Unlocking CRAC Channel Modulation: Plant Metabolite-Derived ORAI1 Inhibitors Targeting E106 for Rheumatoid Arthritis Treatment Through Combined AI-Derived Virtual Screening Approaches

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Rheumatoid Arthritis (RA) is an autoimmune arthropathy that affects over 18 million people globally, causing immense joint pain and swelling. Current treatments (e.g., methotrexate, adalimumab) are associated with serious side effects including hepatotoxicity and bone necrosis. To explore alternative treatment options, a literature review was conducted, revealing that dysregulation of ORAI1, a subunit of the calcium release-activated calcium (CRAC) channel, plays a key role in RA onset. In RA, overactivation of the CRAC channel allows excess calcium influx into T-cells, triggering pro-inflammatory signaling. Specifically, ORAI1's E106 (glutamate) amino acid residue is crucial for calcium ion selectivity of the CRAC channel. Secondary plant metabolites, known for co-evolution with protein targets and favorable biocompatibility, are promising therapeutic candidates for lower toxicity. The research goal was to identify plant metabolites with high binding affinity to the E106 site and minimal off-target effects using computational methods. First, homology modeling was utilized to create the ORAI1 subunits and its active site. Next, virtual screening and docking was conducted using NeoScreen, a novel AI model, alongside Schrodinger GLIDE. Compounds were evaluated based on pharmacokinetics (e.g., Lipinski's rules, polarizability), toxicity profiles (e.g., cytotoxicity, mutagenicity), and overall binding affinity. The lead compound, 1-Desgalloyleugeniin (tannin-derived metabolite), showed the highest affinity and favorable toxicities. Future steps include optimization and nonclinical testing of the lead compound. Targeting the E106 residue for future drug development offers a safer approach for RA and many other autoimmune conditions involving CRAC channel dysfunction.

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