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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

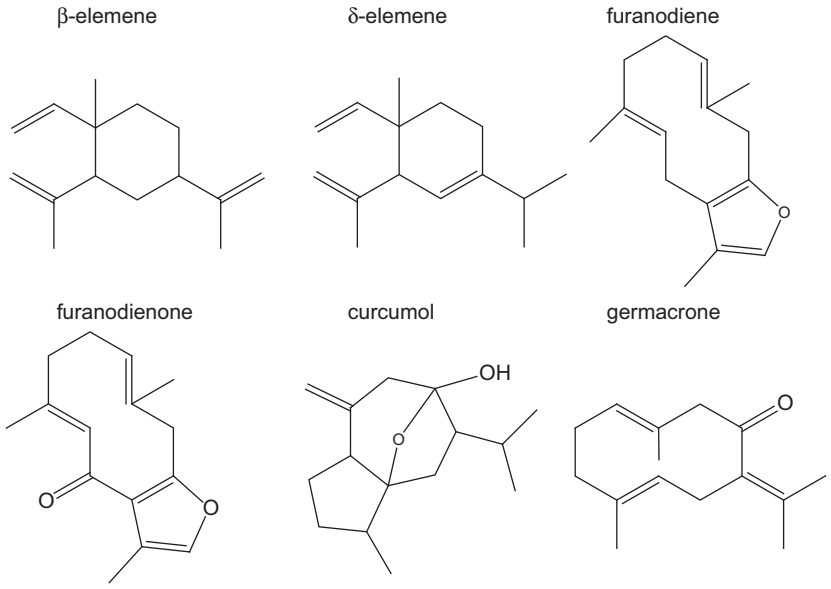

Fig. 2. The chemical structures of β-elemene, δ-elemene, furanodiene, furanodienone, curcumol, and germacrone.

treatment rapidly induces the phosphorylation of Akt and extracellular signal-regulated kinase (ERK), whereas the inhibition of Akt and ERK activation rapidly enhances β-elemene-induced apoptosis, suggesting that Akt and ERK signals are involved in β-elemene-induced cell apoptosis (Li et al., 2011a). Elemene-induced apoptosis in A549 cells is mediated in part by lysosomal membrane permeabilization and lysosomal protease cathepsin D (Li et al., 2011b). Recently, Liu et al. (2011) reported robust autophagy in human gastric cancer MGC803 and SGC-7901 cells treated with β-elemene, which was characterized by a unique cellular morphology and increased levels of light chain 3-II protein. The disruption of autophagy by knocking down Beclin-1 or co-treatment with autophagy inhibitors significantly enhances the anti-cancer effects of β-elemene. Thus, a combination of β-elemene with autophagy inhibitors may be a viable therapeutic option (Liu et al., 2011).

Cell cycle arrest triggered by β-elemene is cell type-dependent. The treatment of glioblastoma cell lines with β-elemene leads to the phosphorylation of p38 mitogen-activated protein kinases (p38 MAPK) and arrests cells in the G_0/G_1 phase, whereas the inhibition of p38 MAPK reverses this β-elemene-mediated anti-proliferation effect (Yao et al., 2008a, 2008b). β-Elemene arrests non-small cell lung cancer cells in the G_2/M phase, which is accompanied by decreased levels of cyclin B1 and phospho-Cdc2 (Thr-161), and increases the levels of p27 and phospho-Cdc2 (Tyr-15) (Wang et al., 2005a). β-Elemene reduces Cdc25C expression but enhances Chk2 expression (Wang et al., 2005a). β-Elemene also blocks the cells at the G_2/M phase in cisplatin-resistant A2780/CP ovarian carcinoma cell lines and enhances cisplatin-mediated G_2/M arrest that is accompanied by the down-regulation of cyclin B1 and Cdc2 expression as well as the elevation of p53, p21, p27, and Gadd45 levels (Li et al., 2005).

β-Elemene inhibits angiogenesis, a vital step in metastasis. At lower doses, β-elemene inhibits the vascular endothelial growth factor (VEGF)-induced sprouting of vessels from the rat aortic ring and microvessel formation in the chorioallantoic membrane of chick embryos (Chen et al., 2011a). The CD34 expression in primary melanomas is suppressed. Moreover, the metastatic melanoma colonies and the melanin content in the lungs are significantly decreased in mice after β-elemene treatment (Chen et al., 2011a).

Drug resistance is an important cause of chemotherapy failure, and combination therapy is one way to enhance the therapeutic effects and to reduce the toxicity of certain drugs. β-Elemene enhances the inhibitory effect of cisplatin on cell proliferation in H460 and A549 cells (Li et al., 2009) as well as androgen-independent prostate carcinoma DU145 and PC-3 cells (Li et al., 2010b). β-Elemene also markedly promotes cisplatin-induced apoptotic cell death via the mitochondrial activation of the caspase-mediated pathway in these cells (Li et al., 2009, 2010b). The interactions of β-elemene with paclitaxel or docetaxel range from slight synergism to synergism, which are related to the augmented cytotoxic efficacy of taxanes through the action of β-elemene (Zhao et al., 2007). β-Elemene-induced alteration of cell membrane permeability, which potentially results in the enhanced cellular uptake of taxanes, may contribute to the synergistic interactions of the combination treatment (Zhao et al., 2007). β-Elemene enhances the aclarubicin-mediated apoptotic effect and the down-regulation of cyclooxygenase-2 (COX-2) by suppressing the activation of the nuclear factor κ-light-chain enhancer of activated B cells (NF-κB) in HL-60 cells (Zheng et al., 2009). Another study showed that a combination of β-elemene and etoposide increases anti-cancer activity, which is mediated by the cleavage of PARP; the up-regulation of Bcl-2-associated x protein (Bax), p53, and p21; and the suppression of cyclin D1 in A549 cells (Zhang et al., 2011a), compared with treatment using β-elemene or etoposide alone. These previous studies demonstrate the potentially beneficial clinical combination of β-elemene with other drugs.

3.1.2. δ-Elemene

δ-Elemene (Fig. 2) is an isomeric compound of β-elemene with a different double bond site (Xie et al., 2011). It exerts anti-cancer activity against several types of cancer cells (Wang et al., 2006; Xie et al., 2009, 2011; Ying et al., 2011) without signs of suppressing normal liver WRL-687 cells (Wang et al., 2006; Xie et al., 2009). δ-Elemene activates the caspase-signaling pathway, thereby activating caspase-3 and the cleavage of PARP in colorectal adenocarcinoma cells and HeLa cells (Wang et al., 2006; Xie et al., 2009). The apoptotic effect of δ-elemene in HeLa cells can be attenuated by L-glutathione or z-DEVD-fmk (Wang et al., 2006). Treatment of NCI-H292 lung cancer cells with δ-elemene increases both p38

MAPK and inducible nitric oxide synthase levels. The over-expression of Bcl-2 or B-cell lymphoma-extra large (Bcl-xL) significantly reduces δ-elemene-triggered apoptosis (Xie et al., 2011).

3.2. Furanodiene

Furanodiene (Fig. 2) is a sesquiterpene that exhibits hepatoprotective, anti-inflammatory, anti-oxidant, and anti-cancer activities (Matsuda et al., 1998; Makabe et al., 2006; Xiao et al., 2007; Zhao et al., 2010). The anti-inflammatory activity of furanodiene is comparable with that of indomethacin, a commonly used anti-inflammatory agent (Makabe et al., 2006). Furanodiene inhibits the growth of HeLa, Hep-2, HL-60, PC-3, SGC-7901, MCF-7, MDA-MB-231, and HT-1080 cancer cell lines (Sun et al., 2009a; Zhong et al., 2012b). In vivo, furanodiene inhibits the growth of sarcoma 180 tumors in mice. The survival of mice was prolonged after intraperitoneal treatment with 10 and 30 mg/kg furanodiene once a day for 7 days (Zheng et al., 2008). Our unpublished data also showed that furanodiene exhibits similar anti-proliferative activities compared to β-elemene in lung cancer cells and inhibits breast cancer growth in vivo, demonstrating its potential application as an alternative to β-elemene (Xu et al., and Zhong et al., unpublished data).

Furanodiene retards HepG2 cancer cell proliferation through G_2/M cell cycle arrest and apoptosis, where the activation of p38 MAPK and the inactivation of the ERK signaling cascades play vital roles (Xiao et al., 2007). Furanodiene also significantly enhances the sub-G_1 peak in human leukemia HL-60 cells, which is accompanied by the activation of the caspase-3, caspase-8, and caspase-9 cascade (Ma et al., 2008). Furanodiene increases both the mRNA and protein levels of tumor necrosis factor receptor 1 (TNFR1) and the soluble TNFR1 receptor effectively inhibits furanodiene-induced apoptosis (Ma et al., 2008). A recent study from our lab revealed that furanodiene enhances the growth-inhibitory and pro-apoptotic activities of tamoxifen by inducing cell cycle arrest and cell apoptosis via CDKs-cyclins and the mitochondrial caspase-dependent and PPARγ-independent signaling pathways in breast cancer cells (Zhong et al., 2012b). Furanodiene exposure significantly inhibits the proliferation of human umbilical vascular endothelial cells and inhibits VEGF-induced proliferation (Zhong et al., 2012a). Exposure to furanodiene inhibits angiogenesis in a zebrafish model, indicating that furanodiene may be a potential anti-angiogenic compound for further study (Zhong et al., 2012a).

3.3. Furanodienone

Furanodienone (Fig. 2) is one of the main bioactive constituents of *Rhizoma Curcumae* that exhibits anti-inflammatory activity (Makabe et al., 2006; Tanaka et al., 2008). Furanodienone inhibits COX-2 more than it does COX-1 (Tanaka et al., 2008). Recent studies show that furanodienone may be a potential lead drug compound for breast cancer therapy, especially against estrogen receptor-α (ER-α)-positive breast cancer (Li et al., 2011c, 2011d). ER-α-negative MDA-MB-231 cells are less sensitive than ER-α-positive MCF-7 and T47D cells to furanodienone (Li et al., 2011d). Furanodienone specifically down-regulates the protein and mRNA expression levels of ER-α without altering ER-β expression (Li et al., 2011d). Knockdown of ER-α decreases the inhibitory effect of furanodienone on cell growth in MCF-7 cells (Li et al., 2011d). Furanodienone causes G_1 cell cycle arrest in BT474 cells and induces apoptosis in SKBR3 cells (Li et al., 2011c). Furanodienone also interferes with epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor-2 (HER-2) signaling in treated cells, shown by the decrease in phosphorylated EGFR, HER-2, Akt, and GSK-3β and the increase in p27 (Li et al., 2011c).

3.4. Curcumol

Curcumol (Fig. 2), a guaiane-type sesquiterpenoid hemiketal (Lou et al., 2010), was first isolated in 1965, and its absolute stereostructure was determined in 1984 (Hikino et al., 1965; Inayama et al., 1984). Curcumol is one of the major components of *Rhizoma Curcumae*, and it is commonly used as a quality control marker (Deng et al., 2006). Though its existence has long been known, there are few pharmacological studies on curcumol, possibly because of its poor water solubility. Curcumol exhibits anti-hepatic fibrosis activity, possibly through the down-regulation of the transforming growth factor-β1 and cytochrome P450 in HSC-T6 cells (Jiang et al., 2005). Curcumol inhibits the proliferation of MCF-7, MM231, HeLa, and OV-UL-2 cancer cells but has negligible effects on normal breast cells (Xu et al., 2005). A dose of 50 μg/mL of curcumol significantly inhibits the total RNA synthesis in MCF-7, MM-231, and HeLa cells (Xu et al., 2005). Curcumol has been reported to cause concentration-dependent cell death in human lung adenocarcinoma ASTC-a-1 cells and to induce G_2/M phase arrest, nuclear fragmentation, phosphatidylserine externalization, and rapid Bax translocation from the cytosol into the mitochondria at 100 μM (Zhang et al., 2011c). Z-VAD-fmk, a broad-spectrum inhibitor of caspases, cannot reduce curcumol-induced apoptosis, indicating that curcumol induces apoptosis via a caspase-independent mitochondrial pathway in ASTC-a-1 cells (Zhang et al., 2011c). Curcumol inhibits the proliferation and induces the apoptosis of nasopharyngeal carcinoma CNE-2 cells, whose mechanism may be related to the down-regulation of NF-κB (Wang et al., 2011).

3.5. Germacrone

Germacrone (Fig. 2) is one of the mandatory indices in the quality control of *Rhizoma Curcumae* essential oils in the Chinese Pharmacopeia (The State Pharmacopoeia Commission of P.R. China, 2005); however, pharmacological studies on this compound are very limited. Germacrone has a potent protective effect on acute liver injury in mice induced by either D-galactosamine/lipopolysaccharides or tumor necrosis factor-α (Matsuda et al., 1998; Morikawa et al., 2002). The anti-cancer properties of germacrone and the related mechanisms were recently reported by our lab (Zhong et al., 2011). Germacrone inhibits cell proliferation, increases lactate dehydrogenase release, mediates G_1 and G_2 cell cycle arrest, and induces mitochondrial membrane potential depolarization in human breast cancer MCF-7 and MDA-MB-231 cells (Zhong et al., 2011). Germacrone treatment increases Bok expression and cytochrome *c* release from the mitochondria without affecting Bcl-2, Bcl-xL, Bax, and Bim protein expression and induces the cleavage of PARP and the activation of caspase-3, caspase-7, and caspase-9 (Zhong et al., 2011); however, the germacrone concentration required to achieve its anti-cancer properties is relatively high (i.e., nearly 200 μM) (Zhong et al., 2011). Recently, Barrero et al. (2011) reported that the synthesis of β-elemene and other bioactive elemenes is possible using germacrone as a renewable starting material and that the synthesis is achieved in only three to five steps with excellent overall yields. This finding suggests that germacrone may be used as a viable starting material for elemene synthesis.

4. Discussion

Among the terpenoids isolated from *Rhizoma Curcumae*, β-elemene is the most widely studied, especially in recent years, while anti-cancer studies on other terpenoids are relatively few. Most of the aforementioned studies focused mainly on the in vitro anti-proliferative properties of these compounds. More studies, especially pertaining to (1) other anti-cancer properties, such as

anti-angiogenic and anti-metastatic activities, and (2) in vivo levels, are urgently needed to determine the potential of these terpenoids in cancer therapy.

Regarding the anti-cancer mechanisms of these terpenoids, their exact targets are still unknown despite many research efforts, especially in recent years. Developments in biology, such as the emergence of the "-omics" technologies, including genomics, transcriptomics, metabolomics, and proteomics, may greatly promote the success of future investigations. For instance, using proteomics, Yue et al. (2008) found that the cytotoxic effect of ganoderic acid D, a natural compound isolated from the traditional Chinese medicine *Ganoderma lucidum*, is associated with the regulated expression of 21 proteins. The direct binding affinity of ganoderic acid D to 14-3-3 zeta was further confirmed through surface plasmon resonance biosensor analysis (Yue et al., 2008). Similar experiments could be performed in the future using the terpenoids from *Rhizoma Curcumae*.

The structural modification of these terpenoids may produce semisynthetic derivatives demonstrating greater activity, with several successful efforts in recent years (Sun et al., 2009b; Xu et al., 2006; Yu et al., 2011). Yu et al. (2011) synthesized five novel piperazine derivatives of β-elemene, which exhibit higher potency than β-elemene in human leukemia HL-60 cells. Xu et al. (2006) also synthesized 14 β-elemene derivatives containing a piperazine, a morpholine, a tetrahydropyrrole, a thiophenylethylamine, or a cyclohexamine group. Most of these derivatives have increased anti-proliferative activity in cancer cells compared with that of β-elemene. Sun et al. (2009b) reported that the anti-proliferative activity of β-elemene monosubstituted amine and Re(CO)3-β-elemene derivatives against HeLa cells is remarkably improved compared with that of the parent β-elemene.

To enhance drug-like features, such as solubility and bioavailability, the drug delivery system may be modified. β-Elemene-loaded microemulsions (Hu et al., 2011), nano-liposomes (Hu and Xu, 2008), and solid lipid nanoparticles (Wang et al., 2005b) have achieved some success. For example, the elemene microemulsion, a clarified and isotropic system that contains 1% elemene, 5% ethanol, 15% propylene glycol, 15% glycerol, and 5% polysorbate 80, was characterized as 57.7 ± 2.8 nm in size (Zeng et al., 2010). This new, easy to prepare formulation provides high entrapment efficiency, excellent clarity, good stability, and improved bioavailability.

5. Conclusion

Rhizoma Curcumae is an important traditional Chinese medicine with "Huoxuehuayu" (promoting blood circulation and removing blood stasis) activity, and its essential oils contribute to several of its pharmacological effects. The chemical composition of *Rhizoma Curcumae* is being gradually clarified; however, the pharmacological activities and the molecular mechanisms remain unclear. Future studies should further clarify the anti-cancer mechanisms and in vivo anti-cancer properties of these terpenoids. Further structural modification studies are also encouraged in order to obtain additional valuable analogs.

An in-depth understanding of their anti-cancer potential, both in vitro and in vivo, and the molecular mechanisms of the terpenoids from *Rhizoma Curcumae*, along with efforts in pharmaceutical chemistry and/or pharmaceutics, may enable the development of new anti-cancer drugs.

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