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Identification of carbazole alkaloids from *Murraya koenigii* as potential main protease inhibitors of SARS-CoV-2 Omicron variant

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Despite of COVID-19 vaccination, immune escape of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants has created an urgent priority to identify additional antiviral drugs. In the short span of two years, SARS-CoV-2 has evolved to raise five variants of concern out of which Omicron has currently become the dominant variant all over the world. Targeting main protease (M^{pro}) expressed by SARS-CoV-2 Omicron variant, is a therapeutic strategy for drug development due to its prominent role in viral replication cycle. Leaves of *Murraya koenigii* are used in various traditional medicinal applications and this plant is known as a rich source of carbazole alkaloids. Previous research reports have shown that the leaves, roots and bark of this plant are high in carbazole alkaloids. Many drug compounds containing a carbazolic core have been discovered, and some have demonstrated antiviral action. Thus, this computational study was designed to investigate the inhibitory potential of carbazole alkaloids from *Murraya koenigii* against M^{pro}. Molecular docking was performed using AutoDock Vina software to determine the binding affinity and molecular interactions of carbazole alkaloids and the reference inhibitor (3WL) in the active site of SARS-CoV-2 Omicron variant M^{pro} (PDB ID: 7TLL). The top scoring compounds were further assessed for physicochemical properties and drug likeness, pharmacokinetic and toxicity (ADME/T) properties, antiviral activity, pharmacophore modeling and molecular dynamics (MD). Two carbazole alkaloids namely, koenine (-7.8 kcal/mol) and girinimbine (-7.6 kcal/mol) displayed a unique binding mechanism that shielded the catalytic dyad (His41 and Cys145) of M^{pro} with stronger binding affinities and molecular interactions than 3WL (-7.2 kcal/mol). Furthermore, the two compounds with high affinity displayed favorable physicochemical and ADME/T properties that satisfied the criteria for oral bioavailability and druggability. The pharmacophore modeling study showed shared pharmacophoric features (aromatic ring, hydrophobic area, hydrogen bond donor/acceptor and positively ionizable region) of those compounds for their biological interaction with M^{pro}. During the molecular dynamics simulation of 100 ns, the MD simulation trajectories of root mean square deviation (RMSD), root mean square fluctuation (RMSF) and radius of gyration (Rg) of top two complexes exhibited high stability. Therefore, koenine and girinimbine from *Murraya koenigii*, may have the potential to restrict SARS-CoV-2 replication by inactivating the M^{pro} catalytic activity thus offering potential hits that may be further structurally modified and evaluated *in vitro* and *in vivo* for the discovery of novel SARS-COV-2 M^{pro} inhibitors.

Keywords: Omicron variant, Main protease, Molecular docking, *Murraya koenigii*, Carbazole alkaloids

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