Title: Discovery of novel MLK4 inhibitors against colorectal cancer through computational approaches

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Abstract: Colorectal cancer (CRC) is a significant health issue globally, affecting approximately 10 % of the world's population. The prevalence of CRC highlights the need for effective treatments and prevention strategies. The current therapeutic option, such as chemotherapy, has significant side effects. Thus, this study investigated the anticancer properties of Sanguinarine derivatives, an alkaloid found in traditional herbs via chemoinformatic approaches. Six Sanguinarine derivatives were discovered through virtual screening and molecular docking to determine their binding affinities against the mixed lineage kinase (MLK4) protein which is responsible for CRC. All the compounds were found to be more effective than standard drug used for colorectal cancer treatment, with Sanguinarine derivative 11 showing the highest affinity. The stability of the drug was confirmed through molecular dynamics simulations at 500 ns. This suggests that compound 11 has a higher chance of replacing 5-Fluorouracil, which is currently a widely used chemotherapy drug. Before molecular dynamics simulations, the pharmacokinetic and chemical properties of Sanguinarine derivatives were determined using pkCSM server and DFT method, respectively. The results support that compound 11 is a good drug candidate, as evidenced by Lipinski's Rule of Five. Therefore, compound 11 is recommended for further analysis via *in vivo* and *in vitro* studies to confirm its efficacy and safety.

Keywords: Colorectal cancer (CRC); Sanguinarine derivatives; Chemoinformatics; Molecular docking; Mixed lineage kinase 4 (MLK4);

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