ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

An *in silico* determination of Drug-Like Molecules from Plant Source to Treat Leprosy- A Neglected Tropical Infectious Disease of India

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ABSTRACT:
In developing countries, awareness towards controlling the infectious diseases with high mortality and morbidity among poor people is neglected. Leprosy otherwise known as Hansen's disease, remains chronic from ancient times which is one among the neglected tropical disease. Though WHO in 1991 set a target to eliminate leprosy by 2000, there are reports recently in 2011 that 41% of cases registered in India. Causative of leprosy is *Mycobacterium leprae* which affects peripheral nerves, skin and multiple internal organs. Treatment involves the usage of dapsone, a bacteriostatic against *M. leprae* for many years until the widespread resistant strains occur. Due to which combination therapy emerged where WHO 1998 prescribed rifampicin with dapsone to treat paucibacillary leprosy and rifampicin and/or clofazimine with dapson for multibacillary leprosy. The difficulties in handling the transmission of leprosy bacilli through inhalation or by direct contact, complete eradication of the disease has not been achieved instead severity being increased. In this perspective, the effective, safe and affordable pharmaceuticals has to be discovered from the plant sources, since they act as reservoir from the ancient period and found as one of traditional medicinal system followed. The plants *Andrographis paniculata* and *Ricinus communis* having traditional background are selected for the present study in order to predict and identify the bioactive principle through *in silico* docking analysis. Through the binding score and hydrogen bond formation, the plant compounds for treating leprosy have to be taken further for drug development process.

KEYWORDS: Neglected Tropical Disease (NTDs), Leprosy, *Mycobacterium leprae*, Dapsone, Medicinal plants, *in silico* docking.

INTRODUCTION:
Leprosy otherwise known as Hansen's disease is categorized as neglected tropical disease (NTDs), which mostly prevail among the poor population of Africa, Asia and America[1]. Hotez *et al*. has reported that one billion people were affected with parasitic, viral and bacterial infections, along with the estimation of death rate as 534 000 and 57 million of disability-adjusted life-years (DALYs)[2].

According to World Health Organization (WHO) the measures of preventing and controlling of NTDs was preventive chemotherapy, intensified case management, control of disease vectors, provision of clean water, sanitation and veterinary public health measures[3]. Albendazole, azithromycin, ivermectin and praziquantel are the largely utilized orally administered drug which has potency to target 90% of NTDs, however, all has its specific side effects[4]. Traditional medicines being the dynamic reservoir has been concentrated worldwide and research are carried out in identifying the potential chemical constituent from it. The present study has focused on medicinal plants like *Andrographis paniculata* and *Ricinus communis* which were called as Siriyaanangai and Amanakkuin Tamil.

The chaperonin 10 is a heat shock protein which plays an important role in ensuring the proper folding of many

Received on 08.03.2017 Modified on 21.05.2017
Accepted on 20.07.2017
Research J. Pharm. and Tech 2017; 10(10):3361-3364.
DOI: 10.5958/0974-360X.2017.00597.2

proteins in bacteria, mitochondria and chloroplasts[5]. Generally, chaperonins consist of two interacting partner proteins, chaperonin60 and chaperonin10, where these proteins are well characterized and studied in the organism *Escherichia coli* as GroEL and GroES, respectively. In the presence of Adenosine Triphosphate (ATP), two molecules of GroES forms a symmetric structure by bounding at both the ends of GroEL cylinder[6,7,8]. The complex formation is expected due to the involvement of presence of mobile loop in each of seven GroES subunits[9,10]. In *Thermoanaerobacterbrockii*, chaperonin10 mediated inhibition of ATP hydrolysis was observed, which is the most required step for the occurrence of protein folding[5]. It is well understood that protein misfolds would lead to the impairment of its biological function[11]. Therefore, the present study has been targeted to inhibit chaperonin10 and to observe the interacting potentiality of chemical constituents from the plants *Andrographis paniculata* and *Ricinus communis*. Both the plants were reported to be used traditionally to heal the leprosy among tribals of Kanyakumari District, where the decoction of whole plant of *A. paniculata* and infusion of *R. communis* roots were used[12].

The global leprosy burden in India was accounted as 59%, especially in the year 2013[13], who also mentioned that, nowadays, population worldwide depend on complementary and alternative medicine (CAM) for remedies and healthcare needs. The traditional way of treatment has its credit in several factors like accessibility and affordability, perhaps, the benefits of herbal treatment was observed in fungal infections, skin conditions and eczema[13].However, at present, clinical evaluation is strongly recommended. On the other hand, discovery and identification of plant-based drugs often requires enormous time and expenditure, which might end up in void. Here, bioinformatics plays a crucial role where the rapid development in high-throughput technologies has paved the way for achieving the goad in stipulated time duration. Moreover, it is cost-effective[14]. The docking method was utilized in the present study to analyze the binding efficiency of chemical constituents from *A. paniculata* and *R. communis* in order to inhibit the function of chaperonin10.

MATERIALS AND METHODS:

Protein Preparation:

The 3D structure of the protein chaperonin10 was retrieved from PDB with corresponding ID, 1P3H. The active sites of the protein was selected based on the literature study, which includes Val3, Ile5, Leu8, Ile88, Pro30, Glu35, Ser71, Arg49, Asp53, Glu52, Glu9, Asp10, Lys11, Ser89, Arg91, Asp92, Tyr73, Ile69, Val93, Leu94, Ala95, Val96 and Val97.

Ligand Molecules:

The structure of chemical constituents identified from the plants, *A. paniculata* and *R. communis* were retrieved from the PubChem database. Along with the drug molecule dapsone used at present for treating leprosy condition was also retrieved to compare with each plant compounds.

The docking analysis was carried out in the software Argus lab. The interactions were observed using the PyMol viewer.

RESULTS AND DISCUSSION:

The G.score, number of hydrogen bonds, interacting residues and bond length for each plant compounds was recorded in table 1. In the present study, the interactions of least scoring compounds alone showed (Fig.1). Among 60 different compounds from *Riccinus communis* and *Andrographis paniculata*, the following compounds were observed with least G. score value. In this study, the docking score upto -6 Kcal/mol were recognized as significant and are tabulated. The compounds like Quercetin-3-O-beta-D-dlucopyranoside, rutin, astragalin, 5,7,3',5'- tetrahydroxy-3,6,8,4-tetramethoxyflavone 3'-glucoside, quercetin from *R. communis* and homoesperetin 7-rutinoside, vindesine of *A. paniculata* had significant docking score. Glu35, Ser71 and Tyr73 are the active site residues involve in the hydrogen bond formation, where Ser71 found interacted with astragalin, Tyr73 with Vindesin and Glu35 actively participated in the interaction with most of the compounds. Apart from the active residues, Ala33, Thr32, Gly74 and Gly75were observed to interact with the plant compounds. Similar to Glu35, the residue Ala33 also involved in interacting with the plant compounds except vindesin and astragalin. The study indicated that both vindesin and astragalin compounds had different interaction profile comparatively to other compounds. The hydrogen bond formation with vindesin was observed to be medium strength, alike to the astragalin and quercetin-3-O-beta-d- glucopyranoside. The residue Ala33 shared bond formation between (O-O) atoms with a bond length of 3.3Å, which is said to be the weaker kind of interaction. The electrostatic interactions were identified as significant in the contribution of stabilized three dimensional architecture either in protein interaction itself or between different biological systems[15]. The docking score of quercetin-3-O-beta-D- glucopyranoside, rutin and homoesperetin 7-rutinoside were -8.36, -8.28 and -8.25 Kcal/mol, respectively. The maximum number of interactions was found with rutin and single interaction with 5,7,3',5'-tetrahydroxy-3,6,8,4-tetramethoxyflavone 3'-glucoside which had 3.2Å length of bond formed with Ala33. According to the scoring functions which are calculated based on the physical potential and knowledge[16] was

predicted to be least in the case of quercetin-3-O-beta-D glucopyranoside, however based on the number of interactions, rutin had 8 interactions.

The residue Glu35 and Tyr73 are reported to be present in the internal diameter at the rim of heptamer base[17]. Therefore, in the present study, the compounds astragalin and vandesin are expected to be localized in the base loop of subunitB, which might have its impact on the movement of base loop and further to inhibit the activity exerted by the protein. This could be confirmed with the further studies on molecular dynamics analysis. Roberts et al. also highlighted that hydrophobic triplet Leu27-Val28-Ile29 in the base loop of heptamer 1 forms a part of β-sheet with heptamer 2, however, none of the plant compounds studied had interactions with the triplet. The compounds interacting with Glu35, Ser71 and Tyr73 might have negative influence towards the role of GroES in facilitating the interheptamer base loop interactions[17].

Table 1: Interactions of plant compounds with Chaperonin10

S. No.	Name of the compound	PubChem ID	Docking Score	No. of hydrogen bonds	Interacting residues	Bond length (Å)
1	Quercetin-3-O- beta-D-glucopyranoside	15959354	-8.36	6	GLY75 (O-H) THR32 (O-H) GLU35 (O-H) GLU35 (O-H) ALA33 (O-H) GLU35 (O-H)	2.0 2.3 2.4 2.8 2.8 1.9
2	Rutin	5280805	-8.28	8	ALA33 (O-H) ALA33 (O-O) THR32 (O-H) GLU35 (O-H) GLU35 (O-H) GLU35 (O-H) ALA33 (O-H) GLY74 (H-O)	2.5 3.3 2.4 2.0 1.9 1.6 2.2 2.6
3	Homoesperetin 7-rutinoside	42607988	-8.25	5	GLY74 (H-O) GLY75 (O-H) ALA33 (O-H) GLU35 (O-H) GLU35 (O-H)	2.0 2.0 1.8 1.8 1.7
4	Vindesine	40839	-7.65	4	GLU35 (O-H) GLU35 (O-H) GLU35 (O-H) TYR73 (H-O)	1.7 2.2 2.6 2.5
5	Astragalin	5282102	-7.55	4	GLU35 (O-H) SER71 (H-O) THR32 (O-H) GLY74 (H-O)	1.9 2.1 1.7 2.5
6	5,7,3’,5’- tetrahydroxy-3,6,8,4-tetramethoxyflavone 3’-glucoside	44260070	-7.04	1	ALA33 (H-O)	3.2
7	Quercetin	5280343	-6.32	5	ALA33 (O-H) GLU35 (O-H) GLY75 (O-H) GLY74 (H-O) GLY74 (H-O)	2.2 2.0 2.2 2.7 2.2

The previous studies on immunoglobulin G response against both 10-kDa and 65-kDa heat-shock protein in leprosy patients indicated that higher percentage of Anti-rML10 (i.e. antibody for *M. leprae* 10-kDa protein) was detected[18]. Therefore, it is suggested that investigations towards inhibition of chaperonin10 (GroES or heat-shock protein) might pave a way in the identification of effective drug for treating leprosy. There are reports that aggregation of chapronin10 (cpn10) into a heptameric structure is required for its biological activity[19] and in this study, the effective binding of plant compounds indicate its inhibitory potency for cpn10. Further studies to determine the stability of the ligand-protein complex for both quercetin-3-O-beta-D glucopyranoside and rutin has to be carried out.

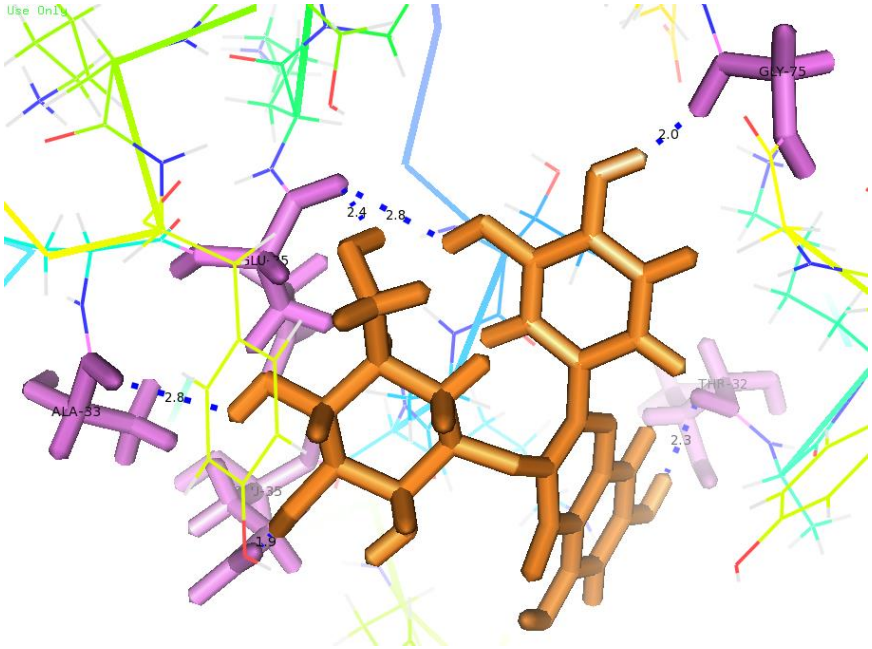

Fig. 1: Interaction of quercetin 3-O- beta-D- glucopyranoside

CONFLICT OF INTEREST:

The authors declare they have no competing interests.

ACKNOWLEDGEMENT:

We acknowledge Vels Institute of Science, Technology and Advanced Studies (VISTAS) for providing us with required infrastructure and support system needed.

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