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Review

Anti-cancer properties of terpenoids isolated from *Rhizoma Curcumae* – A review

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ABSTRACT

Ethnopharmacological relevance: *Rhizoma Curcumae* is a popular type of traditional Chinese medicine whose essential oils are widely used in the treatment of cancer in China. This review aims to systematically summarize and analyze the anti-cancer properties of terpenoids, the main components of essential oils in *Rhizoma Curcumae*, and thus enable the development of new anti-cancer drugs.
Materials and methods: Information on the recent progress of anti-cancer studies on terpenoids isolated from *Rhizoma Curcumae*, including β-elemene, δ-elemene, furanodiene, furanodienone, curcumol, and germacrone, was gathered and analyzed.
Results: Among these terpenoids, β-elemene is the most widely studied, whereas δ-elemene, furanodiene, furanodienone, curcumol, and germacrone have just recently attracted the attention of researchers. The anti-cancer effects of these terpenoids are related to the retardation of cell cycle arrest, the induction of apoptosis, and the inhibition of metastasis or tissue invasion, among others.
Conclusions: Most studies have focused on the in vitro data, and in vivo data is urgently needed. Further insight into the anti-cancer activity and the molecular basis of these compounds, combined with efforts in pharmaceutical chemistry and/or pharmaceutics, will potentially enable the development of new anti-cancer agents.

Contents

1. Introduction

Naturally occurring plant components from traditional herbs are a significant source of potential therapeutic compounds for cancer treatment. *Rhizoma Curcumae* (or Ezhu in Chinese) is a commonly used traditional Chinese medicine according to the

Abbreviations: Bax, Bcl-2-associated x protein; Bcl-xL, B-cell lymphoma-extra large; Bcl-2, B-cell lymphoma 2; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; ER-α, estrogen receptor-α; ERK, extracellular signal-regulated kinase; HER-2, human epidermal growth factor receptor-2; NF-κB, nuclear factor κ-light-chain enhancer of activated B cells; PARP, poly(ADP-ribose) polymerase; p38 MAPK, p38 mitogen-activated protein kinase; VEGF, vascular endothelial growth factor

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Fig. 1. Chinese medicinal material of *Rhizoma Curcumae* (left) and the prepared slices of *Rhizoma Curcumae* (right).

Chinese Pharmacopoeia (Fig. 1). Three species that produce *Rhizoma Curcumae*, namely, *Curcuma phaeocaulis* Valeton, *Curcuma kwangsiensis* S.G. Lee and C.F. Liang, and *Curcuma wenyujin* Y.H. Chen et C. Ling of the family Zingiberaceae, are officially approved for use in Chinese medicine (The State Pharmacopoeia Commission of P.R. China, 2005). These plants have demonstrated wide and diverse medicinal value for almost a thousand years, such as the resolution of blood stasis and the alleviation of pain. In Chinese clinical practice, *Rhizoma Curcumae* has been widely prescribed for the treatment of cardiovascular diseases and cancer, both alone or in combination with other herbs. The yield of *Rhizoma Curcumae* largely depends on agricultural farming, and the *Rhizoma Curcumae* species are mainly distributed in the Zhejiang, Sichuan, Guangxi, Yunnan, and Fujian provinces of China. *Rhizoma Curcumae* Longae (or Jianghuang in Chinese) (The State Pharmacopoeia Commission of P.R. China, 2005), another variety of Chinese medicine, shares several similar properties with *Rhizoma Curcumae*.

2. Chemical composition of *Rhizoma Curcumae*

The bioactive compounds in *Rhizoma Curcumae* can generally be divided into two categories: volatile and non-volatile.

The volatile compounds are almost always distributed in the essential oils of the plant (Li et al., 2002; Yang et al., 2005a, 2005b). These essential oils are considered to be one of the active components of *Rhizoma Curcumae* that are responsible for its strong anti-microbial, anti-inflammatory, neuroprotective, anti-cancer, anti-viral, and anti-thrombotic bioactivities (Makabe et al., 2006; Xiao et al., 2007; Dohare et al., 2008; Tanaka et al., 2008; Chen et al., 2011b; Tan et al., 2011). According to the 2005 Chinese Pharmacopoeia, the acceptable amount of essential oil in *Rhizoma Curcumae* is $\geq$1.5% (The State Pharmacopoeia Commission of P.R. China, 2005). Previous studies have shown that the major active components of the essential oils from *Rhizoma Curcumae* include monoterpenoids and sesquiterpenoids, such as germacrone, elemene, furanodiene, furanodienone, curcumol, curdione, curcumenol, curzerene, camphor, germacrene B, germacrene D, isocurcumenol, and neocurdione (Li and Shen, 2002; Yang et al., 2007).

Curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which possess various pharmacologic activities, are the major non-volatile compounds in *Rhizoma Curcumae* (Alappat and Awad, 2010; Belkacemi et al., 2011; Lu et al., 2011, 2012; Soetikno et al., 2011; Tan et al., 2011). Compared with the volatile compounds, the concentrations of non-volatile compounds are lower in *Rhizoma Curcumae* (Wang et al., 1999). Alkaloids, polysaccharides, and trace elements, such as Zn, Mn, Mg, Fe, P, and Ca, have also been detected in *Rhizoma Curcumae* (Sun and Wang, 1997).

3. Anti-cancer properties of the volatile compounds

3.1. Elemene

Elemene is a sesquiterpenoid mixture of β-, δ-, and γ-elemene with β-elemene (Fig. 2) as the main component. Elemene was isolated from *Rhizoma Curcumae* in the 1980s (Guo, 1983), and its anti-cancer activity was later reported (Fu, 1984). Pharmacological research on elemene, particularly β-elemene, came primarily from the latter part of the 2000s. Elemene has already been approved by China's State Food and Drug Administration as an anti-cancer adjuvant drug and has been prescribed as a part of some cancer treatment regimens in China; however, the exact anti-cancer mechanisms of elemene remain unclear.

3.1.1. β-Elemene

β-Elemene, a natural sesquiterpene extracted from the essential oils of *Rhizoma Curcumae*, accounts for 60–72% of elemene in *Rhizoma Curcumae* (Zhang et al., 2011b). β-Elemene exhibits broad-spectrum anti-cancer activity against many types of cancer cells, including leukemia, brain, breast, prostate, ovarian, cervical, colon, laryngeal, and lung carcinoma cells (Yuan et al., 1999; Zou et al., 2001; Li et al., 2005, 2010a; Wang et al., 2005a; Tao et al., 2006; Yao et al., 2008a; Chen et al., 2010; Zhu et al., 2011). The anti-cancer effects of β-elemene in vitro are concentration dependent, with IC_{50} values of hundreds of micromoles, depending on the cancer cell types. These levels are relatively higher than those of well-known chemotherapy drugs, such as doxorubicin, taxol, camptothecin, and vincristine (Li et al., 2010a; Chen et al., 2011a); however, β-elemene exhibits low toxicity to normal cells (Li et al., 2005; Wang et al., 2005a). The anti-proliferative effects of β-elemene are much weaker against human lung fibroblast CCD-19Lu cells, human bronchial epithelial NL20 cells, and human ovary epithelial IOSE-397 cells compared to the corresponding cancer cell lines (Li et al., 2005; Wang et al., 2005a). β-Elemene has similar inhibitory effects on cell proliferation in both cisplatin-resistant (A2780/CP) and cisplatin-sensitive (A2780) ovarian carcinoma cell lines (Li et al., 2005) and partially reverses drug resistance to adriamycin in breast cancer MCF-7/ADM cells (Hu et al., 2004), demonstrating its underlying anti-multidrug resistant activity. The growth of tumors from transplanted glioblastoma C6 cells in nude mice is inhibited by the intraperitoneal injection of 50 mg/kg of β-elemene for one week (Yao et al., 2008a). The tumor size of the primary melanoma and lung metastasis in mice is remarkably less than that of the control after intraperitoneal treatment with 20 and 50 mg/kg of β-elemene once a day (Chen et al., 2011a). β-Elemene also increases tumor cell immunogenicity by up-regulating the expression of heat shock protein 70 on the tumor cell surface (Wu et al., 1999).

According to previous studies, the inhibition of β-elemene-induced cancer cell proliferation is mainly due to the apoptotic cell death and cell cycle arrest (Li et al., 2005, 2010a; Wang et al., 2005a). β-Elemene appears to trigger apoptosis principally through the mitochondria-mediated caspase activation pathway (Li et al., 2010a; Wang et al., 2005a). β-Elemene exposure decreases the levels of B-cell lymphoma 2 (Bcl-2) protein, increases the release of cytochrome *c*, and activates poly (ADP-ribose) polymerase (PARP), as well as caspase-3, caspase-7, and caspase-9, in lung (Wang et al., 2005a) and prostate (Li et al., 2010a) cancer cells. β-Elemene