## *ABSTRACT*

*Leukemia is characterized by the abnormal proliferation of bone marrow and blood cells that are responsible for approximately 3.1% of cancer-related deaths worldwide. One of the major causes is the overexpression of the BCL-2 protein. Researchers continue to develop effective therapeutic agents capable of inhibiting BCL-2. To date, venetoclax (V) is the only FDA-approved drug targeting BCL-2. However, venetoclax has several limitations, including poor bioavailability and high cost. Therefore, alternative therapeutic agents derived from natural products that are considered safer and more affordable are being explored, for example, andaliman seed. Andaliman seed contains monoterpen compounds such as geraniol (G), geranyl acetate (GA), and limonene (LM). Nevertheless, no in silico studies have yet been conducted to investigate the interactions between andaliman compounds and the BCL-2 protein at the atomic level. Therefore, this study aims to determine the interactions occurring within the complexes based on ligands on complex stability through 200 ns molecular dynamics simulations. The BCL2X protein was employed as the receptor, while ligands geraniol, geranyl acetate, and limonene were used as ligand and venetoclax served as the reference compound. Two computational approaches were applied, namely quantum methods for ligand optimization and classical methods for molecular docking and molecular dynamics simulations. BCL2X...G complex exhibited one hydrogen bond and ten hydrophobic interactions. The BCL2X...GA complex exhibited two hydrogen bonds and six hydrophobic interactions. The BCL2X...LM complex displayed only six hydrophobic interactions. The BCL2X...V complex exhibited three hydrogen bonds, one electrostatic interaction, and eleven hydrophobic interactions. BCL2X...G complex demonstrated the lowest total potential energy due to contributions from* $E_{vdw}$ *and* $E_{electrostatic}$*. The average Rg (~15.8 Å) and RMSD (~4 Å) value of the three andaliman complexes were comparable to those of the BCL2X...V complex. The highest* $\Delta G_{bind}$ *value was observed for the BCL2X...GA complex due to hydrophobic effects, which was further supported by its low SASA value. All the complexes were predominantly composed of α-helix secondary structures. Therefore, the three andaliman compounds exhibited inhibitory potential against BCL-2 comparable to V.*



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