Research Article

Design of Novel Drug Lead Molecules for *Tuberculosis bacilli* Derived from *Chromolaena odorata* Flavonoid

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ABSTRACT

kasA gene plays an important role in the growth of *Mycobacterium Tuberculosis*. Genomics and proteomics attributes of the *KasA* have distinct significance in the development of drug leads. *Chromolaena Odorata* contains certain flavonoids which exhibit moderate anti-tuberculosis activity. This study optimized the action of flavonoids and their modified forms on *kasA* protein by *Insilico* methods. Human Bimolecular Interaction (HBMI) scores and Docking Scores (DS) suggested that four molecules suitable for the specific target. Further analysis of these molecules may give lead candidates for new anti-tb drugs.

Keywords: TB, kasA, Docking Score, Human Bimolecular Interaction.

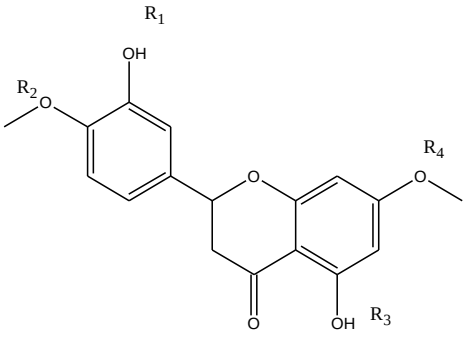
INTRODUCTION

TB (Tuberculosis) is a dreadful and common type disease that usually affects the lungs, while it may affect any part of the body. Treatment of TB should be at least six months and in certain specific circumstances even longer. If treatment is not continuous for a long sufficient period, the living bacteria may cause the patient infectious again, seriously. Effective treatment of tuberculosis has profits both for the single patient and the community in which the patient lives. Analysis of TB routes shows a number of interconnected markers responsible for the disease. Isolation of a potential target for inhibitor is a difficult task. Anti mycobacterial properties of phytochemical constituents were reported in several studies. Interaction between phytochemicals with human proteins may result in activation or inhibition of the protein and causes side effects. Computational tools have been accredited and appreciated as the designing phase of advances in drug development[1]. Docking is commonly used to estimate the binding affinity and activity of molecules towards protein. High value HBMI scores indicate that drugs or drug leads cause side effects in our body. So molecules with low HBMI and high DS may lead to good drug candidate against mycobacteria. This study has been focused to analyze the anti-mycobacterial properties of a flavonoid and some designed molecules from it through the genomics, proteomics and ADMET Analysis.

MATERIALS AND METHODS

kasA (3-oxoacyl-[acyl-carrier protein] synthase) is a known gene involved in fatty acid biosynthesis of tuberculosis[2]. The enzyme *kasA* is vital for the synthesis of mycolic acids[3]. In 1998 Mdluli K, Slayden RA, Zhu Y et al. revealed that sequence alterations at codons 66 (GAT→AAT), 269 (GGT→AGT), 312 (GGC→AGC) and 413 (TTC→TTA) of the kasA gene have been proposed to be mutations associated with *Isoniazid* a standard TB first line drug. This study observed that *kasA* polymorphisms 14.3% INH-resistant isolates (codons 66, 269, 312, and 413). kasA polymorphisms (codons 121, 269, 312 and 387) were identified in 10% of INH resistant isolates, but G312S and G269S was moreover exposed to be a frequent polymorphism among susceptible strains. Lee et al. a study from Singapore studied the existence of *kasA* mutations in 160 isoniazid-resistant and 32 drug-susceptible clinical isolates of *Mycobacterium tuberculosis*[4]. On the basis of above facts this study has been selected *kasA* protein as target proteins.

The proteins of *kasA* genes have been acquired from RSCB Protein Data Bank[5]. Protparam tool was used for the sequence analysis of proteins[6]. Secondary structures of proteins have been analyzed by using SOPMA[7]. Persicogenin, 5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-methoxy-2, 3-dihydrochromen-4-one is a bioflavonoid from *Chromolaena Odorata* reported as moderate anti-tuberculosis activity[8]. Ligand molecules were designed by changing and rearranging the functional groups of Persicogenin and a combinatorial library was formed.



HBMI score of Persicogenin and ligand molecules were predicted by using PASS Online library[9]. The target protein was further subjected to docking with designed molecules and also with persicogenin by using the CDOCKER tool of Accelerys Discovery Studio 2.1 with CHARMm force field[10]. Ligand molecules screened based upon their DS and HBMI. Pharmacokinetic properties of the screened molecules were also examined by computational methods. BLAST analysis was carried out for comparing primary biological sequence information of gene protein and human proteins[11].

RESULTS AND DISCUSSION

Proteins 2WGE, 2WGF, 4C6W, 4C70, 4C71 of *kasA* were retrieved from RSCB Protein Data Bank. All the target proteins have instability index less than 40, sustaining high structural stability. High thermodynamic stability of these protein molecules were understood all over the aliphatic indices which varies from 83 to 87. GRAVY values of 4C6W, 4C70, 4C71 were observed that negative, supports hydrophilic nature of protein molecules. All the proteins have high half life period. All target proteins have high structural stability by observing the values of β-turn and α-helix. The protein characterizations are enlisted in Table1. 4C6W protein was taken as the target protein. Human bimolecular interaction score and docking scores are enlisted in Table2. HBMI and DS of Persicogenin were found to 61.984 and 28.284. Biological activity of Persicogenin is very high in human proteins and its docking interaction with *kasA* protein is medium. Molecules with low HBMI and high DS were found to be [P_1], [P_7], [P_11], [P_19], [P_20], and [P_21]. The results of [P_11] and [P_21] shows that they have less interaction with human proteins together they are very effective against Mycobacterium.

Table 1: Protein Characterization

PDB Code	Half Life	Instability Index	Aliphatic Index	GRAVY	α- Helix (%)	β- Turn (%)
2WGE	30 hrs	35.34	86.15	0.030	33.41	10.34
2WGF	30 hrs	35.34	86.15	0.016	33.41	10.34
4C6W	30 hrs	35.25	83.42	-0.033	32.35	10.71
4C7O	30 hrs	35.25	83.42	-0.033	32.35	10.71
4C7I	30 hrs	35.25	83.42	-0.033	32.12	10.93

Table 2: Comparison of HBMI and Docking Scores (DS)

Name	Functional Groups	HBMI	DS
[Pergin]	R1-OH,R2-OCH3,R3-OH, R4-OCH3	61.984	28.284
[P_1]	R1-NH2,R2-OCH3,R3-NH2, R4-OCH3	6.865	25.002
[P_2]	R1-OH,R2-NH2,R3-OH, R4-NH2	14.291	30.734
[P_3]	R1-OH,R2-OH,R3-OH R4-OCH3	60.926	32.135
[P_4]	R1-OH,R2-OCH3,R3-OH, R4-OH	62.024	29.288
[P_5]	R1-OCH3,R2-OCH3,R3-OCH3, R4-OCH3	33.694	19.886
[P_6]	R1-OH,R2-OH,R3-OH, R4-OH	68.596	30.702
[P_7]	R1-NH2,R2-NH2,R3-NH2, R4-NH2	6.3	25.271
[P_8]	R1-CH2OH,R2-OCH3,R3-OH, R4-OCH3	32.425	30.461
[P_9]	R1-OH,R2-OCH3,R3-CH2OH, R4-OCH3	24.268	33.253
[P_10]	R1-OH,R2-CH2OH,R3-OH, R4-CH2OH	23.487	36.263
[P_11]	R1-CH2OH,R2-CH2OH,R3-CH2OH,R4-CH2OH	2.206	36.263
[P_12]	R1-Cl,R2-OCH3,R3-OH, R4-OCH3	31.58	21.015
[P_13]	R1-OH,R2-OCH3,R3-Cl, R4-OCH3	22.326	24.742
[P_14]	R1-OH,R2-Cl,R3-OH, R4-OCH3	33.29	27.576
[P_15]	R1-OH,R2-OCH3,R3-OH, R4-Cl	27.968	29.888
[P_16]	R1-Cl,R2-Cl,R3-OH, R4-OCH3	31.634	23.119
[P_17]	R1-OH,R2-OCH3,R3-Cl, R4-Cl	13.621	24.359
[P_18]	R1-Cl,R2-Cl,R3-Cl, R4-Cl	8.276	19.736
[P_19]	R1-Cl,R2-Cl,R3-Cl, R4-Cl	8.006	34.966
[P_20]	R1-CH2Cl,R2-OCH3,R3-CH2Cl, R4-OCH3	5.024	25.936
[P_21]	R1-OH,R2-CH2Cl,R3-OH, R4-CH2Cl	7.897	37.749
[P_22]	R1-OH,R2-COOH,R3-OH, R4-OCH3	47.468	33.256
[P_23]	R1-OH,R2-OCH3,R3-OH, R4-COOH	42.943	34.637
[P_24]	R1-OH,R2-COOH,R3-OH, R4-COOH	42.442	39.708

Table 3: ADMETox Studies

Name	Absorption	Solubility	BBB	Hepatotoxicity
[P_1]	0(Good)	-3.62(Good)	3(Low)	0.973(Toxic)
[P_7]	1(Moderate)	-1.605(Optimal)	4(Undefined)	0.980(Toxic)
[P_11]	0(Good)	-1.265(Optimal)	3(Low)	0.973(Toxic)
[P_19]	1(Moderate)	-3.014(Good)	4(Undefined)	0.933(Toxic)
[P_20]	0(Good)	-5.35(Low)	1(High)	0.953(Toxic)
[P_21]	0(Good)	-4.585(Low)	2(Medium)	0.933(Toxic)

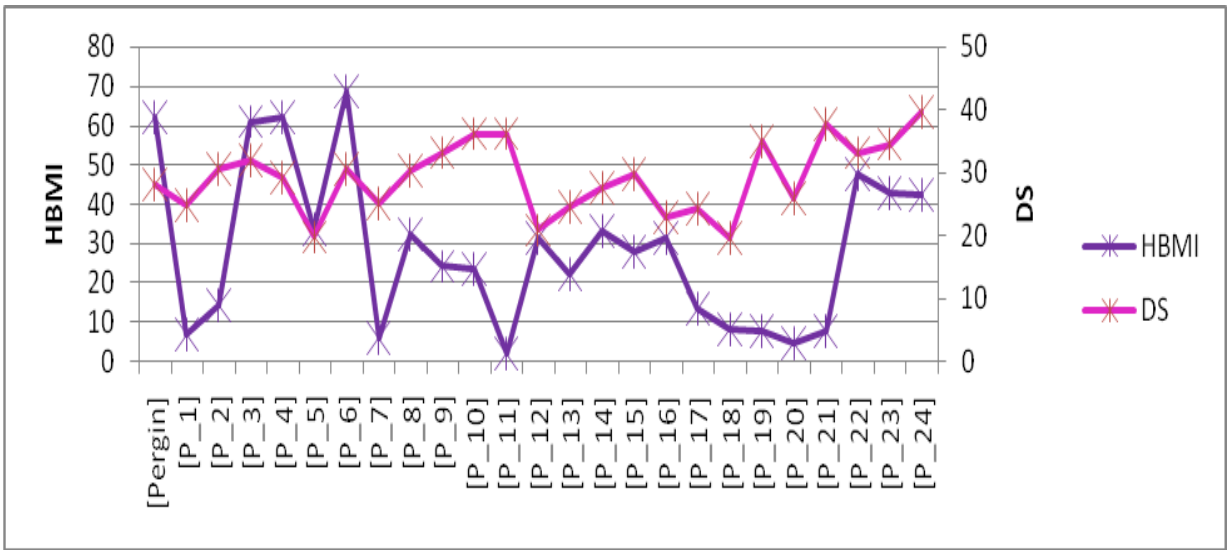


Figure 2: Comparison of HBMI and DS

ADMETox studies showed that [P_7], [P_19] have poor Pharmacokinetic properties. [P_1] has good absorption and solubility. It has low BBB character. Absorption and Solubility of [P_11] and [P_20] are good enough. But the BBB of [P_20] was observed as high. BLAST analysis suggested that none of the SNP's were similar to *kasA* sequence.

CONCLUSION

Tuberculosis is one of the oldest and dreadful diseases affecting mankind. With the global stretch of drug resistance, the need for development of new drugs is of prime importance. Computational tools helps in identifying better drug leads that are effective and also may help in cutting down the high costs. The designed molecules, [P_11] and [P_21] have the most activity against *Mycobacterium tuberculosis* and also drug lead character. These molecules can be used as very likely lead candidates for developing effective anti-tuberculosis drugs.

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