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Evaluation of Fibrates for Anticancer Activity – An *Insilico* Approach

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Abstract

Cancer is a major cause of death throughout the world, and cancer therapy remains a big medical challenge in terms of both its therapeutic efficacy and safety. Therefore, to find out safe anticancer drugs has been major goal for medical scientists. Fibrates class of drugs plays an important role in decreasing the levels of serum cholesterol and triglycerides while increasing the levels of high-density lipoproteins. Recently, several studies have reveals that fibrates may also have anticancer effects via a variety of pathways involved in apoptosis, cell-cycle arrest, invasion, and migration. *Insilico* approaches have been applied to evaluate the potential interaction between the target and the fibrate derivatives.

Keywords; fibrates, lipid-lowering, anticancer, drug repurposing.

INTRODUCTION

Cancer is considered to be a group of diseases caused by loss of cell cycle control. It is associated with uncontrolled growth of abnormal cells with the ability to invade local tissues and metastasis which are proliferating individually throughout the body. These abnormal cells are also termed as cancer cells, malignant cells, or tumor cells. Treatments of cancer includes surgery, radiation, chemotherapy, hormone therapy, immune therapy and targeted therapy. A large number of chemo preventive agents were used in the treatment of various cancers, but they produce side effects that prevent their extensive usage. Chemotherapy and radiation therapy are major clinical treatment used for the control of early stages of tumor but these methods can put patients under a lot of strain and further damage their health. The therapeutic effects of anticancer drugs are excreted by various mechanisms like, inhibiting cancer activating enzymes, stimulating DNA repair mechanism, promoting production of protective enzymes, inducing antioxidant action and by enhancing activity of the immune cells [1].

Drug repurposing, also termed as drug repositioning, it is an alternative drug development strategy predicated on the reuse of existing drugs for new pharmacological indication. New cancer treatments are being developing, but to bring these drugs to the market is a very slow and expensive process. Repurposing is an affordable and safe treatment approach to reuse available licensed non-cancer drugs as a new anticancer agent [2]. Drug repurposing have the potential to make clinically important contributions to oncology, and could offer important socio-economical benefits for more sustainable healthcare systems in the long term. Drug repurposing is also referring to the identification or finding the new indication from existing drug and the application of newly identified drugs to the treatment of disease other than its original pharmacological action[3]. The principle of poly pharmacology is the basis for the drug discovery. A direct application of poly pharmacology is drug repurposing which is also referred to as drug repurposing, drug reprofiling and therapeutic switching. Generally, drug repurposing refers to the reinvestigation of existing drugs for new therapeutic intervention. In order to expand our knowledge and drug repurposing is a very productive method in drug discovery and development. It is useful for identifying and classifying drugs based on their actions to multiple therapeutic targets or their action to non-therapeutic target. Drug repurposing is an alternative approach in drug discovery and development[4].

Fibrates class of drugs has been widely used in the treatment of hypercholesterolemia and hyperlipidemia. The lipid-lowering effect of fibrates is believed to be mediated through its stimulation of peroxisome proliferator-activated receptor α (PPARα). In addition to its lipid-lowering function, fibrates also have pleiotropic effects[5]. For instance, fibrates were found to not only slow the progression of diabetic retinopathy and other microvascular complications in patients with type 2 diabetes but also protect against retinopathy, nephropathy, and cardiac pathological changes in type 1 diabetes[6]. Most recently, PPARα-specific agonists were reported to have anticancer effects in a large number of human cancer types, such as acute myeloid leukemia, chronic lymphocytic leukemia, and solid tumors, including those of the liver, ovary, breast, skin, and lungs. Furthermore, fibrates also inhibits the proliferation of cell lines derived from breast and oral tumors, melanoma, lung carcinoma, glioblastoma, and fibrosarcoma. Therefore, this review mainly focuses on some recent developments in the anticancer actions of fibrates[7,8].

The mammalian or mechanistic target of rapamycin (mTOR) is a serine/threonine kinase that acts through two structurally and functionally distinct protein complexes, mTOR complex1 (mTORC1) and mTOR complex2 (mTORC2), to identify and integrate multiple intracellular and environmental signals. mTOR signaling is generally involved in regulating cell survival, cell growth, cell metabolism, protein synthesis and autophagy, as well as homeostasis. The pathological relevance of dysregulation of mTOR signal was illustrated in many human diseases, especially in human cancers. As reported, mTOR is over activated in more than 70% of cancers. Over the past few years, it has been extensively demonstrated in animal models and clinical patients of cancer that mTOR dysfunction contributes to tumorigenesis[9]. When the m-TOR inhibition is occurs the cell division is arrested as

which will leads to prevention of rapid cell growth inside the body [10].

Therefore, we hypothesized that the mechanism by which fibrates suppresses oral tumor development might mediate metabolic changes through regulation of the down-regulation of mTOR activity through activation of AMPK signaling. In this study, we aimed to explore the anti-tumorigenic effect of fibrates by docking with mTOR receptor.

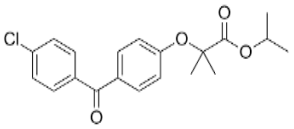
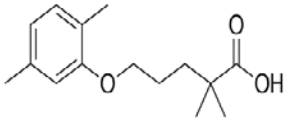
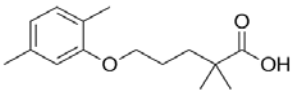
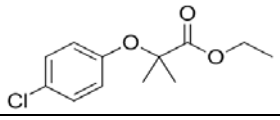
MATERIALS AND METHODS

Docking studies of fibrate derivatives were performed using Auto dock vina pyrx virtual screening tool, against the selected cancer macromolecules, where alteration of expression of each macromolecule corresponds to a different anticancer mechanism.

Data source – Ligand

The 3D structure of ligand or drug like compound was retrieve from Pubchem. It contains the chemical structure of small organic molecules and information on their biological activities. The chemical structure and molecular formula are given in the table 1.

Table 1: Selected drug candidates for in-silico drug design

Name of the drug	Chemical structure	Molecular formula
Fenofibrate		C20H21ClO4
Benzafibrate		C15H22O3
Gemfibrozil		C15H22O3
Clofibrate		C12H15ClO3

Data source – Protein

Proteins are the large biomolecules or macromolecule consists of one or more long chain residues of amino acids. The 3D structure of the protein can be retrieved from the database named Protein Data Bank (PDB). The crystal structure of the investigational scaffold protein Human epidermal growth factor receptor mTOR has been downloaded from RCSB protein data bank bearing the PDB code 2GAQ (Figure). All the small and the non-essential water molecules were removed. Finally hydrogen atoms were merged to the target receptor molecule using pyMOL.

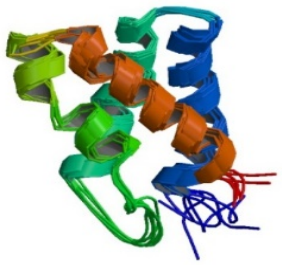


Figure I: 3D structure of protein

Format conversion of ligand

Openbabel- 2.3.2/obgui.exe was used to convert SDF 3D structure of ligand in to PDB format. Protein preparation and molecular visualization PyMOL is open source software, which used for the target preparation as well as for the visualization of small molecules. PyMOL can produce high quality 3D image of small molecules and biological macromolecules such as proteins.

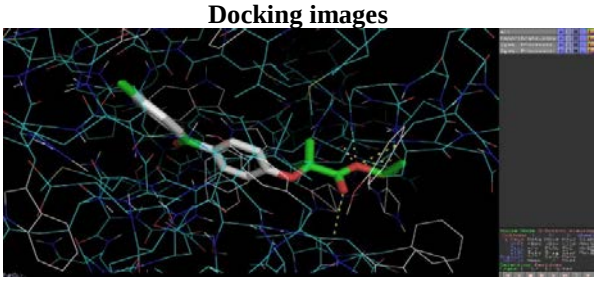
Molecular docking

Virtual screening is a computational technique used in drug discovery to search libraries of small molecules in order to identify those structures which are most likely to bind to drug target, typically a protein receptor or enzyme. Autodock vina Pyrx virtual screening tool was used to perform the molecular docking [10].

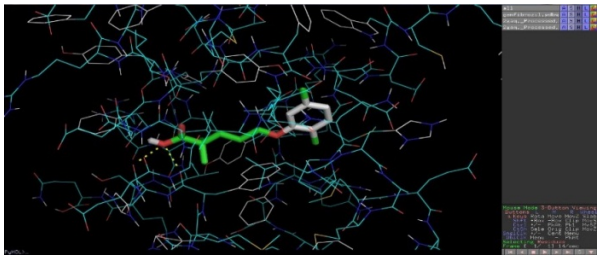
RESULTS AND DISCUSSION

Three different derivatives of the fibrates was used for the docking studies, they are fenofibrate, benzafibrate, gemfibrozil and clofibrate respectively. Fenofibrate have five hydrogen bond interaction, bezafibrate have 6 and gemfibrozil have 2 hydrogen bond interaction, bezafibrate found to be have more number of hydrogen bond interaction. Molecular docking details are summarized in table Docking images were shown in figure I, II, and III.

Docking images



FigureII. Docked image of Fenofibrate



FigureIII. Docked image of Gemfibrozil

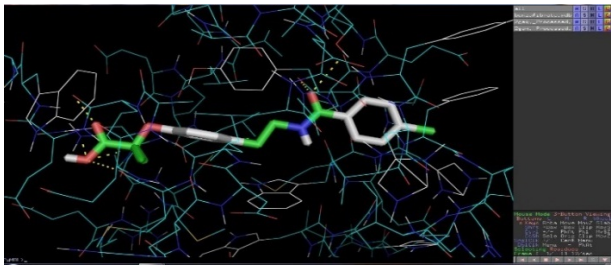


Figure. IVDocked image of Benzafibrate

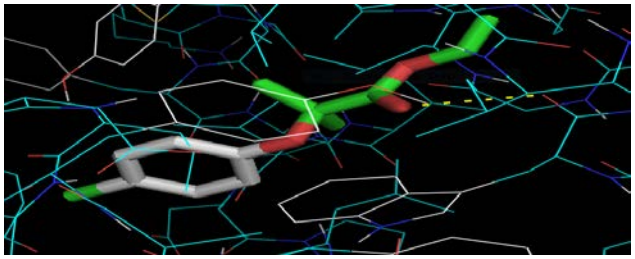


Figure. V Docked image of Clofibrate

Table 2: Molecular docker Scores and Number of Hydrogen Bond Interaction

Drug	No. of Hydrogen bond interaction	Docking Score
Fenofibrate	5	-6.5
Benzafibrate	6	-6.9
Gemfibrozil	2	-5.8
Clofibrate	1	-5

CONCLUSION

From the docking result the benzafibrate have more hydrogen bond interaction with the target molecule, than the other two fibtrate derivatives, and also the same bezafibrate have more binding affinity than the other fibrate derivatives and also found that the fibrates produces its anticancer activity by binding with the mTOR receptor and downregulate the particular receptor. In the fibrate derivatives the benzafibrate is found to be having more anticancer activity.

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