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3-Epi-Betulinic Acid Acetate as A Drug Candidate for Tuberculosis

Neetu Patra and Jyoti Prakash Rath*
School of Applied Sciences, Centurion University of Technology and Management, Odisha, India

ABSTRACT

Tuberculosis continues to worry mankind. Because of the sharp increase in multi and total drug resistant cases the scientific community is looking for new drugs for *Tuberculosis*. The presence of *Rhamnosyl* residue in the cell wall of *Mycobacterium tuberculosis* pathogen and absence in human host projects the enzymes for its biosynthesis as possible drug targets. The presented work focuses on finding out possible plant based inhibitors for *Rhamnose* biosynthetic enzyme RmlC. 126 plant based anticancer compounds were obtained from NPACT database. The compounds were then evaluated for their binding affinity to RmlC through molecular docking procedure. 3-epi-betulinic acid acetate was found to be the best candidate inhibitor for RmlC and thus can work as a putative drug for Tuberculosis.

KEY WORDS: DOCKING, DRUG, NPACT, PLANT, TUBERCULOSIS.

INTRODUCTION

Tuberculosis continues to pose a threat to mankind (WHO's Global Tuberculosis Report, 2019). The disease is caused by *Mycobacterium tuberculosis* (Mtb) (WHO's Global Tuberculosis Report, 2019, Barberis et al., 2017). Last thirty years has seen a steady increase in Tuberculosis cases largely because of a concomitant increase in HIV-AIDS (WHO's Global Tuberculosis Report, 2019, Barberis et al., 2017). India carries the largest burden of Tuberculosis cases (WHO's Global Tuberculosis Report, 2019). Moreover, multidrug and total drug resistant cases magnify the problem manifold (WHO's Global Tuberculosis Report, 2019, Barberis et al., 2017). Therefore, there is a growing appeal to find out new drugs for this disease. The cell wall of Mtb is one of the validated drug targets (Babaoglu et al., 2003). α-L-rhamnosyl-(1→3)-α-D-N-acetyl-glucosaminosyl-1-phosphate, a disaccharide linker is present in Mtb cell wall (Babaoglu et al., 2003, Dong et al., 2007). The outer mycolyl arabinogalactan layer is connected to the peptidoglycan layer by this linker (Babaoglu et al., 2003, Dong et al., 2007, Ma Y et al., 2002). Therefore, this linker is crucial for structural integrity of the cell wall (Ma Y et al., 2002). As the rhamnosyl residue present in the linker is unique to *Mycobacterium tuberculosis* and absent in human host therefore the enzymes responsible for its biosynthesis can work as possible drug targets (Ma Y et al., 2002). The biosynthesis of the L-rhamnosyl residue is being carried out by four enzymes i.e. RmlA (glucose-1-phosphate thymidyl transferase), RmlB (dTDP-D-glucose 4, 6-dehydratase), RmlC (dTDP-6-deoxy-D-xylo-4-hexulose 3, 5-epimerase) and RmlD.

(dTDP-6-deoxy-D-xylo-4-hexulose reductase) those work in sequential manner (Nikaido H et al., 1965). However, as structure is available for RmlC and it is much specific to its substrate, therefore it gives an edge to RmlC as the drug target over other enzymes (Ma Y et al., 2002). As finding a new drug is a time consuming and a cumbersome process. Therefore, we thought of adopting

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*Corresponding Author: jyotiprakash.rath@cutm.ac.in
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a drug repositioning approach i.e. evaluating existing drugs for new therapeutic values. This study focuses on evaluating some known plant derived anticancer agents present in the NPACT database for their efficacy in inhibiting RmlC (Mangal et al., 2013).

MATERIAL AND METHODS

Molecular docking software used: ArgusLab 4.0.1. (Thompson et al., 2004) was used for molecular docking of compounds against RmlC. The target protein RmlC (PDB ID: 2IXC) with bound substrate analogue was retrieved from the Protein Data Bank (www.rcsb.org/pdb). Amino acid residues within 5 A0 radius of the bound substrate analogue were considered as the active site. Water molecules and the substrate analogue were then removed. As the protein is a functional dimer therefore two polypeptide chains were retained removing the other two.

Figure 1: NPACT00219 (3-epi-Betulinic acid acetate) with highest binding energy docked to the active site of RmlC.

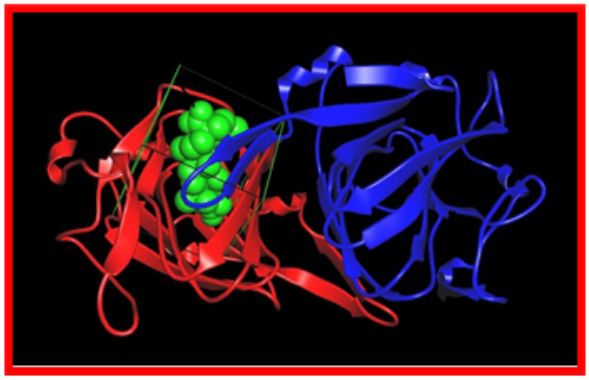

Table 1. Top ten NPACT molecules with high binding energy.

Sl. No.	NPACT ID	Name of the molecule	Binding energy (Kcal/mol)
1	NPACT00219	3-epi-betulinic acid acetate	-15.78
2	NPACT00585	Friedelan-1,3-dione	-14.32
3	NPACT00057	1-O-formyl-4'-demethoxy-3',4'-methylenedioxy-methyl rocaglate	-13.12
4	NPACT00959	Squamostatin-D	-12.94
5	NPACT00332	Betulin	-12.42
6	NPACT00051	18-beta-Glycyrrhetic acid	-12.35
7	NPACT00390	Caracasine	-12.19
8	NPACT00201	candenatenin B	-12.06
9	NPACT01390	7-hydroxycadallin	-12.04
10	NPACT00556	Erlangerins B	-11.88

The anti cancer compounds listed for cervix cancer in Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target database (NPACT, http://crdd.osdd.net/raghava/npact/) were considered for docking (Mangal et al., 2013). All 116 molecules listed as anti cervix cancer NPACT database were retrieved. These compounds were then docked to the active site of RmlC one by one and the resultant binding energy was recorded. Top ten molecules with high binding energy were then recorded (Table 1).

RESULTS AND DISCUSSION

The top ten ligands appear to bind to RmlC properly (Table 1). However, as 3-epi-betulinic acid acetate, NPACT00219 having highest interaction energy (-15.78 Kcal/mol) binds to the active site efficiently thus it is supposed to be a lead drug for Tuberculosis (Figure 1).

CONCLUSION

Since 3-epi-betulinic acid acetate (NPACT00219) is found to have highest interaction energy and it is interacting with the active site efficiently therefore it is supposed to be a lead drug for Tuberculosis. However, in vivo experimental study will garner more support for the work.

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