INNOVATIVE 7-O-SUBSTITUTED CHRYSIN DERIVATIVES AS VEGFR-2 INHIBITORS: A NATURAL PRODUCT-BASED ANTICANCER THERAPY

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Abstract:

Introduction

VEGFR-2, critical target in cancer therapy, facilitating tumor angiogenesis, yet existing inhibitors face toxicity and resistance issues. Chrysin, flavonoid with anticancer properties, has VEGFR-2 characteristics but suffers from poor pharmacokinetics. A series of 7-O-substituted chrysin derivatives was designed to enhance binding and drug-like properties by incorporating key hydrogen-bonding groups and hydrophobic elements, informed by VEGFR-2 structural analysis.

To design and assess novel chrysin derivatives through computational predictions and molecular docking; synthesize and characterize selected derivatives; and evaluate their antioxidant and anticancer activities in vitro, to identify effective candidates that exhibit favorable pharmacokinetics and safety.

Methods

Chrysin derivatives featuring alkylamino and ester substituents were designed using molecular docking against VEGFR-2. ADMET profiling was conducted to anticipate pharmacokinetics and toxicity. Selected derivatives were synthesized via alkylation and esterification, and characterized using UV, IR, NMR, and mass spectrometry. Antioxidant activity evaluated using DPPH assay, while anticancer efficacy against MCF-7 cells assessed through cell viability assays, comparing IC50 values with those of ascorbic acid and sorafenib.

Results

Docking studies indicated strong binding affinities, particularly for ester derivatives. ADMET predictions suggested favorable drug-like characteristics. **C7** demonstrated remarkable antioxidant activity, exceeding both chrysin and ascorbic acid. In anticancer tests, C7 and C8 displayed significant cytotoxicity (IC50 = 1.0 and 1.5 µM), outperforming chrysin and nearing sorafenib efficacy.

Conclusion

The improved bioactivity and predicted safety of C7 and C8 highlight efficacy of rational structural modifications in optimizing natural products. Their dual antioxidant and anticancer properties underscore their potential as lead compounds for VEGFR-2-targeted breast cancer treatments. Chrysin derivatives, particularly C7 and C8, exhibit promising VEGFR-2 inhibitory activity and therapeutic potential, supporting their further investigation as multifunctional anticancer agents. Building on these findings, future efforts will focus on developing suitable formulations to improve their solubility, stability, and bioavailability

Keywords: Chrysin derivatives, Antioxidant, Anticancer, VEGFR-2 inhibition

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