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Mathematical Modeling of Histone Deacetylases to Predict their Response against Belinostat Drug Treatment for Smooth Muscle Cells Proliferation

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Abbreviations:

HDACs: Histone Deacetylases; SMCs: Smooth Muscle Cells; ASMC: Advanced Smooth Muscle Cell; NICD: Notch Intracellular Domain; QSARs: Quantitative Structure-Activity Relationship; ODE: Ordinary Differential Equation; DNA: Deoxyribonucleic Acid; FDA: Food and Drug Administration; CSL: CBF1/RBP-J, Su(H), Lag-1

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1. Abstract

1.1. Background: The family of enzymes known as histone deacetylases (HDACs) serves as an objective target for regulating the phenotypic of smooth muscle cells (SMCs) and advanced smooth muscle cells (ASMCs). HDAC activity may be inhibited to alter SMC proliferation, which alters the Notch Signaling pathway and causes certain cancers to grow in the body. Clinical studies are being conducted on oral and injectable forms of belinostat, which is being utilized to treat a wide range of solid and hematologic malignancies either as a monotherapy or in combination with other active medications.

1.2. Methods: This information was used to create the Notch signaling pathway model. To determine the expression levels of the mutant HDAC complex and its expression upon drug induction, modeling and simulations were done.

1.3. Results: To normalize the translation of the SMC phenotype, Belinostat 600 mg/ml was administered into the model. Once the model was exposed to belinostat on the fourth day of therapy, it was noticed that the expression of HDAC began to rise.

1.4. Conclusion: This research study can be used in the future as part of in vitro drug discovery and development.

2. Introduction

Histone deacetylases (HDACs) are well-known for catalyzing the deacetylation of an acetyl-lysine found inside the NH2-terminal tail of core histones [1]. A few transcription factors have distinct histone acetyltransferase activity. GCN5-related N-acetyl transferase, MYST, and cAMP reaction component binding protein (CREB/p300) families are among these groups [2]. Changes in histone acetyltransferases and HDACs are identified in several human cancers. Fundamental structural alterations in HDACs linked to cancer are infrequent. The increase in the quantity of HDAC2 and HDAC3 proteins in colon cancer has been linked to the increased expression of several HDACs [3]. HDAC1 expression is elevated in gastric cancer, while decreased expression of HDAC5 and HDAC10 is associated with a poor prognosis in lung cancer [4]. Oncogenic translocation protein complexes activate HDACs in many types of lymphomas and leukemia. HDAC2 truncating mutations have been discovered in two colon cancer cell lines and two endometrial cancer cell lines [5].

The histone deacetylase enzyme family essentially inhibits translation. HDACs have a significant mechanism of tumor suppressor gene silencing in illnesses, which has led to the use of HDAC inhibitors as anticancer therapies. HDACs serve as a specific target

for the control of smooth muscle cell (SMC) and advanced smooth muscle cell (ASMC) phenotypes. Inhibiting HDAC activity can alter SMC proliferation, leading to a mutant Notch Signaling pathway and the development of specific cancers in the body [6]. The Notch signaling pathway is an intracellular signaling mechanism that is essential for proper embryonic development in all metazoan living beings [7, 8]. It is required for various developmental and physiological processes, such as cell fate decision, cell separation, tissue development and formation, cell proliferation, and cell death. The Notch pathway was named after the mutant Drosophila, which has multiple notches of missing tissue at the tips of its blade-like wings. Single transmembrane proteins in the Notch family function as nuclear transcriptional regulators and cell surface receptors. Mammals have been shown to contain four Notch receptors, numbered from 1 to 4, so far [9].

The activation of Notch signaling occurs whenever cells expressing Delta or Serrate Notch receptors come into interaction with one another. The activation of Notch signaling results in two crucial proteolytic cleavage events [10]. The first cleavage is carried out by the ADAM group of metalloproteases, whereas the second cleavage is carried out by the gamma-secretase complex (presenilin, nicastrin, PEN2, and APH1) [7]. The second cleavage results in the production of the Notch Intracellular Domain (NICD), which subsequently moves into the nucleus and functions as a transcriptional co-activator. To activate DNA binding protein, which in turn promotes the gene expression for SMC proliferation, NICD heterodimers with the DNA binding proteins CSL, CBF1, Su ((H), and LAG-1 [11].

HDACs serve as a target for SMC phenotypic growth, and their inhibition can alter SMC proliferation [12]. HDACs have been linked to Notch signaling in neural crest cells, which provide ascend to subpopulations of blood vessel SMCs [13]. HDAC3 deficiency hampered the formation of blood vessel SMCs in the aortic curve, and this deformation was associated with decreased Jagged1 expression. As a result, HDAC mutations inhibit Notch-mediated SMC differentiation [6, 14]. Belinostat has been shown in preclinical tests to potentially treat a wide range of solid and hematologic malignancies as a monotherapy or in combination with other active medicines; both oral and injectable forms of the medication are being tested in clinical trials. In a dose design, belinostat administration inhibited cell growth and multiplication and caused cell cycle arrest. It also inhibits HDAC activity in tumor and other cell-related genes. [15].

2.1. Significant Rationale: This work focuses on the mathematical modeling of the Notch signaling system and Belinostat induction to inhibit HDAC activity to promote Notch-interceded SMC differentiation.

3. Material and Methods

This segment discusses using the Notch signaling system to test the effects of mutant HDACs on the production of other proteins. Belinostat is used to treat HDAC mutations because it inhibits the aberrant activity of HDACs. The Notch signaling pathway model is presented first, followed by the Belinostat profiling, which is mathematically figured out and analyzed. Figure 1 depicts the complete technique of the selected approach.

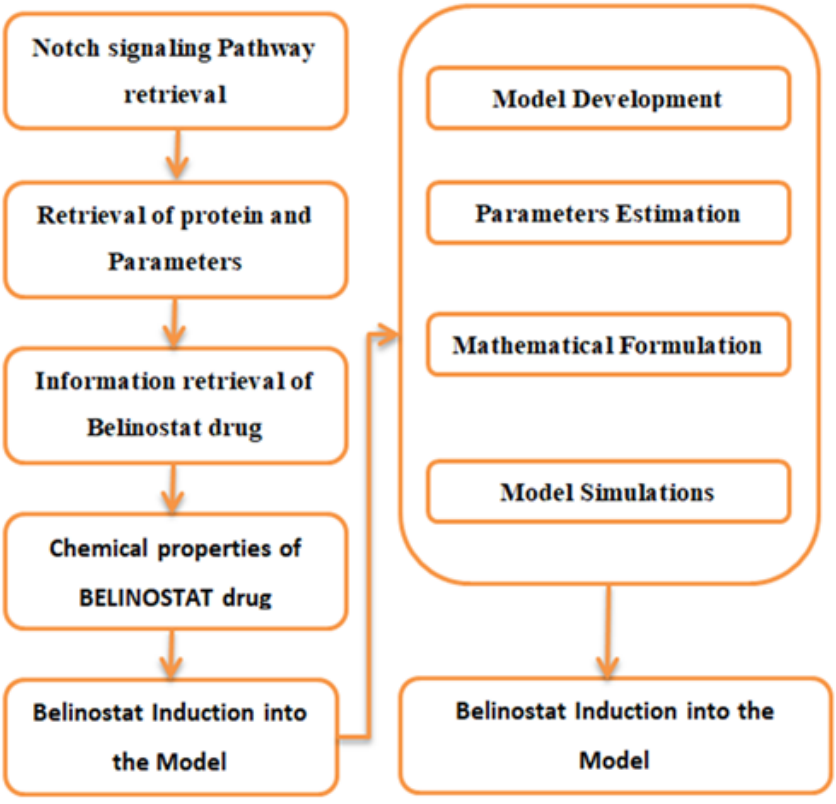

Figure 1: The detailed flowchart of Methodology

3.1. Notch Signaling Pathway Retrieval and Model Development

The KEGG database was used to construct a diagrammatic depiction of the Notch signaling pathway. The Notch signaling pathway was developed in Matlab's Simbiology package. The term "Notch Signaling" often refer to a specific conserved molecular process shared by many animals. Notch signaling involves the activation of Notch cell surface receptors by interaction with ligands of the DSL family, which comprises Delta and Serrate/Jagged in humans and Drosophila [16]. KEGG is a knowledge repository for the systematic exploration of gene functions, combining genomic data with higher-order functional data such as gene, enzyme, and protein functional data [17].

3.2. Retrieval of Protein Parameters Involved in the Notch Signaling Pathway

The Protparam tool was used to collect the parameters of all proteins. Parameters are the particular size or weight stated in units. The ProtParam program is used to determine the physiochemical properties of molecules found in Swiss-Prot or TrEMBL, as well as proteins provided by the user [18]. The molecular weight, hypothetical PI, amino acid composition, atomic composition, extinction coefficient, predicted half-life, instability index, aliphatic index, and grand average of hydropathicity are among the metrics calculated in this study.

3.3. Information Retrieval of Belinostat drug

Belinostat data was gathered from a drug bank database. Dug Bank is a database that contains precise FDA data about drug compounds, as well as their targets and metabolite activity data, in silico discovered drug targets, docking and screening methodologies, drug metabolism predictions, drug interactions, and general pharmaceutical use instructions [19]. Belinostat has FDA approval and is now in stage II clinical studies to potentially treat a wide range of solid and hematologic malignancies as a monotherapy or in combination with other dynamic medicines, both oral and injectable. Unfortunately, the pharmacokinetics and ADMES of Belinostat have not been described in the literature. Belinostat is an experimental small drug that inhibits the HDAC protein [20]. Figure 2 shows the chemical structure of the medication Belinostat.

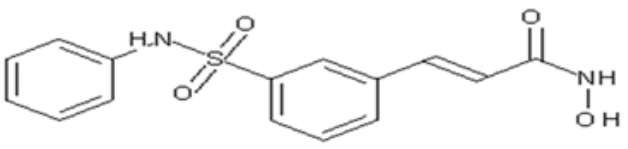

Figure 2: the chemical structure of Belinostat drug

3.4. Chemical Properties of BELINOSTAT drug

All of Belinostat's chemical characteristics, including its logP, refractive index, acid PKA, water solubility, dissociation constant, and other QSARs, were created using an online chemical modeling environment. It is an online program that aims to automate and enhance the QSAR modeling process. The prediction of new medications' organic and physicochemical characteristics greatly reduces the scope of test estimations since the development of new pharmaceuticals heavily relies on computational approaches supported by these computational systems. [21].

3.5. Estimation of Parameters and Formulation of Mathematical Equations

The parameters of the pathway and Belinostat were examined using Simbiology simulations and the established ordinary differential equation (ODE). The ODEs were generated by an ODE solver toolkit based on the Runge- Kutta estimating approach, which is dependent on well-defined and unambiguous emphases for the discretized solution of ODEs. The Appendix section contains all the differential equations. Model simulations were carried out using the Fminsearch method.

3.6. Developed Model Simulations

The model was then simulated to assess the change in expression levels of several genes caused by the impact of aberrant HDAC complex activity. Essentially, simulation modeling is the process of creating and disassembling a computational model of a physical model to predict its execution in reality.

3.7. Induction of Belinostat into the Model

The Belinostat drug was then introduced into the model to begin the HDACs inhibited expression for SMC growth, and simulations were run to analyze the changing behavior of the proteins involved in the pathway by assessing their expressions.

4. Results

Model-based research is changing the way researchers and experts operate by allowing them to organise wet lab tasks for the PC [22]. Keeping in mind the above assertion, the diagrammatic representation of the Notch signaling route was retrieved from the KEGG database, and the same diagrammatic representation of the pathway was produced in the model of the notch signaling pathway in a Simbiology toolbox of Matlab program. Figure 3 shows the model.

When the cells of Notch receptors (Delta or Serrate) come into interaction with each other in the Model (Figure 3), Notch signaling is activated. When Notch signaling is activated, two key processes of proteolytic cleavage occur [12]. The first cleavage is performed by the ADAM group of metalloproteases, whereas the second cleavage is performed by the gamma-secretase complex (presenilin, nicastrin, PEN2, and APH1) [7]. The second cleavage results in the formation of the Notch Intracellular Domain (NICD), which subsequently translocates to the nucleus and functions as a transcriptional co-activator. NICD heterodimerizes with the DNA binding protein CSL, CBF1, Su ((H) and LAG-1) to activate DNA binding protein, which subsequently triggers gene expression for SMC proliferation. For all of the model's components (proteins), numerous parameters have been discovered, as indicated in Table 1.

To run model simulations, each protein's parameter was required. Once the parameters had been discovered and allocated to the model, they were tested for their ability to accurately characterize the model's behavior using the ODE solver and Fminsearch using the formula in Eq. (1).

$$[t, y] = ode\,23\,([t, y] = ode\,23(odefun, tspan, y\,0, options)) \quad (1)$$

$$\frac{d(notch)}{dt} = 1/[Notch\ Signaling\ Pathway] * ([Delta + FringeActivity] * Fringe * Delta + Serrate + TACE + [y - Secretase\ complex] + Dvl + Numb - Notch) \quad (2)$$

$$\frac{d(fringe)}{dt} = 1/[Notch\ Signaling\ Pathway] * (-[Delta + FringeActivity] * Fringe * Delta) \quad (3)$$

$$\frac{d(Delta)}{dt} = 1/[Notch\ Signaling\ Pathway] * (-[Delta + FringeActivity] * Fringe * Delta) \quad (4)$$

$$\frac{d(Serrate)}{dt} = 1/[Notch\ Signaling\ Pathway] * (-SerrateActivity * Serrate) \quad (5)$$

$$\frac{d(TACE)}{dt} = 1/[Notch\ Signaling\ Pathway] * (-TACEActivity * TACE) \quad (6)$$

$$\frac{d([y - Secretase\ complex])}{dt} = 1/[Notch\ Signaling\ Pathway] * (-[y - SecretaseComplexActivity] * [y - Secretase\ complex]) \quad (7)$$

$$\frac{d(dvl)}{dt} = [Notch\ Signaling\ Pathway] * (-DvlActivity * Dvl) \quad (8)$$

$$\frac{d(Numb)}{dt} = 1/[Notch\ Signaling\ Pathway] * (-NumbActivity * Numb) \quad (9)$$

$$\frac{d(Deltex)}{dt} = 1/[Notch\ Signaling\ Pathway] * (NotchActivity * Notch) \quad (10)$$

$$\frac{d(CSL)}{dt} = 1/[Notch\ Signaling\ Pathway] * (NICDActivity * Notch + CoActivators - CSL + HDACcorepressorComplex - DNAActivity * CSL) \quad (11)$$

$$\frac{d(CoActivators)}{dt} = 1/[Notch\ Signaling\ Pathway] * (-CoActivatorsActivity * CoActivators) \quad (12)$$

$$\frac{d(SKIP)}{dt} = 1/[Notch\ Signaling\ Pathway] * (CSLActivity * CSL) \quad (13)$$

$$\frac{d(HDACcorepressorComplex)}{dt} = 1/[Notch\ Signaling\ Pathway] * (-HDAC\ corepressor\ Complex\ Activity * HDAC\ corepressor\ Complex) \quad (14)$$

$$\frac{d(DNA)}{dt} = 1/[Notch\ Signaling\ Pathway] * (DNAActivity * CSL - DNAActivity * DNA) \quad (15)$$

$$\frac{d\left(\left[Hes\frac{1}{5}\right]\right)}{dt} = 1/[Notch\ Signaling\ Pathway] * (DNAActivity * DNA) \quad (16)$$

$$\frac{d(PreTalpha)}{dt} = 1/[Notch\ Signaling\ Pathway] * (DNAActivity * DNA) \quad (17)$$

The vector function odefun clarifies the genes or perhaps proteins activity, tspan represents the simulation time, and y0 represents the differential circumstances state variable. Both y0 and tspan show the particular time interval and initial conditions of the route. The fminsearch work reduced the possibility of mistakes and assigned model components to their respective parameters (Table 1). The ODE solver also improved the response rates, lowering the possibility of errors and bringing the rate values considerably closer to the stated values.

Initially, simulations were run for the aberrant pathway model (Figure 4) without Belinostat induction to establish the degree of protein and complex expression. The X-axis represents hours, while the Y-axis represents expression rates. The simulation period was set to 28 days, and the simulation was carried out.

Figure 4 shows that the HDAC complex reduced from 4 x 105 to 0 on the fourth day after mutation, whereas the DNA binding protein (Maroon line) expression rose from 0.5 x 105 to 4 x 105 after the fifth day. Similarly, the gene expression level for SMC proliferation was on 0 due to decreased expression of HDAC corepressor complex. The expression of DNA binding protein (light maroon color line) also resulted in a decrease from 1 x 105 to 0 after the third hour of mutation development, causing a decrease in HES 1/5 (blue color line) from 3 x 10 5 to 0 at the fourth hour, inhibiting SMC proliferation. TACE, Pre-T-alpha, Dvl, for example, are highly expressed genes. The parameters of the Belinostat for its induction into the Notch model were obtained through its clinical trial data [23], and are shown in Table 2.

The physicochemical features of compounds, such as dissolvability, strength, dose regimens, solid-state properties, fragment coefficient, and ionization constant(s), must be understood to build a medicine formulation technique [24].

The 600 milligrams/milliliter (mg/ml) dosage of Belinostat obtained from the [23] was inducted into the model at a daily dose base for the first 5 days and then after every 4th day for a 28-day cycle and the model was simulated, a continuous decrease in the HDACs expression level was observed, as well as the DNA binding protein, which is required for SMC proliferation. Figure 5 depicts the simulation findings.

Following Belinostat induction, the simulation period was set to a 28-day cycle, with the x-axis indicating time in days and the y-axis representing protein expression levels in a pathway model. The HDAC complex increased from 4 x 105 immediately to 0 on the fourth day of drug induction, and the expression of DNA binding protein (light maroon color line) decreased from 1 x 105 to 0 after the third day of drug induction, causing a decrease in HES 1/5 (blue color line) from 3 x 105 to 0 at the fourth hour, which starts SMC proliferation. Similarly, the gene expression level for SMC proliferation was enhanced from 0 to 4 x 105, confirming Belinostat's effectiveness as an HDAC inhibitor.

The model generated about 16 differential equations, which are displayed in the Appendix section. Several standards in science and engineering are concerned with the connections between changing quantities. Since that rates of advancement are scientifically represented by derivatives, it should come as no surprise that such criteria are typically developed utilizing differential circumstances. [25].

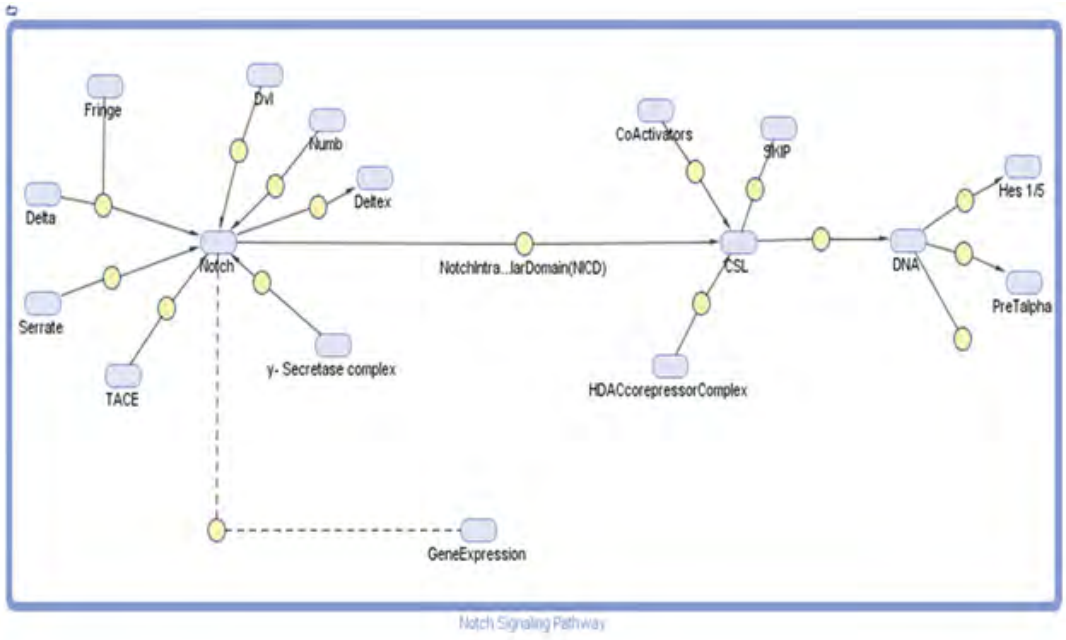

Figure 3: The Developed model of Notch Signaling Pathway. The proteins or genes are represented by rectangular shapes, and the reaction between them is given by yellow spheres. The interactions are represented by arrowheads.

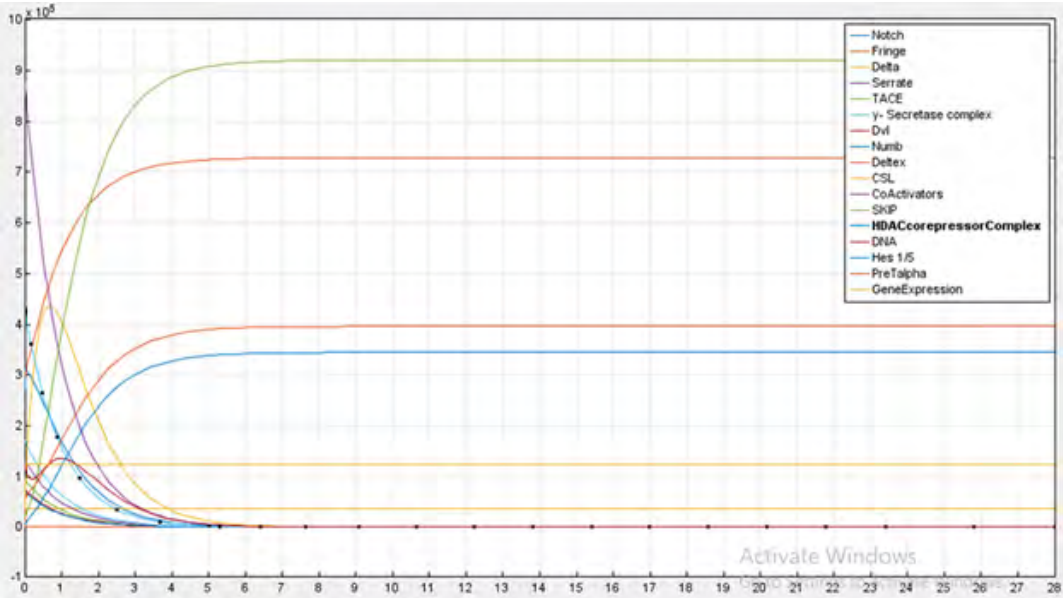

Figure 4: The analysis of model simulations before applying Belinostat doses. Each gene expression is characterized by a colored line. The level of HDAC complex expression is symbolized by the dotted line.

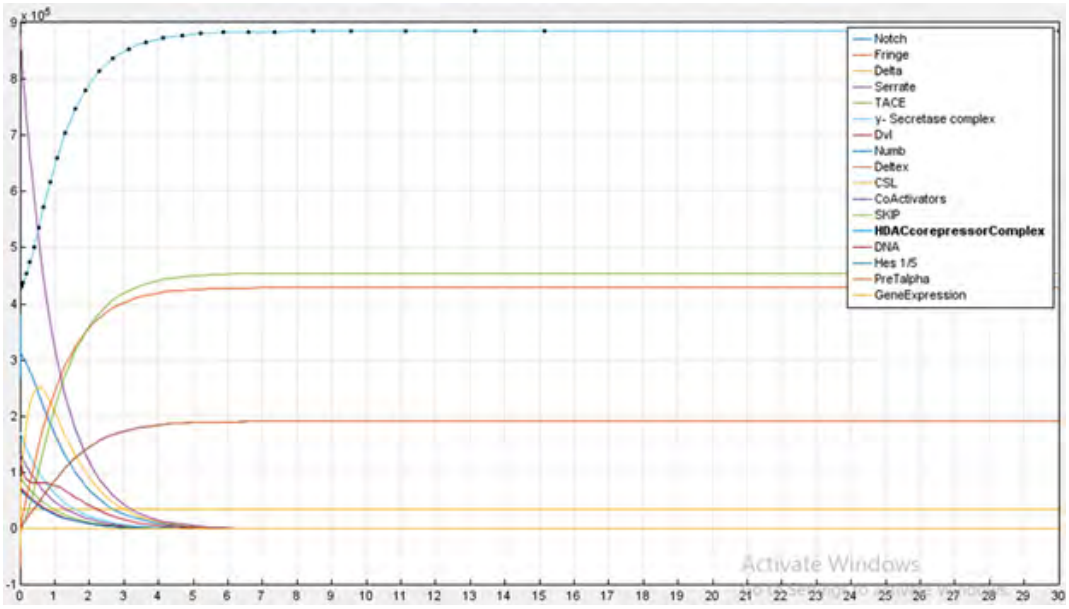

Figure 5: The simulation results of Notch Signaling pathway model after applying 600 mg Belinostat, HDAC expression is highlighted by black dots.

Table 1: Names of proteins involved in the Notch signaling pathway, the parameters developed for them, and values assigned to all the proteins of the pathway.

SPECIES	Units	PARAMETERS	VALUES	Units
Fringe	Molecule	Fringe Activity	41773.2	1/hour
Delta	Molecule	Delta Activity	78055.5	1/hour
Serrate	Molecule	Serrate Activity	133798.5	1/hour
Tace	Molecule	Tace Activity	93020.9	1/hour
Notch	Molecule	Notch Activity	272504.6	1/hour
CSL	Molecule	CSL Activity	56750.5	1/hour
Y-secretase complex	Molecule	Y-secretase complex Activity	172103.8	1/hour
Co-activators	Molecule	Co-activators Activity	877643.6	1/hour
SKIP	Molecule	SKIP Activity	56750.5	1/hour

DNA	Molecule	DNA Activity	120414.7	1/hour
Pre-T-alpha	Molecule	Pre-Activity	120414.7	1/hour
HDAC co-repressor complex	Molecule	HAC Co-repressor Complex Activity	429755.4	1/hour
Deltex	Molecule	Deltex Activity	272504.6	1/hour
Gene Expression	Molecule	RAS/MAPK Activity	10000	1/hour
Dvl	Molecule	Dvl Activity	75186.7	1/hour
Numb	Molecule	Numb Activity	70803.8	1/hour
Hes1/5	Molecule	Hes Activity	120414.7	1/hour

Table 2: Dose escalation scheme and other parameters of Belinostat

Drug	Dose(mg/ml)	Molecular weight	Predicted LD_{50}	Chemical Formula	Water solubility	Reference
Belinostat	600-1000	318.35 g/mol	6000 mg/kg	$C_{15}H_{14}N_2O_4S$	0.14 mg/mL	[23]

5. Discussions

Belinostat has been approved by the FDA for the treatment of numerous malignancies, including lymphomas, and is now in stage II clinical studies. Belinostat is a new small drug under research that inhibits the enzyme histone deacetylase [26]. Belinostat has been shown in preclinical tests to have the potential to treat a wide range of solid and hematologic malignancies as a monotherapy or in combination with other dynamic medicines; both oral and injectable versions of the medication are being tested in human trials. In a dose design, belinostat administration inhibited cell growth and multiplication and caused cell cycle arrest. It also inhibits HDAC activity in tumor and other cell correspondence genes [20].

Belinostat has been tested in clinical trials to treat non-Hodgkin lymphoma, which is caused by an imbalance in HDAC expression. Non-lymphomas Hodgkin's are a diverse group of cancers that arise from the lymphoid framework [27]. NHL, like other cancers, develops through a multi-step series of inherited alterations that cause a specific growth of the hazardous malignant clone. Intermittent translocations, which occur at various phases of B-cell separation, are typically the beginning of malignant alterations. These translocations result in the erroneous articulation of oncogenes, which govern the processes of cell multiplication, survival, and differentiation [28].

This scientific study focuses on the formalization of notch-interceded SMC proliferation. Using mathematical modeling, the expression levels of a few genes, their complexes, and their effects on SMC proliferation have been noted, along with a few differential conditions, the impact of HDAC complex has been examined to determine the changed expressions of HDAC complex after Belinostat induction. The fundamental goal of this research was to better understand the mechanism of interaction between many genes and/or proteins. The pathway model was created and simulated in simbiology. The simulation findings (Figure 3) show how a gene might influence the expression levels of others by interacting with them.

Consideration of treatment routes is required to improve the creation of viable medications for their early identification and diagnosis. Biological pathways are typically modeled to investigate system sub-adventures, determine gene expression patterns, and forecast the consequences of various changes induced in cells [29]. In this way, this study discovered the expression level of HDAC co-repressor complex when it is mutated, and the diagrammatical representation of a specific pathway makes it easy to understand the proper dosage regimen, as well as how a drug can change the expression of a specific gene, so the Belinostat 600 mg/ml dose was identified and given to HDAC complex. The drug increases HDAC expression, confirming that it is used to treat abnormal HDAC activities; simulations revealed that when the parameters were entered into the model both before and after Belinostat induction, the drug induction provided better simulation results than the simple drug simulations. When the simulations were run after the settings were applied, none of the typical errors occurred. As a result, we propose that Belinostat 600 mg/ml be administered to individuals whose SMC growth is hampered by aberrant HDAC complex activities.

6. Conclusion

Using a mathematical modeling approach, this study determined the expression level of the HDAC co-repressor complex when it is altered. The HDAC co-repressor complex expression levels were measured before and after the Belinostat 600 mg/ml treatment. The model also included the development of 16 differential equations. The rise in HDAC expression indicates that Belinostat can cure the mutations of the HDAC complex, which suppresses the growth of smooth muscle types in Lymphoma after being mutated. This study work can also be employed in drug development and formulation in-vitro.

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8. Competing interests: None of the authors has any competing Interests.

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