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Peruvoside targets apoptosis and autophagy through MAPK Wnt/β-catenin and PI3K/AKT/mTOR signaling pathways in human cancers

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ABSTRACT

Aim: To investigate the cytotoxic effect of Peruvoside and mechanism of action in human cancers.
Main methods: Cell viability was measured by MTT assay and the cell cycle arrest was identified by FACS. Real-time qPCR and western blotting studies were performed to identify important gene and protein expressions in the different pathways leading to apoptosis. Immunofluorescence was performed to understand protein localization and molecular docking studies were performed to identify protein-ligand interactions.
Key findings: Peruvoside showed significant anti-proliferative activities against human breast, lung, and liver cancer cells in dose-dependent manner. The anti-cancer mechanism was further confirmed by DNA damage and cell cycle arrest at the G0/G1 phase. Dysregulation of Wnt/β-catenin signaling with Peruvoside treatment resulted in inhibition of cyclin D1 and c-Myc also observed in this study. Furthermore, we identified that Peruvoside can inhibit autophagy by PI3K/AKT/mTOR signaling and through downregulating MEK1. Moreover, Peruvoside has the ability to modulate the expressions of key proteins from the cell cycle, MAPK, NF-kB, and JAK-STAT signaling. *In silico* studies revealed that Peruvoside has the ability to interact with crucial proteins from different biochemical signaling pathways.
Significance: Our results demonstrated that Peruvoside has the ability to inhibit cancer cell proliferation by modulating the expression of various key proteins involved in cell cycle arrest, apoptosis, and autophagic cell death. Clinical data generated from the present study might provide a novel impetus for targeting several human cancers. Conclusively, our findings suggest that the Peruvoside possesses a broad spectrum of anticancer activity in breast, lung, and liver cancers, which provides an impetus for further investigation of the anticancer potentiality of this biomolecule.

1. Introduction

Cancer remains undefeated in the history of mankind with mortality rates of 10 million in the year 2018 [1]. Characterization of cancer can be done as unlimited growth, metastasis, and invasion of the cells [2]. Reportedly, synthetic drugs are the only option for cancer therapy but synthetic drug kills cancer cells as well as normal cells. Therefore, there is an urgent need for the identification of novel drugs or to use the existing drugs for new therapeutic indications through drug repurposing [3]. Plants remain as one of the important sources for various drugs for many diseases including cancer [4,5]. Among them, cardiac glycosides (CGs) are one of the ancient drugs, initially used for heart failure [6] and their activities towards cancer cells are novel. The current study was aimed to identify the cytotoxicity of a novel cardiac glycoside (Peruvoside) and to understand the mechanism action in breast, lung, and liver cancer cell lines.

CGs are natural chemical compounds extracted from plants and some animal species [7]. The well-recognized mechanism of CGs is to inhibit sodium/potassium (Na+/K+)-ATPase and increases intracellular sodium ions [8]. Na^+/K^+-ATPase is a P-type pump that

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