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Lanatoside C Induces G2/M Cell Cycle Arrest and Suppresses Cancer Cell Growth by Attenuating MAPK, Wnt, JAK-STAT, and PI3K/AKT/mTOR Signaling Pathways

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Abstract: Cardiac glycosides (CGs) are a diverse family of naturally derived compounds having a steroid and glycone moiety in their structures. CG molecules inhibit the α-subunit of ubiquitous transmembrane protein Na^+/K^+-ATPase and are clinically approved for the treatment of cardiovascular diseases. Recently, the CGs were found to exhibit selective cytotoxic effects against cancer cells, raising interest in their use as anti-cancer molecules. In this current study, we explored the underlying mechanism responsible for the anti-cancer activity of Lanatoside C against breast (MCF-7), lung (A549), and liver (HepG2) cancer cell lines. Using Real-time PCR, western blot, and immunofluorescence studies, we observed that (i) Lanatoside C inhibited cell proliferation and induced apoptosis in cell-specific and dose-dependent manner only in cancer cell lines; (ii) Lanatoside C exerts its anti-cancer activity by arresting the G2/M phase of cell cycle by blocking MAPK/Wnt/PAM signaling pathways; (iii) it induces apoptosis by inducing DNA damage and inhibiting PI3K/AKT/mTOR signaling pathways; and finally, (iv) molecular docking analysis shows significant evidence on the binding sites of Lanatoside C with various key signaling proteins ranging from cell survival to cell death. Our studies provide a novel molecular insight of anti-cancer activities of Lanatoside C in human cancer cells.

Keywords: Cardiac glycosides; Na^+/k^+-ATPase; G2/M phase; apoptosis; autophagy; molecular docking

1. Introduction

In Asia, about 8.7 million cases were reported by the end of 2018 with more than 100 different types of cancers, among which 1.57 million reports are from developing countries such as India. Breast and lung cancers are the leading causes for the number of cancer-related deaths [1]. Regrettably, cancers exhibit poor survival rates even after continuous treatment, showing more resistance to conservative cytotoxic agents and ineffectiveness of drugs. Consequently, developing an active therapeutic approach to treat advanced forms of cancer is always an essential issue [2]. Cardiac glycosides (CGs) are among such therapeutic options, which are profusely available from plant and animal sources [3] and clinically used to treat congestive heart diseases. Recent epidemiological studies showed the anti-cancer and anti-viral activities of CGs in several types of cancers and viral diseases [4]. The available CGs are