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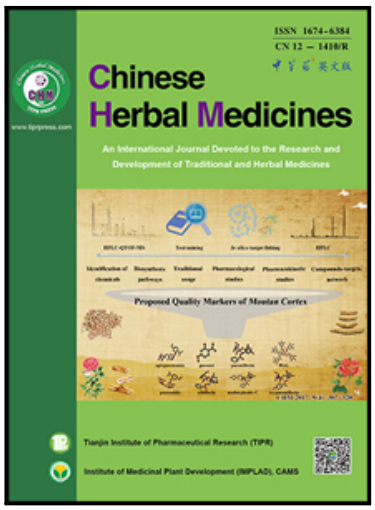

Ergosta-7,22-diene-2β,3α,9α-triol(EGDT) from Ganoderma lucidum inhibits nasopharyngeal carcinoma cells by blocking EGFR signaling pathway

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ACCEPTED MANUSCRIPT

Ergosta-7,22-diene-2β,3α,9α-triol(EGDT) from Ganoderma lucidum inhibits nasopharyngeal carcinoma cells by blocking EGFR signaling pathway

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Abstract

Objective To investigate the efficacy and mechanism of EGDT against NPC cell lines. **Methods** MTT assay was used to assess cell proliferation inhibition of EGDT; The apoptotic induction and cell cycle arrest were detected by flow cytometry; Western blot was adopted to detect the protein levels; Quantitative Real-time PCR was used to determine the mRNA expressions; The NPC xenografts were established to evaluate the tumor growth inhibition of EGDT; Immunohistochemistry was applied to analyze the EGFR expression in the tumor tissues. **Results** EGDT showed proliferation inhibition on the NPC cell, induced G0/G1 phase arrest and cell apoptosis *in vitro*. EGDT decreased the protein and mRNA levels of EGFR and its downstream RAF/MEK/ERK and PI3K/AKTpathways in time- and dose-dependent manner. Furthermore, EGDT also showed a sound antitumor activity in NPC xenograft *in vivo.* **Conclusion** The treatment of EGDT displays EGFR and its mediated downstream signaling pathway blockade through decreasing the protein and mRNA levels, suggesting a promising strategy in treating human NPC.

Key words: Ergosta-7-22-diene-2β,3α,9α-triol; nasopharyngeal carcinoma; epidermal growth factor receptor; antitumor.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating in the epithelial cells of nasopharynx, with special epidemiology, pathology and clinical characteristics differing from other head and neck squamous cell carcinomas (HNSCC) (Wei and Sham, 2005). The risk of NPC is highest occurs in Southeast Asia, especially southern China, with the annual incidence rate of about 20 per 100 000 people in the last 30 years (Caponigro et al, 2010). Due to the lack of early symptoms and reliable diagnostic markers for early detection, 60-70% of patients with NPC are not diagnosed until the disease reaches an advanced stage. Radiotherapy and chemotherapy are the standard treatment for NPC patients, although some trials showed encouraging results with over 90%local control rate, the recurrence and/or distant metastasis remain the major patterns of disease failure (Wu et al, 2014). Therefore, the development of novel therapeutic strategies against NPC still needs to be explored.

Overexpression of epidermal growth factor receptor (EGFR) has been reported in 85% of NPC tissues, and is associated with tumor metastasis, recurrence and poor survival in NPC patients (Tulalamba and Janvilisri, 2012; Chou et al, 2008; Ma et al, 2014). The PI3K/AKT/mTOR signaling is a key downstream pathway of EGFR, which is vital in the intracellular signaling of apoptosis and pathogenesis of cancer (Li et al, 2016; Tetsu et al, 2015). Another important EGFR downstream signaling route is the RAF/MEK/ERK pathway, which functions critically in the regulation of cell proliferation and survival (Fitzgerald et al, 2015; Nisimova et al, 2014). EGFR activation of these pathways results in enhanced proliferation, angiogenesis, invasion, and metastasis in NPC tumor, as well as inhibition of apoptosis (Ooft et al, 2015; Sun et al, 2014). Therefore, the inhibition of EGFR as well as its downstream pathways has been considered to be a potent strategy in NPC therapies.

Ganoderma lucidum (Levss exFr.) Karst, a medicinal fungus belonging to Basidiomycetes, Aphyllophorales, Ganodermataceae, is widely used in Oriental medicine to maintain health and improve longevity. Nowadays, *G. lucidum* and related products are used widely as not only health food, but also clinical drugs for the prevention and treatment of cancer, hepatopathy, hypertension, arthritis, neurasthenia, acute and chronic bronchitis and so on (Pan et al, 2013; Paterson, 2006; Heleno et al, 2013; Boh, 2013; Wu et al, 2013; Shi et al, 2013). Most of the anticancer effects of *G. lucidum* may be resulted in the stimulation of the immune system by polysaccharides (Liang et al, 2014; Zhu et al, 2007) or cytotoxic effects of triterpenes (Thyagarajan et al, 2010; Grienke et al, 2011). Although the function of steroid compounds from *G. lucidum* had not aroused great attention, its antitumor activity should not be neglected. The ergosterol peroxide (EPO), widely found in *G. lucidum*, inhibit inflammatory responses in RAW264.7 macrophages and growth of HT29 colon adenocarcinoma cells (Kobori et al, 2007). 5α,8α-Epidioxy-22E-ergosta-6,9(11),22-trien-3β-ol, a sterol extracted from the Fermentation Mycelia of *G. lucidum*, has been reported to suppress growth of HL60 leukemia and HT29 colon adenocarcinoma cells (Chen et al, 2009; Kobori et al, 2006). Herein, a sterol of Ergosta-7-22-diene-2β,3α,9α-triol (EGDT) from *G. lucidum* (Levss ex Fr.) Karst were purified, and its tumor suppressive efficacy on the NPC cell lines were studied. The data shows a potent anti-NPC ability of EGDT, which probably acts through the blockade of EGFR and its downstream pathways.

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