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Identification of β-cycloidal-derived mono-carbonyl curcumin analogs as potential interleukin-6 inhibitor to treat wound healing through QSAR, molecular docking, MD simulation, MM-GBSA calculation

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ABSTRACT

Interleukin-6 (IL-6) is a cytokine that involved in the different phases of wound healing. It is responsible for promoting inflammation, regulating tissue repair scar formation, stimulating the production of extracellular matrix components and recruiting immune cells to the wound site. Therefore, suppressing IL-6 is beneficial for wound healing. However, no small molecules are currently available in the market against the IL-6. As a result, this research gap motivates us to find a potential inhibitor. This study aimed to investigate the wound healing potential of novel β-cycloidal-derived mono-carbonyl curcumin analogs reported in the literature through screening a series of computational studies. The calculated pIC50 value of 18 compounds (below 10) showed that all compounds may have potential therapeutic efficacy. Molecular docking studies revealed that compound C12 (−45.6044 kcal/mol) bound most strongly in the active site of IL-6 compared to the FDA-approved drug clindamycin (−42.3223). The Molecular Dynamic (MD) simulation displayed that lead compound C12 had the highest stability in the active site of IL-6 compared to the reference drug clindamycin. Furthermore, MMGBSA results indicated that C12 (−20.28 kcal/mol) had the highest binding energy compared to clindamycin (−8.36 kcal/mol). The ADMET analysis predicted that C12 are favourable for drug candidates. This study recommended compound C12 as a lead IL-6 inhibitor for future testing and development as therapeutics for wound healing.

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Wound healing; β-cycloidal-derived mono-carbonyl curcumin analogs; IL-6; QSAR; molecular docking; MD simulation

1. Introduction

Wound healing is a complex biological reaction involving four stages: haemostasis, inflammation, proliferation, and remodeling. They involve diverse cells and tissues, as well as the interaction of various sub-stages, mediators, cytokines, enzymes, and growth factors (Kandhare et al., 2016; Strodtbeck, 2001). Previous studies demonstrated that any disturbance to these sequential processes might upset this balance, thereby affecting the normal pace of wound healing (Cullen et al., 2002). Notably, one key factor in the regulation of wound healing is interleukin 6 (IL-6), which acts as a proinflammatory cytokine that has a potential role in the pathogenesis and physiology of inflammatory processes such as wound healing (Nada et al., 2023). A study reported that IL-6 plays a crucial role in promoting inflammation, recruiting immune cells to the wound site, and stimulating the production of extracellular matrix components (Legiawati et al., 2018). Additionally, its help to regulate the balance between tissue repair and scar formation, ensuring proper healing of the wound. The inflammation develops within 24 h following the wound and might last for two weeks or longer. During this stage, neutrophils and macrophages come to the site of action and destroy debris and microorganisms *via* the phagocytosis process. The proinflammatory cytokines released by macrophages, such as IL-6, assist in wound healing (Bodas & Shinde, 2021). Deregulation of the normal wound healing process causes wound healing to be delayed (typically for more than 6–8 wk), resulting in a chronic wound (Li et al., 2007). Nowadays, chronic wounds represent a huge burden not just for individuals but also for healthcare systems. Chronic wounds are characterized by prolonged inflammation, hypoxia, biofilm formation,

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