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Cinnamaldehyde induces apoptosis and reverses epithelial-mesenchymal transition through inhibition of Wnt/β-catenin pathway in non-small cell lung cancer

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ABSTRACT

Cinnamaldehyde, the main chemical component of the essential oil separated from the traditional herb Cinnamomum cassia, has been demonstrated to be an efficient cytotoxic agent against several human cancers. The present experiment showed that cinnamaldehyde dose-dependently depresses the proliferation of three types of NSCLC cells and induces cell apoptosis in vitro and in vivo. Moreover, cinnamaldehyde attenuated $CoCl_2$-induced EMT and decreased matrix metalloprotease (MMP) family while the in vivo study showed the same trend. Mechanistically, cinnamaldehyde imitated the suppressive effect of XAV939 on cell motility and EMT which could be impaired by LiCl. Collectively, our research demonstrated for the first time that cinnamaldehyde is able to inhibit NSCLC cell growth by inducing apoptosis and reverse EMT through terminating Wnt/β-catenin pathway, which might supply further insight into cinnamaldehyde-mediated anti-tumor effect against NSCLC for better prognosis.

1. Introduction

Lung cancer remains the most frequently diagnosed malignancy with more than 1.8 million new cases per year and the leading cause of cancer-related mortality in both sexes responsible for approximately 1.59 million yearly deaths worldwide (Torre et al., 2015; Chen et al., 2016a), among which non-small cell lung cancer (NSCLC) accounts for nearly 85% of the cases (Oser et al., 2015). Despite satisfactory curative effect presented by conventional therapeutics including surgery, chemotherapy, radiotherapy and targeted therapy, the five-year survival rate of patients with advanced NSCLC is less than 15%, usually culminating in treatment failure due to high aggressiveness (Minguet et al., 2016; Coate et al., 2009). Therefore, it is extremely urgent that elaborate investigation on new valid chemotherapeutic ingredients for NSCLC should be performed for innovative therapeutic applications.

In solid tumors, abnormalities of tumor vascular structure and function as well as increased oxygen consumption resulted from expeditious cell proliferation further cause regions where there is inadequate oxygen delivery, a condition named hypoxia, to benefit tumor progression and therapy resistance which is mostly mediated by hypoxia-inducible factors (HIFs) (Gilkes et al., 2014). Importantly, cancer cells undergo epithelial-mesenchymal transition (EMT) during adapting to hypoxia, a process authorizes cell invasion and migration. In time of EMT, polar epithelial cells go through enormous phenotypic alteration and lose the polarity to transform into mesenchymal cells, weakening contact with ambient matrix and cell–cell junctions while initiating infiltrative and metastatic characteristics (De Craene and Berx, 2013).

Of late, several signaling pathways have established themselves as EMT regulators while increasing data authenticates the participation of Wnt/β-catenin pathway on account of the presence of E-cadherin/β-catenin complex who paves way for steady adherent junctions (Gujral et al., 2014; Wu et al., 2016; Shukla et al., 2016; Wang et al., 2014). In the meantime, there is a crucial association between hypoxia and Wnt/β-catenin signaling while recent

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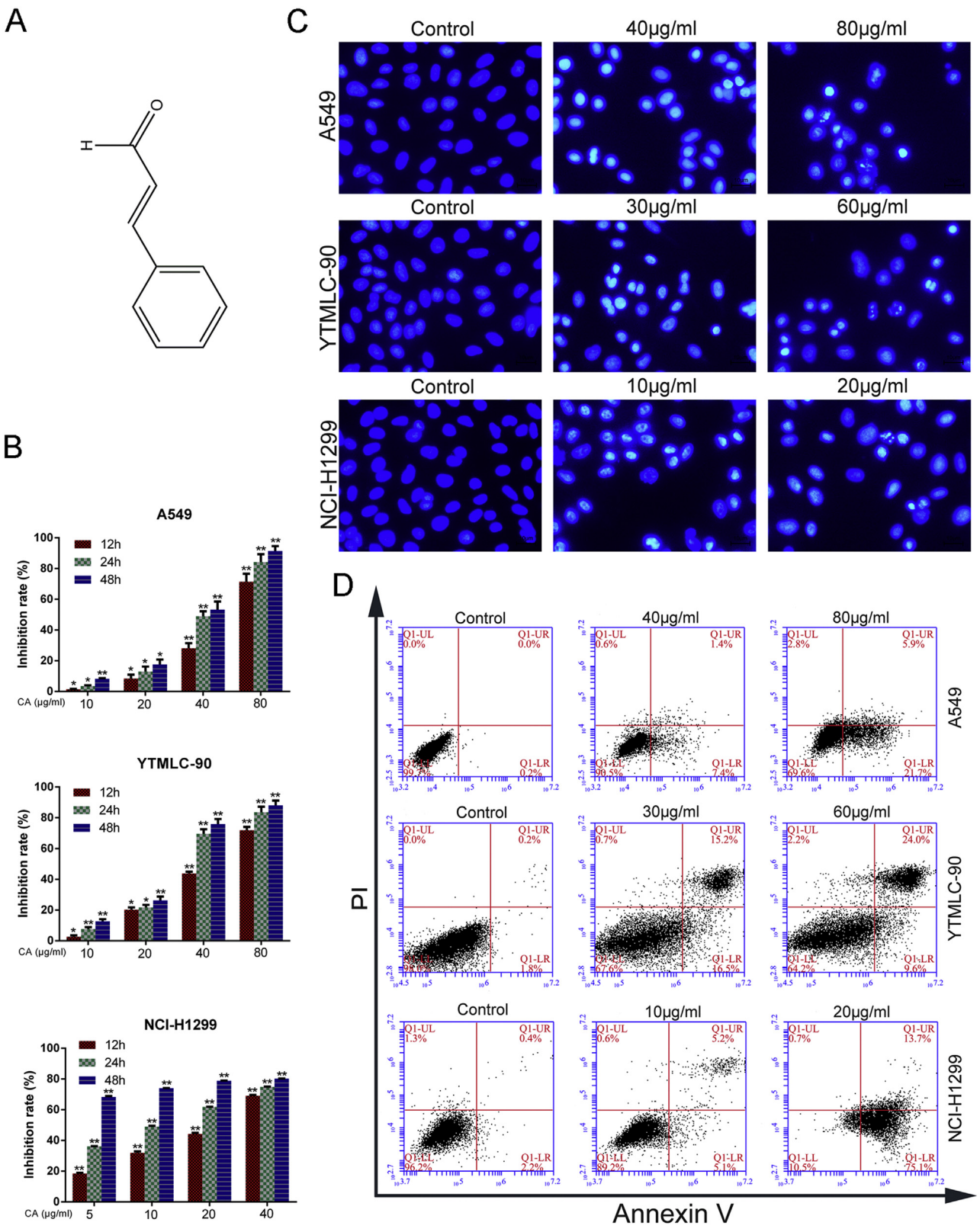

Fig. 1. CA prohibits NSCLC cell proliferation and induces apoptosis. (A) Chemical structure of cinnamaldehyde. (B) Cells were incubated with CA for 12, 24 and 48 h respectively and the inhibitive rates were measured by MTT assay. Results are presented as mean ± SD from three independent experiments. (C) Cells were treated with CA for 24 h, nuclei were characterized by Hochest 33258 staining and investigated under fluorescent microscopy (Magnification, ×200). (D) After treatment with CA for 24 h, cells were stained with FITC-conjugated Annexin V and PI for flow cytometric analysis. Viable (AV negative/PI negative); early apoptotic (AV positive/PI negative); late apoptotic (AV positive/PI positive); necrotic (AV negative/PI positive).