Identification of novel drugs for inhibition of nuclear factor κ-B protein to treat inflammation-based obesity using computational techniques

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Submitted by:

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Contents

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS, ABBREVIATIONS

Abbreviation	Definition
(NF-κB	Nuclear Factor Kappa B
WAT	White Adipose Tissue
RBP4	Retinol-Binding Protein 4
TNF-α	Tumor Necrosis Factor-Alpha
MCP-1	Monocyte Chemotactic Protein 1interleukin
IKB1	Inhibiting Components
JNK	Jun N-Terminal Kinase
IKK	NF-Kb-Activating Kinase
IKK-β	I Kappa B Kinase Beta
MAPK	Mitogen-Activated Protein Kinase
TLRs	Toll-Like Receptor
TNF	Tumor Necrosis Factor
SOSA	Selective Optimization of Side Activities
IRS	Insulin Receptor Substrates

ABSTRACT

Inflammation brought on by obesity is linked to several clinically significant consequences, such as insulin resistance, Type 2 diabetes, hypertension, and non-alcoholic fatty liver disease . Adipose tissue plays a crucial role in this process, even though the reason and the participating molecules are still not fully understood . Coordinating controllers of immune and inflammatory reactions, nuclear factor kappa B (NF-κB) transcription factors are genetically conserved . They are crucial in progression of cancer and other metabolic diseases .

The IKK/NF-κB signalling has been shown in numerous studies to play a critical role in the induction and maintenance of the inflammatory state that underpins metabolic disorders like type 2 diabetes and obesity . Recently, a crucial function for immune cells, in producing the inflammation, brought on by fat, has been discovered . It may be possible to find treatment targets, that can reduce the problems related to obesity by specifying the cellular and molecular entities of obesity caused by inflammation .

In this paper, we have focused on molecular mechanisms and pathways related to obesity-based diabetes type-2 and worked on a list of multiple drugs which are commonly approved for different diseases like cancer and hypertension, etc . that can be repurposed to cure diabetes type-2 led by inflammation-based obesity . Out of 250 drugs, Telmisartan, an anti-hypertension drug, and Dolutegravir, which is an anti-viral drug resulted as the best binding drug to inhibit NF κ-B and stop the onset of disease .

Keywords—obesity, inflammation, diabetes, molecular docking, drug-repurposing .

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CANDIDATE'S DECLARATION

I, SHRISTI SHARMA, 2K21/BIO/05, student of M . Tech (Bioinformatics), hereby declare that the project Dissertation titled " Identification of novel drugs for inhibition of nuclear factor κ-B protein to treat inflammation-based obesity using computational techniques" which is submitted by me to the Department of Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology, is original and not copied from any source without proper citation . This work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition .

Place: Delhi

Date: 13th June 2023

Shristi Sharma

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CERTIFICATE

I hereby certify that the Project Dissertation titled " Identification of novel drugs for inhibition of nuclear factor κ-B protein to treat inflammation-based obesity using computational techniques" which is submitted by Shristi Sharma, 2K21/BIO/05 [Department of Biotechnology], Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology, is a record of the project work carried out by the students under my supervision . To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere .

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Shristi Sharma

Place: Delhi **SHRISTI SHARMA**

Date: 13th June 2023

INTRODUCTION

Being obese is presently the sixth most important risk factor adding to the overall burden of disease globally, making obesity the most significant public health problem for the upcoming years. White adipose tissue (WAT) is prone to low-grade inflammation due to persistent innate immune system activation, which increases the risk of insulin resistance, decreased glucose tolerance, and even diabetes [1]. Leptin, resistin, adiponectin, retinol-binding protein 4 (RBP4), as well as many cytokines and immune-associated substances like tumor necrosis factor-alpha (TNF-α), monocyte chemotactic protein 1interleukin (IL) 1, and IL-6, are among the many substances that the adipose tissue is known to secrete. (MCP-1) [2].

Inflammation is a prevalent trait that is usually involved in the pathophysiology of several obesity-associated diseases, even though it is probable that there are numerous molecular pathways connecting obesity to its consequences [3]. Main inflammatory signaling molecules, both extracellular as well as intracellular, have received a lot of attention recently in attempts to define the impacts of obesity on specific organs and general metabolism. More recent research has revealed immune cells, particularly monocytes, and macrophages, to be key players in the inflammation and problems brought on by fat. Obesity greatly contributes to the inflammation of fatty tissue by increasing the quantity and activity of macrophages in that tissue [4].

Recent studies have connected the development of insulin resistance brought on by fat to molecular networks that regulate inflammation. The multi-protein transcription factor shortly known as NF-kB regulatory targets includes inflammatory proteins like MCP-1, and TNF-α.

Numerous inflammatory stimuli, which comprise activation of Toll-like receptors, exposure to UV radiation, reactive oxygen species, and proinflammatory cytokines, resulting in the phosphorylation and breakdown of the NF-kB inhibitory component. After being liberated from its inhibiting components like IKB1 or IKB2 moves into the nucleus, the NF-kB complex turns active and translocate to the nucleus where it starts NF-kB-dependent transcription in a cell-type-specified pattern [5].

The NF-κB also known as nuclear factor kappa B and Jun N-terminal kinase or JNK systems, as well as the I kappa B kinase beta IKK-β, which maintains inflammatory responses through activation of NF-κB, are primarily involved in the pro-inflammatory effects of cytokines through intracellular signaling pathways in obesity. In the tissues that respond to insulin in obese and high-fat-fed animals, signaling cascades involving IKK- and NF-κB are triggered.

CHAPTER 1:

LITERATURE SURVEY

In recent years, there has been a growing interest in identifying novel drugs that can effectively inhibit the nuclear factor κ-B (NF-κB) protein to treat inflammation-based obesity . This area of research has gained significance due to the increasing prevalence of obesity and its associated health complications . Computational techniques have emerged as powerful tools in the drug discovery process, allowing for the screening of large chemical libraries and the repurposing of existing drugs to target NF-κB and mitigate inflammation . Numerous studies have employed virtual screening and molecular docking simulations to identify potential drug candidates with anti-inflammatory properties . These computational approaches enable the prediction of ligand-protein interactions and the assessment of binding affinities, providing valuable insights into the potential effectiveness of the identified compounds . Through this literature survey, it becomes evident that computational techniques offer a promising avenue for the discovery of novel drugs for the treatment of inflammation-based obesity by specifically targeting NF-κB . [6] Further validation through in vitro and in vivo studies is necessary to assess the efficacy and safety of these drug candidates, with the ultimate goal of developing effective therapeutic interventions for this prevalent health issue .

Furthermore, the literature survey reveals several key findings related to the identification of novel drugs for the inhibition of NF-κB protein in the context of inflammation-based obesity . Studies have explored different strategies to target NF-κB, such as direct binding to its active site or modulating the upstream signaling pathways involved in its activation . Virtual

screening of chemical databases, including PubChem, drug bank, and ChEMBL, has been conducted to identify potential drug candidates with anti-inflammatory properties . Molecular docking simulations have played a crucial role in assessing the binding affinity and interaction between the identified compounds and NF-κB . By leveraging computational techniques, researchers have successfully identified compounds that exhibit promising inhibitory effects on NF-κB, potentially leading to the development of effective therapeutic interventions for inflammation-based obesity . Moreover, in silico approaches have not only accelerated the drug discovery process but also saved valuable time and resources by minimizing the need for extensive experimental screening . However, it is important to note that further preclinical and clinical research is essential to validate the efficacy, safety, and pharmacokinetic properties of these potential drug candidates.

Overall, the literature survey demonstrates the significant progress made in the identification of novel drugs for the inhibition of NF-κB to address inflammation-based obesity, emphasizing the potential of computational techniques in advancing drug discovery efforts in this field [6] .

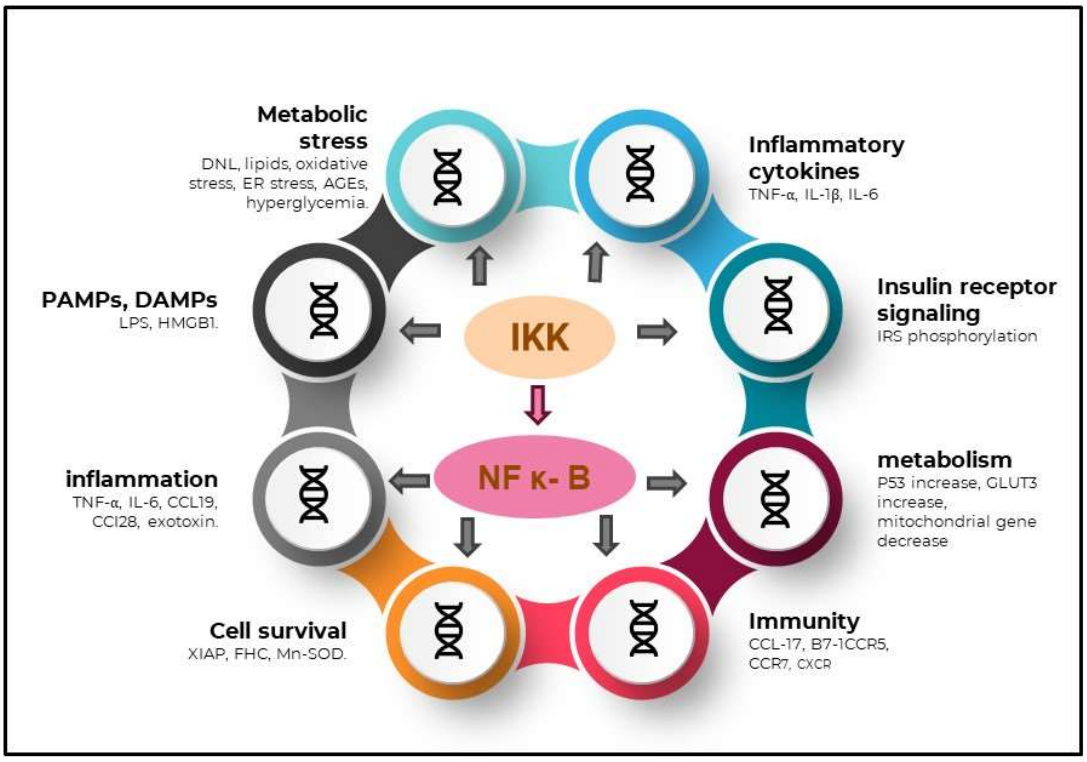

Figure 1: Pathways linking inflammation, obesity, insulin action

ROLE OF NF-κB IN INFLAMMATION

Nuclear Factor kappa B, also known as NF-B, is an important player in the control of inflammation. By regulating the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules, it functions as a mediator of inflammatory responses . This transcription factor is activated in response to cytokines, infections, and oxidative stress, among other stimuli . When NF-B is activated, it moves into the nucleus and encourages the transcription of genes related to inflammation and immunological responses. NF-B is connected to metabolic illnesses such as obesity and insulin resistance via the way that inflammation and these ailments interact with one another. Increased NF-B activity is linked to the persistent low-grade inflammation found in adipose tissue in obese people, which results in insulin resistance and poor glucose metabolism. Additionally, via modulating immune cell activation, differentiation, and the generation of antimicrobial peptides, NF-B plays a crucial part in controlling immunological responses. Autoimmune disorders and immunological dysfunction can be brought on by NF-B signalling dysregulation .NF-B has become a potential therapeutic target for a variety of inflammatory disorders due to its crucial involvement in inflammation.

ROLE OF NF K-B IN OBESITY AND DIABETES TYPE-2

The IKK/NF-κB signaling pathway is necessary for the interaction between the metabolic process, inflammation, and insulin activity . Most metabolic stress signals that result in insulin resistance or pancreas cell dysfunction, whether they are caused by intracellular or extracellular stressors, focus on the NF-κB-activating kinase (IKK), and the other major

inflammatory kinase, JNK mitogen-activated protein kinase (MAPK) . IKK is a key component of the signaling networks that are triggered by metabolic stress sensors, TLRs, and cytokine receptors . TNF, IL-1, and IL-6 are among the inflammatory genes whose production is regulated by this factor[6] .

The IKK kinases have a significant contribution in anomalies of insulin metabolism and overeating via a number of different mechanisms . In the residing tissue macrophages and metabolically active cells, as adipocytes and hepatocytes, IKK-mediated NF-B activation causes macrophage recruitment, activation, and differentiation, as well as the beginning and maintenance of an inflammatory response that leads to insulin resistance in obese persons [7].

The major metabolic effect of insulin on the target sites is mediated by direct serine phosphorylation of insulin receptor substrates (IRSs), which takes place when IKK is triggered by cytokine-evoked inflammation signals or metabolic stress .

The stimulation of IRS during metabolic inflammation, however, appears to depend more on JNK1 than IKK . The pancreatic islet's core metabolism networks are affected by the IKK/NF-B pathway, which also makes peripheral insulin sensitivity worse [8] . As a consequence of metabolic stress and proinflammatory signals, it promotes islet mortality and cell failure in insulin-resistant people, impairing the ability of cells to make compensatory insulin and leading to glucose intolerance and type 2 diabetes in its most extreme form .

It has become an urgent need to retrieve some novel drugs which can be used to treat inflammation caused by NF-κB that leads to multiple diseases . Here we are focusing on Diabetes type-2 disease and extracting drugs by performing virtual screening and molecular docking using a drug re-purposing approach .

CHAPTER 2:

Molecular Docking-Based and Protein Structure Approaches In Drug Discovery and Development

Protein interactions with bioactive small molecules play a significant role in determining their biological effects. To study these interactions, computer software is utilized to create three-dimensional models of the target protein and the drug. This process, known as molecular docking, is widely employed in drug discovery to optimize binding affinities within the active site of the target protein, such as an enzyme's pocket, with the goal of enhancing the drug's effectiveness. Given the extensive use of molecular docking, it is not uncommon to observe drug repositioning efforts based on this approach. Since many compounds have interactions with multiple proteins, the objective is to identify potential off-targets by screening against three-dimensional protein structures in databases. If the predicted off-targets are relevant to the disease, the drug can be repurposed accordingly.

Recent studies have focused on comparing the similarities between binding sites to approximate the biochemical and physical reality of protein interactions more closely. For example, it was discovered that synapsin I, a protein involved in neurotransmitter release regulation, could be a new target for the drug staurosporine, which is known to bind the Pim-1 kinase. This finding was experimentally validated in vitro, although further investigation is needed to determine the pharmacological significance of this new target.

In an inverse screening study, a researcher docked a single compound against multiple binding sites to characterize the off-target binding landscape of kinase inhibitors. These drugs, commonly used in cancer therapy, are known for their "promiscuous" behavior. The virtual screening revealed a previously unknown enzyme, PDK1, as an off-target of indirubin. This prediction was confirmed through in vitro experiments using a phenotypic cell proliferation assay, validating the reliability of the approach and providing insights into the side effects of kinase inhibitors.

Another study focused on addressing drug-resistant tuberculosis using molecular docking methods. In certain cases, the bacteria responsible for this condition develop resistance to conventional drugs, making it challenging to eradicate the pathogen. The researchers employed a workflow called selective optimization of side activities (SOSA), which involves gradually shifting the focus from the original drug indication and optimizing a compound across different protein families. This methodology includes extracting binding sites from three-dimensional protein structures, identifying similar binding sites across the proteome using a search algorithm, and conducting manual docking analysis to ensure the feasibility of physical interactions. Through this pipeline, the research group predicted that the approved drugs entacapone and tolcapone, typically prescribed for Parkinson's disease, exhibit potent activity against enoyl-acyl carrier protein reductase, an enzyme crucial for fatty acid synthesis in Mycobacterium tuberculosis. These predictions were experimentally validated in vitro using commercially available tablets. Notably, the introduction of the novel mode of action of these two compounds could overcome drug resistance in Mycobacterium tuberculosis, providing a valuable treatment option for affected patients.

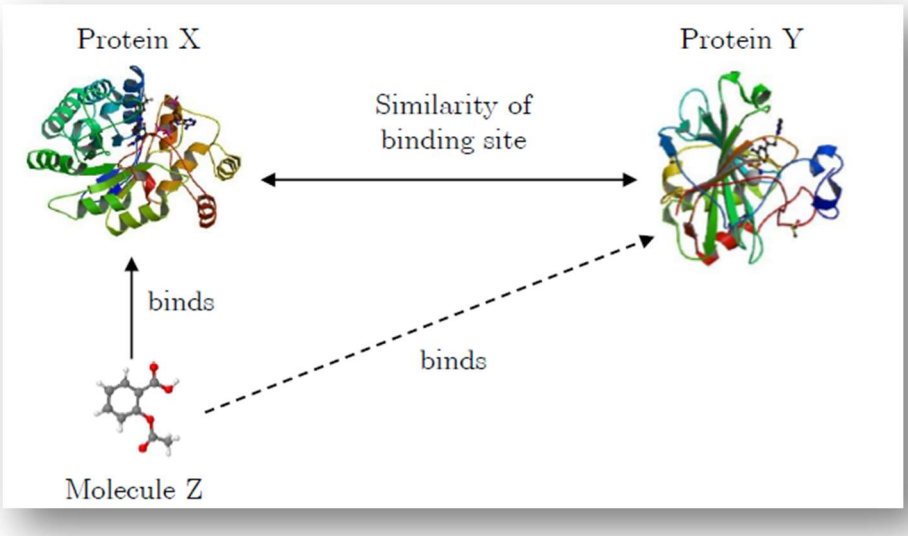

Figure 2: In drug repositioning efforts, the comparison of protein structures and their corresponding binding sites is crucial . A scoring function is utilized to assess the similarities between binding sites . The assumption is that similar binding sites have the potential to bind the same ligand . For instance, if protein X and protein Y have similar binding sites, and molecule Z binds to protein X, it is reasonable to hypothesize that molecule Z may also bind to protein Y . Relevant illustrations from the Protein Data Bank can be utilized to support these hypotheses .

Despite the mentioned accomplishments, molecular docking strategies utilized in drug repositioning encounter certain limitations. Firstly, the availability of three-dimensional (3D) structural data is crucial. Although databases like the Protein Data Bank (PDB) contain a substantial number of records, they are still far from encompassing the entire proteome. Secondly, automatically identifying a binding site can be a challenging task, particularly when the protein structure lacks the crystallized ligand. Lastly, the generation of a significant number of false positives by all methodologies necessitates the need for experimental and manual validations to assess the accuracy of predictions. Additionally, even a slight variation in a single in automated analysis and alignment of structures. Amino acid can profoundly impact the pharmacology of the binding site, presenting challenges.

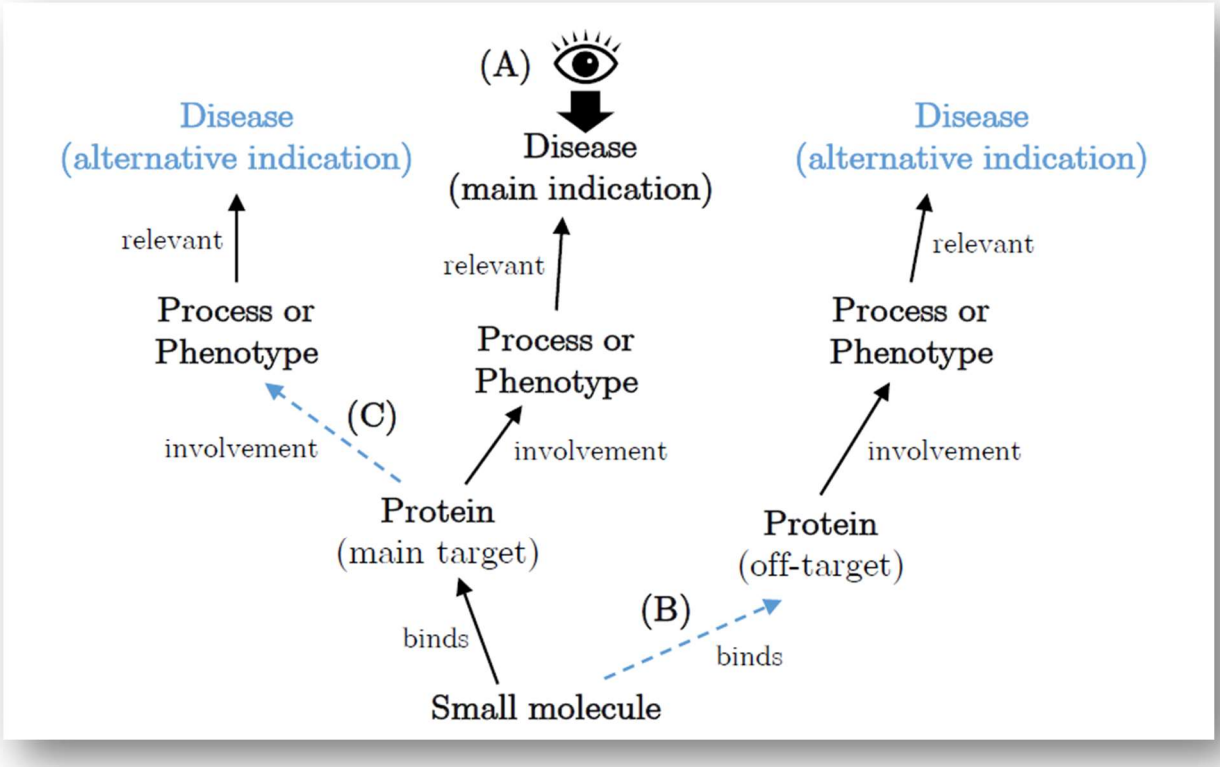

Figure 3: Drug Discovery Process and Opportunities for Drug Repositioning

In the process of drug discovery, represented by the blue pathway, biological evidence identifies a specific protein's involvement in a disease of interest. Subsequently, a series of chemicals undergo screening to assess their bioactivity. Promising molecules that demonstrate potency and safety against the target protein are developed into drugs indicated for the disease. This traditional approach aligns with Paul Ehrlich's principles, emphasizing the importance of chemical specificity to enhance pharmacological control. The concept of a "magic bullet" symbolizes the ideal therapeutic compound.

However, drug repositioning opens up alternative opportunities, as indicated by the dashed lines. Small molecules identified during the drug discovery process may also bind to other proteins, known as off-targets, which could be associated with different diseases. This repositioning hypothesis allows for the exploration of new therapeutic indications for existing drugs. Additionally, the main protein target initially identified may participate in alternative biological processes relevant to other diseases, presenting additional avenues for drug repositioning.

Both traditional drug discovery and drug repositioning contribute to the search for effective treatments, either through the development of specific drugs or the repurposing of existing ones.

In conclusion, protein-based approaches are arguably the most accurate methodology for investigating the physical interaction between a drug and a protein target. Docking approaches provide a comprehensive and detailed understanding of the biochemical complexities involved, despite the inherent challenges in modeling. It is important to emphasize that the identification of off-target proteins does not always guarantee repositioning opportunities, and the results should be interpreted within a broader biological context.

PROCEDURE FOR USING AUTODOCK VINA

For Vina to execute, both the ligand and receptor structures must be available in pdbqt file format . The pdbqt format is an extension of the pdb file format, but it includes information about polar hydrogens, which are typically not present in pdb files due to the limitations of structure determination methods . To create a pdbqt file, the AutoDock Tools program is utilized . This program calculates the positions of hydrogens based on a given pdb protein structure and adds them to the file .

Additionally, it is necessary to define a search area within the receptor . This search area is specified by its size and coordinates in three-dimensional space[12] . Vina will only explore docking possibilities within this defined search area . AutoDock Tools provides a feature called "gridbox" that assists in visualizing the search area and aids in its selection .

The docking experiments using Vina were conducted on a computer network called ABEL, which offers increased computational power for handling large amounts of data . Prior to running the experiments, the ligand and receptor pdb files were converted to pdbqt format using AutoDock Tools . A configuration file for AutoDock Vina was then created, which included information about the ligand, receptor, search area, computer resources, and output details . The docking experiments were initiated by executing the configuration file . It is important to note that ABEL is a Linux-based computer network, so executing commands may involve additional steps compared to running on a personal Windows computer .

The output of a completed Vina experiment is a modified ligand structure provided in a pdbqt file . This file contains the docked structure of the ligand to the receptor, indicating potential modifications compared to the input structure and changes in the coordinates of the atoms . Vina generates up to nine results from each docking experiment, and all structures are stored in a single pdbqt file, viewable using visualization programs like PyMOL or AutoDock Tools . In addition to the docked structures, the output includes data related to the docking process, such as the theoretical binding affinity and two measures of result proximity (RMSD measures) . The binding affinity provides insight into the strength of the binding, with smaller values indicating stronger binding . A positive affinity suggests thermodynamically unfavorable binding and may indicate a false positive result .

Measuring the structure Quality:

The Ramachandran plot, also known as the Sasisekharan-Ramakrishnan-Ramachandran plot, is a widely used method for assessing the quality of protein structures . It provides valuable information about the torsion angles present in a protein by plotting them against the sterically "allowed" angles . The allowed torsion angles are determined based on various chemical constraints . Specifically, the psi and phi angles are influenced by the energetically favorable conformations of the side chains, while the omega angle is typically fixed at 180° . [13]

METHODOLOGY

A. Retrieval of literature data

Before performing the experimental and computational work, a literature survey was done to collect information and the recent research done on target proteins and diseases . This was done using PubMed, google scholar, and other online literature databases present . A filter was applied for the work done in the last 5 years and the data was studied from the extracted papers .

B. Exploration of drugs

The drugs were taken from official databases like PubChem, drug bank, ChEMBL, etc . these are specific databases that contain detailed information regarding the drugs . PubChem is an online database that comprises information related to chemical molecules and their functionality against biological assays . It is handled by the National Center for Biotechnology Information . Drug bank is handled and maintained by the university of Alberta and is used for the study of drugs and in-silico-based drug discovery . ChEMBL is a chemical database that provides information about the impact of biochemical compounds on the human brain . The

blood-brain barrier permeability was checked using the BBB predictor CB ligand which is an online website .

C . Retrieval of the target protein

The main targeted protein i . e . nuclear factor κ-B was taken from UniProt which is an online database for their protein structure and their functional behavior . The 3-D structure was saved in PDB format .

D . Preparation of receptor and ligand

The target was prepared in open Babel, which is an application of Auto Dock Vina, where the water molecules were removed and the hydrogen atoms along with Kollman charges were introduced to bring the target to its native state . It was then saved in PDB format . The ligands were also converted and saved to PDB format .

E . Molecular docking

The receptors and ligands were docked using the Auto Dock Vina, which is a modeling and simulation software used in bioinformatics and in-silico works .

As the molecular docking is completed, all the binding energies are analyzed and the 10 best biding scores are extracted in a list . These 10 drugs provide us with the best results and the drug with the best binding score is described in the upcoming portions of the paper .

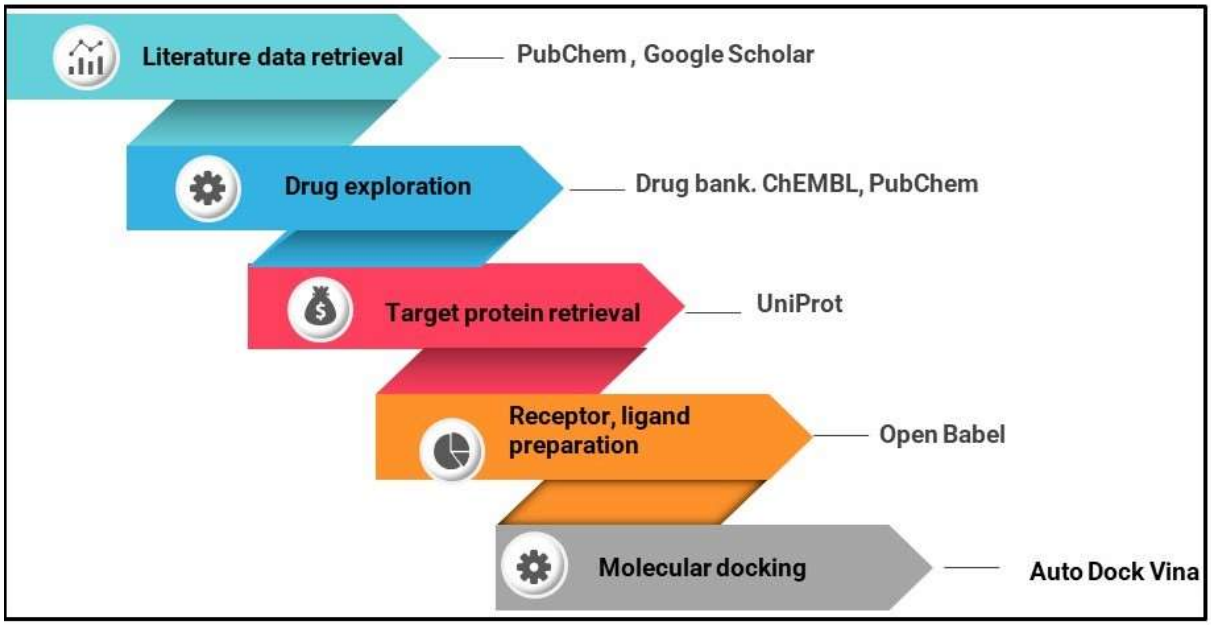

Figure 4 : Diagrammatic representation of methodology

CHAPTER 3:

RESULTS

After the in-silico work was done, we found two compounds with the best and same binding energies . They are Telmisartan with ChEMBL ID 1017, and Dolutegravir with ChEMBL ID 1229211 . Both of these drugs gave -8 . 6kcal/mol as binding affinity . Other drugs on the list are Dasabuvir, Tecovirimat, Eplerenone, Cabotegravir, Olmesartan Medoxomil, Bictegravir, Atorvastatin, Saxagliptin, Spironolactone . All these drugs cleared the blood-brain barrier permeability and are approved by FDA .

A . Telmisartan

Telmisartan is an anti-hypertensive drug, whose drug bank accession number is DB00966 . It is sold under the brand name Actelsar Hct, Pritor, Micardis, Micardis-hct, and Twynsta . It is a small molecule whose chemical formula is C33H30N4O2 . It is an angiotensin II receptor blocker that causes the tightening of vessels . Usually, this medication is taken orally once a day, but in some rare medical conditions, it depends on the advice of the doctors .

This medicine has several side effects on the patient's health like nausea, fever, dizziness, sinus pain, sore throat, fatigue, diarrhea, back pain, upset stomach, muscle pain, and many more . This drug has been repurposed to treat inflammation-based obesity which is leading to Diabetes type-2

B . Dolutegravir

Dolutegravir is an anti-viral drug used to treat the symptoms of viral fever . Its drug bank accession number is DB08930 and is FDA approved for the usage of public . It is sold under the brand names Dovato, Juluca, Tivicay, and Triumeq and is an HIV- integrase inhibitor . The chemical formula for Dolutegravir is C20H19F2N3O5 and is monoisotopic . It was developed by ViiV Healthcare and provides the best results with minimal toxicity . Dolutegravir

is an oral medication that should be taken once or twice a day daily or with the prescription and recommendation of doctors . It shows several side-effects on health like body pain, muscle cramps, headache, nausea, vomiting, dizziness, etc .

ChEMBL ID	Compound Name	Binding Affinity	RMSD UB/LB
CHEMBL1017	TELMISARTAN	-8 . 6	0/0
CHEMBL1229211	DOLUTEGRAVIR	-8 . 6	0/0
CHEMBL3137312	DASABUVIR	-8 . 4	0/0
CHEMBL1257073	TECOVIRIMAT	-8 . 4	0/0
CHEMBL1095097	EPLERENONE	-8 . 3	0/0
CHEMBL2403238	CABOTEGRAVIR	-8 . 2	0/0
CHEMBL1200692	OLMESARTAN MEDOXOMIL	-8 . 2	0/0
CHEMBL3989866	BICTEGRAVIR	-8 . 1	0/0
CHEMBL1487	ATORVASTATIN	-8 . 1	0/0
CHEMBL385517	SAXAGLIPTIN	-8	0/0
CHEMBL1393	SPIRONOLACTONE	-8	0/0

Table 1: : List of top ten drugs with their binding affinities

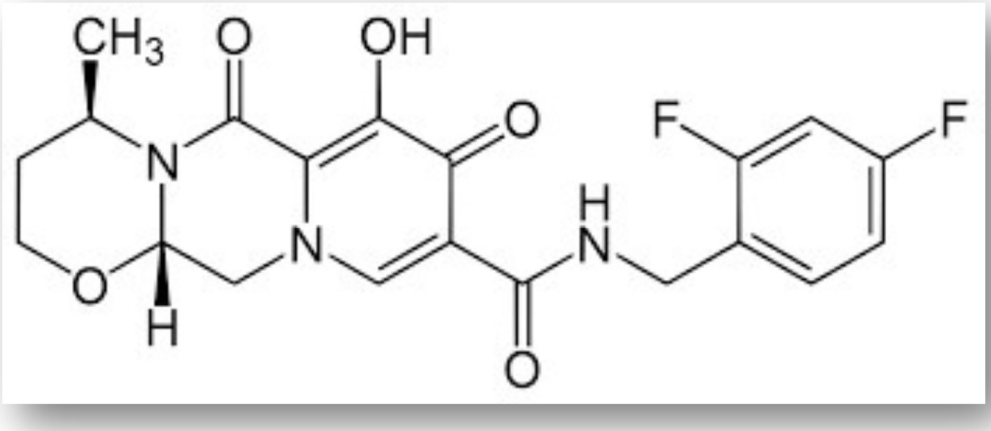

Figure 5: Chemical structure of Dolutegravir

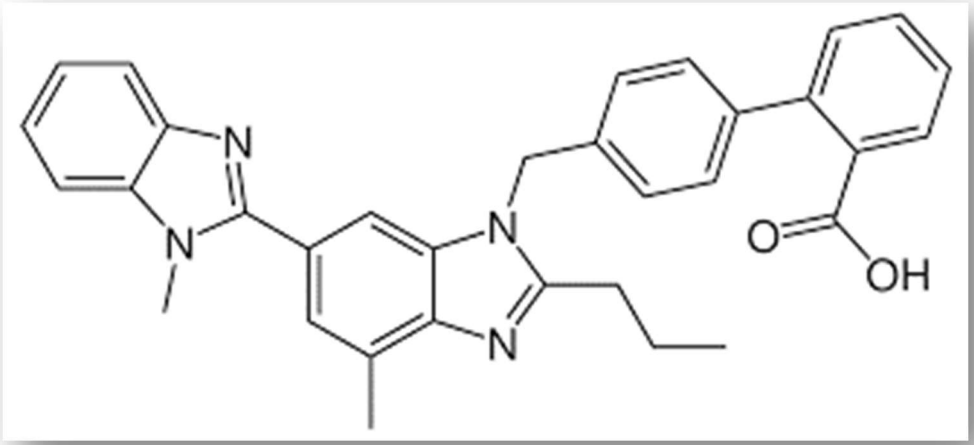

Figure 6: Chemical structure of Telmisartan

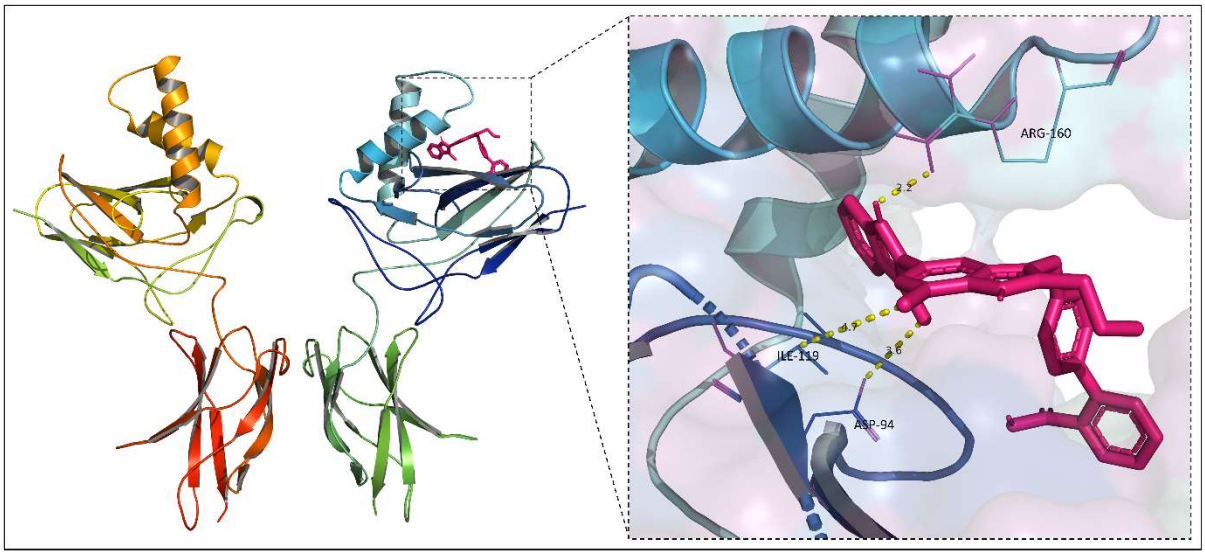

Figure 7: NF-κB with Telmisartan, active site interacts with ASP-94, ILE-119, and ARG-160 .

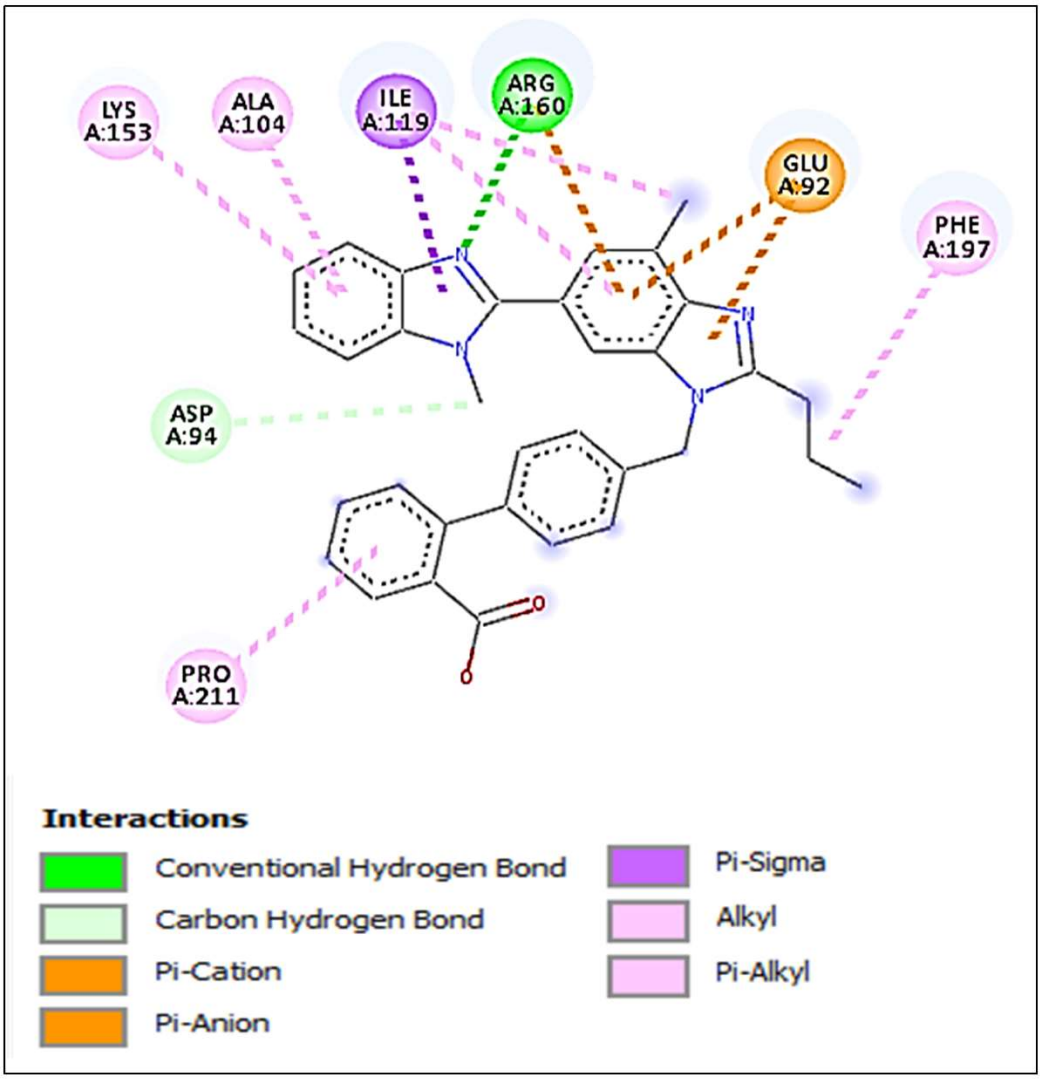

Figure 8 : 2D interaction diagram of Telmisartan with the active residues .

DISCUSSION

The development of drugs targeting inflammation-based obesity is an area that requires urgent attention within the healthcare sector . While numerous drugs are available in the market to address diabetes and obesity, there is a significant scarcity of drugs specifically designed to combat inflammation in the context of obesity[14] . Therefore, it is imperative for the healthcare industry to invest in research and development efforts to discover novel drugs using both traditional methodologies and cutting-edge technologies, such as in-silico approaches .

One of the notable advantages of in-silico studies is their ability to expedite the drug discovery process while reducing the associated costs . By utilizing computational techniques, researchers can simulate the binding affinities and interactions between potential drug candidates and their target molecules . This not only saves valuable time but also prevents resources from being wasted on experimental studies that may yield negative or inconclusive results . However, it is crucial to emphasize that in-silico studies should serve as a preliminary step, and subsequent validation through simulations and wet lab research is essential to confirm the findings .

The drugs identified in this paper, namely Telmisartan and Dolutegravir, hold promise as potential therapeutic options for inflammation-based obesity . However, it is imperative to subject these drugs to rigorous preclinical and clinical research to evaluate their efficacy, safety, and long-term effects . This comprehensive evaluation will provide substantial evidence to establish these drugs as strong contenders in the list of therapeutic interventions for inflammation-based obesity and its associated metabolic disorders, particularly type 2

diabetes .Moreover, it is important to highlight the potential of combination therapy and drug repurposing in the context of inflammation-based obesity . By targeting multiple pathways and utilizing existing drugs approved for other indications, researchers can explore synergistic effects and maximize therapeutic outcomes . The drugs mentioned in this study, such as Dasabuvir, Tecovirimat, Eplerenone, Cabotegravir, Olmesartan Medoxomil, Bictegravir, Atorvastatin, Saxagliptin, and Spironolactone, exhibit properties that make them potential candidates for repurposing . However, further investigation is necessary to ascertain their suitability for treating inflammation-based obesity and the associated metabolic disorders .

In conclusion, the development of drugs to address inflammation-based obesity is of utmost importance in the healthcare field . In-silico approaches offer valuable tools for preliminary screening and identification of potential drug candidates . However, it is crucial to perform subsequent validation through simulation and wet lab research . The drugs highlighted in this paper, particularly Telmisartan and Dolutegravir, show promise, but further preclinical and clinical studies are essential to establish their effectiveness and safety . Additionally, exploring combination therapies and repurposing existing drugs provides a viable approach to enhance treatment outcomes . By advancing research efforts, conducting comprehensive studies, and integrating multidisciplinary approaches, the healthcare industry can effectively combat inflammation-based obesity and its associated metabolic disorders, thereby improving the overall health and well-being of individuals affected by these conditions .

CONCLUSION

Various drugs are present in the market which deals with diabetes and obesity issue but drugs for inflammation-based obesity are very rare . It is the need of the healthcare sector to research new drugs either by traditional methods or using the latest technology and performing combination therapy and drug repurposing . The current healthcare landscape encompasses a wide range of drugs aimed at addressing diabetes and obesity-related issues . However, when it comes to inflammation-based obesity, the availability of effective drugs is significantly limited [15] . This presents a pressing need within the healthcare sector to embark on comprehensive research endeavors, employing both traditional methodologies and cutting-edge technologies such as in-silico approaches, as well as exploring combination therapy and drug repurposing strategies .

In-silico approaches hold tremendous potential in accelerating the drug discovery and development process, offering notable advantages over traditional experimental methods . One significant advantage lies in the time and cost savings associated with in-silico studies . By employing computational models and virtual screening techniques, researchers can swiftly evaluate a vast number of potential drug candidates, thereby narrowing down the pool of options for further investigation . This circumvents the arduous and resource-intensive process of conducting numerous experimental trials that often yield negative or inconclusive results .

Nevertheless, it is crucial to note that in-silico studies should not be considered as standalone solutions . While they offer valuable insights into the potential efficacy of drug candidates,

validation through simulation and subsequent wet lab research is imperative . Combining computational analyses with real-world experimentation allows for a comprehensive evaluation of the drug's behavior, efficacy, and safety profile .

Moreover, the drugs proposed in the research paper should undergo rigorous pre-clinical and clinical investigations to establish their efficacy and safety profiles in real-world scenarios . These crucial steps are essential to ascertain the drugs' therapeutic potential and position them as strong contenders in the realm of healing drugs . Pre-clinical studies involving in vitro and in vivo experiments can provide valuable data on the drugs' mechanisms of action, pharmacokinetics, and potential adverse effects . Subsequently, clinical trials involving human subjects can further evaluate the drugs' safety, efficacy, and optimal dosing regimens .

By combining the power of in-silico approaches with rigorous pre-clinical and clinical research, the development of novel drugs to combat inflammation-based obesity can be accelerated . This multifaceted approach enables researchers to identify potential drug candidates, investigate their molecular interactions, and gain insights into their therapeutic potential . Ultimately, this comprehensive research endeavor holds the promise of contributing to the development of effective treatments for inflammation-based obesity, addressing a critical gap in the current therapeutic landscape .

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Identification of novel drugs for inhibition of nuclear factor κ-B protein to treat inflammation-based obesity using computational techniques

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***Abstract*— Inflammation brought on by obesity is linked to several clinically significant consequences, such as insulin resistance, Type 2 diabetes, hypertension, and non-alcoholic fatty liver disease. Adipose tissue plays a crucial role in this process, even though the reason and the participating molecules are still not fully understood. Coordinating controllers of immune and inflammatory reactions, nuclear factor kappa B (NF-κB) transcription factors are genetically conserved. They are crucial in progression of cancer and other metabolic diseases.**

The IKK/NF-κB signalling has been shown in numerous studies to play a critical role in the induction and maintenance of the inflammatory state that underpins metabolic disorders like type 2 diabetes and obesity. Recently, a crucial function for immune cells, in producing the inflammation brought on by fat, has been discovered. It may be possible to find treatment targets that can reduce the problems related to obesity by specifying the cellular and molecular enteties of obesity caused by inflammation.

In this paper, we have focused on molecular mechanisms and pathways related to obesity-based diabetes type-2 and worked on a list of multiple drugs which are commonly approved for different diseases like cancer and hypertension, etc. that can be repurposed to cure diabetes type-2 led by inflammation-based obesity. Out of 250 drugs, Telmisartan, an anti-hypertension drug, and Dolutegravir, which is an anti-viral drug resulted as the best binding drug to inhibit NF κ-B and stop the onset of disease.

Keywords—obesity, inflammation, diabetes, molecular docking, drug-repurposing.

I. INTRODUCTION

Being obese is presently the sixth most important risk factor adding to the overall burden of disease globally, making obesity the most significant public health problem for the upcoming years. White adipose tissue (WAT) is prone to low-grade inflammation due to persistent innate immune system activation, which increases the risk of insulin resistance, decreased glucose tolerance, and even diabetes [1]. Leptin, resistin, adiponectin, retinol-binding protein 4 (RBP4), as well as many cytokines and immune-associated substances like tumor necrosis factor-alpha (TNF-α), monocyte chemotactic protein 1interleukin (IL) 1, and IL-6, are among the many substances that the adipose tissue is known to secrete. (MCP-1) [2].

Inflammation is a prevalent trait that is usually involved in the pathophysiology of several obesity-associated diseases, even though it is probable that there are numerous molecular pathways connecting obesity to its consequences [3]. Main inflammatory signaling molecules, both extracellular as well as intracellular, have received a lot of attention recently in attempts to define the impacts of obesity on specific organs and general metabolism. More recent research has revealed immune cells, particularly monocytes, and macrophages, to be key players in the inflammation and problems brought on by fat. Obesity greatly contributes to the inflammation of fatty tissue by increasing the quantity and activity of macrophages in that tissue [4].

Recent studies have connected the development of insulin resistance brought on by fat to molecular networks that regulate inflammation. The multi-protein transcription factor shortly known as NF-kB regulatory targets includes inflammatory proteins like MCP-1, and TNF-α. Numerous inflammatory stimuli, which comprise activation of Toll-like receptors, exposure to UV radiation, reactive oxygen species, and proinflammatory cytokines, resulting in the phosphorylation and breakdown of the NF-kB inhibitory component. After being liberated from its inhibiting components like IKB1 or IKB2 moves into the nucleus, the NF-kB complex turns active and translocate to the nucleus where it starts NF-kB-dependent transcription in a cell-type-specified pattern [5].

The NF-κB also known as nuclear factor kappa B and Jun N-terminal kinase or JNK systems, as well as the I kappa B kinase beta IKK-β, which maintains inflammatory responses through activation of NF-κB, are primarily involved in the pro-inflammatory effects of cytokines through intracellular signaling pathways in obesity. In the tissues that respond to insulin in obese and high-fat-fed animals, signaling cascades involving IKK- and NF-κB are triggered.

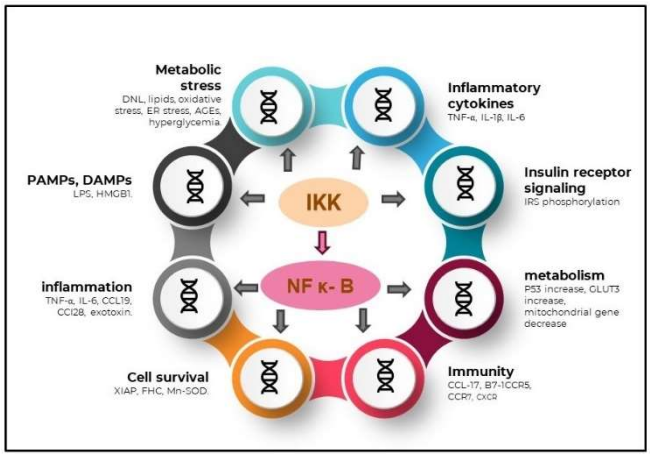

Fig 1. Pathways linking inflammation, obesity, insulin action

II. ROLE OF NF K-B IN OBESITY AND DIABETES TYPE-2

The IKK/NF-κB signaling pathway is necessary for the interaction between the metabolic process, inflammation, and insulin activity. Most metabolic stress signals that result in insulin resistance or pancreas cell dysfunction, whether they are caused by intracellular or extracellular stressors, focus on the NF-κB-activating kinase (IKK), and the other major inflammatory kinase, JNK mitogen-activated protein kinase (MAPK). IKK is a key component of the signaling networks that are triggered by metabolic stress sensors, TLRs, and cytokine receptors. TNF, IL-1, and IL-6 are among the inflammatory genes whose production is regulated by this factor[6].

The IKK kinases have a significant contribution in anomalies of insulin metabolism and overeating via a number of different mechanisms. In the residing tissue macrophages and metabolically active cells, as adipocytes and hepatocytes, IKK-mediated NF-B activation causes macrophage recruitment, activation, and differentiation, as well as the beginning and maintenance of an inflammatory response that leads to insulin resistance in obese persons [7]. The major metabolic effect of insulin on the target sites is mediated by direct serine phosphorylation of insulin receptor substrates (IRSs), which takes place when IKK is triggered by cytokine-evoked inflammation signals or metabolic stress.

The stimulation of IRS during metabolic inflammation, however, appears to depend more on JNK1 than IKK. The pancreatic islet's core metabolism networks are affected by the IKK/NF-B pathway, which also makes peripheral insulin sensitivity worse [8]. As a consequence of metabolic stress and proinflammatory signals, it promotes islet mortality and cell failure in insulin-resistant people, impairing the ability of cells to make compensatory insulin and leading to glucose intolerance and type 2 diabetes in its most extreme form.

It has become an urgent need to retrieve some novel drugs which can be used to treat inflammation caused by NF-κB that leads to multiple diseases. Here we are focusing on Diabetes type-2 disease and extracting drugs by performing virtual screening and molecular docking using a drug re-purposing approach.

III. METHODOLOGY

A. *Retrieval of literature data*

Before performing the experimental and computational work, a literature survey was done to collect information and the recent research done on target proteins and diseases. This was done using PubMed, google scholar, and other online literature databases present. A filter was applied for the work done in the last 5 years and the data was studied from the extracted papers.

B. *Exploration of drugs*

The drugs were taken from official databases like PubChem, drug bank, ChEMBL, etc. these are specific databases that contain detailed information regarding the drugs. PubChem is an online database that comprises information related to chemical molecules and their functionality against biological assays. It is handled by the National Center for Biotechnology Information. Drug bank is handled and maintained by the university of Alberta and is used for the study of drugs and in-silico-based drug discovery. ChEMBL is a chemical database that provides information about the impact of biochemical compounds on the human brain. The blood-brain barrier permeability was checked using the BBB predictor CB ligand which is an online website.

C. *Retrieval of the target protein*

The main targeted protein i.e. nuclear factor κ-B was taken from UniProt which is an online database for their protein structure and their functional behavior. The 3-D structure was saved in PDB format.

D. *Preparation of receptor and ligand*

The target was prepared in open Babel, which is an application of Auto Dock Vina, where the water molecules were removed and the hydrogen atoms along with Kollman charges were introduced to bring the target to its native state. It was then saved in PDB format. The ligands were also converted and saved to PDB format.

E. *Molecular docking*

The receptors and ligands were docked using the Auto Dock Vina, which is a modeling and simulation software used in bioinformatics and in-silico works.

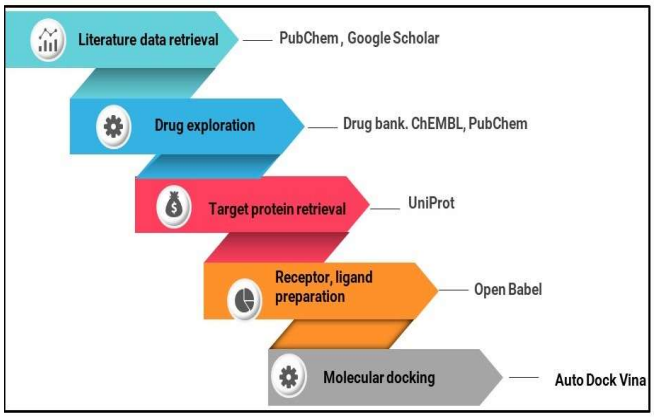

Fig. 2 Diagrammatic representation of methodology

As the molecular docking is completed, all the binding energies are analyzed and the 10 best biding scores are extracted in a list. These 10 drugs provide us with the best results and the drug with the best binding score is described in the upcoming portions of the paper.

IV. RESULTS

After the in-silico work was done, we found two compounds with the best and same binding energies. They are Telmisartan with ChEMBL ID 1017, and Dolutegravir with ChEMBL ID 1229211. Both of these drugs gave -8.6kcal/mol as binding affinity. Other drugs on the list are Dasabuvir, Tecovirimat, Eplerenone, Cabotegravir, Olmesartan Medoxomil, Bictegravir, Atorvastatin, Saxagliptin, Spironolactone. All these drugs cleared the blood-brain barrier permeability and are approved by FDA.

A. *Telmisartan*

Telmisartan is an anti-hypertensive drug, whose drug bank accession number is DB00966. It is sold under the brand name Actelsar Hct, Pritor, Micardis, Micardis-hct, and Twynsta. It is a small molecule whose chemical formula is

C33H30N4O2. It is an angiotensin II receptor blocker that causes the tightening of vessels. Usually, this medication is taken orally once a day, but in some rare medical conditions, it depends on the advice of the doctors. This medicine has several side effects on the patient's health like nausea, fever, dizziness, sinus pain, sore throat, fatigue, diarrhea, back pain, upset stomach, muscle pain, and many more. This drug has been repurposed to treat inflammation-based obesity which is leading to Diabetes type-2.

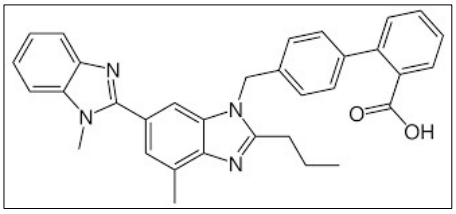

Fig. 3: Chemical structure of Telmisartan

Table 1: List of top ten drugs with their binding affinities

ChEMBL ID	Compound Name	Binding Affinity	RMSD UB/LB
CHEMBL1017	TELMISARTAN	-8.6	0/0
CHEMBL1229211	DOLUTEGRAVIR	-8.6	0/0
CHEMBL3137312	DASABUVIR	-8.4	0/0
CHEMBL1257073	TECOVIRIMAT	-8.4	0/0
CHEMBL1095097	EPLERENONE	-8.3	0/0
CHEMBL2403238	CABOTEGRAVIR	-8.2	0/0
CHEMBL1200692	OLMESARTAN MEDOXOMIL	-8.2	0/0
CHEMBL3989866	BICTEGRAVIR	-8.1	0/0
CHEMBL1487	ATORVASTATIN	-8.1	0/0
CHEMBL385517	SAXAGLIPTIN	-8	0/0
CHEMBL1393	SPIRONOLACTONE	-8	0/0

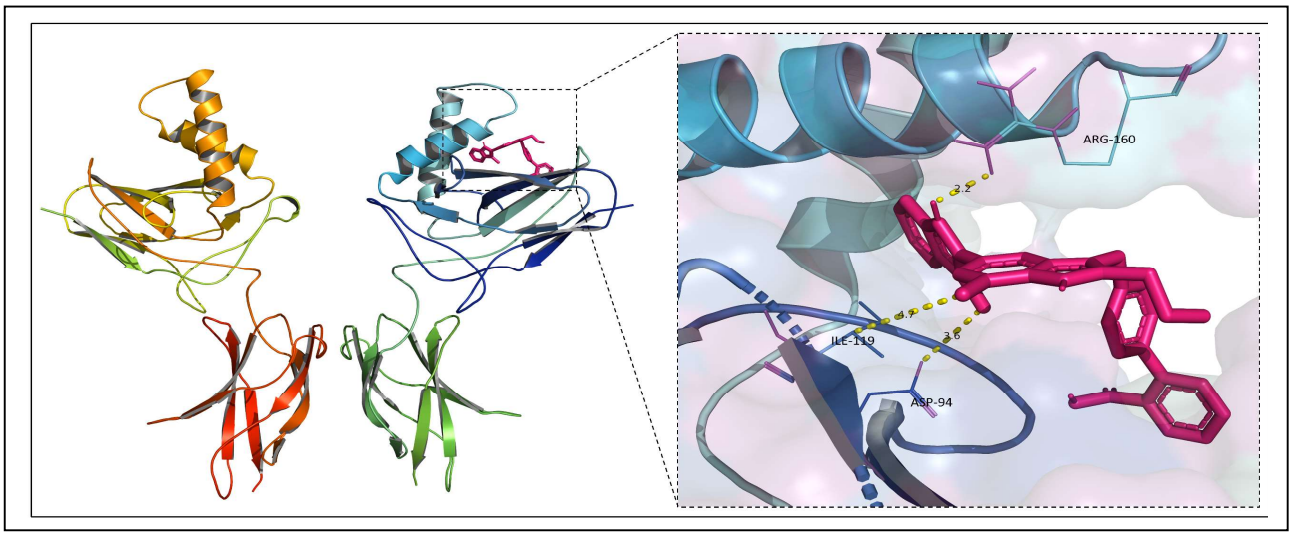

Fig. 4: NF-κB with Telmisartan, active site interacts with ASP-94, ILE-119, and ARG-160.

B. *Dolutegravir*

Dolutegravir is an anti-viral drug used to treat the symptoms of viral fever. Its drug bank accession number is DB08930 and is FDA approved for the usage of public. It is sold under the brand names Dovato, Juluca, Tivicay, and Triumeq and is an HIV- integrase inhibitor.

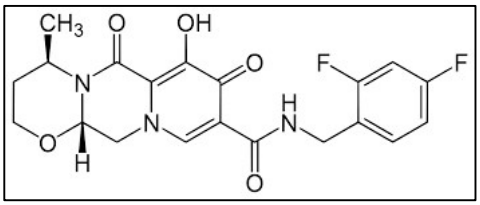

Fig. 5: Chemical structure of Dolutegravir

The chemical formula for Dolutegravir is C20H19F2N3O5 and is monoisotopic. It was developed by ViiV Healthcare and provides the best results with minimal toxicity. Dolutegravir is an oral medication that should be taken once or twice a day daily or with the prescription and recommendation of doctors. It shows several side-effects on health like body pain, muscle cramps, headache, nausea, vomiting, dizziness, etc.

V. DISCUSSION AND CONCLUSION

Various drugs are present in the market which deals with diabetes and obesity issue but drugs for inflammation-based obesity are very rare. It's the need of the healthcare sector to research new drugs either by traditional methods or using the latest technology and performing combination therapy and drug repurposing. These in-silico approaches are highly beneficial as they save the time as well as money that is spent on unknown experimental works which provide negative results in the end. In silico studies should be performed and for the validation simulation and wet lab research should be done. The drugs suggested in the paper should be pre-clinically and clinically researched and tested so that they can be strong contenders in the list of healing drugs.

Acknowledgment

We would like to thank the department of biotechnology of Delhi Technological University for constantly guiding and supporting us in the work.

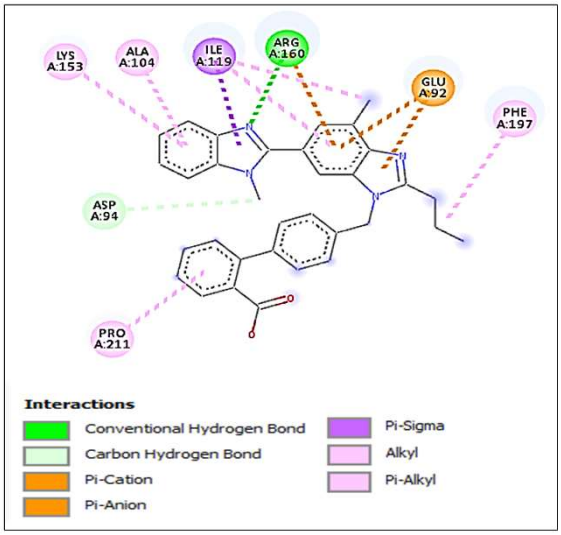

Fig. 6: 2-D Interaction diagram of Telmisartan with the active residues.

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