carter et al., 2009; Vaser et al., 2016)

Table.1. – tools used for driver gene study.

As a result, each approach to driver gene prediction has a certain level of representative intensity in identifying the genes of the true cancer driver, and this concludes the key concerns(Pon & Marra, 2015).

Hence, the researcher evaluated total 41,948 important mutations by using a variety of different methodologies: namely frameshift mutations (1,935), missense mutations (26,448), splice site mutations (832), and in-frame insertion (115) and in-frame deletion mutations (563). Consequences of these studies, the researcher has recorded 63 driver genes that have a clear association with subtypes of breast cancer: basal (19.86%), regular (14.23%), Her2 (15.82%) Luminal A (28.06%) and Luminal B (22.01%) types of breast cancer. The findings indicate that 24 genes have previously been linked to commonly familiar breast cancer driver genes, while the left 39 genes have never been identified or communicated as potential breast cancer drivers (Rajendran & Deng, 2017).

Furthermore, all of the information we've covered comes from DNA sequencing of the majority of cancers. Intra-tumoral heterogeneity is known to be caused by genetic instability within individual cancers, and epigenetic modifications can increase

heterogeneity even further. Numerous features of tumorigenesis, comprising clonal development, metastasis, recurrence, drug resistance, and cancer-driver switch-off during cancer progression, could be affected by these events. Hence, utilization of bulk DNA for sequencing can unquestionably conceal intra-tumoral heterogeneity. As some recent studies have shown, sequencing DNA derived from individual cancer cells could be able to overcome this flaw (Brouwer et al., 2016; Gerlinger & Gore, 2012; K. T. Kim et al., 2016; Navin et al., 2011). The collation between BRCA driver genes and published genes has been depicted in fig.2.

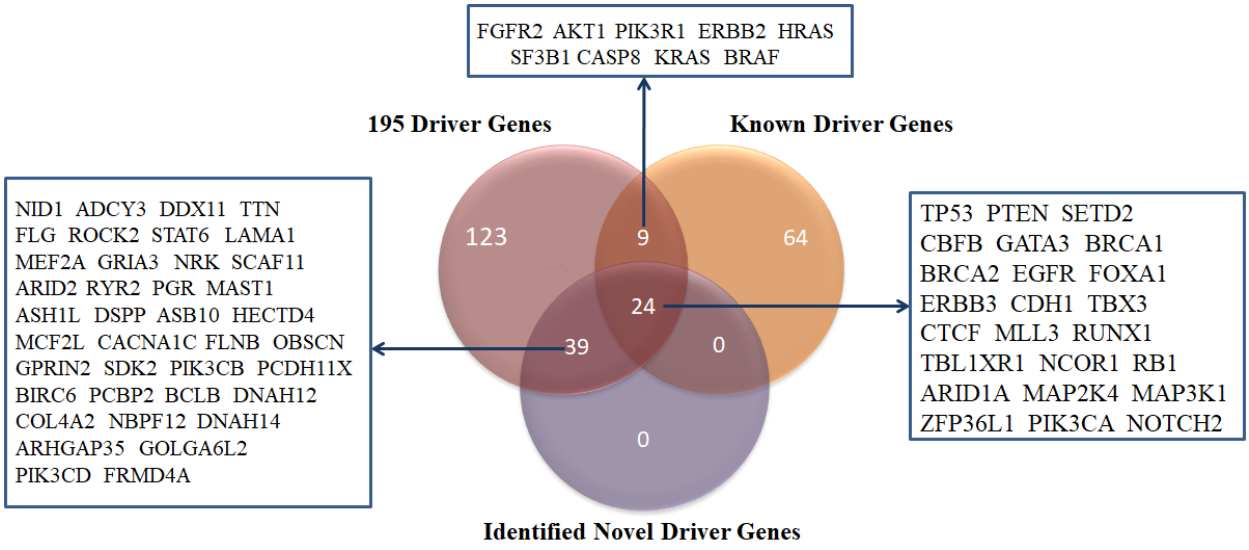


Fig.3- Comprehensive collation between identified BRCA driver genes and published genes (Van Ginneken et al., 2011)**.**

2.1.2. Role of AI in Breast Cancer Diagnosis

If diagnosed early, breast cancer may be treated successfully. It is also important to have sufficient techniques to test for the earliest signs of breast cancer(Tarique et al., 2015). For breast cancer screening and diagnosis, there are different imaging methods available, mammography, ultrasound, and thermography are some of the important them (*American Cancer Society [Webpage on the Internet]. How Is Breast Cancer*

Diagnosed? 2014. Available from: Http://Www.Cancer.Org/ Cancer/Breastcancer/Detailedguide/Breast-Cancer-Diagnosis. Accessed September 20, 2017., n.d.). Since, these methods focused on early detection to get the best outcomes for breast cancer, it is important to get a diagnosis as soon as possible. Breast cancer imaging approaches have also been evolved to improve chances of early detection and reduce the risk of needless biopsy (Jalalian et al., 2013). The different stage for the image processing has been depicted in fig.3. In recent many AI techniques have been used for image processing some of them has been shown in fig.4.

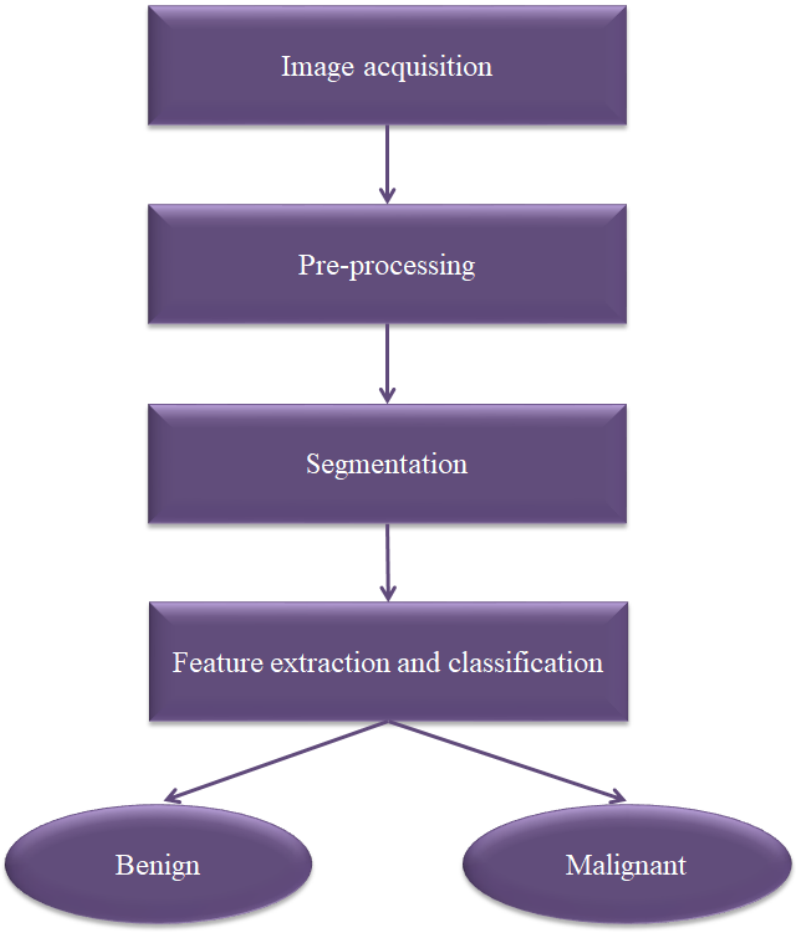


Fig.4- Image processing stages for cancer detection(Sadoughi et al., 2018)**.**

Introduction Of Different Image Processing AI Techniques

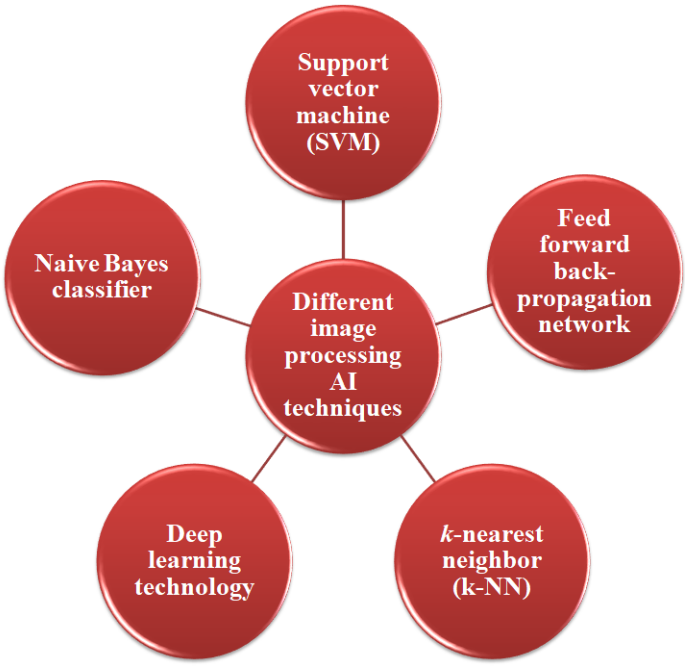


Fig.5- Diagrammatic representation of different image processing AI techniques(Kumari & Singh, 2018)***.***

2.1.2.1.Support Vector Machine (SVM)

Vladimir Vapnik was the first to implement Support Vector Machines (SVMs) for two-class classification. Essentially, the goal of this algorithm is to discover the best conclusion hyperplane for maximising the isolate margin between data points of different groups. The decision boundary (optimal hyperplane) is defined by the middle of the separation margin, and the data points nearest to it are support vectors. Kernel methods include SVMs because they only rely on data through dot-products, they can work in high-dimensional spaces. As a result of this It has two main advantages: enables creation of nonlinear resolved boundaries and the classification of data that does not have a clear fixed-dimensional vector space representation (PEDRO HENRIQUES ABREU and

MIRIAM SEOANE SANTOS,CISUC, Departmentof Informatics Engineering, Faculty of Sciences and Technology of Coimbra University, Portugal MIGUEL HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016). The most commonly utilized method for detecting breast cancer is SVM. This method is clever one among the learning algorithms inspired by statistical learning theory, and it has been applied into the machine learning set in recent decades. Hence, issue of overfitting in the training data is minimized, and broad training set with small subsets of training points can be reported. Additionally, with no need to create separate hypotheses, this technique will work on optional functions(Sadoughi et al., 2018).

2.1.2.2.*K*-Nearest Neighbor (K-NN)

By minimising a similarity measure, the supervised classification algorithm k-Nearest Neighbors (KNN) selects the k closest neighbours of a point. (PEDRO HENRIQUES ABREU and MIRIAM SEOANE SANTOS,CISUC, Departmentof Informatics Engineering, Faculty of Sciences and Technology of Coimbra University, Portugal MIGUEL HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016) k-NN choose category of K records belonging to a training data set that has the most data that are similar to the examine data and agrees on examined data class built on their rank or mark supremacy. Straightforwardly, this approach chooses the rank with the most records in the chosen neighborhood (AhmedMedjahed et al., 2013). Slothful learning algorithm is KNN's main drawback. There is no such thing as a "model" since the training data is not used to make any generalisations. As a result, whenever KNN explore for each occasion closest neighbours, must traverse the whole dataset, which can be time-consuming in large databases. Additional problem is determining the best number of neighbours (k) and the best distance metric to utilize. To achieve the best results, this necessitates a thorough examination of the dataset and the advancement of many KNN models (PEDRO HENRIQUES ABREU and MIRIAM SEOANE SANTOS,CISUC, Departmentof

Informatics Engineering, Faculty of Sciences and Technology of Coimbra University, Portugal MIGUEL HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016).

2.1.2.3.Genetic Algorithm As Optimizer

Genetic Algorithm finds the answer that finest matches the data from a population of single possible answer using the "survival of the fittest" philosophy, similar to how animals adapt to their surroundings through evolution. A fitness function decides which answer must be held and which must be discarded. A new population is created at the end of each generation, and all individuals' fitness values are estimated on the ground of their success in the problem domain (PEDRO HENRIQUES ABREU and MIRIAM SEOANE SANTOS,CISUC, Departmentof Informatics Engineering, Faculty of Sciences and Technology of Coimbra University, Portugal MIGUEL HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016).
In the forecast of a BC recurrence problem, GAs may be utilized as an optimization tool for other algorithms, like artificial neural networks (ANN). Consider a population of 40 randomly generated ANNs and a fitness function based on the ANN's success as a BC recurrence problem classifier (PEDRO HENRIQUES ABREU and MIRIAM SEOANE SANTOS,CISUC, Departmentof Informatics Engineering, Faculty of Sciences and Technology of Coimbra University, Portugal MIGUEL HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016). Without affecting the final result negatively, this algorithm will easily search a collection of large solutions and remove bad suggestions. Since the genetic algorithm follows its own set of rules, it can be used to solve problems that are classified as abnormal (Dheeba & Selvi, 2011; *Russell 1959.Pdf*, n.d.). This operation is replicated until the best ANN is established or greatest number of generations is reached (PEDRO HENRIQUES ABREU and MIRIAM SEOANE SANTOS,CISUC, Departmentof Informatics Engineering, Faculty of Sciences and Technology of Coimbra University, Portugal MIGUEL

HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016).

2.1.2.4.Naive Bayes Classifier

When making a conclusion, the Naive Bayes (NB) classifier hold into account the possibility distribution of patterns in each class, presuming that predictors (features) and performance have a probabilistic relationship (class) (PEDRO HENRIQUES ABREU and MIRIAM SEOANE SANTOS,CISUC, Departmentof Informatics Engineering, Faculty of Sciences and Technology of Coimbra University, Portugal MIGUEL HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016). The posteriori probability of a given pattern depicted by x belonging to class ωi, P ($\omega 1 \mid x$), is determined by Bayesian classification. In the case of a binary classification difficulty with two posterior chances, P ($\omega 1 \mid x$) and P ($\omega 2 \mid x$), the NB conclusion rule takes into account that

—If $P(\omega 1 \mid x) > P(\omega 2 \mid x)$, then **x** belongs to $\omega 1$;

—If $P(\omega 1 \mid x) < P(\omega 2 \mid x)$, then **x** belongs to $\omega 2$.

If P (1 | x) = P (2 | x), the decision is unpredictable. The well-known Bayes' law (equation 1) is used to calculate the posteriori probabilities.

$$P(\omega i \mid \mathbf{x}) = \frac{p(\mathbf{x} \mid \omega i)\, P(\omega i)}{p(\mathbf{x})}, \quad (1)$$

P (ωi) the earlier chances of class ωi which is a probability approximation for pattern x belonging to ωi ; $p(\mathbf{x} \mid \omega i)$ is the possibility of x, which may be evaluated by utilizing the Probability Density Function (pdf) of x; and p(x) is the total probability of x, which can be calculated utilizing Equation (2) (PEDRO HENRIQUES ABREU and MIRIAM SEOANE SANTOS,CISUC, Departmentof Informatics Engineering, Faculty of Sciences

and Technology of Coimbra University, Portugal MIGUEL HENRIQUES ABREU, Portuguese Institute of Oncology of Porto, Portugal BRUNO ANDRADE,CISUC, 2016).

$$\mathrm{p(x)} = \sum_{i=1}^{c} \quad p(\mathbf{x} \mid \omega i)\, P\,(\omega i). \qquad (2)$$

The benefit is that, to approximate the necessary classification parameters, this model needs a small amount of training data (Karabatak, 2015).

2.1.2.5.Deep Learning Technology

The deep learning network includes additional layers of image processing than the traditional machine learning classifiers based on image features. Every individual layer is a standard neural network, like convolutional neural network. Rather than utilizing a series of manually or automatically determined image characters computed from images, the deep learning network uses the image itself as a single input (Christian Szegedy, Wei Liu, Yangqing Jia, Pierre Sermanet1 et al., 2015). With lower layer networks, efficient image characteristics are automatically learned and extracted. As a result, higher layer networks utilize the derived characters patterns to classify images into separate target categories (Abdel-Zaher & Eldeib, 2016). The advantages and limitations of deep learning technology have been shown in table.2.

advantages	limitations
• Supporting radiologists as a second translator after the radiologist in the process of analysis and screening • Reduces the amount of false positives, obviates the need for unnecessary biopsy, and saves money. • lessen the patient's test time by evaluating and documenting the results in seconds.	• difficulty choosing the function of the kernel for a problem. • The machine's poor performance in training and tests. • In the test point, lower covariance. • Trouble selecting the necessary parameters of the kernel. • That the model takes plenty of memory space to run. • Allows you to run the model using one of two parametric or nonparametric approaches. • Reliance on the issue of the position of each learning machine

Table.1-Conclusion of the image processing AI technique(Sadoughi et al., 2018)**.**

2.1.2.6.Breast Cancer Invasiveness With DNA Methylation Biomarkers Computational Identification

A range of malignancies are closely related to cancer-specific modifications of DNA methylation (Cui et al., 2015; Hatada, 2010; Nones et al., 2014; G. Wang et al., 2018). Recent studies examining genomic lesions of primary and metastatic cancers have shown tumor metastasis and progression can be accounted for by certain specific changes in DNA methylation (Chiam et al., 2014; Vitale et al., 2017). In the research described here, built on the DNA methylation pattern of breast cancer, researcher deduced whether tumors are invasive or noninvasive. To distinguish the differentially methylated CpG sites between the two classes, the researcher used two differential methylation analysis approaches. After shrinking these characterisitics, a methylation-based invasiveness classifier was created to distinguish between invasive and non-invasive primary breast

cancer. The research offers molecular support to assess the invasiveness of breast cancer and demonstrates the possible influence of clinical decision-making using this method (C. Wang et al., 2020). However, since breast cancer is extremely heterogeneous illness, this approach has some limitations, so for samples from various subclasses, a fixed classifier can have different predictive precision (Reyngold et al., 2014).

2.1.2.7.Gene Chip And Next-Generation Sequencing

The gene chip may simultaneously analyze loads of nucleic acid fragments, and it is commonly used in the diagnosis of BC. The gene chip is utilized to track and investigate the condition of nucleic acids in BC cells and tissues, and can additionally scan a large number of samples to identify potential diagnostic biomarkers for BC. As is well known, a high-density oligonucleotide microarray is basically a gene chip (Bliss et al., 2018; Burns et al., 1998; Hao et al., 2018). In situ synthesis and direct point technique are two approaches for chip preparation at present (Li et al., 2017). Researchers discovered pathways for doxorubicin resistance in BC using gene chip technology and screened these primary genes for BC therapy (M. H. Kim et al., 2017). However, gene chip limitations exist, like problems in synthesizing probes, simple presence of positive signals, and particularly complex extraction of nucleic acid (He et al., 2020).

Metzker has put forward next-generation sequencing (NGS) (Metzker, 2010). This approach makes a great contribution to collecting data about the genome sequence and may help find sites of mutant genes. At present, NGS is commonly used in the diagnosis of BC. However, short reads of around 200-500 bp are the primary restriction of NGS. Single-molecule sequencing may provide long read lengths, straight RNA sequencing, straight base modification recognition, etc., but NGS can easily deal with mismatch at present and is not appropriate for satellite DNA research (Jeoung Won Bae, Kwang Ho Choi, Han Gyum Kim, 2000).

2.2. Bioinformatics

Recent come up discipline, bioinformatics brings together information science, mathematics, and biology to assist address biological questions. Creation of software tools and algorithms, as well as the analysis and elucidation of biological data utilizing diviersity of software tools and algorithms, are the two key components of bioinformatics (Maloy, Stanley, and Kelly Hughes, 2013).

2.2.1 Finding New Dual Inhibitors For Raf/Extracellular-Signal-Regulated Kinase (ERK)

Many studies have found that Raf/MEK/ERK signalling pathway is overactive in tumours, and that targeting Raf/MEK/ERK pathway can help treat breast cancer (Robin D.Lester‡MinjiJo‡W. MarieCampana§Steven L.Gonias, 2005; Saini et al., 2013; Serra et al., 2011). The ERK MAPK pathway inhibitor has been utilized for cancer therapy. Mitogen-activated protein kinase (MAPK) cascades are associated with the management of normal cell survival, growth and differentiation (Ahronian et al., 2015; Endo et al., 2013; Ingeson-Carlsson et al., 2015; Izrailit et al., 2013). Interestingly, utilization of Raf or MEK inhibitors that target ERK signalling in the therapy of breast cancer has recently shown optimistic clinical activity (Kirouac et al., 2013; Saini et al., 2013; Zhao et al., 2012).

A worldwide PPI network comprising many other PPIs was computer-built utilizing internet resources of protein-protein interaction (PPI).To develop the array of true-positive gene pairs, comprising 14,892 from Homo MINT among 6240 proteins (Zanzoni et al., 2002); 39,044 out of 9619 proteins from HPRD (Hermjakob et al., 2004) ; 37,710 out of 8982 proteins from BioGRID(Stark et al., 2006); 8044 out of 4073 proteins from BOND; and 34,935 out of 8849 proteins from IntAct (Lu et al., 2007). Researcher extracted these physical protein protein interactivity from manually generated PPI databases (Zanzoni et al., 2002). Researchers subsequently reformed this network into a sub-network of RAF/MEK/ERK, containing 929 edges and 812 nodes. In addition,

a proteomics-dependent RAF/ERK-modulated PPI network based on BL-EI001-treated MCF-7 cells was built by researchers, including 132 interactions and 95 differentially expressed proteins. Prominence, researchers established that RAF1 controlled 18 ERK1 interactors, and ERK1 regulated 38 RAF1 interactors. These findings have thus shown that RAF/MEK/ERK-self-reliant pathways in breast cancer can control the programmed cell death activity (Chen et al., 2017).

2.2.2 Network Based Approach For Lead Compound Identification

Recognition of therapeutic methods for cancer treatment is a time-consuming, expensive, and inefficient method. According to conservative figures, getting a new drug to market require time around 15 years and $800 million to $1 billion (Adams & Van Brantner, 2006). Drug repositioning is the recognition of novel targets for current drugs, is becoming more appealing method of therapeutic discovery. Repositioned medication doesn't require the six to nine years of progress time needed for novel drugs, rather going straight to preclinical research and clinical trials, decreasing risk and costs (Ashburn & Thor, 2004). Systems biology has made significant strides in recent years in solving basic biological problems and resulting in real-world medical and drug creation applications (Y. Wang et al., 2012).

The network principle is highlighted in network-based computational systems biology, which emphasises the interactivity between biomolecules. A network is usually made up of nodes and edges, and it is mathematically defined by graph theory (Barabási & Oltvai, 2004). Biological molecule, such as RNA, gene, metabolite, protein or pathway, may be a node. A phenotype level node, like disease or drug, may also be a node. A complex interaction between two nodes can be represented by an edge, like protein-protein interactivity, a drug-disease therapeutic association, a drug-protein target association, and many other.

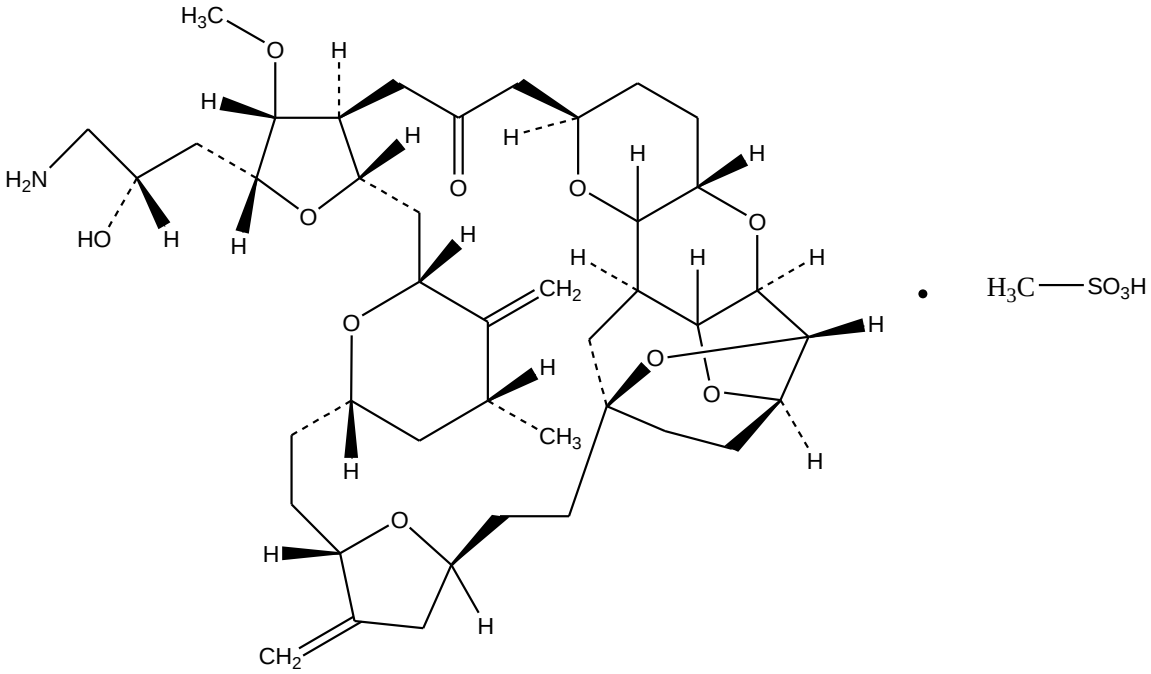
Reconstruction of biomolecular and cellular networks has become possible thanks to the growth of various high-throughput biology data, like miRNA expression data, gene expression data, and drug-target data. There are several network-based approaches for predicting new drug indications (L. Yu et al., 2015; L. Yu, Ma, et al., 2016; L. Yu, Su, et al., 2017; L. Yu, Wang, et al., 2016; L. Yu, Zhao, et al., 2017).

Many recent studies have shown that drugs can control microRNA (miRNA) expression, and that small molecular drugs can target mature miRNAs as well as their precursors (Bose et al., 2012; Z. Liu et al., 2008; Srinivasan et al., 2013; S. Xu, n.d.). As a result, the researchers propose miTS, a novel approach for forecast possible drugs for diseases based on miRNA data and disease tissue specificity. In this research using breast cancer as a case study the data of the Comparative Toxicogenomics Database benchmark, clinical reports, KEGG pathway enrichment analysis, literature mining, and overlapping genes between enhanced pathways are all evaluated. Among top 30 drugs, the researcher found five novel drugs are depicted in table.3. and chemical structure in fig.5.for breast cancer (L. Yu et al., 2018).

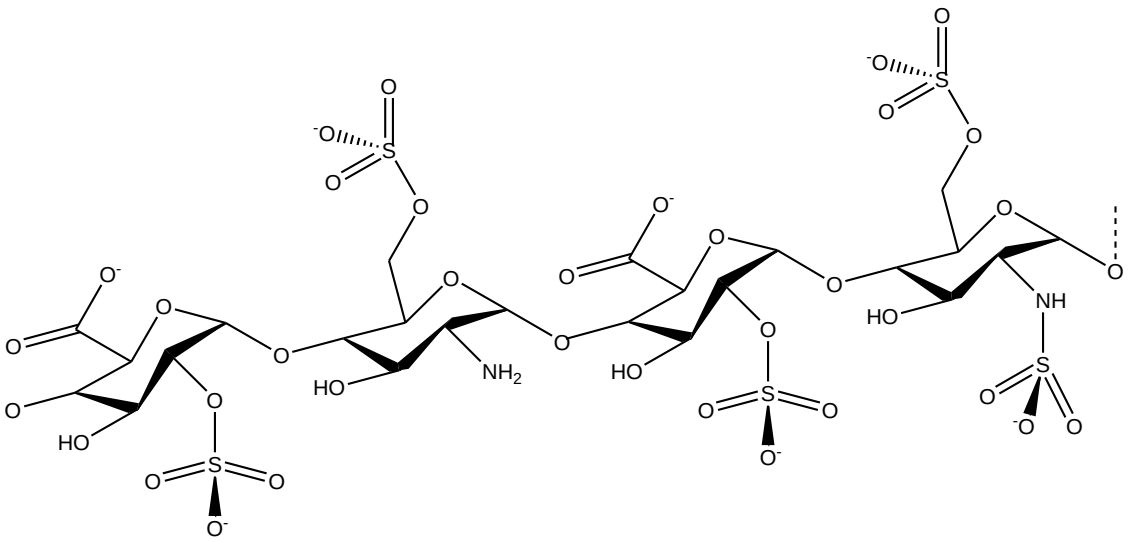
Drug names	**Drugbank ID**	**Original indications**
Eribulin mesylate	DB08871	anticancer drug
Nadroparin	DB08813	anticoagulan
Regorafenib	DB08896	oral multi-kinase inhibitor
Pralatrexate	DB06813	anticancer drug

Tenecteplase	DB00031	tissue plasminogen activator

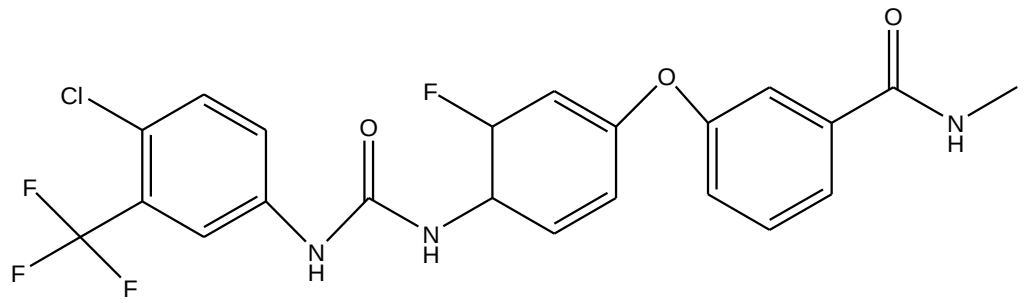
Table.2- The five potential drugs with Drugbank ID(L. Yu et al., 2018)**.**



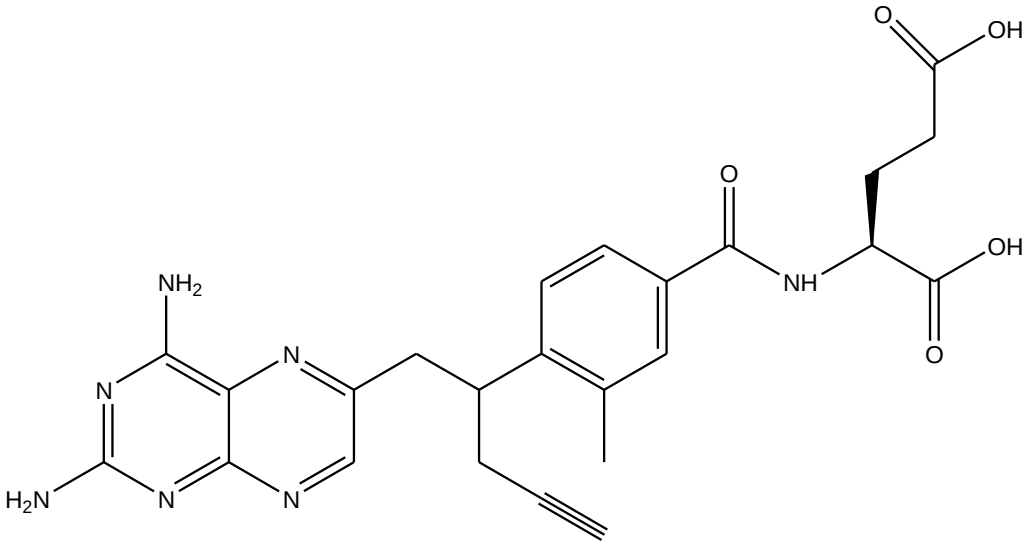
Eribulin mesylate



Nadroparin



Regorafenib



Pralatrexate

Fig.-5- Potent drugs structures utilized in Bioinformatics (L. Yu et al., 2018)

The result analysis shows that all the 5 drugs shows potent activity and further studies can be done. In specific Regorafenib (DB08896) shares fifteen KEGG pathways with breast cancer, all of which have very low p-values. Regorafenib also has a clear association with breast cancer, whether in literature curation or

clinical confirmation. Regorafenib appears to be genuinely successful medication, deserving of further investigation, according to all available facts (L. Yu et al., 2018).

2.3. Molecular Docking

Molecular docking is the examination of how two or more molecular structures interact. Docking, in its simplest form, is a molecular simulation technique for predicting how protein interchanges with small molecules. The capacity of a protein or nucleic acid to associate with small molecules to form supramolecular complex has big impact on protein's dynamics, which can either help or hurt its biological function. Molecular docking describes actions of small molecules in the unalterable pockets of target proteins (Roy, Kunal, Supratik Kar, 2015).

2.3.1. Apoptosis-Inducing Mechanisms With New ERK Inhibitor (BL-EI001)

Here in breast cancer new small molecule ERK inhibitor backed by sequence of experimental validation and computational design was identified by the researcher, suggesting that BL-EI001 could be favorable apoptosis-inducing drug for potential treatment of breast cancer. A sequence of candidate small molecule inhibitors from Drug Bank and ZINC were computer-screened by researchers. Researchers selected a candidate small-molecule compound E1 on the basis of MTT assay of 3 types of breast cancer cells and synthesized a sequence of E1 derivatives and finally identified new ERK inhibitor (BL-EI001) in breast cancer cells through further MTT assay. In addition, in order to additionally confirms the synthesized BL-EI001, researchers used MD simulation to bind ERK better than E1, suggesting that BL-EI001 is a strong ERK inhibitor. And it was observed that BL-EI001 anti-proliferative interest was significantly enhanced (IC50 = 5 μM, 24 h). Therefore, by integrating theoretical prediction and experimental screening, a new ERK inhibitor (BL-EI001) has been conveniently engineered and located as a

candidate anti-tumor drug to have impressive anti-growth interest against breast cancer cells (B. Liu et al., 2015).

2.3.2. Interest Of Novel Plumbagin Hydrazones

The anti-proliferative interest of novel plumbagin hydrazonates against oestrogen receptor-positive MCF-7 and triple negative MDA-MB-468 and MDA-MB-231 breast cancer cell lines was evaluated, and they showed higher inhibitory interest than the parent plumbagin compound. Molecular docking observations showed that the hydroxyl groups on the side chains of plumbagin and hydrazonate favour further hydrogen bonding interactivity with amino acid residues in the p50-subunit of the NF-B protein, inhibiting NF-B expression and possibly explaining the modified anti-proliferative behaviour. These compounds were discovered additionally selective against triple negative breast cancer cells, and they may be used to develop potential plan against triple negative breast cancers, which are notorious for their high drug resistance and poor prognosis in breast cancer patients (Dandawate et al., 2012).

2.3.3. Investigation Of Determined Phytochemicals Of Furanocoumarins

In this study the researcher selected the phyto-compounds named as BER, XAN, ANG, IMP, and PSO. The selection was done on the foundation of leading docking scores against breast cancer. Since the beginning and development of breast cancer is caused by specific cellular downstream signaling pathways initated by the activation of PR, ERα, EGFR and HER-2 receptors. Therefore, phyto-chemical validation was also done on those signaling pathways using in-vitro assays (F. Wang et al., 2017).

The present study concludes that five determined furanocoumarin compounds, BER, ANG XAN, PSO, and IMP, thought to be influential anti-breast cancer agents antagonistic towards ER, PR, mTOR and EGFR, based on binding affinities demonstrated by docking studies and in-vitro assays. In-vitro and in-vivo research on breast cancer models can also be performed to additionally

explore compounds for breast cancer treatment and prevention (Acharya et al., 2019).

2.3.4. Studying Novel Benzofuran And Furo[3,2-G]Chromone-Build Cytotoxic

The researcher is working on the combining a novel class of benzofurans and 5H-furo[3,2-g]chromones with additional heterocyclic functionalities, with the aim of developing novel antiproliferative candidates antagonist to MCF-7 breast cancer cells with p38 MAP kinase inhibitory task. In contrast to doxorubicin, the biological data revealed that MCF-7 breast cancer cell lines are significantly more responsive to most of the prepared compounds. Furthermore, compounds VIIIa,b, VIa,b, VIIa,b, IIa,b, Va,b, and XIc inhibited p38 MAPK in vitro with potencies approximate to the standard reference SB203580. Compound VIa induced G2/M phase arrest and programmed cell death in MCF-7 cancer cells, as well as activation of caspases-9 and -3, according to cell cycle analysis and apoptosis detection results. The mostly allowable association between the calculated docking scores of fitness and the biological data of p38 MAP kinase inhibition was rationalised by gold molecular docking studies. For additional functionalization, optimization, and in-depth biological observation, the novel produced benzofuran and 5H-furo[3,2-g]chromone derivatives may observed as novel favorable nuclei in anti-breast cancer chemotherapeutics (Amin et al., 2018).

2.4. Quantitative Structure-Activity Relationship (QSAR)

This approaches are useful in predicting the biological effects of chemicals using mathematical and statistical relationships (Peter, Swathik Clarancia, 2019).

2.4.1. QSAR Model For Alignment-Free Prediction

Discussed here work cover the first QSAR model for one hundred twenty-two proteins linked to human breast cancer (HBC), which were discovered experimentally from a database of over ten thousand human proteins. The one hundred twenty-two

proteins associated with HBC and a control series of two hundred proteins not associated with HBC (non-HBCp) were compelled to fold in an HP lattice network in this analysis. Collections of electrostatic potential parameters (nk) were determined from these networks to numerically represent every protein. The application of nk as a starting point for LDA resulted in a QSAR method or model to distinguish b/w non-HBCp and HBCp which perhaps be used to evaluate the participation of a certain protein or gene in HBC. The model was also subjected to validation procedures, which had an outer estimation sequence and the assessment of thousand non-HBCp series. In every case, strong classification levels were reached, with
values reaching 80% (SANTIAGO VILAR, HUMBERTO GONZA´ LEZ-DI´AZ,* LOURDES SANTANA, 2008).

2.4.2. QSAR Modeling Of Indazole Derivatives As Antagonizes Of Estrogen Receptor Alpha (ER-A)

The use of multiple linear regression was applied to fifty-four indazole derivatives in order to setup a QSAR model. The DFT-B3LYP technique with basis set 6-311G was used to determine the chemical reactivity, structure, and properties of the compounds. This research included global reactivity descriptors, molecular docking and ADME charactertics on a collection of twenty-one selective oestrogen receptor degraders compounds that represent the most active compounds in the set of data. The fitted and observed biological behaviours were in good agreement using the MLR regression equation. The obtained method has strong anticipated strength as well as healthy if the average R2Boots is higher than 0.5. Furthermore, an average R2pred (0.57) standards of about 0.6 can be used as a measure of strong external predictability (Zekri et al., 2020).

2.4.3. QSAR Studies Of Phenylindoles As Cytotoxic Antimitotic Agents

R-group QSAR,regression-based as well as linear discriminant examined based 2D QSAR researches , CoMSIA 3D-QSAR study and kernel-based partial least square (KPLS) tests were used to conduct a validated relative molecular modelling research on a collection of derivatives of phenylindole.As dependent variables,

antiproliferative actions against two breast cancer cell lines (MCF7 & MDA-MB-231) had been used independently. Various

E-state measures and pharmacophoric demands of essential replacements were illustrated by RQSAR review. The finest 2D-QSAR model is determined using three machine learning methods: ANN, SVM and MLR. The value of various topological descriptors, physicochemical and structural descriptors, had been portrayed in the two-dimensional QSAR models. Although RQSAR studies revealed the fingerprint need of different alternative, KPLS examination revealed the fingerprint demand for the whole molecule.

The CoMSIA tool clarifies these elucidations by showing how minor differences in these arrangements of molecule can impact biological activity. Various modelling methods observations corroborated each other. Present QSAR research may be used to develop drugs used against miotic's in cancer (NilanjanAdhikaria,Amit KumarHaldera,AchintyaSaha,KrishnaDas Sahac, 2015).

CHAPTER-3

CONCLUSION

Over a period of time, breast cancer emerged as the second most diagnosed and prime reason for cancer death in women worldwide. However, our understanding of breast cancer cause, prediction, diagnosis, or in drug development studies needed to be modified. Which via traditional approaches was next to impossible things therefore the use of computational approaches became a need of an hour. With computational approaches like artificial intelligence, bioinformatics, QSAR studies, molecular docking which were discussed here the unsolved questions related to breast cancer are no more unsolved. In addition with the time and resources which were used in traditional approaches to studying drug discovery, diagnosis, and prediction for breast cancer were significantly reduced when computational approaches are used. Like in present computational approaches opened some doors, in future also with advancement in computational approaches it can be expected that it will open many more doors and will become more beneficial.

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