Identification of Potential Inhibitors for Mycobacterial Uridine Diphosphogalactofuranose-Galactopyranose Mutase Enzyme: A Novel Drug Target through In Silico Approach

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Abstract

Background: The Mycobacterium tuberculosis (MTB) uridine diphosphogalactofuranose (UDP)-galactopyranose mutase (UGM) is an essential flavoenzyme for mycobacterial viability and an important component of cell wall. It catalyzes the interconversion of UDP-galactofuranose into UDP-galactofuranose, a key building block for cell wall construction, essential for linking the peptidoglycan and mycolic acid cell wall layers in MTB through a 2-keto intermediate. Further, as this enzyme is not present in humans, it is an excellent therapeutic target for MTB. Thus, inhibition of this UGM enzyme is a good approach to explore new anti-TB drug. This study aims to find novel and effective inhibitors against UGM from reported natural phytochemicals and ZINC database using virtual screening approach. Methods: In this study, 148 phytochemicals with reported antitubercular activity and 5280 ZINC compounds with 70% structural similarity with the natural substrate of UGM (UDP-galactopyranose and UDP-galactofuranose) were screened against UGM. Results: In virtual screening, 19 phytochemicals and 477 ZINC compounds showed comparatively better binding affinity than natural substrates. Among them, best 10 compounds from each group were proposed as potential inhibitors for UGM based on the binding energy and protein-ligand interaction analysis. Among phytochemicals, three compounds, namely, tiliacorine, amentoflavone, and 2'-nortiliacorinine showed highest binding affinity (binding energy of −10.5, −10.4, and −10.3 Kcal/mol, respectively), while among ZINC compounds, ZINC08219848 and ZINC08217649, showing highest binding affinity (binding energy of −10.0 and −9.7 Kcal/mol, respectively) toward UGM as compared to its substrates. Conclusion: These selected compounds may be proposed as potential inhibitors of UGM and need to be tested in TB culture studies in vitro to assess their anti-TB activity.

Keywords: Glf, mycobacterium tuberculosis, phytochemicals, uridine diphosphogalactofuranose-galactopyranose mutase, virtual screening

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Methods:

In this study, 148 phytochemicals with reported antitubercular activity and 5280 ZINC compounds with 70% structural similarity with the natural substrate of UGM (UDP-galactopyranose and UDP-galactofuranose) were screened against UGM. In virtual screening, 19 phytochemicals and 477 ZINC compounds showed comparatively better binding affinity than natural substrates. Among them, best 10 compounds from each group were proposed as potential inhibitors for UGM based on the binding energy and protein-ligand interaction analysis. Among phytochemicals, three compounds, namely, tiliacorine, amentoflavone, and 2'-nortiliacorinine showed highest binding affinity (binding energy of −10.5, −10.4, and −10.3 Kcal/mol, respectively), while among ZINC compounds, ZINC08219848 and ZINC08217649, showing highest binding affinity (binding energy of −10.0 and −9.7 Kcal/mol, respectively) toward UGM as compared to its substrates.

Conclusion:

These selected compounds may be proposed as potential inhibitors of UGM and need to be tested in TB culture studies in vitro to assess their anti-TB activity.

Introduction:

Mycobacterium tuberculosis (MTB) remains a major health problem worldwide with 10.4 million new patients and 1.4 million deaths in 2015.[1] Further, increasing incidence of multidrug-resistant cases of TB and difficulty in treating these cases requires urgent need to find novel and effective anti-TB drug. Although anti-TB drugs such as isoniazid, rifampicin, ethambutol, and streptomycin were introduced till the 1980s, reporting 98% chances of cure,[2] they have major serious side effects such as psychosis, mental confusion, coma, convulsive seizures, vasculitis, clinical hepatitis, and peripheral neuropathy.[3] Recent increase in cases of HIV and TB coinfection has caused more serious problem with drug-resistant and multidrug-resistant TB.

There are many drug targets reported in MTB, but more effective drugs with minimal side effects against those important targets are the need of the day for effective TB control. MTB uridine diphosphogalactofuranose (UDP)-galactopyranose mutase (UGM), also known as Glf, is a flavoenzyme containing 399 amino acids in its protein sequence and catalyzes the interconversion of UDP-galactopyranose into UDP-galactofuranose containing 399 amino acids in its protein sequence and catalyzes the interconversion of UDP-galactofuranose into UDP-galactofuranose. Sanders et al. reported that UDP-Galf is the precursor of the D-galactofuranose (Galf) residues found in MTB cell wall.

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in the MTB cell. It is also involved in different pathways such as galactose metabolism, amino sugar and nucleotide sugar metabolism, biosynthesis of UDP-galactofuranose and mycolyl-arabinogalactan-peptidoglycan complex, and super pathway of UDP-glucose-derived O-antigen building blocks biosynthesis.\[5,6\] The overexpression of MTB UGM (Glf) enzyme is also reported to contribute to isoniazid resistance. The computational study by Nayak et al. reported that overexpression of Glf may lead to NADH binding, and as a result, it may not be available to Ndh for forming NAD+, required for INH-NAD adduct formation and thus leading to INH resistance.\[7\] Further, Glf is very essential for mycobacterial viability\[8\] and is reported to be a suitable drug target because there is no comparable enzyme present in humans\[9\] and also UGM residues are antigenic in humans.\[10,11\] Thus, it is proposed that UGM inhibitors can block mycobacterial cell growth,\[9\] and its inhibition is a good approach in designing novel anti-TB drugs.\[12\] In the present study, virtual screening approach is explored to find suitable inhibitors from phytochemicals and ZINC compounds for UGM to inhibit growth of the pathogenic mycobacteria.

**METHODS**

**Hardware and software**

Dell workstation with Windows operating system, having hard disc of 500 GB and 6 GB RAM, was used for this *in silico* study. Further, computational analysis was performed using bioinformatics tools such as Modeller9v14, AutoDock Tools 1.5.4,\[13\] AutoDock Vina 1.1.2,\[14\] PyMol molecular visualization packages, and online resources.

*Mycobacterium tuberculosis uridine diphosphogalactofuranose-galactopyranose mutase enzyme*

The amino acid sequence of MTB UGM enzyme (NCBI Accession No.-NP_218326.1) was retrieved from NCBI (http://www.ncbi.nlm.nih.gov) in FASTA format for further analyses.

**Homology modeling of Glf**

Homology modeling technique was used to predict the three-dimensional (3D) structure of Glf using Modeller\[15\] software. As the experimentally determined structures of Glf (PDB ID: 4RPQ)\[16\] enzyme have some missing residues, its 3D structure was predicted using its amino acid sequence and 4RPQ as template. The 3D structure was subjected for structure validation using ProSA-web,\[17\] Protein Quality Predictor (ProQ),\[18\] and RCSB validation server.\[19\]

**Ligand preparation**

*Phytochemicals*

One hundred forty-eight phytochemicals with reported antitubercular activity were identified from online resources\[20\] and literature.\[21-26\] The chemical structure files were retrieved from NCBI PubChem database\[27\] in SDF format.

**ZINC compounds**

Five thousand two hundred and eighty compounds were retrieved from ZINC database\[28,29\] in SDF format having 70% structural similarity with the natural substrate (UDP-galactopyranose and UDP-galactofuranose) of UGM. All these structures (phytochemicals and ZINC compounds) were then converted to PDBQT format using Open Bable 2.3.2.\[30\]

**Receptor preparation**

AutoDock Tools 1.5.4 program (ADT, Molecular Graphics Lab at The Scripps Research Institute, North Torrey Pines Road, La Jolla, California) was used to prepare receptor molecule (Glf) by adding all hydrogen atoms into the carbon atoms of the receptor. Kollman charges were also assigned, and the entire receptor molecules were converted to protein data bank extension file format (PDBQT).

**Virtual screening**

All the ligand datasets were subjected to virtual screening along with the natural substrates of UGM, i.e., UDP-galactopyranose and UDP-galactofuranose, using AutoDock Vina 1.1.2\[31\] virtual screening program. All the ligands were docked against the target protein on the binding site of substrate. A grid of 60, 60, and 60 points in x, y, and z directions was centered on the reported substrate binding site residues of enzyme (PHE157, THR162, TRP166, TYR191, ASN282, ARG292, TYR328, and TYR366). The grid box dimensions of previous parameter optimized dockings were implemented. Docking energies calculated during the run were extracted using in-house developed Perl script. Ligands showing binding energy less than that of UDP-galactopyranose and UDP-galactofuranose were selected for further studies.

**Visualization and interaction analysis**

PyMol molecular graphics system (www.pymol.org) and LigPlot\[32\] tool were used to visualize the protein-ligand interactions.

**RESULTS AND DISCUSSION**

The cell envelope of MTB is made up of three major components: mycolic acid, arabinogalactan and peptidoglycan complex, and a polysaccharide-rich capsule-like material.\[33\] MTB UDP-galactofuranose (UDP-Galf) is a vital component for the synthesis of arabinogalactan that covalently connects with the mycolic acids and peptidoglycan complex.\[4,12\] It is also involved in biosynthesis of UDP-galactofuranose, mycolyl-arabinogalactan-peptidoglycan complex, and UDP-glucose-derived O-antigen building blocks.\[5,6,34\] Further, UDP-galactopyranose also known as UDP-alpha-D-galactose, a common component of bacterial O-antigens,\[35\] reported to be involved in galactose metabolism, amino sugar, and nucleotide sugar metabolism pathway and also used for synthesis of essential structures such as lipopolysaccharides core, a major component of the outer membrane of Gram-negative bacteria, protecting the membrane from certain kinds of chemical attacks and also induces a strong response from animal immune systems.\[36\]
As UGM catalyzes the interconversion of UDP-galactopyranose to UDP-galactofuranose, an essential intermediate of the mycobacterial cell wall biosynthesis,\[^{10,35}\] it is a suitable drug target of MTB. In this study, we explored novel phytochemicals with reported anti-TB activity against UGM, so as to propose potential drug candidates for TB.

**Homology modeling and structure validation**

The stereochemistry of Glf model\[^{7}\] (Figure 1a) (Procheck analysis) revealed that 94.8% of residues were situated in the most favorable region and 4.6% were in additional allowed region, whereas 0.6% of the residue fell in the generously allowed region of the Ramachandran plot [Figure 1b]. ProSA-web evaluation of Glf model revealed a compatible Z score value of −10.1 [Figure 1c] and LG score of 5.013 as predicted by the ProQ.

**Virtual screening and interaction analysis**

In virtual screening, it was observed that the UDP-galactopyranose, the natural substrate of UGM, binds with UGM with binding energy of −8.5 Kcal/mol. Subsequently, 41 phytochemicals out of 148 and 477 ZINC compounds out of 5280 showed comparatively better binding affinity than natural substrate. Further, these selected phytochemicals were subjected for hydrogen bond interaction analysis using in-house developed Perl script and PyMol software. The 10 top ranked phytochemicals [Table 1 and Figure 2] and ZINC compounds [Table 2 and Figure 3] showing less binding energy as compared to substrate and having hydrogen bond interaction with substrate binding site of UGM were proposed as potential inhibitors for UGM.

*Tiliaeora triandra*, the native edible plant of Southeast Asia, has been used as antipyretic, detoxication, anti-inflammatory, anticancer, antimycobacterial, and immune modulator agent.\[^{36}\] Sureram et al. also observed the inhibitory effect of tiliacorinine, 2'-nortiliacorinine, and tiliacorine, isolated from the edible plant, *T. triandra*, against 59 clinical isolates of multidrug-resistant MTB.\[^{37}\] In our *in silico* study, we also observed the high binding affinity of tiliacorine toward UGM that binds in the enzyme substrate binding core [Figure 3a] with high binding energy of −10.5 Kcal/mol as compared to both the natural substrates (UDP-galactopyranose and UDP-galactofuranose).

![Figure 1: (a) 3D model, (b) Ramachandran plot, (c) Z plot of uridine diphosphogalactofuranose-galactopyranose mutase](image)

| PubChem ID   | Compound name              | Binding energy (Kcal/mol) | No. of H-bonds | Hydrophilic interacting residue          |
|--------------|----------------------------|--------------------------|----------------|-----------------------------------------|
| CID: 442369  | Tiliacorine                | −10.5                    | 1              | GLU315                                  |
| CID: 5281600 | Amentoflavone              | −10.4                    | 6              | GLU143, PHE157, TRP166, ASN177, ASN282  |
| CID 14527219 | 2-nortiliacorine          | −10.3                    | 1              | PRO329                                  |
| CID: 53260757| Mauritine M               | −9.8                     | 5              | MET104, GLN165, TRP166, ARG261          |
| CID 5280637  | Luteoloside                | −9.3                     | 9              | GLU143, TYR154, PRO174, THR162, ASN177, ASN282, ASN284 |
| CID: 5281675 | Orientin                  | −9.2                     | 9              | GLN165, TRP166, ASN177, ARG261, ARG180  |
| CID: 96710   | Aristolactams             | −9.1                     | 3              | ASN46, LEU367, MET369                   |
| CID 131684   | Ramontoside               | −9.0                     | 7              | ALA64, HIS65, LEU66, ASN282, TYR366     |
| CID: 5316802 | Kanzanol C                | −9.0                     | 5              | MET104, PRO182, AEG184                  |
| CID: 84298   | Asperuloside              | −8.6                     | 6              | ASN46, TYR62, HIS65, LEU66, TYR328, TYR366 |
| CID 18068    | UDP-galactopyranose       | −8.5                     | 14             | ASN46, TYR62, ALA64, HIS65, HIS89, TRP166, TYR191, ARG292, TYR328, TRP366, LEU367, ASP368, MET369 |
| CID: 44570701| UDP-galactofuranose       | −8.4                     | 17             | ASN46, TYR62, ALA64, HIS65, LEU66, GLN165, TRP166, TYR191, ARG292, TYR328, TYR366, LEU367, ASP368, MET369 |

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of UGM, i.e., −8.5 Kcal/mol and −8.4 Kcal/mol, respectively. Further, 2'-nortiliacorinine binds with UGM with binding energy of −10.3 Kcal/mol, revealing it as possible potential inhibitor of UGM. The phytochemical, amentoflavone (AMF), has been reported to exhibit antiangiogenic and anti-inflammatory functions.\[^{38,39}\] Kuete et al. also reported the antimycobacterial activity of kanzanol C (KAN) and AMF along with three other flavonoids from Dortenia barteri such as isobachalcone, 4-hydroxylochocarpin, and stipulin.\[^{40}\] The Mauritine M, is a cyclic alkaloid isolated from the plant, Ziziphus mauritiana has been reported to have antimycobacterial activity against MTB.\[^{41}\] Further, luteoloside is a flavonoid isolated from Gentiana macrophylla and also found in dandelion coffee, Ferula varia, Fueracea foetida, Campanula persicifolia, Campanula rotundifolia, Cynara scolymus, etc., reported to have antibacterial and anticancer activity.\[^{42,43}\] Orientin is a water-soluble flavonoid C-glycoside, which is commonly extracted from some medicinal plants such as Ocimum sanctum,\[^{44-46}\] Phyllostachys nigra (bamboo leaves),\[^{47-49}\] Passiflora species (passion flower),\[^{50,51}\] Trollius species

Figure 2: Docking interaction of uridine diphosphogalactofuranose-galactopyranose mutase with phytochemicals with known anti-TB activity: (a) tiliacorine, (b) amentoflavone, (c) 2'-nortiliacorinine, (d) Mauritine M, (e) luteoloside, (f) orientin, (g) aristolactams, (h) ramontoside, (i) kanzanol C, (j) asperuloside, (k) uridine diphosphogalactofuranose-galactopyranose, and (l) uridine diphosphogalactofuranose-galactofuranose obtained through LigPlot tool

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(Golden Queen)\cite{52,53} and Jatropha gossypiifolia (bellyache bush)\cite{54}. Orientin has reported to possess different medicinal properties such as antioxidant, antiaging, antiviral, antibacterial, anti-inflammation, vasodilatation and cardioprotective, antiadipogenesis, analgesic, radiation protective, neuroprotective, and antidepressant-like effects.\cite{55} Ramontoside, isolated from the heartwood of Flacourtia ramontchi, has several pharmacological activities including anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, antimalarial, antidiabetic, antiasthmatic, and antibacterial activity.\cite{56,57} In our study, we also observed the high binding affinity of AMF, Mauritine M, luteoloside, orientin, aristolactams, ramontoside, KAN, asperuloside, etc., \cite{Table 1} toward UGM as compared to natural substrates. Thus, these phytochemicals may be proposed as potential inhibitors of UGM and subjected to further study so as to propose possible anti-TB drugs. Further,

\textbf{Figure 3}: Docking interaction of uridine diphosphogalactofuranose-galactopyranose mutase with ZINC compounds: (a) ZINC08219848, (b) ZINC08217649, (c) ZINC85541479, (d) ZINC30724067, (e) ZINC49803938, (f) ZINC30727361, (g) ZINC85574422, (h) ZINC24612443, (i) ZINC30724655, (j) ZINC87520281, (k) UDP-galactopyranose, and (l) uridine diphosphogalactofuranose-galactofuranose obtained through LigPlot tool.
In our study, we also employed computational techniques for structure-based drug screening to identify potential inhibitors from large number of compounds against pathogenic organism such as MTB before going for in vitro culture study to test their anti-TB activity.

## Conclusion

The UGM of MTB catalyzes the conversion of UDP-galactopyranose into UDP-galactofuranose and vice versa. Both the substrates play an important role in cell wall biosynthesis and also associate with different important metabolic pathways of MTB. Thus, in this study, we explored 148 different phytochemicals with known anti-TB activity and 5280 ZINC compounds with 70% structural similarity with natural substrates of UGM, so as to identify potential inhibitors for UGM through virtual screening approach. Further, we have proposed 10 top ranked inhibitors from each group having better binding affinity than UGM, an important drug target of MTB. The in silico screening approach has been useful in identifying potential inhibitors from large number of compounds against pathogenic organism such as MTB before going for in vitro culture study to test their anti-TB activity.
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Conflicts of interest
There are no conflicts of interest.

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