We investigate induction of apoptosis by xanthohumol on Ca Ski cervical cancer cell line. Xanthohumol is a prenylated chalcone naturally found in hop plants, previously reported to be an effective anticancer agent in various cancer cell lines. The present study showed that xanthohumol was effective to inhibit proliferation of Ca Ski cells based on IC\textsubscript{50} values using sulforhodamine B (SRB) assay. Furthermore, cellular and nuclear morphological changes were observed in the cells using phase contrast microscopy and Hoechst/PI fluorescent staining. In addition, 48-hour long treatment with xanthohumol triggered externalization of phosphatidylserine, changes in mitochondrial membrane potential, and DNA fragmentation in the cells. Additionally, xanthohumol mediated S phase arrest in cell cycle analysis and increased activities of caspase-3, caspase-8, and caspase-9. On the other hand, Western blot analysis showed that the expression levels of cleaved PARP, p53, and AIF increased, while Bcl-2 and XIAP decreased in a dose-dependent manner. Taken together, these findings indicate that xanthohumol-induced cell death might involve intrinsic and extrinsic apoptotic pathways, as well as downregulation of XIAP, upregulation of p53 proteins, and S phase cell cycle arrest in Ca Ski cervical cancer cells. This work suggests that xanthohumol is a potent chemotherapeutic candidate for cervical cancer.

1. Introduction

Cervical cancer is a global health problem affecting women. According to the available data, 99.7% of all cervical carcinomas occur due to infection by human papillomavirus (HPV), especially HPV-16 and HPV-18, which World Health Organization identified as high risk carcinogenic agents. HPV affects body cells by integrating with the host's genome and inducing cellular dysregulation, such as increased DNA synthesis, cell proliferation, and cellular response to growth and differentiation factors, which eventually lead to the development of cervical cancer [1]. Two viral genes, E6 and E7, are expressed in HPV-positive cervical cancer cells. Their gene products are known to activate telomerase, prevent death of human primary epithelial cells, and inactivate major tumor suppressors (p53 and pRB proteins) [2]. Despite the growing availability of HPV vaccines, screening tests, and approved therapies, cervical cancer remains highly prevalent among women worldwide, ranking fourth, after breast, colorectal, and lung cancers [3].

A number of molecularly targeted agents were reported to modulate angiogenesis, growth factor receptors, cell cycle, and inflammation in cervical cancer signaling pathways. Amongst these are the chemotherapeutic agents currently used as advanced and metastatic cervical cancer treatment options, such as cisplatin, paclitaxel, topotecan, cetuximab, and bevacizumab. However, at present, the use of these agents results in medical complications and different grades of toxicities, such as nausea, vomiting, pain, fatigue, and anemia [4]. Thus, an effective and safe therapy for cervical cancer is urgently needed.

Xanthohumol (Figure 1), a prenylated chalcone isolated from the female hop plant, Humulus lupulus, was reported to have \textit{in vitro} antiproliferative and apoptosis-inducing properties on prostate, ovarian, breast, and endometrium cancer cell lines [5]. It has been posited that xanthohumol might provide therapeutic strategies against hormone-dependent breast cancer by suppressing breast cancer cell survival [6]. Inhibition of DNA synthesis, induction of cell cycle arrest