

Selective cytotoxicity of non-small cell lung cancer cells by the withaferin A-fortified root extract of Ashwagandha involves differential cell-cycle arrest and apoptosis

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Abstract

Withaferin A (WFA) isolated from the root and leaf extracts of *Withania somnifera* (Ashwagandha, ASH) has been shown to exhibit promising anti-tumor properties. Even though WFA is cytotoxic to a variety of cancer cell types, it is also toxic to normal cells. To selectively chemosensitize cancer cells to WFA, we have utilized a novel approach of fortifying the crude root ASH extract with WFA (FASH) and compared the effects of WFA and FASH on normal and non small cell lung cancer (NSCLC) cells. WFA-induced cytostatic and apoptotic effects on normal and NSCLC cells were accompanied by an increased oxidative stress induced lipid peroxidation and GSSG/GSH ratio. While FASH potentiated the cytotoxic effects of WFA on NSCLC cells, they were significantly inhibited in normal cells. The protective effects of FASH on normal cells were associated with the up regulation of antioxidant enzymes, alteration in the expression and functions of cell cycle, and apoptosis related proteins. The anti-apoptotic effects of FASH on normal cells were exerted via the activation and phosphorylation of AKT, ERK1/2 and BAD. Overall, we demonstrate that FASH selectively chemo sensitizes NSCLC through a differential modulation of oxidative stress induced signaling. These findings provide a novel strategy to target a variety of cancers.

Keywords: Ayurveda, Ashwagandha, *Withania somnifera*, withaferin A, lipid peroxidation, antioxidant

Introduction

Withania somnifera Dunal, commonly known as Ashwagandha (ASH) is a plant belonging to the Solanacea family. It has been safely used for centuries in Indian Ayurvedic medicine for the treatment of a variety of ailments (Mishra, 2000). Intensive research has now confirmed its antioxidant, anti-inflammatory, immune-modulating, and anti-stress prop-