Introduction

Tuberculosis (TB), a tropical disease caused by Mycobacterium tuberculosis (M. tuberculosis) remains a public health concern due to the emergence and evolution of multidrug-resistant strains. To overcome this issue, reinforcing the effectiveness of first-line antituberculosis agents using targeted drug delivery approach is an option. Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH), a common virulence factor found in the pathogenic microorganisms has recently been discovered on the cell-surface of M. tuberculosis, (Malhotra et al., 2017) allowing it to be used as a drug target for TB. This study aims to discover active small molecule(s) that target GAPDH and eventually enhance the delivery of antituberculosis drugs directly against M. tuberculosis.

Methods

Ten compounds with reported in vitro and/or in vivo activities against GAPDH were evaluated for their binding interactions through molecular docking studies using AutoDock 4.2 program. The compound with the best binding energy was then modified to further produce 13 derivatives and these derivatives were re-ranked against GAPDH using previous protocols. BIOVIA Discovery Studio Visualizer 2019 was used to explore the ligand-receptor interactions between the derivatives and GAPDH.

Results & Discussion (1)

C (curcumin) showed the highest activity with the estimated binding energy of -7.85 kcal/mol followed by F (folic acid) and H (konicid acid) (-7.68 and -7.62 kcal/mol, respectively).

Results & Discussion (2)

Konicid acid and curcumin has been reported as good GAPDH inhibitors in other studies, so these results were expected. (Kato, Sakai and Endo, 1992; Gómez et al., 2019) However, even though folic acid is a popular targeting agent for anti-cancer drugs, it is not known to bind to GAPDH. Hence, we decided to further research folic acid to see whether it can be used as a targeting agent for GAPDH.

F7 (folic acid N-hydroxysuccinimide ester) showed the highest activity with the estimated ΔGbind of -9.22 kcal/mol followed by F8 (p-(tert-butyl-N-(6-aminohexyl)carbamate) folic acid) with estimated ΔGbind of -8.92 kcal/mol.

Conclusions

Folic acid and the two derivatives F7 and F8 have a huge potential to be developed as the targeting agent against the GAPDH receptor. Further study is currently on-going to evaluate the effectiveness of these molecules through ELISA study and subsequently on the Mycobacterium itself.

Figure 1: Docking results of selected compounds with GAPDH

Figure 2: 2D diagram of ligand-protein complex of folic acid

Figure 3: Docking results of folic acid derivatives with GAPDH

Figure 4: 2D diagram of ligand-protein complex of F7

Figure 4 showed that the addition of N-hydroxysuccinimide allowed F7 to fill a binding cavity that folic acid could not, resulting in additional van der Waals interactions that lead to an increase in binding affinity. However, attempts at extending the glutamic acid component of folic acid resulted in decreased binding affinity, as evidenced by F9, F10, F11, F12, and F13.

Literature cited