RESEARCH PAPER

Integrated Network Pharmacology and Molecular Docking Approach to Explore the Therapeutic Potential of Flavopiridol in Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a progressive, chronic, metabolic disease characterized by peripheral insulin resistance, defects in insulin secretion that progress with gradual loss of pancreatic beta-cells, and chronic hyperglycemia. A variety of underlying pathophysiological processes contribute to its pathogenesis including abnormal adipokine and cytokine signaling, chronic low-grade adipose tissue inflammation, impaired mitochondrial function, and abnormalities in the transcriptional regulation of adipogenesis and glucose homeostasis. To tackle this, researchers used a combo of network pharmacology and molecular docking to hunt down key targets for Flavopiridol in fighting Type 2 Diabetes Mellitus and to figure out how it locks onto important proteins. Network pharmacology pointed out ten main genes that play a role in causing Type 2 Diabetes Mellitus, with enrichment analysis showing main signalling pathways, namely CCNH, CDK2, CDK4, CDK6 and GSK3B. After that, five proteins were singled out for closer inspection based on their docking scores – basically how well they would fit together. When put to the test, Flavopiridol connected strongest with CCNH (-6.28 kcal/mol), followed by CDK2 (-5.28 kcal/mol), and GSK3B (-5.08 kcal/mol). Flavopiridol created sturdy bonds with these enzyme targets with hydrogen bonds, non-covalent interactions, hydrophobic and van der Waals forces. This approach hits the key processes behind Type 2 Diabetes Mellitus. These results point to Flavopiridol as a good candidate for developing new Flavopiridol treatments, which deserve testing in cells and clinical trials.

Keywords: Diabetes mellitus, Flavopiridol, Phytoconstituents, Network Pharmacology, Molecular Docking

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1. Introduction

One of the major global challenges faced in the 21st century is the growing burden of Type 2 Diabetes Mellitus which falls under non-communicable diseases. The 11th edition of the International Diabetes Federation (IDF) Diabetes Atlas report indicates that as of 2024, one in every nine adults had diabetes globally; a total number that has surpassed 500 million and is estimated to reach nearly 900 million in 2050[1,2]. Diabetes resulted in an estimated 3.4 million deaths in 2024, i.e. One death every nine seconds, and global health expenditure for diabetes was around USD 1.015 trillion, an increase by 338% over the past seventeen years[1]. Surprisingly, approximately 43% of adults with diabetes-nearly 252 million-were undiagnosed, while almost 90% of all diabetic population was in low- and middle-income countries, thereby representing a large unmet medical need that is expected to rise[2]. The majority of all cases of diabetes (over 90%) are Type 2 Diabetes Mellitus and it is considered to be influenced by a multifactorial synergy involving sociodemographic, economic, environmental, dietary and genetic factors. In a complementary approach, analyses from Global Burden of Disease studies have demonstrated that the death rate and burden of disability adjusted life years (DALYs) associated with Type 2 Diabetes Mellitus have been steadily increasing from 1990 to 2021, and have been highest in the low- and lower-middle Socio-Demographic Index regions, suggesting a sustained increased trend through 2044 . Type 2 Diabetes Mellitus is a chronic and progressive metabolic disease characterized by peripheral insulin resistance, defectively regulated pancreatic -cell insulin secretion due to progressive dysfunction of the beta cells, and consequently, chronic hyperglycemi[4]. In its complex pathophysiology, disrupted adipokine and cytokine signalling, chronic low-grade inflammation in adipose tissue, mitochondrial dysfunction and impaired transcriptional regulation of adipogenesis and glucose metabolism play significant roles[5]. The current first-line pharmacotherapy for Type 2 Diabetes Mellitus such as biguanides, sulphonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists typically interact with only one target and or pathway in the disease network. However, with such a polygenic and multi-pathway complicated disease, the traditional one-drug-one-target approach often has limits and is frequently associated with tolerability issues, such as weight gain, water retention, digestive system intolerance, or cardiovascular adverse effects[5].

Flavopiridol (alvocidib) is an ideal example of a repurposed, well-characterized small molecule that our multi-target framework is perfectly designed to test. A semisynthetic flavonoid alkaloid structurally based on rohitukine (a natural chromone alkaloid isolated from Indian medicinal plant *Dysoxylum binectariferum* (*Amoora rohituka*)) the drug was the first pan-cyclin-dependent kinase (CDK) inhibitor tested in humans, back in 1994[6,7]. As an ATP-competitive inhibitor, it potently targets and binds CDK9, with more general activity against CDK1, CDK2, CDK4, CDK6 and CDK7, leading to blockage of cell-cycle progression at the G1/S and G2/M phase transition, and inhibition of RNA polymerase II-mediated transcriptional elongation by blocking the positive transcription elongation factor b (P-TEFb)[7,8]. This activity lead to Flavopiridol obtaining FDA and EMA orphan drug status for chronic lymphocytic leukemia and acute myeloid leukemia where it is still undergoing clinical trials (including in combination regimens such as FLAM (flavopiridol, cytarabine, mitoxantrone))[9,10]. Furthermore, this broad targeting, along with its anti-proliferative and anti-inflammatory properties has enabled it to be tested for use in non-cancerous conditions, such as rheumatoid arthritis and atherosclerotic plaque formation, more recently it has shown activity in the metabolic disease area: in a range of cell lines, flavopiridol was found to inhibit adipocyte differentiation by downregulating PPAR, C/EBP and its downstream lipogenic target genes and also suppressing insulin stimulated AKT/mTOR signalling during early adipogenesis; in addition it enhanced the adipose tissue mitochondrial function and it ameliorated adipose tissue inflammation and improved glucose tolerance, insulin sensitivity and serum lipids in diet induced obese mice; finally and importantly it showed it has promise as an orally active and potent therapy for T2DM/diabesity by promoting an anti-inflammatory and pro-sensitizing phenotype in the adipose tissue and improving overall metabolic health; given that flavopiridol has already achieved orphan status for an established safety and pharmacokinetic profile from the FDA, development of this drug as therapy for T2DM/diabesity would offer a comparatively cheap and rapid route to drug-development compared with de novo drug-discovery approaches[11].

Increasingly, the integration of network pharmacology and molecular docking methods have been successfully utilized to understand the multi-target effects of natural products and repurposed drugs on Type 2 Diabetes Mellitus. In one prominent example of large-scale integrated application, network pharmacology, molecular docking, ADMET prediction and molecular dynamics studies on fourteen major genes linked to Type 2 Diabetes Mellitus uncovered a number of natural product compounds, e.g., curcumin, chelerythrine, ursolic acid, and the class of CDK-inhibitor compounds, such as alvocidib (flavopiridol) and rohitukine, with higher binding affinities to selected targets than that of several existing antidiabetic agents. This work revealed inhibition of cyclins dependent kinases as an upcoming, mechanistically sound approach for Type 2 Diabetes Mellitus drug discovery. As such, the network pharmacology coupled with molecular docking strategies were applied to screen out and validate the molecular targets that mediate the possible anti-diabesity and antidiabetic properties of the candidate drug, forming the basis of future in vivo and in vitro experimental verification.

2. Materials and methods

This research took place in two phases using a smart methodology based on network pharmacology. Phase one consisted of collecting overlapping genes associated with Type 2 Diabetes Mellitus and Flavopiridol from different databases. In phase two, multiple analyses were performed using the overlapping genes, including enrichment analyses and Protein-Protein Interactions (PPI).

2.1 Targets of Diabesity and Flavopiridol

The genes related to Type 2 Diabetes Mellitus were obtained from the GeneCards database (https://www.genecards.org/, accessed on 11 February, 2025)[12]. The molecular structure of Flavopiridol was retrieved using the PubChem database (https://pubchem.ncbi.nlm.nih.gov, accessed on 11 February, 2025). The canonical smiles of the drug was searched to obtain the target of Flavopiridol in PubChem database (https://pubchem.ncbi.nlm.nih.gov, accessed on 11 February, 2025), and subsequently assessed the pharmacokinetic parameters through the SwissADME[13] and Molsoft[14] (https://www.swissadme.ch/, https://molsoft.com/mprop/, accessed on 11 February, 2025) and SwissTargetPrediction[15] and SuperPred[16] (swisstargetprediction.ch and https://prediction.charite.de/subpages/target_prediction.php, accessed on 11 February, 2025) online data sites to predict its potential targets. The common names of the gene targets of Flavopiridol were obtained from the STRING database (https://string-db.org/, accessed on 11 February, 2025)[17].

2.2 Screening of intersection targets and construction of PPI network

The targets of Flavopiridol and Type 2 Diabetes Mellitus - related targets were taken intersected in Venny 2.1.0[18] (https://bioinfogp.cnb.csic.es/tools/venny/, accessed on 11 February, 2025). Finally, the intersecting targets obtained are potential targets of Flavopiridol for Type 2 Diabetes Mellitus prevention. The intersection targets are imported into STRING (https://string-db.org/, accessed on 11 February, 2025) to construct the PPI network. The .tsv file of the PPI network was obtained and imported into Cytoscape 3.10.3[19,20]for analysis and visualization. In CytoHubba, the core targets are obtained according to the importance of the nodes. The core targets were visualized.

2.3 GO and KEGG Enrichment analysis

Core targets were imported into DAVID (https://davidbioinformatics.nih.gov/, accessed on 11

February, 2025)[2] to obtain the results of GO and KEGG enrichment analysis[22,23]. The screening criteria were $p < 0.05$, and the enriched signalling pathway contained multiple core targets. All entries of BP, CC and MF were selected in this study, respectively. The collated data were imported into the ShinyGO v0.85.1[24] (https://bioinformatics.sdstate.edu/go/) for visualization and analysis.

2.4 Construction of drug-target-pathway network

The signalling pathways were filtered based on its involvement in the Type 2 Diabetes Mellitus generation from all the pathways involve with $p < 0.05$. Data of Flavopiridol, signalling pathways and core targets were made into network .xlsx file type and were imported into Cytoscape for visualization. The Flavopiridol-core target-pathway network was constructed. The yellow diamond represents Flavopiridol, the pink rectangle represents the core target, and the orange rectangle represents the signalling pathway.

2.5 Molecular Docking

2.5.1 Ligand Preparation

The three-dimensional (3D) structures of Flavopiridol was retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) in SDF format, which was further converted into .pdb format using OpenBabel (v3.1.1, accessed on 12 February, 2025)[25].

2.5.2 Receptor Preparation

The hubb genes namely, CCNH(3BLR)[26], CDK2(1W98)[27], CDK4(7SJ3)[28], CDK6(5L2I)[29] and GSK3B(1PYX)[30] were retrieved from RCSB Protein data bank (https://www.rcsb.org/). AutoDock tools (v4.2)[31] was used for preparation of proteins and ligand by deleting water, adding polar hydrogens, checking missing atoms, adding Kollman charges and calculating partial charges on the protein. The final protein prepared files were saved in .pdbqt format for further docking analysis and visualization using BIOVIA Discovery Studio (v25.1.0.24284)[32].

3. Results

3.1 Information on target acquisition

A total of 8,157 genes related to Type 2 Diabetes Mellitus were collected from the GeneCards database according to the standard of having a relevance score (Gifts ≥70) more significant than the median. A total of 100 and 44 approved targets of Flavopiridol were acquired from the SwissTargetPrediction and SuperPred databases, respectively. Duplicates were removed through the common names and UniProt IDs from the targets to acquire a total of 131 Flavopiridol targets. After data collection, there were 77 potential targets with Flavopiridol-related targets with Type 2 Diabetes Mellitus through Venny 2.1.0. **(Figure1A).**

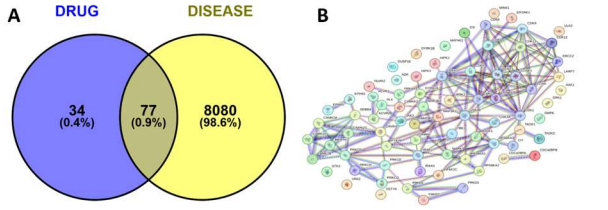

Figure 1(A) Venn diagram of intersection targets between Flavopiridol-Type 2 Diabetes Mellitus (B) Establishment of PPI network for intersection targets

3.2 Establishment of PPI network and selection of core targets

77 intersecting targets were input to String, and a PPI network (**Figure1B**) containing 77 nodes, 56 edges, and a PPI enrichment p-value < 1.0e-16 was established. The .tsv file of the PPI network was downloaded and imported into Cytoscape 3.10.3 for visualization and analysis (**Figure2A**). The intersecting targets were ranked from largest to smallest according to the degree value using the CytoHubba plugin. The top 10 intersecting targets were selected as core targets for Flavopiridol in the prevention of Type 2 Diabetes Mellitus. The core targets (hub genes) are visualized (**Figure2B**). The circles represent the core targets for screening, and the redder the colour of the circle, the greater the importance. The 10 core targets include CCNH, CDK2, CDK5, CCNE1, CCND3, CDK4, CDK6, CDK1, GSK3B and CCNT1.

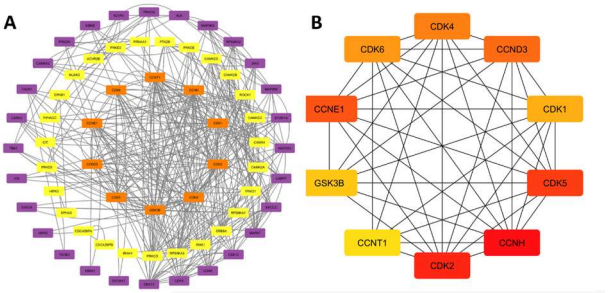

Figure 2(A) Graphical display of intersection targets (B) Visualization of core target hubb genes.

3.3 Results of enrichment analysis

Core targets were imported into DAVID for GO and KEGG enrichment analysis. The results of GO enrichment analysis of core targets included 62 entries, BP (Biological Process):33, CC (Cellular Component):13, MF (Molecular Function):16. The top 20 items in each category were selected for visual analysis through ShinyGO database. The biological processes involved in the 10 core targets were mainly cell division, mitotic cell cycle, rhythmic process, protein phosphorylation, gene expression, signal transduction etc. (**Figure3A**). They mainly act on the cyclin-dependent protein kinase holoenzyme complex, nucleoplasm, nucleus, cytosol, cyclin D3-CDK4 complex, cyclin D3-CDK6 complex etc. (**Figure3B**). They are involved in molecular functions including cyclin-dependent protein serine/threonine kinase activity, cyclin

binding, ATP binding etc. (**Figure3C**). 26 signaling pathways were identified by KEGG enrichment analysis of core targets, and 10 important signaling pathways were visualized and analyzed. The main signaling pathways involved directly in Flavopiridol-Type 2 Diabetes Mellitus target include p53 signaling pathway, Cellular senescence, PI3K-Akt signaling pathway, Human T-cell leukemia virus 1 infection etc. **(Figure 4)**. The results of KEGG enrichment analysis suggest that Flavopiridol may prevent Type 2 Diabetes Mellitus mainly through the above pathways.

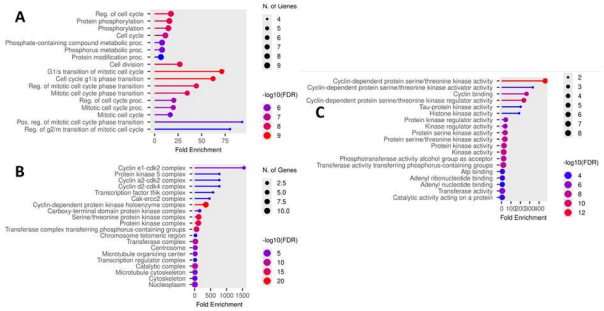

Figure 3(A, B, C) Visualization results of GO enrichment analysis for BP (Biological Process), CC (Cellular Component), MF (Molecular Function)

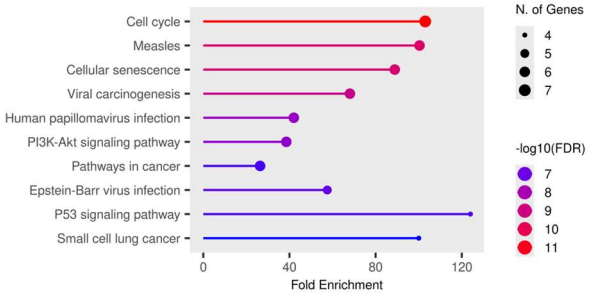

Figure 4 Visualization and signalling pathways results of KEGG enrichment analysis

3.4 Drug-target-pathway network

The pathways were filtered again from KEGG analysis data, which were specific to Type 2 Diabetes Mellitus only, and 11 pathways were established. The core targets, Flavopiridol and KEGG enrichment pathways were categorized and organized to construct the drug-target-pathway network in Cytoscape 3.10.3 (**Figure 5**). In **Figure 5**, the yellow diamond represents Flavopiridol, the pink rectangle represents the core target, and the orange rectangle represents the pathway in which the core target was enriched.

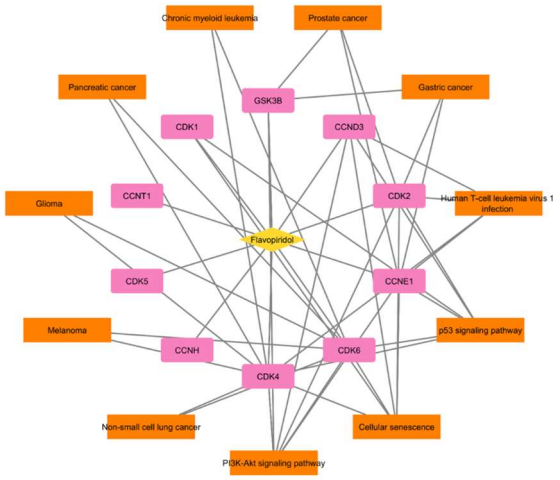

Figure 5 Visualization results of drug-pathway-target relationship network

3.5 Molecular Docking

Ten hub genes were predicted by network pharmacology to be crucial molecules for the pathogenesis of acne. Molecular docking has been implemented to verify the binding affinity of Flavopiridol with the target hub proteins. Docking not only provides the connection between network-based prediction and molecular-level confirmation but also verifies the binding characteristics of Flavopiridol with some key proteins for Type 2 Diabetes Mellitus. It will verify the compound's potential action mechanism and further support the other in-vitro and in-vivo experiments.

The docking scores and 2D interaction analysis of five hubb genes namely CCNH(3BLR), CDK2(1W98), CDK4(7SJ3), CDK6(5L2I) and GSK3B(1PYX) show different ligand-protein interactions, indicating the difference in inhibitory ability. From the figures and Table 1, the binding energies of the drugs determined with molecular docking, lower values (more negative) indicate higher affinity.

Table.1: Docking scores for vitamin E succinate and its interactions with the enzymes.

LIGAND	PDB ID OF THE PROTEIN	DOCKING ENERGY	MAJOR BINDING POCKETS
Flavopiridol	CCNH	-6.28	TTRP221, HIS202, ILE212, LYS206

	CDK2	-5.28	LYS110, TYR281, LEU113, ARG114, PRO280
	GSK3B	-5.08	PPHE67, GLY202, PRO294, ARG96, PHE293
	CDK4	-4.48	GGLU312, GLU342, LYS159, ASP345, ASP341
	CDK6	-3.98	GLN103, TYR108, VAL112, PRO113, PRO118

To compare binding strengths, the interaction energy between Flavopiridol and other hub proteins was calculated. Flavopiridol showed better affinity towards CCNH (-6.28 kcal/mol) and CDK2 (-5.28kcal/mol) than any other hubb genes. Therefore, Flavopiridol is a potentially better inhibitor towards hub targets.

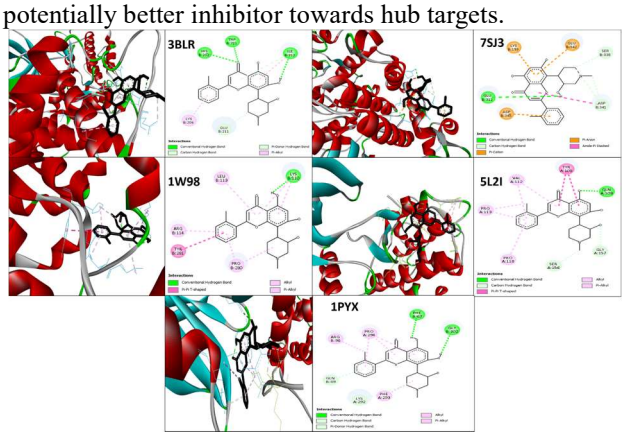

Figure 6: Comparative two-dimensional and three-dimensional molecular interaction diagrams of Flavopiridol docked against target proteins, CCNH(3BLR), CDK2(1W98), CDK4(7SJ3), CDK6(5L2I) and GSK3B(1PYX).

4. Discussion

Flavopiridol (alvocidib), an FDA-approved CDK inhibitor against pan-CDKs developed initially for blood cancers, has recently emerged as a promising candidate for repositioning as a Type 2 Diabetes Mellitus and obesity ("diabesity") therapy. It was reported in a 2024 research that flavopiridol potently blocked the differentiation of adipocytes across cell models through the inhibition of adipogenic transcription factors PPAR and C/EBPα, arrested the cell cycle in the G1/S stage in the process of mitotic clonal expansion, deactivated the AKT/mTOR pathway, and increased the mitochondrial activity in differentiated adipocytes – with 135 times efficacy more potent than that of the parent compound rohitukine[11].

This anti-adipogenic, insulin-sensitizing profile correlates with a separately confirmed interaction of the CDK family of kinases with insulin resistance. For instance, feeding high-fat diets has been found by Choi et al to stimulate adipose tissue-specific Cdk5 activation and subsequently to promote PPAR phosphorylation at serine 273, thereby compromising the expression of obesity related genes, such as the reduction in adiponectin levels (which is normalized by standard anti-diabetic drugs such as rosiglitazone). Following this observation, a class of non-agonist PPAR ligands was generated that targets CDK5 to block phosphorylation and thus improves insulin sensitivity, and another group has identified a regulatory ERK/CDK5 pathway, inhibition of which effectively prevents insulin resistance in obese mice[5,33].

Taken together, these findings support the proposed reasonable scheme of CDK, CDK5 and GSK3 polypharmacology of flavopiridol converging to regulate adipose development, inflammation of the adipose tissue, and insulin signalling – critical elements in the development of Type 2 Diabetes Mellitus pathophysiology. However, studies remain preclinical, and the toxicity profile of flavopiridol established from the oncology dose range suggests that careful dose-optimization and safety assessment be made before any clinical studies for metabolic disease use could be contemplated.

The docking results add structural evidence for the potential multi-target action of flavopiridol in the context of Type 2 Diabetes Mellitus. The strongest binding affinity detected for CCNH (-6.28 kcal/mol) is particularly noteworthy given that flavopiridol was already co-crystallized in a structural complex with the CDK9/Cyclin H-associated P-TEFb complex, confirming the robustness of the docking methodology and reinforcing CCNH as a highly plausible mediator for flavopiridol transcriptional and anti-inflammatory functions in adipocytes. The moderate to strong binding for CDK2 (-5.28 kcal/mol) is also consistent with the known role of flavopiridol as a pan-CDK inhibitor responsible for arresting the cell cycle in the G1/S phase during the clonal expansion phase of adipogenesis, a cellular event known to contribute to flavopiridol anti-adipogenic activity.

Similarly, binding at GSK3B (-5.08 kcal/mol) utilizing ATP-binding residues of the target (PHE67, ARG96, PHE293) is consistent with known regulation of insulin signalling and glycogen synthesis by GSK3 in Type 2 Diabetes Mellitus and suggests that flavopiridol might target this pathway along with the well characterized CDK

Targets of this kinase. In comparison, lower binding energies were seen for CDK4 (-4.48 kcal/mol) and CDK6 (-3.98 kcal/mol). This indicates that these targets, although are part of the network pharmacology hub set, may not be as important in driving the anti-diabesity action of flavopiridol as the aforementioned CCNH, CDK2, GSK3B targets.

Hence, a tiered mechanism where cell-cycle arrest through CCNH/CDK2 targeting and insulin signalling disruption through GSK3 Targeting act as the main and most favourably interacting targets of flavopiridol is suggested as a mechanism contributing to its anti-diabesity properties.

In summary, the findings of the study are consistent with the network pharmacology prediction, and the most favourable target interactions indicate CCNH, CDK2, and GSK3 as priority targets for further validation, whereas CDK4 and CDK6 could serve as synergistic/secondary targets.

Data Availability

Not applicable

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Ethics declaration

Not applicable

Conflict of Interest

The author declares no conflict of interest

Contributions

Conceptualization: Shallu Sharma, Vishal M Balaramnavar; Investigation: Shallu Sharma, Taru Mishra; Writing: Shallu Sharma, Taru Mishra. All authors read and approved the final manuscript.

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