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Strophanthidin Attenuates MAPK, PI3K/AKT/mTOR, and Wnt/β-Catenin Signaling Pathways in Human Cancers

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Lung cancer is the most prevalent in cancer-related deaths, while breast carcinoma is the second most dominant cancer in women, accounting for the most number of deaths worldwide. Cancers are heterogeneous diseases that consist of several subtypes based on the presence or absence of hormone receptors and human epidermal growth factor receptor 2. Several drugs have been developed targeting cancer biomarkers; nonetheless, their efficiency are not adequate due to the high reemergence rate of cancers and fundamental or acquired resistance toward such drugs, which leads to partial therapeutic possibilities. Recent studies on cardiac glycosides (CGs) positioned them as potent cytotoxic agents that target multiple pathways to initiate apoptosis and autophagic cell death in many cancers. In the present study, our aim is to identify the anticancer activity of a naturally available CG (strophanthidin) in human breast (MCF-7), lung (A549), and liver cancer (HepG2) cells. Our results demonstrate a dose-dependent cytotoxic effect of strophanthidin in MCF-7, A549, and HepG2 cells, which was further supported by DNA damage on drug treatment. Strophanthidin arrested the cell cycle at the G2/M phase; this effect was further validated by checking the inhibited expressions of checkpoint and cyclin-dependent kinases in strophanthidin-induced cells. Moreover, strophanthidin inhibited the expression of several key proteins such as MEK1, PI3K, AKT, mTOR, Gsk3α, and β-catenin from MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin signaling. The current study adequately exhibits the role of strophanthidin in modulating the expression of various key proteins involved in cell cycle arrest, apoptosis, and autophagic cell death. Our *in silico* studies revealed that strophanthidin can interact with several key proteins from various pathways. Taken together, this study demonstrates the viability of strophanthidin as a promising anticancer agent, which may serve as a new anticancer drug.

Keywords: cardiac glycoside, strophanthidin, Na^+/K^+-ATPase, G2/M phase, apoptosis, autophagy

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INTRODUCTION

Cancer denotes an assembly of diseases that share a collective overall phenotype, irrepressible cell progression, and proliferation which can affect any organ in humans (1). Cancer is the most prominent cause of death worldwide, with 1.7 million new cases per annum, and is likely to extend to 26 million by 2030 (2). Among all the cancers, breast cancer, and lung cancer are the most affected