Anti-breast cancer potential of *Sterculia quadrifida* phytochemicals: MMP inhibition and apoptosis activation

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ABSTRACT

Breast cancer progression is driven by uncontrolled proliferation and metastatic dissemination, processes in which matrix metalloproteinases (MMPs) and apoptosis resistance play critical roles. This study evaluated three isolates from Sterculia quadrifida for their anti-invasive and anticancer mechanisms, with emphasis on MMP inhibition and apoptosis induction. In vitro assays demonstrated that aurone exhibited the strongest and broadest inhibition of MMP-2, MMP-3, and MMP-9, suppressing each isoform by approximately 69-70% at 200 µg/mL, whereas the phenylpropanoid showed moderate inhibition (54-56%) and the phenolic compound displayed weaker activity (36-41%). Fluorescence-based assays confirmed enzymatic blockade, with aurone-treated wells approaching baseline relative fluorescence units (RFU), while the pan-MMP inhibitor NNGH achieved approximately 95% inhibition. Mechanistic analyses revealed that aurone robustly induced intrinsic mitochondrial apoptosis across multiple breast cancer cell lines, as evidenced by Bax upregulation, Bcl-2 downregulation, an increased Bax/Bcl-2 ratio, activation of caspase-9, processing of executioner caspases (caspase-3 or caspase-7), and enhanced PARP cleavage, including in p53-mutant backgrounds. Aurone further enforced G1 phase arrest through suppression of Cyclin D1, CDK4/6, and phosphorylated Rb, accompanied by upregulation of p21^Cip1 and p27^Kip1. Concurrently, decreased phosphorylation of Akt and ERK1/2 indicated attenuation of pro-survival signaling pathways. Collectively, these findings demonstrate that S. quadrifida aurone exerts dual anti-invasive and antiproliferative effects through coordinated MMP inhibition, reactivation of mitochondrial apoptosis, and G1 checkpoint regulation, highlighting its potential as a multi-target anticancer candidate.

Keywords: Aurone, G1 cell cycle arrest,intrinsic apoptosis, matrix metalloproteinases (MMPs), *Sterculia quadrifida*