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SHORT COMMUNICATION

Cuminum cyminum fruits as source of luteolin-7-*O*-glucoside, potent cytotoxic flavonoid against breast cancer cell lines

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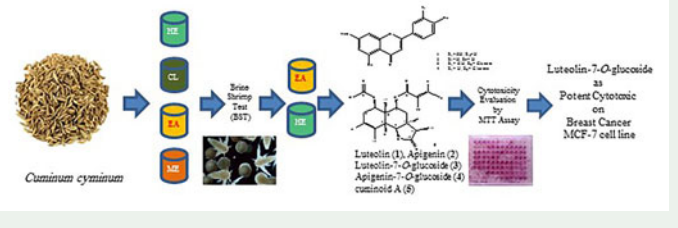
ABSTRACT

Cuminum cyminum is famous for its spicy fruits used for culinary and therapeutic properties worldwide. Brine shrimp test was performed for detecting cytotoxic fractions and subfractions. Ethyl acetate (EA) and hexane (HE) fractions demonstrated LC_{50} of 52.40 and 60.77 μg/ml against *Artemia salina* while other fractions showed no toxicity (LC_{50}> 500 μg/ml). Bioguided elucidation of EA and HE fractions were carried out and cytotoxicity of pure compounds were investigated against breast cancer cell lines (MCF-7 and MDA-MB-231) and normal cell line (NIH/3T3) by MTT assay. Four flavone structures as luteolin, apigenin, luteolin-7-*O*-glucoside and apigenin-7-*O*-glucoside from EA and cuminoid A from HE were purified and identified. Luteolin-7-*O*-glucoside demonstrated potent anticancer activities against MCF-7 cell line (IC_{50} of 3.98 μg/ml) with selectivity index of 8.0. In conclusion, flavonoids especially luteolin-7-*O*-glucoside play a significant role in cytotoxic effect of *C. cyminum* fruits and can be introduced as candidate for chemopreventive and chemotherapeutic drugs.



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1. Introduction

The fruits of *Cuminum cyminum*, cumin seeds, are old famous medicinal and culinary plant from Apiaceae family. The fruits of cumin are used as second most popular spice after *Piper nigrum* worldwide (Mnif and Aifa 2015) and cultivated in Iran and many other countries (Kaur and Sharma 2012). It is used in Iranian traditional medicine for treatment of several disorders (Nostro et al. 2005; Deepak 2013).

Cuminaldehyde was known as active antibacterial and hypoglycemic compound of cumin essential oil (Lee 2005; Gohari and Saeidnia 2011). Its anti-osteoporotic and antioxidant effects were related to existence of phytoestrogens and monoterpene alcohols, respectively (Shirke et al. 2008; De Martino et al. 2009). Immunomodulatory properties of cumin belong to the presence of flavonoid glycosides, large amounts of iron, vitamin C and A (Chauhan et al. 2010). The stomach, colon, uterine, cervix and hepatomas cancer prevention ability of cumin fruits could be related to modulation of carcinogens metabolisms (Aruna and Sivaramakrishnan 1992; Gagandeep et al. 2003). EHP (2-ethyl-6-heptylphenol), the only elucidated anticancer compound of cumin, exhibited good cytotoxicity against six cancer cell lines while it showed no toxicity against normal cell line (Mekawey et al. 2009).

The purpose of present study was isolation and identification of chemical compounds from *C. cyminum* extract via bioguided fractionation.

2. Results and discussion

From past to present, natural products play a notable role in process of drug discovery. In the cancer area, over 75% of small molecules approved by FDA are not synthetic and actually 49% of them are natural or directly derived from them (Newman and Cragg 2016). Present study focused on isolation and identification of pure compounds from cytotoxic fractions of cumin fruits.

Cytotoxicity of fractions and subfractions of *C. cyminum* fruits was evaluated by Brine Shrimp Test (BST) and reported in Table S1. According to considerable correlation between BST and *invitro* cytotoxicity tests, BST was approved by National Cancer Institute (NCI, USA) as a pre-screening method for detecting anticancer drugs (Meyer et al. 1982). LC_{50} value of EA and HE were calculated equal to 52.40 and 60.77 μg/ml, respectively which were comparable to pure cytotoxic alkaloid of berberine hydrochloride with LC_{50} of 26 μg/ml (Gohari et al. 2009). Seven subfractions of EA and HE with mortality percentage upper 50% were selected for further investigation and elucidation of their compounds. Luteolin (**1**), apigenin (**2**), luteolin-7-*O*-glucoside (**3**) and apigenin-7-*O*-glucoside (**4**) from potent cytotoxic EA subfractions and cuminoid A (**5**) from active HE subfraction were isolated and identified by spectroscopic methods (Figure 1).

Cytotoxicity of pure compounds was reported against two human breast adenocarcinoma (MCF-7 and MDA-MB-231) and normal (NIH/3T3) cell lines by MTT assay (Table S2). Following the standard of NCI, pure compounds with IC_{50} lower than 4 μg/ml were considered active on selected cancer cell lines (Goodarzi et al. 2017). According to this criterion, only luteolin-7-*O*-glucoside revealed potent anticancer activities against MCF-7 (IC_{50} of 3.98 μg/ml). On the other hand, compounds with selectivity

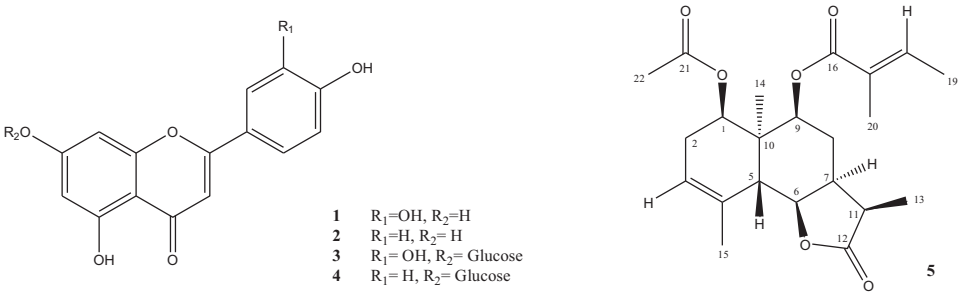

Figure 1. Structure of pure compounds; Luteolin (**1**), Apigenin (**2**), Luteolin-7-*O*-glucoside (**3**), Apigenin-7-*O*-glucoside (**4**) and cuminoid A (**5**).

index (SI) higher than 10 was classified as selective whereas those with SIs between 1 and 10 were categorized as non-selective (Goodarzi et al. 2017). In present research, all tested compounds showed non-selective cytotoxic effects against MCF-7 cell line but among them, SI of luteolin-7-*O*-glucoside was higher (equal 8.0) and the manner could be considered near selective. Luteolin-7-*O*-glucoside and apigenin-7-*O*-glucoside showed non-selective effects against MDA-MB-231cell line, (SIs equal 1.11 and 1.14, respectively).

Induction of apoptosis by activating ROS/endoplasmic reticulum stress, mitochondrial dysfunction, decreasing nitrite levels and superoxide anion radicals were suggested as molecular mechanisms of luteolin anticancer activity on colon and glioblastoma cancer cell lines (Wang et al. 2017; Vukovic et al. 2018). Another study revealed the role of luteolin on inhibition the activity and reduction the protein expression of Anoctamin 1 (ANO1) channels in prostate cancer (PC-3) cells (Seo et al. 2017). Luteolin ability for targeting cancer stem cells, prevention of cancer cell invasiveness and treatment of liver cancer was observed in previous research (Tsai et al. 2016; Zhang et al. 2016).

In present investigation, aglycone and glycoside forms of same flavonoids were elucidated. Sugar position could change cellular uptake of flavonoid and consequently their inhibitory activity on cancer cell lines. In previous investigations, luteolin-7-*O*-glucoside exhibited antiproliferative effects on HepG2 and COLO320DM cancer cells by G2/M cell cycle arrest, ROS generation and caspase signaling pathway and chemopreventive efficacy in experimental *in vivo* model (Baskar et al. 2011; Hwang et al. 2013).

3. Conclusion

Consumption of *Cuminum cyminum* fruits as a spice in foods has a significant role in prevention of different chronic diseases including cancers. Paying attention to anti-cancer investigation of cytotoxic compounds of cumin fruits is important. Potent cytotoxic activity of luteolin-7-*O*-glucoside and its less toxicity against normal cells (high selective index) indicated it can be introduced as future candidate for design of chemopreventive and chemotherapeutic drugs.

Disclosure statement

The authors declare that there is no conflict of interest.

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