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Original Article

The Effect of Sophoridine on NSCLC by Down Regulation of mTOR and NOTCH1

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ABSTRACT

Introduction: Sophoridine, an alkaloid compound which is isolated from various plant species like *Sophora alopecuroides* and *Sophora flavescens*. It identified to have potential pharmacological properties, including anti-inflammatory, anticancer and antiviral activities. The effect of the sophoridine on mTOR and NOTCH1 pathways that are critical in NSCLC is not well understood. **Materials and Methods:** In order to assess the virtual interaction of mTOR and NOTCH1 with sophoridine, we employed molecular docking. We also performed an *in vitro* analysis using the NSCLC cell line (A549) using MTT, RT-PCR, western blot and wound healing assays. **Results and Discussion:** We report strong interaction of sophoridine with mTOR and it exhibited cytotoxic effect on NSCLC cells, causing downregulation of the mTOR and NOTCH1 genes. We used a wound-healing assay to assess its impact on cell migration in NSCLC cells and our findings confirmed that sophoridine significantly (p= 0.0265) inhibits cell migration in A549 cells. **Conclusion:** Our study indicates sophoridine to be potential anti-cancer drug in NSCLC cell via inhibition of mTOR and NOTCH1 axis.

Keywords: Sophoridine, Natural compound, NSCLC, mTOR and NOTCH1.

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INTRODUCTION

Sophoridine, an alkaloid chemical, is naturally present in numerous plant species, most notably those classified within the Sophora genus. It is classified as quinolizidine alkaloids and has generated considerable interest owing to its pharmacological properties.[1-3] Sophoridine possesses an extensive array of biological properties, as evidenced by research findings. These include antiviral, anti-cancer, anti-inflammatory and neuroprotective effects. In cancer research, sophoridine has not only exhibited potential as a therapeutic agent, but also holds promise, particularly in Non-Small Cell Lung Cancer (NSCLC). In addition to its aforementioned mechanisms of action against cancer cells, sophoridine inhibits proliferation, suppresses metastasis, induces apoptosis (programmed cell death) and possesses anti-angiogenic properties, according to scientific research. Given its unique characteristics, sophoridine emerges as a highly auspicious subject for further investigation in the realm of cancer treatment.[4-7]

The NOTCH and mTOR (mechanistic Target of Rapamycin) signaling pathways are of paramount importance in both cancer initiation and progression. The mTOR pathway regulates cellular processes such as proliferation, apoptosis, metabolism and cellular growth, while the NOTCH pathway plays a remarkable role in cell fate determination, differentiation and proliferation. Both pathways can interact and influence one another, thereby contributing to the intricate nature of cancer biology.[8-10] It has been reported that both NOTCH1 and mTOR play crucial roles in numerous cellular processes, including proliferation, apoptosis, metabolism and cellular growth. NOTCH signalling can have both oncogenic and tumor-suppressive roles, depending on the cellular context and cancer type. In case of colon cancer and lung cancer NOTCH genes is associated with development of drug resistance, although in neuroendocrine tumors its paradoxical role is reported. Prior research has indicated the existence of communication between the mTOR and NOTCH pathways in cancer[8,11] By regulating the processing and expression of NOTCH

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receptors and ligands, mTOR signaling is capable of altering NOTCH activity. Conversely, NOTCH signaling has the capacity to influence mTOR activity through various mechanisms, including the regulation of downstream effectors or components of the mTOR pathway. Also, in breast cancer cells it is reported that NOTCH1 have vital role in p53 inhibition via mTOR dependent PI3K-Akt/PKB axis and promotes chemoresistance. Enhanced treatment resistance and the development of cancer may be profoundly affected by this interaction. Simultaneously targeting both pathways and combining them with other therapeutic approaches may yield synergistic effects and improve the clinical outcomes of cancer patients.[12-14]

Overall, sophoridine represents a natural compound with noteworthy pharmacological characteristics, suggesting its potential as a starting point for creating innovative therapeutics targeting various diseases, including cancer. Regarding NSCLC, the anticancer potential of sophoridine has yet to be thoroughly investigated thus far. We aim to explore the impact of sophoridine on the mTOR and NOTCH axis in Non-Small Cell Lung Cancer (NSCLC).

MATERIALS AND METHODS

Molecular docking

Molecular docking is a computational approach used to predict the binding affinity and orientation of the molecule with protein.[15,16] We employed molecular docking to determine the binding affinity and identify the interaction residues of mTOR and NOTCH1 with sophoridine. The 3D protein structures of mTOR (4JSV) and NOTCH1 (5FMA) were obtained from RCSB-PDB, while the structure of sophoridine (CID 165549) was taken from PubChem. Both proteins and ligand were prepared before docking using AutoDock tools version 1.5.7. All water molecules were removed, hydrogen atoms and Kollmann charges were added to the structure and Chain B and Chain A of Notch1 and mTOR were selected for docking with grid box values shown in Table 1 and the outcomes were assessed using Discovery Studio software. Further ADMET analysis was done to analyse toxicological and pharmacological properties of the sophoridine (Supplementary file 1).

Cell culture

The National Center for Cell Sciences in Pune, India, gave us the Non-Small Cell lung carcinoma cell, A549. The cells were grown in RPMI-1640 medium from Gibco, NY, USA, which had 100 U/mL penicillin-streptomycin from Hyclone, UT, USA and 10% fetal bovine serum from Gibco, NY, USA added to it. In a cell culture incubator set to 37°C with 5% CO_2, the cell lines were kept alive. A cell culture incubator set to 37°C and 5% CO_2 was used to keep the cell lines alive.

MTT Assay

We used the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay to figure out how cytotoxic sophoridine was. Overnight, A549 cells were seeded into microtitre plates at a density of 5,000-10,000 cells/well. In addition, for 48 hr, the cells were mixed with sophoridine ranging from 0 to 20 mM, as previously described by Lin *et al.* (2010).[17] Every well was supplemented with 20 µL of MTT solution (5 mg of MTT/mL in Phosphate-Buffered Saline, PBS) following the treatment period. As a further 4 hr, the plates were maintained at 37°C. Each well's formazan crystals were broken up by adding 150 µL of Dimethyl Sulfoxide (DMSO). Microplate readers (BioTek, Winooski, VT, USA) were used to measure the absorbance at 570 nm. The cell viability percentage was determined in comparison to the control group that was not treated. (Figure 1).

Wound healing Assay

The migratory capacity of the cell is assessed through a wound healing assay. Approximately one million cells are placed in a six-well plate and allowed to grow until they cover 90-95% of the plate's surface. The culture is disrupted by a sterile 1 ml pipette tip after treatment with sophoridine, resulting in a scratch. The images were captured at the 0, 24 and 36 hr time points using a microscope.

Real Time-PCR

The TRIZOL method was used to extract total RNA from both treated and untreated A549 cells. Using a NanoDrop spectrophotometer, the concentration and purity of the RNA were ascertained. Additionally, a reverse transcription kit (Verso cDNA synthesis Kit) and the extracted RNA were used as templates for cDNA synthesis, which was carried out according to the manufacturer's protocol. Afterwards, the mRNA expression levels of target genes were analyzed using quantitative RT-PCR. Primers were specifically designed for the gene of interest (Table 2) and ACTB was used as a housekeeping gene for normalization. The standard protocol was followed to carry out the PCR amplification using a real-time PCR system[2]

Western Blot

Cell lysis was accomplished by means of RIPA lysis buffer. NSCLC (A549) proteins were extracted by spinning the lysate in a centrifuge. A 10% SDS gel was used to resolve the protein of an equivalent concentration. It was also possible to prevent non-specific binding by transferring the protein to a nitrocellulose

Table 1: Illustrates that Chain B and Chain A of Notch1 and mTOR were chosen for docking with the grid box.

Protein target	Coordinates (X×Y×Z)	Grid box size (X×Y×Z)
mTOR	70.03×-3.967×-57.164	126×126×126
NOTCH1	46.640×31.451×63.255	126×126×126

Table 2: **Presents the sequence of the target gene, the size of the product, and the annealing temperature.**

Primer	Sequence	Product size	Annealing temperature
NOTCH1	F- 5'-CAGACTATGCCTGCAGCTGTG-3'	596	60°C
	R- 5'-GCAGTTGTAGGTGTTCACGC-3'		
mTOR	F- 5'-CGCGAACCTCAGGGCAAG-3'	564	60°C
	R- 5'-GAAGGTAGGGACGCTGATGG-3'		
ACTB	F- 5'-GTCATTCCAAATATGAGATGCGT-3́	121	60°C
	R-5́- GCTATCACCTCCCCTGTGTG-3́		

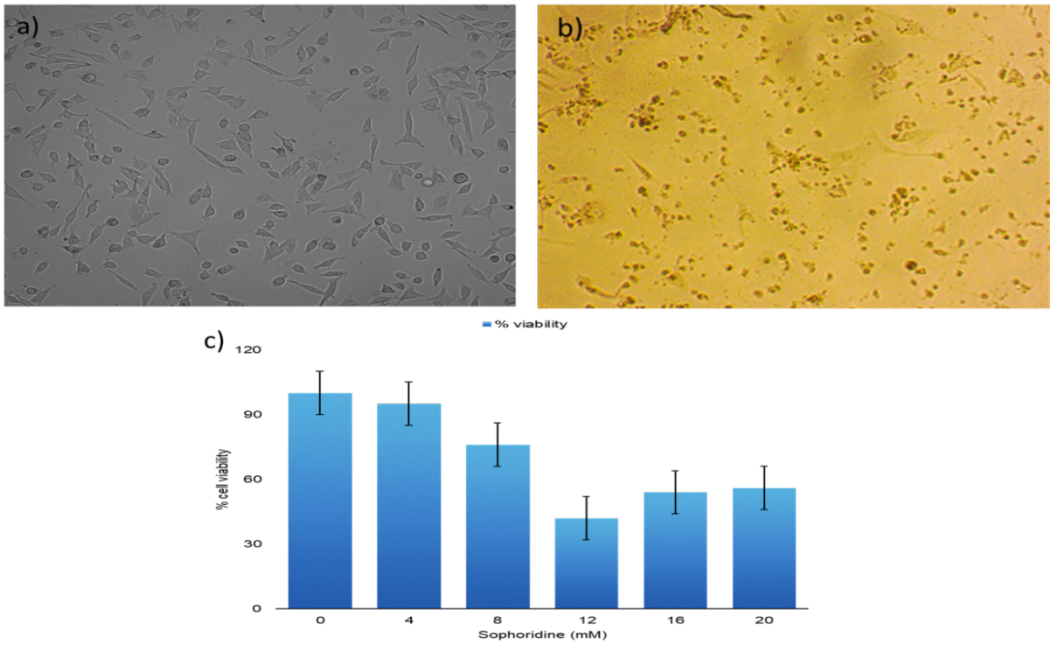

Figure 1: Effect of sophoridine on cell viability of A549 cells; (a) and (b) represents the change in morphology of untreated and treated cells respectively. (c) A bar graph represents the decrease in cell viability in dose dependent manner.

membrane and then blocking it with fat-free milk. Overnight, the primary antibody was incubated with the target proteins. The next step was to incubate the membrane for an hour with the suitable secondary antibodies that were HRP-conjugated. Chemi luminescence (Bio-Rad) was used to observe the blots.

Statistical Analysis

Appropriate statistical tests were implemented using GraphPad Prism 8, SPSS and Microsoft Office Excel. For all analyses, significance was established when $p<0.05$.

RESULTS

Molecular Docking

The molecular docking method was used as a virtual screening tool to determine the binding affinities of sophoridine with the predefined biological targets, mTOR and NOTCH1. Figure 2 shows that according to the docking analysis conducted using Autodockvina, the interaction score between sophoridine and mTOR was higher than that between sophoridine and NOTCH1.

Sophoridine induces cell death lung cancer cell lines

To determine whether sophoridine is cytostatic or cytotoxic, we used a cell viability assay on the A549 cells. We also used different concentrations of sophoridine to determine how the cells' viability changed with dose. The half-maximum Inhibitory Concentration (IC_{50}) was similar to what has been reported in previous literature.[17] The effect of sophoridine on cell metastasis ability was assessed using a wound-healing assay. Our results exhibited the significant effect of sophoridine in reducing the cell migration ability of A549 cells. When we compared the sophoridine-treated cells with the untreated cells, the number of cells that migrated was significantly ($p=0.0265$) reduced in the treated cells.

Sophoridine reduces mTOR and NOTCH1 expression

In A549 cells, a Reverse Transcription-Polymerase Chain Reaction (RT-PCR) was performed and the transcriptional levels of mTOR and NOTCH1 were checked. The purpose of this experiment was to determine the effect that sophoridine has on

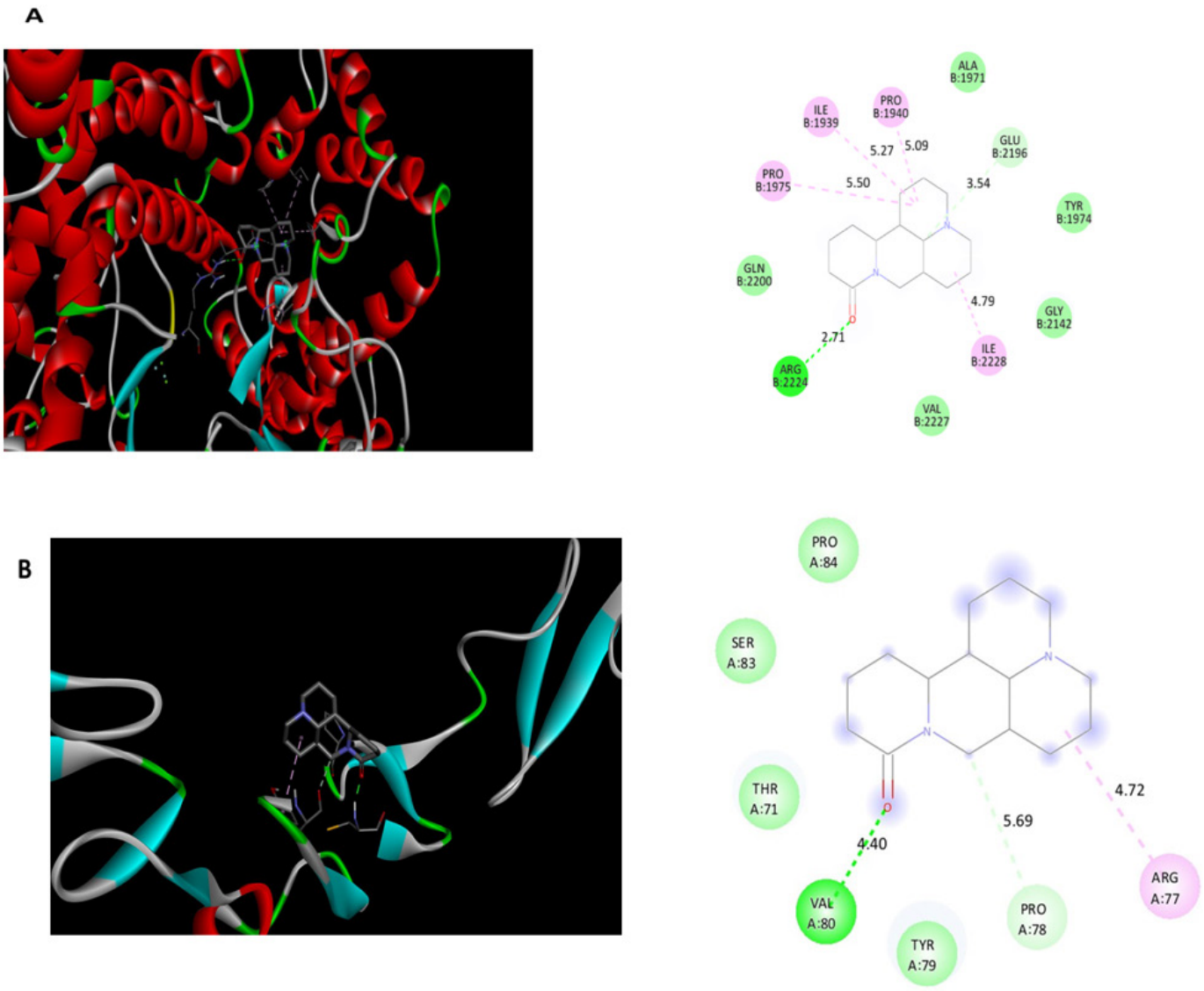

Figure 2: Structural representation of sophoridine interaction with (A) mTOR and (B) NOTCH1.

the mTOR and NOTCH1 axis. It was discovered that the levels of mTOR and NOTCH1 mRNA expression in the A549 cells that were treated with sophoridine were 4.3 and 2.7 times lower, respectively, when compared to the control samples (Figure 3). Additionally, western blot analysis was utilized in order to validate the levels of expression of mTOR and NOTCH1 at the protein level. Nevertheless, the levels of NOTCH1 did not exhibit any noteworthy alterations, despite the fact that there was a Significant decrease ($p<0.05$)in the levels of mTOR in the A549 cells that were treated with sophoridine in comparison to the control group. We found that sophoridine had a significantly more significant impact on the inhibition of mTOR than NOTCH1 did (Figure 4). This was the result of our *in vitro* studies, which confirmed the findings of the docking experiment.

DISCUSSION

Even though there have been improvements in how NSCLC is treated, the high death rate that comes with it makes it a major public health risk. On the other hand, some of the biggest problems in treating non-small cell lung cancer are that it is resistant to targeted medicines, immunotherapy doesn't always work, people are diagnosed late and they need more personalized treatment plans.[18-21] Numerous pharmacological effects have been demonstrated for sophoridine, an active quinolizidine alkaloid compound. According to prior research, Sophoridine has strong anticancer effects.[22,23] The essential molecular pathways still have not been fully elucidated. This study shows that sophoridine inhibits the mTOR and NOTCH1 axis in A549 cells. There has not yet been a complete understanding of the fundamental molecular pathways. Through the evidence presented in this study, we have

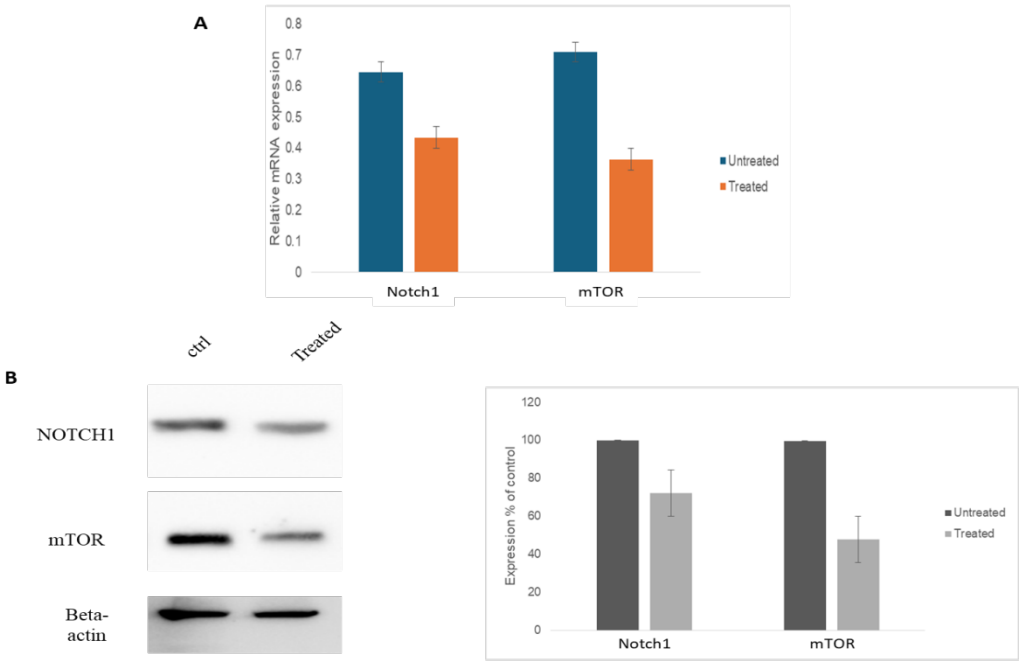

Figure 3: expression analysis of NOTCH1 and mTOR in sophoridine treated and untreated control A549 cells (A) mRNA expression analysis graph for NOTCH1 and mTOR (B) western blot analysis for NOTCH1 and mTOR.

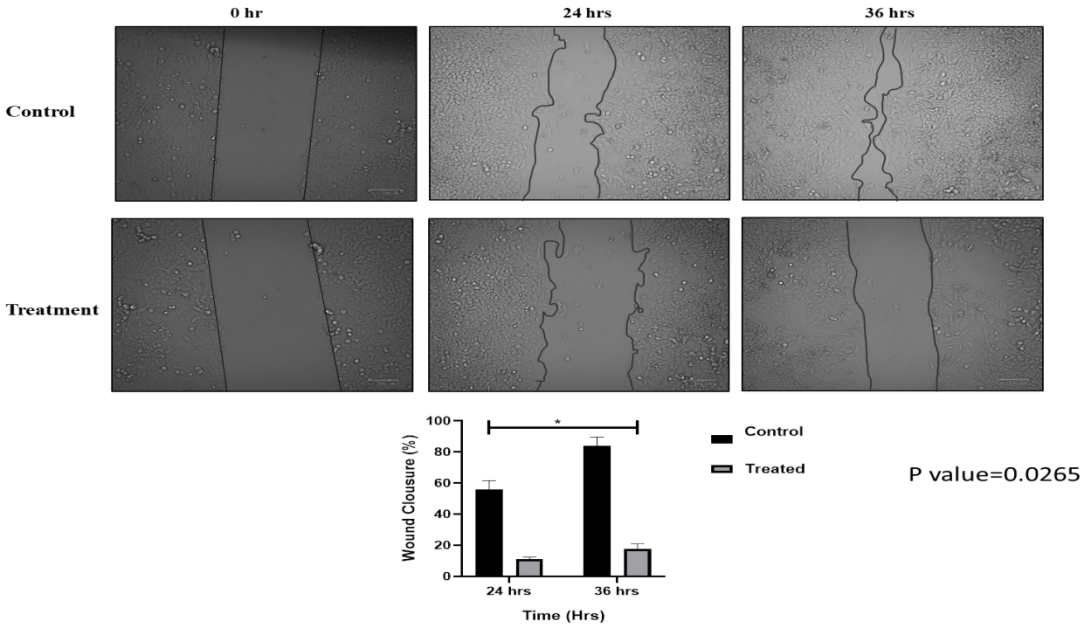

Figure 4: Wound healing assay determined the cell migration in A549 with sophoridine treatment and control.

demonstrated that sophoridine significantly inhibits the mTOR and NOTCH1 axis in A549 cells.

In order to determine whether or not sophoridine possesses cytotoxic properties, we conducted a cell viability test on A549 cells. The results of this test revealed that treatment with sophoridine led to the death of the cells. In the previously published literature, sophoridine inhibited cell migration in gastric cancer cells.[3] In order to evaluate its effect on cell migration in NSCLC cells, we performed a wound-healing assay and our results verified the inhibitory effect of sophoridine on cell migration in A549 cells. On the other hand, additional research was carried out to understand sophoridine's underlying mechanism of action. It has been demonstrated in previous research that the mTOR and NOTCH1 proteins play an essential part in the progression and proliferation of non-small cell lung cancer.[24-26] Hence, we used computational methods and *in vitro* experiments to study how

sophoridine affected the expression levels of certain biological factors, namely mTOR and NOTCH1. An investigation into the potential for sophoridine to bind with mTOR and NOTCH1 was carried out using the molecular docking method. According to our findings, the binding potential of sophoridine with mTOR was significantly higher than that of NOTCH1. Also, the structure of the sophoridine and the mTOR protein was found to have multiple interactions between their respective residues. Research on breast cancer cells has previously investigated using sophoridine to induce autophagy and apoptosis by inhibiting mTOR signalling.[27] Our results from the computational study were further validated by the results of the *in vitro* study that we conducted. Therefore, it was discovered that the levels of mTOR and NOTCH1 mRNA were decreased in A549 cells that had been treated with sophoridine. However, the only significant change observed was in the transcriptional level of mTOR. In addition, we carried out western blotting to assess the impact that sophoridine had on mTOR and NOTCH1 at the protein level. Similar to the findings of the transcriptional analysis, we discovered that the levels of mTOR protein were the only ones significantly reduced in the A549 cell lines treated with sophoridine compared to the control group that was not treated. The results of our *in vitro* study provided additional confirmation of the findings of the molecular docking experiment and we observed that sophoridine had an inhibitory effect on mTOR at the same time. Our outcomes were consistent with those of earlier studies on the anticancer potential of sophoridine. These studies found that sophoridine inhibited the activity of mTOR in HepG2 and TNBC cells.[27,28]

CONCLUSION

Sophoridine exhibited cytotoxic activity in the A549 NSCLC cell line. It exerts a strong inhibitory effect on mTOR protein in comparison to NOTCH1. Sophoridine shows great potential as a natural pharmaceutical molecule. Further investigations are required to enhance comprehension of the molecular mechanism of sophoridine biophysical analysis. In vivo studies will be beneficial in obtaining more profound understanding.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NSCLC: Non-Small Cell Lung Cancer; **A549 cells:** Non-Small Cell Lung Cancer cells; **mTOR:** The mammalian target of rapamycin; **NOTCH1:** Neurogenic locus notch homolog protein 1; **MTT:** 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **RT-PCR:** reverse transcription-polymerase chain reaction; **HepG2:** Hepatocellular carcinoma cell lines; **DMSO:** Dimethyl sulfoxide; **TNBC:** Triple-negative breast cancer.

SUMMARY

Our results unveiled a promising potential in sophoridine, showing its cytotoxic potential in NSCLC cell line (A549). The computational and invitro studies highlight its significant inhibitory effect on mTOR protein as compared to NOTCH1. Our findings projects sophoridine to be promising natural compound, however to better understand the mechanism of action of sophoridine biophysical analysis and *in vivo* studies will be helpful in providing better insight.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No ethical approval is necessary for the cell lines that have already been established. Thus, there is no requirement for ethical approval.

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