The protein Ezrin, is a member of the ERM family (Ezrin, Radixin and Moesin) that links the F-actin to the plasma membrane. The protein is made of three domains namely the FERM domain, a central α-helical domain and the CERMAD domain. The residues in Ezrin such as Ser66, Tyr145, Tyr353 and Tyr477 regulate the function of the protein through phosphorylation. The protein is found in two distinct conformations of active and dormant (inactive) state. The initial step during the conformation change is the breakage of intramolecular interaction in dormant Ezrin by phosphorylation of residue Thr567. The dormant structure of human Ezrin was predicted computationally since only partial active form structure was available. The validation analysis showed that 99.7% residues were positioned in favored, allowed and generously allowed regions of the Ramachandran plot. The Z-score of Ezrin was −7.36, G-factor was 0.1, and the QMEAN score of the model was 0.61 indicating a good model for human Ezrin. The comparison of the conformations of the activated and dormant Ezrin showed a major shift in the F2 lobe (residues 142-149 and 161-177) while changes in the conformation induced mobility shifts in lobe F3 (residues 261 to 267). The 3D positions of the phosphorylation sites Tyr145, Tyr353, Tyr477, Tyr482 and Thr567 were also located. Using targeted molecular dynamic simulation, the molecular movements during conformational change from active to dormant were visualized. The dormant Ezrin auto-inhibits itself by a head-to-tail interaction of the N-terminal and C-terminal residues. The trajectory shows the breakage of the interactions and mobility of the CERMAD domain away from the FERM domain. Protein docking and clustering analysis were used to predict the residues involved in the interaction between dormant Ezrin and mTOR. Residues Tyr477 and Tyr482 were found to be involved in interaction with mTOR.

Keywords: Ezrin, FERM domain, homology modeling, targeted molecular dynamics