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In-silico investigation of inhibition of TGF-β1 signalling pathway by C-glycosidic Ellagitannins, a bioactive molecule from the plant *Osbekia octandra* for their potential as a treatment option for hepatic fibrosis

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Liver fibrosis is a lethal disease caused by the activation of the canonical TGF-β1 pathway upon chronic stimulation by pro-inflammatory cytokines. Thus, the in-silico observation of potent natural compounds in the development of advanced medicines for liver fibrosis is essential. The main objective of the study was to investigate the in-silico inhibition of the TGF-β1 pathway by C-glycosidic ellagitannin bio-active molecules of the *Osbeckia octandra* plant, based on binding interactions and binding energies. Initially, the crystal structures of TGF-β1 pathway proteins, TGF-β receptor I and TGF-β receptor II, were obtained via homology modelling and subjected to binding site analysis. The structures of five different ellagitannins (ligands) Casuarinin, Casuarin, Castalegine, Vescalagine, and Epi-punicacortien A were geometrically optimized. All ligands were docked with each receptor and their binding affinities were compared with commercial drugs, Silmitasertib (for TGF-β receptor I) and ITD-1 (for TGF-β receptor II) with the best pose along with binding interactions. The TGF-β receptor I and TGF-β receptor II crystal structures were selected based on the highest GMQE values of 0.84 and 0.81, respectively. The automated docking results showed that Casuarinin, Casuarin, Castalegine, Vescalegine, and Epi-punicacortien A had binding affinities of -9.5, -9.0, -8.2, -8.3, and -9.3 kcal/mol, respectively, towards TGF-β receptor I, compared to the commercial drug Silmitasertib, which showed -10.0 kcal/mol. For TGF-β receptor II, the ligands showed binding affinities of -9.8, -9.3, -8.7, -9.0, and -8.2 kcal/mol, respectively, while ITD-1 showed a binding affinity of -8.9 kcal/mol. Since Casuarinin showed a high and comparable binding affinity towards both TGF-β receptors compared to the commercial drugs, this study suggests that Casuarinin is a potential candidate that can be further developed as an oral capsule or infusion to treat liver fibrosis.

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