

## **Abstract**

According to the Center for Disease Control and Prevention, as of August 23, 94 countries had confirmed 42,954 Monkeypox Virus cases. As specific monkeypox drugs are not yet developed, the treatment depends on repurposed FDA-approved drugs. According to a recent study, the Monkeypox outbreak is caused by a strain with a unique mutation, raising the likelihood that the virus will develop resistance to current drugs by acquiring mutations in the targets of currently used drugs. The probability of multiple mutations in two or more drug targets at a time is always low than mutation in a single drug target. Therefore, we identified 15 triple-targeting FDA-approved drugs that can inhibit three viral targets, including topoisomerase1, p37, and thymidylate kinase, using high throughput virtual screening approach. Further, the molecular dynamics simulation analysis of the top hits such as Naldemedine and Saquinavir with their respective targets reveals the formation of stable conformational changes of the ligand-protein complexes inside the dynamic biological environment. We suggest further research on these triple-targeting molecules to develop an effective therapy for the currently spreading Monkeypox.

**Keywords: Monkeypox, Drug repurposing, molecular docking, molecular dynamics**