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Food-compatible Reaction-synthesized Flavone Dimer ZHL10 Suppresses Triple-negative Breast Cancer Growth in Cellular and Xenograft Models

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Abstract

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype characterized by high metastatic potential, limited targeted therapeutic options, and poor clinical outcomes [1]. The development of structurally novel flavonoid-based compounds using food-compatible synthetic strategies may provide new opportunities for identifying safer bioactive candidates for cancer intervention. ZHL10 is a flavone dimer synthesized using an oxygen-mediated oxidative coupling reaction in alkaline water, based on a previously reported catalyst-free and food-compatible strategy for the synthesis of flavone dimers [2]. In this study, we investigated the anti-cancer effects of ZHL10 against TNBC using two-dimensional cell culture, three-dimensional tumor spheroids, and an *in vivo* xenograft model.

ZHL10 markedly inhibited the viability of TNBC cells in a concentration-dependent manner. In MDA-MB-231 and MDA-MB-468 cells, ZHL10 reduced cell proliferation, as evidenced by decreased EdU incorporation, and induced apoptotic cell death. In three-dimensional TNBC spheroids, ZHL10 suppressed spheroid growth, indicating its inhibitory effects under a tumor-like microenvironment. Importantly, ZHL10 demonstrated significant anti-tumor efficacy in a TNBC xenograft model. Compared with the vehicle control group, ZHL10 treatment markedly delayed tumor progression and reduced final tumor burden. The reduction in tumor growth was accompanied by decreased tumor size and tumor weight at the endpoint, supporting the *in vivo* anti-TNBC activity of ZHL10. Moreover, ZHL10-treated mice maintained stable body weight throughout the treatment period, and no obvious abnormalities were observed in major organs based on preliminary histological examination. These findings suggest that ZHL10 exhibits promising *in vivo* efficacy with a favorable preliminary safety profile.

Mechanistically, transcriptomic profiling and pathway enrichment analysis were first performed to explore the molecular basis underlying the anti-TNBC activity of ZHL10. The analysis revealed marked modulation of survival- and proliferation-related signaling networks. To further investigate potential protein targets, a combination of target prediction, cellular thermal shift assay, and pathway validation experiments was conducted. These analyses supported the engagement of ZHL10 with a key pathway-associated protein and demonstrated suppression of downstream oncogenic signaling in TNBC cells and xenograft tumor tissues. These findings suggest that ZHL10 may exert its anti-TNBC effects through target engagement-mediated disruption of tumor-promoting signaling pathways.

Overall, this study demonstrates that food-compatible reaction-synthesized flavone dimer ZHL10 effectively suppresses TNBC growth in both cellular and xenograft models. The robust tumor suppression observed *in vivo*, together with the absence of obvious systemic toxicity, supports the further development of ZHL10 as a flavonoid-based anti-cancer candidate for triple-negative breast cancer intervention.

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References

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