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Condurango-glycoside-A fraction of *Gonolobus condurango* induces DNA damage associated senescence and apoptosis via ROS-dependent p53 signalling pathway in HeLa cells

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Abstract *Gonolobus condurango* plant extract is used as an anticancer drug in some traditional systems of medicine including homeopathy, but it apparently lacks any scientific validation. Further, no detailed study is available to suggest whether condurango-glycoside-A (CGA), a major ingredient of condurango serves as a potent anticancer compound. Therefore, we investigated apoptosis-inducing ability of CGA against cervix carcinoma cells (HeLa). β-galactosidase-activity and DNA damage were critically studied at different time points; while induced DNA-damage was observed at 9–12th hours, senescence of cells appeared at a later stage (18th hour after CGA treatment), implicating thereby a possible role of DNA damage in inducing premature cell senescence. Concurrently, the number of cells undergoing apoptosis increased along with increase in reactive oxygen species (ROS) generation. Expression of p53 was also up-regulated, indicating that apoptosis could have been mediated through p53 pathway. DCHFDA (4′,6-Diamidino-2-phenylindole dihydrochloride) assay, acridine orange/ethidium bromide staining and annexin V/PI assay results collectively confirmed that apoptosis was induced by increased ROS generation. Reduction in proliferation of cells was further evidenced by the cell cycle arrest at G0/G1 stage. Expression profiles of certain relevant genes and proteins like p53, Akt, Bcl-2, Bax, cytochrome *c* and caspase 3 also provided evidence of ROS mediated p53 up-regulation and further boost in Bax expression and followed by cytochrome *c* release and activation of caspase 3. Overall results suggest that CGA initiates ROS generation, promoting up-regulation of p53 expression, thus resulting in apoptosis and pre-mature senescence associated with DNA damage.

Keywords Condurango-glycoside-A · DNA damage · Senescence · Apoptosis · HeLa cells

Introduction

Cundurango or condurango (*Gonolobus condurango*) is native of South America and belongs to the milkweed family (Apocynaceae). It was first introduced into the United States in 1871 to treat stomach cancer and syphilis [1, 2]. While it was never really proven effective for cancer during those early years through any scientific study, its use continued since then in various traditional and complementary medicines as a remedy for many types of stomach and digestive problems [3]. It is also used as a remedy to calm nervous and upset stomach, relieve stomach pain, nausea and intestinal gas [3]. Besides, condurango has also been documented for its anti-inflammatory and anti-oxidant actions in animal studies [4]. The extract contains a group of novel glycosides and steroids; along with tannin, small quantities of a strychnine-like alkaloid, caoutchouc, condurangin, condruit, essential oil, phytosterin, resin, and sitosterol [5, 6]. The anti-tumour activity of some of these novel compounds was first reported in the 1980s [7]. However, the mechanism behind this activity still remains unknown, as its efficacy has not been investigated systematically so far.

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