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New Chemotherapeutic Agents: Monoterpenes and Fatty Acid Synthase Inhibitors

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http://dx.doi.org/10.5772/62283

Abstract

Colorectal cancer (CRC) is one of the most common cancers in the world. Around 90% of CRC deaths are caused by metastasis, and systemic chemotherapy is the last hope for patients with unresectable metastases of CRC. Although recent systemic chemotherapy advances have prolonged survival in patients with unresectable CRC, the effectiveness, cost, and side effects of the chemotherapeutic agents still need to improve. The use of plant-, microbial-, or fungal-derived natural products for medical benefits is playing an important role globally, such as in anti-cancer drugs and antibiotics.

The cancer cells are different from normal cells in many points. In contrast to normal cells, most of the fatty acids in malignant cells are derived from de novo lipogenesis that emphasizes the importance of up-regulation of endogenous lipid biosynthesis in malignant transformation.

Several anti-cancer drugs available on the market today, such as Taxol, Oncovin, Navelbine, and Vumon, trace their origins to plants. Monoterpenes of several essential oils from plants possess medical benefits. Various monoterpenes such as d-limonene, geraniol, 1,8-cineole, and perillyl alcohol (POH) are effective for CRC in in vitro and animal experiments.

Fatty acid synthase (FASN), the key enzyme of de novo lipogenesis, is significantly up-regulated in many cancers including CRC. In normal adults, FASN is mainly expressed in cells with lipid metabolisms such as liver and adipose tissues. The expression of FASN has been found to be up-regulated in various human cancer cells including CRC. Lipogenesis by cancer cells provides proliferative and survival advantages and drug resistance against chemotherapeutic agents. Inhibition of lipogenesis targeting FASN induces apoptosis selectively in human cancer cells both in vitro and in vivo. The differential expression of FASN between cancer cells and normal cells makes FASN a suitable target for cancer treatment. The pharmacological FASN inhibitors are cerulenin, C75, C93, orlistat, luteolin, epigallocatechin-3-gallate (EGCG), triclosan, capsaicin, curcumin, and so on.
In this chapter, we discuss the usefulness of monoterpenes and FASN inhibitors against CRC for the novel chemotherapeutic agents.

**Keywords:** fatty acid synthase inhibitor, monoterpe, colorectal cancer, chemothera-
py, cerulenin

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1. Introduction

Colorectal cancer (CRC) is one of the most common cancers in the world, and about 90% of CRC deaths are caused by metastasis, not by primary solid tumors [1]. Despite recent advances, systemic chemotherapy for metastatic disease is considered palliative, and long-term survivors are rarely seen treated only by chemotherapy [2]. Natural products are the most successful strategy to discover new agents used in anti-cancer therapy and more than two-thirds of the drugs used in cancer treatment [3]. A large number of studies have focused on the efficacy of essential oils and their chemical constituents as bioactive new products [4], especially cancer treatment [5, 6]. The essential oils are a mixture of volatile lipophilic substances: monoterpenes, sesquiterpenes, and phenylpropanoids. These substances have many biological activities such as analgesic, anti-convulsant, anti-inflammatory [6, 7, 9], and anti-tumor activities [10–14]. Monoterpenes of several essential oils from plants possess medical benefits. The various monoterpenes, such as limonene, geraniol, 1,8-cineole, and perillyl alcohol (POH), are effective for CRC in in vitro and animal experiments [15].

2. Monoterpenes

Terpenes are the largest class of plant-derived secondary metabolites, and they are the main component of essential oils [16, 17]. Monoterpenes are the largest class of terpenes [18]. The therapeutic properties of monoterpenes are anti-allergic, anti-inflammatory, anti-cancer, and so on [19]. The basic structure of monoterpenes consists of two isoprene units (C5H8)$_2$. Monoterpenes exist in many forms in nature, such as hydrocarbons, alcohols and their glycosides, ethers, aldehydes, ketones, carboxylic acids, and esters [15]. Monoterpenes are classified as acyclic, monocyclic, and bicyclic according to the ring formation. The important acyclic monoterpenes, which have anti-tumor effects, are myrcene and geraniol [20]. The important monocyclic monoterpenes with anti-tumor effects are linalyl acetate, camphor, thymol, carvacrol, POH, d-limonene, and many others. POH and d-limonene are said to inhibit the development of several types of carcinomas as they were in Phase I and II clinical testing, respectively [21, 22]. The bicyclic monoterpenes that have anti-tumor effects are 1,8-cineole (eucalyptol), and α- and β-pinene [23, 24].
3. Monoterpene and colorectal cancer

In this chapter, we reviewed monoterpenes with anti-CRC activity. The monoterpenes presented in this chapter were selected with reference to effects shown in specific experimental models for evaluation of anti-tumor activity and/or by complementary studies aimed to elucidate mechanisms of action shown in Table 1.

| Compound       | Mechanism                  | Animal/cell line tested | IC50, etc          | Reference |
|----------------|----------------------------|-------------------------|--------------------|-----------|
| Acyclic        |                            |                         |                    |           |
| Geraniol       | Cell cycle arrest/5FU      | Caco-2                  | 200 μM (Caco-2 IC30) | [26]     |
|                | synergy                    |                         |                    |           |
|                | Cell cycle arrest          | Caco-2                  | 400 μM (70% inhibition) | [27]     |
|                | ERK1/2 inactivation        | Caco-2                  | 400 μM (60% reduction of PKC activity) | [28]     |
|                | Synergistic with 5FU       | TC-118/Swiss nu/nu mouse | 5FU 20 mg/kg, geraniol 150 mg/kg | [29]     |
|                | Thymidylate synthase       |                         | 53% tumor reduction |           |
| Monocyclic     |                            |                         |                    |           |
| Alpha terpineol| Cell cycle arrest,         | HCT-116 (p53+/+, −/−)   | 1 mM               | [30]     |
|                | apoptosis                  |                         |                    |           |
| Linalyl acetate|                            |                         |                    |           |
| Camphor        |                            |                         |                    |           |
| Carvacrol      | Anti-oxidant activity      | Caco-2, K562, HepG2     | 150–200 μM (IC50 of K562) | [31, 32] |
|                | Cytotoxic effect           | Caco-2                  | 600 μM (IC50)      | [34]     |
| Thymol         | Anti-oxidant activity      | DMH/DSS carcinogenesis rat | 50 mg/kg         | [35]     |
|                | Cytotoxic effect           | Caco-2                  | 700 μM (IC 50)) | [34]     |
|                | Apoptosis                  | HL60                    | 75 μM (12 h), 50 μM (24 h) | [36]     |
| TQ             | Apoptosis, Wnt signal      | Apc<sup>min</sup> rat   | 375 mg/kg BW 12 w (polyp decrease) | [38]     |
|                | Apoptosis                  | HCT-116 xenograft       | 5 mg/kg (3 times/week ip) | [39]     |
|                | ERK JNK, apoptosis by ROS  | Caco-2                  | 15.0 μM (IC50 24 h) | [40]     |
|                |                            | HCT-116                 | 30 μM (IC50 24 h)  |           |
|                |                            | LoVo                    | 38 μM (IC50 24 h)  |           |
|                |                            | DLD-1                   | 42 μM (IC50 24 h)  |           |
### Table 1. Monoterpene and colorectal cancer.

| Compound          | Mechanism                                  | Animal/cell line tested | IC50, etc         | Reference |
|-------------------|---------------------------------------------|-------------------------|-------------------|-----------|
| HT-29             | 110 μM (IC50 48 h)                          |                         |                   | [41]      |
| MDA-MB-231        | viability 16.0 ± 5.6% (96 h)                |                         |                   | [41]      |
| TQ (8 mg/kg p.o.) | protect cardiotoxicity                      |                         |                   | [42]      |
| HT-29             | 46.8 μM to 39.0 μM (with DOX)               |                         |                   | [43]      |
| SW480, HT-29      | 100 ppm, 74.2% reduction of SW480          |                         |                   | [44]      |
| Azoxymethane,     | 0.5% d-limonene decreases ACF formation    |                         |                   | [45]      |
| F344 rat          |                                             |                         |                   |           |
| colon cancer      | 3.2 mM viability 30% decrease              |                         |                   | [46]      |
| CRC patients      | 0.5 mg/m²/day                               |                         |                   | [47, 48] |
| HT-29             | 50 μM (IC50)                                |                         |                   | [49]      |
| Azoxymethane      | 2 g/kg decrease cancer incidence to 1/3    |                         |                   | [50]      |
| HCT-116           | 0.5 mM (IC50)                               |                         |                   | [51]      |
| CRC patients      | 1200–1600 mg/m²/day                         |                         |                   | [52–56]  |
| RKO               | 50 mg/kg reduced tumor weight as 1/3        |                         |                   | [24]      |

3.1. Geraniol

Geraniol is an acyclic monoterpene. Geraniol is one of the main components of geranium oil, and its content is about 20% [25]. Geraniol shows a cytotoxic effect in Caco-2 colon cancer cells [26–28]. Geraniol decreases the expression of p44/p42 ERK and has an anti-tumor effect in Caco-2 cells [28]. In addition, geraniol has a synergistic anti-tumor effect combined with 5-fluorouracil in TC-118 human colorectal tumors [29].

3.2. Alpha terpineol, linalyl acetate, and camphor

Alpha terpineol, linalyl acetate, and camphor are monocyclic monoterpene, and they are the bioactive components of Lebanese sage (Salvia libanotica) essential oil [30]. Linalyl acetate is found in many flowers and spice plants. Camphor is found in the wood of the camphor laurel.
These three components cause inhibition of the growth of the human colon cancer cell lines (HCT-116 p53+/+ and p53−/−) and were inactive on FHs74 Int normal human intestinal cell lines [30]. It has been demonstrated that alpha terpineol, linalyl acetate, and camphor synergize to induce cell cycle arrest and apoptosis, mainly through mitochondrial damage (cytochrome c release), caspase activation, and PARP cleavage in human CRC cells [30].

3.3. Carvacrol

Carvacrol is a monocyclic monoterpenol constituent of essential oils produced from the aromatic plant *Oreganum vulgarea* sp. Carvacrol has a cytotoxic effect in K562, HepG2, and Caco-2 cells [31, 32]. It inhibits the proliferation and migration of the two-colon cancer cell lines HCT-116 and LoVo. Cell invasion was suppressed after carvacrol treatment by decreasing the expression of matrix metalloprotease-2 (MMP-2) and MMP-9. Carvacrol treatment also caused cell cycle arrest in the G2/M phase and decreased cyclin B1 expression. Finally, carvacrol-induced cell apoptosis in a dose-dependent manner [33]. Carvacrol promotes the endogenous anti-oxidant system and suppresses inflammation in DMH/DSS-induced rats and reduces the tumor formation of colitis-associated CRC [34].

3.4. Thymol

Thymol is a monocyclic monoterpenol and can be found in the oil of thyme. Thymol presents a cytotoxic effect in several cell lines, such as HepG2, V79, and Caco-2 human colon cancer cells [35]. The cytotoxic effect of thymol on human leukemia cell HL-60 appears to be associated with induction of cell cycle arrest at sub G0/G1 phase and apoptotic cell death. Thymol induced apoptosis in HL-60 cells involves both caspase-dependent and caspase-independent pathways [36].

3.5. Thymoquinone

Thymoquinone (2-methyl-5-isopropyl-1,4-benzoquinone) is a monocyclic monoterpenol present in the seed oil of the plant *Nigella sativa* L. (Renunculaceae family), commonly known as black cumin or black seed that is widely consumed as a condiment in many societies [37]. Thymoquinone possesses anti-proliferative and pro-apoptotic activities in several cancer cell lines [37]. Thymoquinone decreased the number of large polyps in the intestine, activated GSK-3-β, increased membrane localization of β-catenin, and reduced nuclear expression of c-myc in in vivo experiments of Apc<sup>min</sup> mice [38]. Thymoquinone reduced the size of xenograft tumors, induced apoptosis, and inhibited tumor cell proliferation in HCT-116 human colon cancer cell xenograft tumor growth in NMRI mice [39]. Reactive oxygen species and activation of ERK and JNK signaling were involved in thymoquinone-induced apoptosis in a panel of human colon cancer cells (Caco-2, HCT-116, LoVo, DLD-1, and HT-29) [40]. Encapsulation of thymoquinone into nanoparticles enhances the anti-proliferative effect in HT-29 cells [41]. Thymoquinone boosted the effect of doxorubicin by reducing its cardiotoxicity in several cancer cell lines including the CRC cell line HT29 [42, 43].
3.6. D-limonene

Limonene is a monocyclic monoterpen, and it is a major constituent of citrus oils. It has optical isomers, d-limonene and l-limonene, and d-limonene has a more lemon-like odor and therapeutic effects. D-limonene is contained in citrus volatile oil, and the citrus volatile oil induces apoptosis and has an anti-angiogenic effect against colon cancer SW480 and HT-29 [44]. D-limonene also inhibited the development of colonic aberrant crypt foci (ACF) induced by azoxymethane in F344 rats, which suggests that this monoterpenoid might be a chemopreventive agent for colonic carcinogenesis in rats [45]. D-limonene suppressed the viability of LS174T colon cancer cells in a dose-dependent manner and caused a dose-dependent apoptotic cell death. D-limonene decreased the levels of Akt pathway, activated caspase-3 and caspase-9 and PARP cleavage in a dose-dependent manner [46]. A group of 32 patients with solid tumors registered and completed Phase I study of administration of d-limonene orally. The maximum tolerated dose was 8 g/m² per day, and nausea, vomiting, and diarrhea were dose-limiting factors [47]. Three individuals with colorectal carcinoma with d-limonene suspended progression of the disease for over 6 months [47]. D-limonene at a dosage of 0.5 g/m²/day was able to halt progression of cancer for 9 months in a patient diagnosed with locally advanced mucinous cystadenocarcinoma of the appendix. A patient with presacral recurrence of an adenocarcinoma in the sigmoid colon experienced a minor reduction (<50%) in tumor size at a dose of 0.5 g/m²/day for 12 months. Another patient with local retrovesical recurrence of colorectal adenocarcinoma remained stabilized on 1 g/m²/day (2 g/day) for 7.5 months [47, 48].

3.7. Perillyl alcohol (POH)

POH is a monocyclic monoterpen, and it is derived from limonene. POH is a naturally occurring dietary monoterpen isolated from the essential oils of lavender, peppermint, and other plants. It has an anti-tumor effect in several cancer cell lines including the HT-29 colon cancer cell line [49]. Dietary POH at 1 or 2 g/kg greatly reduced the incidence and the number of invasive adenocarcinomas of the colon of rats injected with azoxymethane [50]. To establish the molecular mechanisms of POH, cell cycle and cell cycle regulatory proteins were studied in HCT-116 human colon cancer cells. POH exerted a dose-dependent inhibitory effect on cell growth correlated with a G1 arrest [51]. Phase I and II clinical trials using POH were started [21, 22, 52–55]. In seven Phase I clinical trials, POH was administered orally to cancer patients with advanced malignancy. POH was given in divided doses ranging from 2,400 to 16,200 mg per day (equivalent to approximately 40–270 mg/kg). Treatment duration varied with each patient but was generally between 2 and 9 months. Nausea, vomiting, eructation, and satiety were dose-limiting factors in several of these trials [21]. Meadows et al. conducted Phase II study in patients with metastatic CRC [56]. The authors found that oral POH administration did not have clinical anti-tumor activity when used for patients with advanced colorectal carcinoma, despite preclinical evidence of anti-cancer activity. Instead of oral administration, POH was administered through nasal inhalation to recurrent glioma patients, and these studies not only demonstrated clinical activity of POH but also revealed that long-term intranasal inhalation of the compound was very well tolerated over several years of daily use [21, 57, 58].
3.8. 1,8-cineole (eucalyptol)

1,8-cineole (eucalyptol) is a bicyclic monoterpene, which comprises up to 90% of the essential oil of some species of the generic product Eucalyptus oil. 1,8-cineole has several effects such as anti-inflammatory, anti-oxidant, and anti-atherosclerotic activity in vitro and in vivo. 1,8-cineole has a cytotoxic effect in Hep G2, HeLa, MOLT-4, K-562, and CTVR-1 cell lines [59]. 1,8-cineole was reported to have moderate anti-oxidant and cytotoxic properties and pronounced analgesic and anti-tumor activity [60]. Murata et al. showed that the human CRC cell line RKO expressed phosphoserine 473-Akt constitutively and treatment with 1,8-cineole dephosphorylated Akt. 1,8-cineole treatment activated p38 and dephosphorylated Akt, which induced caspase-3 cleavage and resultant cleavage of PARP and finally caused apoptosis. In a xenograft mouse model, 1,8-cineole therapy showed tumor shrinkage [24].

3.9. α- and β-pinene

α- and β-pinene are bicyclic monoterpenes. They are natural compounds isolated from pine needle oil. Bhattacharjee and Chatterjee [61] promoted the identification of proapoptotic, anti-inflammatory, anti-proliferative, anti-invasive, and potential anti-angiogenic activities of α-pinene, β-pinene, d-limonene, and geraniol by employing a dual reverse virtual screening protocol. The anti-tumor activity of α-pinene on the BEL-7402 hepatoma cell line in vitro and in vivo and the mechanisms involved were investigated. The results showed that liver cancer cell growth was inhibited obviously in vitro and in vivo: Chk1 and Chk2 levels were up-regulated; and Cyclin B, CDC25, and CDK1 levels were down-regulated [62].

3.10. Conclusion of monoterpenes

Several studies have shown in vitro and in vivo anti-tumor activity of monoterpenes derived from many essential oils obtained from plants. This chapter shows that many monoterpenes are being examined for in vitro and in vivo anti-tumor activity of CRC. In addition, two of the monoterpenes, d-limonene and POH, were moved on to Phase I and II clinical trials, which indicates the safety of monoterpenes for clinical use. There are many monoterpenes that show anti-tumor effects in vitro and in vivo, and with additional research some monoterpenes act to inhibit the proliferation and to induce tumor cell death in clinical use.

4. Fatty acid synthase (FASN) inhibitors

Fatty acid synthase (FASN), the key enzyme of de novo lipogenesis, is significantly up-regulated in many cancers including CRC [63, 64]. In normal adults, FASN is mainly expressed in cells with lipid metabolisms, such as liver and adipose tissues [65]. Under a usual diet, the de novo fatty acid synthesis in normal cells is rarely needed and the FASN protein level is low [66]. FASN is a 270-kDa cytosolic enzyme containing seven catalytic domains [67]. FASN synthesizes palmitate from one acetyl-CoA, seven malonyl-CoAs, and seven NADPHs [65, 66]. The expression of FASN has been found to be up-regulated in various human cancer cells including...
CRC [68–70]. FASN is elevated in ACF compared with normal colonic mucosa [71]. Lipogenesis by cancer cells gives proliferative and survival advantages and drug resistance against chemotherapeutic drugs [72]. An increased expression of lipogenic enzymes is associated with a more aggressive metastatic phenotype in CRC [73]. Inhibition of lipogenesis targeting FASN induces apoptosis selectively in human cancer cells both in vitro and in vivo [74–76]. The differential expression of FASN, together with the different responses to FASN inhibition between cancer cells and normal cells, makes FASN a suitable target for cancer treatment. The pharmacological FASN inhibitors are cerulenin, C75, C93, orlistat, luteolin, and epigallocatechin-3-gallate (EGCG). Triclosan [77], capsaicin [78], and curcumin [79] are reported to inhibit FASN and have anti-tumor effect. There are several newly developed agents, such as TVB-3567 [80], TVB-3166 [81], and GSK2194069 [82].

| Compound | Mechanism | Animal/cell line tested | IC50, etc | Reference |
|----------|-----------|--------------------------|-----------|-----------|
| Cerulenin | Akt inhibition | Colon 26 liver metastasis/Balb-c mouse | 30 mg/kg reduces 50% of liver metastasis | [93] |
| Akt inhibition, synergistic with oxaliplatin | RKO/xenograft in SCID mouse | Cerulenin 15 mg/kg, oxaliplatin 2.5 mg/kg | [94] |
| Malonyl-co A independent apoptosis | RKO | 10 μg/ml | [101] |
| C75 | Malonyl-co A independent apoptosis | RKO | 10 μg/ml | [101] |
| Orlistat | ER stress, synergistic with thapsigargin | HT-29 | Orlistat 25 μM, thapsigargin 25 nM | [114] |
| Luteolin | Cell cycle arrest, apoptosis | HT-29 | 60 μM 83% decrease of survival at 72 h | [121] |
| SIP, ceramide, Akt inhibition | Caco-2 | 100 μM more than 50% decrease at 48 h | [122] |
| Synergic effect with aspirin, iNOS, COX2 inhibition | DMH rat carcinogenesis | 0.2 mg/kg/weekly for 15 weeks | [123] |
| β-catenin, GSK-3-β, cyclin D1 inhibition | Mouse, azoxymethane administration | 1.2 mg/kg orally | [124] |
| EGCG | Cell proliferation, apoptosis | HCT-15 | 100 μM (IC50) | [125] |
| VEGF/VEGFR axis | SW837 mouse xenograft | 0.01% EGCG drinking | [133] |
| HES1, Notch 2 | HT-29 mouse xenograft | 5 mg/kg intragastrically | [135] |
| Clinical trials | Polyp relapse decreasing | 1.5–2.5 g green tea extract/daily | [137] |

Table 2. FASN inhibitors and colorectal cancer.
In this chapter, we reviewed FASN inhibitors with anti-CRC activity. The FASN inhibitors presented in this chapter were selected with reference to effects shown in specific experimental models for evaluation of anti-tumor activity and/or by complementary studies aimed to elucidate mechanisms of action shown in Table 2.

4.1. Cerulenin

Cerulenin is the first-known FASN inhibitor, which is isolated from the culture filtrate of the fungus Cephalosporum caerulens [83–86]. It was originally used as an anti-fungal antibiotic and is a potent non-competitive irreversible inhibitor of FASN by binding to the active site of the KS domain [87–89]. Cerulenin treatment significantly decreases fatty acid synthesis and induces selective cytotoxicity in various types of cancer cells [90–92]. Murata et al. [93] revealed the anti-tumor activities of cerulenin in murine colon cancer cell lines Colon 26 and CMT 93. Shiragami et al. [94] evaluated the anti-tumor effect of cerulenin in murine colon cancer cell lines Colon 26 and CMT 93. Overexpression of FASN has been seen to cooperate with survival pathways, including the phosphatidylinositol-3-kinase (PI3K)/Akt pathway. CRC cell lines expressed FASN and phosphorylated Akt constitutively, and the treatment of CRC cells with cerulenin suppressed FASN expression, dephosphorylated constitutive activated Akt, and increased cleaved caspase-3 in murine CRC cell lines Colon 26 and CMT 93, and in human CRC cell line HCT-116 and RKO cells [93, 94]. FASN has a major role in the synthesis of phospholipids including phosphatidylinositol trisphosphate (PIP3) [95]. PIP3 binds to Akt and activates kinase phosphoinositide-dependent protein kinase-1 (PDK-1) with high affinity, and the phosphorylation of Akt is dependent on PIP3 [95]. In an in vivo experiment, Murata et al. [93] evaluated the potential effectiveness of cerulenin for metastatic liver tumors of the CRC cell line. Shiragami et al. [94] revealed the synergistic effect of cerulenin in combination with oxaliplatin, which means that reduction is possible when combined with cerulenin in the CRC treatment. Recently, Chang et al. revealed cerulenin down-regulated energy metabolism and PI3K/Akt/mTOR signaling pathway using human CRC cell lines HT-29 and LoVo [96]. Bauerschlag et al. [97] revealed that relative to normal fallopian tube tissue, ovarian cancer tissue had 1.8-fold FASN overexpression and cell lines had around 100-fold protein overexpression. In the ovarian cancer cell lines, cerulenin markedly decreased FASN expression and cell viability and induced apoptosis. Unlike concomitant administration, sequential cerulenin/cisplatin treatment reduced cisplatin’s half-maximal inhibitory concentration up to 54% in a cisplatin-resistant cell line [97].

4.2. C75

C75 is a cerulenin-derived, semi-synthetic FASN inhibitor lacking cerulenin’s reactive epoxy group [98], and C75 is more chemically stable than cerulenin [98]. C75 has significant anti-tumor effects against many types of cancer cells, such as the human breast [98], prostate [91], and ovary [99] as well as renal carcinoma in xenograft animal models [100]. Li et al. reported that both C75 and cerulenin produce rapid, potent inhibition of DNA replication and S-phase progression in human cancer cells, as well as apoptotic death. They also revealed that these
FASN inhibitors reduce cyclin A-, B1-associated kinase activities, and p53, p21 accumulation which cause growth arrest at G1 and G2 [101]. Cerulenin and C75 were useful against p53 mutations [101]. They discussed that accumulation of malonyl-CoA was independent of apoptosis induction, and they estimated that the effect of these agents has resulted from product depletion [101].

4.3. C93

In addition to inhibiting FASN, C75 stimulates fatty acid oxidation by activating carnitine O-palmitoyltransferase-1 (CPT1) [102]. Activation of CPT1 contributes to the reduction of neuropeptide Y expression in the hypothalamus [102, 103]. The limiting toxicity of C75 is due to this stimulation of fatty acid oxidation rather than the inhibition of FASN. C93, which was designed to specifically inhibit FAS without affecting CPT1 activity [104]. Orita et al. revealed that C93 inhibited FASN of four human lung cancer cell lines: LX7, H1975, H460, and A549. Moreover, C93 inhibited subcutaneous and orthotopic H460 xenograft tumor without causing anorexia and weight loss in the treated animals [105]. They found that higher levels of FAS expression were observed in 77% of the squamous cancers, 96% of the adenocarcinomas, and 94% of Barrett’s lesions with high-grade dysplasia, when compared with the levels in normal esophageal epithelium and non-dysplastic Barrett’s mucosa. Mice with Colo680N esophageal squamous cell carcinoma cell xenograft were treated C93, which significantly inhibited the growth of orthotopic xenograft tumors without causing anorexia and weight loss in the treated animals [106].

4.4. Orlistat

Orlistat is an anti-obesity drug approved by the US Food and Drug Administration. Orlistat is also reported to inhibit FASN [107]. Orlistat is the only long-term option for obesity treatment in the United States, and it is the only approved weight loss drug in Europe [108]. Orlistat is a synthetic hydrogenated derivative of lipstatin, produced by the fungus Streptomyces toxytricini [109]. It partially inhibits gastric lipase, pancreatic lipase, and carboxyl ester lipase enzymes that work by hydrolyzing the dietary triglycerides into fatty acids and monoglycerides, which are absorbed by the mucosa of the gastrointestinal tract [110]. Orlistat reduces the absorption of ingested fat and increasing its excretion in the feces [111]. The main anti-obesity action of orlistat is in helping to reduce caloric intake in individuals [112]. Orlistat also helps individuals to reduce the fat content of their diet, as diets rich in fatty products will lead to more adverse effects, such as diarrhea and fecal incontinence [108, 112]. Several studies have shown that orlistat exhibits anti-tumor effects in many cancer cells including human CRC cell line HT-29 in vitro and in vivo by inhibiting FASN activity [107, 113–115]. Treatment of tumor cells with orlistat-induced ER stress, which is further confirmed by the increased expression of the ER stress–regulated genes CHOP, ATF4, and GRP78. FAS inhibitors cooperate with the ER stress inducer thapsigargin to enhance tumor cell killing. These results provide the first evidence that FASN inhibitors induce ER stress and establish an important mechanistic link between FASN activity and ER function [114]. Yang et al. revealed that orlistat induced an ATF4-
dependent transcriptional induction of REDD1 (also known as Rtp801 or DDIT4), a known mTOR inhibitor and works as a novel caspase-2 regulator in the ovarian cancer. REDD1 positively controls caspase-2-dependent cell death of ovarian cancer cells by inhibiting mTOR, and this is the main pathway of orlistat-induced cell death in ovarian cancer [116]. Agostini et al. revealed that orlistat inhibited the orthotopic tongue squamous cell carcinoma in the BALB/c nude mice. In an in vivo experiment, the drug was able to decrease both the volume and proliferation indexes of the tongue orthotopic tumors and, importantly, reduced the number of metastatic cervical lymph nodes by 43% [117].

4.5. Luteolin

Luteolin, 3′,4′,5,7-tetrahydroxyflavone, is found in a variety of vegetables, fruits, and medicinal herbs. Luteolin has been shown to function as an anti-oxidant, anti-inflammatory, and anti-cancer agent [118]. Additionally, luteolin induces cell cycle arrest and apoptosis in the liver and lung cancer cell lines [119, 120]. Lim do et al. indicated that luteolin inhibited HT-29 cell proliferation by inducing cell cycle arrest and apoptosis [121]. Luteolin exerts toxic effects on colon cancer cells by inhibiting both S1P biosynthesis and ceramide traffic, inhibiting Akt activation [122]. The supplantations of luteolin in addition to aspirin in the treatment of DMH-induced carcinogenesis in rats reflect a better effect than the use of aspirin alone [123]. Luteolin suppresses both iNOS and COX-2 expressions and plays an anti-inflammatory role during the administration of azoxymethane in mice [124]. Luteolin decreased the expressions of β-catenin, phospho GSK-3-β, and cyclin D in HCT-15 cells. Luteolin also promoted cell cycle arrest at the G2/M phase and induced apoptosis in HCT-15 cells. Furthermore, Western blot analysis showed that luteolin treatment enhanced the expression of Bax and caspase-3, whereas the expression of Bcl-2 was suppressed [125].

4.6. Epigallocatechin gallate (EGCG)

EGCG, which is green tea polyphenol, inhibits the activity of FASN [126, 127]. EGCG induces apoptosis in human breast and prostate cancer cells [128–130]. It is also the major biologically active component that inhibits cell proliferation and induces apoptosis in HCT-116 and SW-480 human CRC cells [131]. EGCG suppresses FASN expression and downstream PI3K/Akt pathway [132]. EGCG activates stress signals, such as c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK), and induces apoptosis in CRC cell lines [131]. EGCG has also been reported to inhibit the growth of human CRC cells in subcutaneous xenograft models [133–135]. Maruyama et al. revealed that EGCG strongly reduces liver metastasis of human CRC in SCID mice [136].

Epidemiologically, green tea consumption of >10 cups daily reduced CRC risk in Japanese [137]. A double-blind, placebo-controlled study with green tea in Italian patients showed a successful prevention of prostate cancer. The progression of prostate cancer in men with high-grade prostate intraepithelial neoplasia, the main premalignant lesion of prostate cancer, was significantly prevented by oral administration of green tea catechins, 600 mg/d for 1 year [138]. Shimizu et al. conducted a randomized trial to determine the preventive effect of green tea
extract (GTE) supplements on metachronous colorectal adenomas by raising green tea consumption in the target population from an average of 6 cups (1.5 g GTE) daily to 10 cups equivalent (2.5 g GTE) by supplemental GTE tablets. To 136 patients with colorectal polyp resection, they performed colonoscopy to confirm no polyps in the colorectum 1 year later. Then they randomized into two groups, i.e., GTE group and control group. The incidence of metachronous adenomas at the endpoint colonoscopy was 31% (20 of 65) in the control group and 15% (9 of 60) in the GTE group (relative risk, 0.49; 95% confidence interval, 0.24–0.99; \( P < 0.05 \)). The size of relapsed adenomas was also smaller in the GTE group than in the control group \( (P < 0.001) \). No serious adverse events occurred in the GTE group. They concluded that GTE is an effective supplement for the chemoprevention of metachronous colorectal adenomas [137]. The multicenter RCT trial to investigate EGCG for reducing colon polyp recurrence in elderly people was performed, which was called minimizing the risk of metachronous adenomas of the colorectum with GTE (MIRACLE). The clinical trial was a randomized, placebo-controlled, multicenter trial to investigate the effect of diet supplementation with GTE containing 300 mg of EGCG on the recurrence of colon adenomas. Patients who had undergone polypectomy for colonic polyps were randomized to receive either GTE containing 150 mg of EGCG two times daily or a placebo over the course of 3 years. Incidence, number, and histology of adenoma at endpoint colonoscopy at 3 years will be compared in both groups [139].

4.7. Triclosan

Triclosan has the U.S. Food and Drug Administration approval as a bactericide in personal hygiene products (toothpaste, mouth rinse, hand wash, soaps, and deodorant) and has been used since 1968 [77]. Triclosan has an established safety profile with minimal toxicity in rats, dogs, baboons, and humans; no significant weight loss is associated with triclosan treatment; and triclosan is not a genotoxic or mutagenic compound [77]. Triclosan has excellent oral bioavailability and stability in plasma [140]. Triclosan also acts as a FASN inhibitor to inhibit enoyl reductase of FASN [141], and it showed chemo-preventative activity in a rat mammary carcinogenesis model [142]. Similarly, treatment of male rats with triclosan did not induce significant changes in body weight at any of the test doses [143]. Recently, Sadowski et al. evaluated triclosan as a repurposed drug against prostate cancer cells and compared its activity to C75 and orlistat, two well-known FASN inhibitors [77, 144]. In this comparative study, Sadowski et al. discovered that triclosan is a superior alternative to C75 and orlistat in inducing cell death of prostate cancer cells through inhibition of FASN [77].

4.8. Capsaicin

Capsaicin (trans-8-methyl-N-vanillyl-6-non-enamide) is the major component in hot chili peppers and several types of red peppers of the genus *Capsicum*. It constitutes approximately 40–60% of the six natural capsaiciniod contents of this herb [145, 146]. It is commonly and frequently consumed worldwide as a spice, food additive, and as a drug for traditional medications. Capsaicin is a specific and potent anti-carcinogenic agent through the apoptosis pathway in both in vitro and in vivo cancer models, whereas it does not induce cytotoxicity
in normal cells [147–151]. Impheng et al. revealed that capsaicin also acts as FASN inhibitor [78]. Capsaicin decreased FASN expression and inducing apoptosis in HepG2 cells. The lipogenic enzyme FASN, not ACC and ACLY, is proposed to be the particular target of capsaicin to induce apoptosis in HepG2 cells. This study also suggests that an accumulation of malonyl-CoA, as a result of a reduction of fatty acid synthesis, is a critical proapoptotic factor that inhibits CPT-1 activity, leading to accumulation of ceramide which in turn induces apoptosis [78].

4.9. Curcumin

Curcumin is a hydrophobic polyphenol derived from the rhizome of Curcuma longa. It possesses various pharmacological activities, such as respiratory conditions, inflammation, liver disorders, diabetic wounds, and certain tumors [152]. Curcumin has chemopreventive and therapeutic properties against many tumors in both in vitro and in vivo models [153–158]. Curcumin suppresses cell proliferation and inflammation, induces apoptosis, and sensitizes tumor cells to cancer therapies, and it also suppresses invasion, angiogenesis, and metastasis of cancer cells [159]. It was found that curcumin showed both fast-binding and slow-binding inhibitions to FASN in vitro. Curcumin inhibited FASN with an IC50 value of 10.5 μg/ml non-competitively with respect to NADPH and partially competitively against both substrates Ac-CoA and Mal-CoA [160]. Compared with the known FASN inhibitors 14, 175 and EGCG, curcumin was generally more potent [126]. Curcumin-induced HepG2 cell apoptosis by inhibiting intracellular FASN activity and down-regulating FASN expression and mRNA level. Sodium palmitate-rescued, curcumin-induced apoptosis in HepG2 cells confirmed that apoptosis related to inhibition of FASN [79].

4.10. Newly developed agents

TVB-3567 [80] and TVB-3166 [81] are newly developed FASN inhibitors provided from 3-V Biosciences, which inhibit many kinds of cancer cell lines, such as CRC cell lines, COLO-205, and HT-29 [81]. GSK2194069 was identified from a high-throughput screen of the GSK compound collection, and this agent inhibits cell growth of A549 cells [82].

4.11. Conclusion of FASN inhibitors

Several studies have shown in vitro and in vivo anti-tumor activity of FASN inhibitors. This chapter shows that many FASN inhibitors are being examined for in vitro and in vivo anti-tumor activity of CRC. In addition, one of the FASN inhibitors, EGCG, has moved on to clinical trials aimed at preventing Colon polyp recurrence, which indicates the safety of monoterpenes for clinical use. Other FASN inhibitors are effective in in vitro/in vivo researches, and the clinical trials of using these reagents are expected, but still need more research. Newly developed agents, such as TVB-3166, TVB-3567, and GSK2194069, are expected to become new candidates for chemotherapeutic agents against unresectable cancers.
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References

[1] Gupta GP and Massague J. Cancer metastasis: building a framework. Cell 127: 679–695, 2006.

[2] Tachimori A, Yamada N, Amano R, et al. Combination therapy of S-1 with selective cyclooxygenase-2 inhibitor for liver metastasis of colorectal carcinoma. Anticancer Res 28: 629–638, 2008.

[3] Efferth T. Cancer therapy with natural products and medicinal plants. Planta Medica 76: 1035–1036, 2010.

[4] De Sousa DP. Medicinal Essential Oils: Chemical, Pharmacological and Therapeutic Aspects. 1st edition. New York, NY: Nova Science Publishers, 2012.

[5] Rasoanaivo P, Randriana RF, Maggi F, et al. Chemical composition and biological activities of the essential oil of Athanasia brownie Hochr. (Asteraceae) endemic to Madagascar. Chem Biodivers 10: 1876–1886, 2013.

[6] Zapata B, Betancur LG, Duran C, and Stashenko E. Cytotoxic activity of Asteraceae and Verbenaceae family essential oils. J Essential Oil Res 6: 50–57, 2014.

[7] de Sousa DP. Analgesic-like activity of essential oils constituents. Molecules 16: 2233–2252, 2011.

[8] de Almeida RN, de Fátima Agra M, Maior FNS, and de Sousa DP. Essential oils and their constituents: anticonvulsant activity. Molecules 16: 2726–2742, 2011.

[9] da Silveira e SáRita de Cássia, Nalone AndradeLuciana, de OliveiraRafael dos Reis Barreto, and de SousaDamião Pergentino. A review on anti-inflammatory activity of phenylpropanoids found in essential oils. Molecules 19: 1459–1480, 2014.

[10] Su YC, and Ho CL. Composition, in-vitro anticancer, and antimicrobial activities of the leaf essential oil of Machilus mushaensis from Taiwan. Nat Prod Commun 8: 273–275, 2013.

[11] Manjamalai A, and Grace VMB. The chemotherapeutic effect of essential oil of Plectranthus amboinicus (Lour) on lung metastasis developed by B16F-10 cell line in C57BL/6 mice. Cancer Invest 31: 74–82, 2013.
[12] Ashour HM. Antibacterial, antifungal, and anticancer activities of volatile oils and extracts from stems, leaves, and flowers of *Eucalyptus sideroxylon* and *Eucalyptus torquata*. Cancer Biol Therap 7: 399–403, 2008.

[13] Medina-Holguín AL, Holguín FO, Micheletto S, Goehle S, Simon JA, and O’Connell MA. Chemotypic variation of essential oils in the medicinal plant, *Anemopsis californica*. Phytochemistry 69: 919–927, 2008.

[14] Kathirvel P, and Ravi S. Chemical composition of the essential oil from basil (*Ocimum basilicum* Linn.) and its in vitro cytotoxicity against HeLa and HEP-2 human cancer cell lines and NIH 3T3 mouse embryonic fibroblasts. Nat Prod Res 26: 1112–1118, 2012.

[15] Sobral MV, Xavier AL, Lima TC, and de Sousa DP. Antitumor activity of monoterpenes found in essential oils. Sci World J 953451, 2014.

[16] Balcerzak L, Lipok J, Strub D, and Lochyński S. Biotransformations of monoterpenes by photoautotrophic micro-organisms. J Appl Microbiol 117: 1523–1536, 2014.

[17] Velankar HR, and Heble MR. Biotransformation of (L)-citronellal to (L)-citronellol by free and immobilized *Rhodotorula minuta*. Electron J Biotechnol 6: 90–130, 2003.

[18] Gounaris Y. Biotechnology for the production of essential oils, flavours and volatile isolates. A review. Flavour Fragr J. 25: 367–386, 2010.

[19] Schewe H, Mirata MA, Holtmann D, and Schrader J. Biooxidation of monoterpenes with bacterial monooxygenases. Process Biochem 46: 1885–1899, 2011.

[20] Mitić-Culafić D, Zegura B, Nikolić B, Vuković-Gacić B, Knezević-Vukcević J, and Filipic M. Protective effect of linalool, myrcene and eucalyptol against t-butyl hydroperoxide induced genotoxicity in bacteria and cultured human cells. Food Chem Toxicol 47: 260–266, 2009.

[21] Chen TC, Da Fonseca CO, and Schönthal AH. Preclinical development and clinical use of perillyl alcohol for chemoprevention and cancer therapy. Am J Cancer Res 5: 1580–1593, 2015.

[22] Wang G, Tang W, and Bidigare RR. Terpenoids as therapeutic drugs and pharmaceutical agents. In: Zhang L, Demain AL (Eds.), Natural Products: Drug Discovery and Therapeutic Medicine. Totowa: Humana Press, pp. 197–227, 2005.

[23] Girola N, Figueiredo CR, Farias CF, Azevedo RA, Ferreira AK, Teixeira SF, Capello TM, Martins EG, Matsuo AL, Travassos LR, and Lago JH. Camphene isolated from essential oil of *Piper cernuum* (Piperaceae) induces intrinsic apoptosis in melanoma cells and displays antitumor activity in vivo. Biochem Biophys Res Commun 467: 928–934, 2015.

[24] Murata S, Shiragami R, Kosugi C, Tezuka T, Yamazaki M, Hirano A, Yoshimura Y, Suzuki M, Shuto K, Ohkohchi N, and Koda K. Antitumor effect of 1, 8-cineole against colon cancer. Oncol Rep 30: 2647–2652, 2013.

[25] Maruyama N, Takizawa T, Ishibashi H, Hisajima T, Inouye S, Yamaguchi H, and Abe S. Protective activity of geranium oil and its component, geraniol, in combination with
vaginal washing against vaginal candidiasis in mice. Biol Pharm Bull 31: 1501–1506, 2008.

[26] Carnesecchi S, Langley K, Exinger F, Gosse F, and Raul F. Geraniol, a component of plant essential oils, sensitizes human colonic cancer cells to 5-Fluorouracil treatment. J Pharmacol Exp Therap 301: 625–630, 2002.

[27] Carnesecchi S, Schneider Y, Ceraline J, et al. Geraniol, a component of plant essential oils, inhibits growth and polyamine biosynthesis in human colon cancer cells. J Pharmacol Exp Therap 298: 197–200, 2001.

[28] Carnesecchi S, Bradaia A, Fischer B, et al. Perturbation by geraniol of cell membrane permeability and signal transduction pathways in human colon cancer cells. J Pharmacol Exp Therap 303: 711–715, 2002.

[29] Carnesecchi S, Bras-Gonçalves R, Bradaia A, Zeisel M, Gossé F, Poupon MF, and Raul F. Geraniol, a component of plant essential oils, modulates DNA synthesis and potentiates 5-fluorouracil efficacy on human colon tumor xenografts. Cancer Lett. 215: 53–59, 2004.

[30] Itani WS, El-Banna SH, Hassan SB, et al. Anti-colon cancer components from Lebanese sage (Salvia libanotica) essential oil: mechanistic basis. Cancer Biol Therap 7: 1765–1773, 2008.

[31] Horváthová E, Sramková M, Lábaj J, and Slamenová D. Study of cytotoxic, genotoxic and DNA-protective effects of selected plant essential oils on human cells cultured in vitro. Neuro Endocrinol Lett 27: 44–47, 2006.

[32] Horvathova E, Turcaniová V, and Slamenova D. Comparative study of DNA-damaging and DNA-protective effects of selected components of essential plant oils in human leukemic cells K562. Neoplasma 54: 478–483, 2007.

[33] Fan K, Li X, Cao Y, Qi H, Li L, Zhang Q, and Sun HD. Carvacrol inhibits proliferation and induces apoptosis in human colon cancer cells. Anticancer Drugs 26: 813–823, 2015.

[34] Arigesavan K, and Sudhandiran G. Carvacrol exhibits anti-oxidant and anti-inflammatory effects against 1, 2-dimethyl hydrazine plus dextran sodium sulfate induced inflammation associated carcinogenicity in the colon of Fischer 344 rats. Biochem Biophys Res Commun 461: 314–320, 2015.

[35] Slamenová D, Horváthová E, Sramková M, and Marsálková L. DNA-protective effects of two components of essential plant oils carvacrol and thymol on mammalian cells cultured in vitro. Neoplasma 54: 108–112, 2007.

[36] Deb DD, Parimala G, Saravana Devi S, and Chakraborty T. Effect of thymol on peripheral blood mononuclear cell PBMC and acute promyelotic cancer cell line HL-60. Chem Biol Interact 193: 97–106, 2011.
[37] Kundu J, Chun KS, Aruoma OI, and Kundu JK. Mechanistic perspectives on cancer chemoprevention/chemotherapeutic effects of thymoquinone. Mutat Res 768: 22–34, 2014.

[38] Lang M, Borgmann M, Oberhuber G, Evstatiev R, Jimenez K, Dammann KW, Jambrich M, Khare V, Campregger C, Ristl R, and Gasche C. Thymoquinone attenuates tumor growth in ApcMin mice by interference with Wnt-signaling. Mol Cancer 12: 41, 2013.

[39] Gali-Muhtasib H, Ocker M, Kuester D, Krueger S, El-Hajj Z, Diestel A, Evert M, El-Najjar N, Peters B, Jurjus A, Roessner A, and Schneider-Stock R. Thymoquinone reduces mouse colon tumor cell invasion and inhibits tumor growth in murine colon cancer models. J Cell Mol Med 12: 330–342, 2008.

[40] El-Najjar N, Chatila M, Moukadem H, et al. Reactive oxygen species mediate thymoquinone-induced apoptosis and activate ERK and JNK signaling. Apoptosis 15: 183–195, 2010.

[41] Ganea GM, Fakayode SO, Losso JN, Van Nostrum CF, Sabliov CM, and Warner IM. Delivery of phytochemical thymoquinone using molecular micelle modified poly(D, L lactide-co-glycolide) (PLGA) nanoparticles. Nanotechnology 21: 285104, 2010.

[42] Al-Shabanah OA, Badary OA, Nagi MN, Al-Gharebly NM, Al-Rikabi AC, and Al-Bekairi AM. Thymoquinone protects against doxorubicin-induced cardiotoxicity without compromising its antitumor activity. J Exp Clin Cancer Res 17: 193–198, 1998.

[43] Effenberger-Neidnicht K, and Schobert R. Combinatorial effects of thymoquinone on the anti-cancer activity of doxorubicin. Cancer Chemotherap Pharmacol 67: 867–874, 2011.

[44] Chidambara Murthy KN, Jayaprakasha GK, and Patil BS. D-limonene rich volatile oil from blood oranges inhibits angiogenesis, metastasis and cell death in human colon cancer cells. Life Sci 91: 429–439, 2012.

[45] Kawamori T, Tanaka T, Hirose Y, Ohnishi M, and Mori H. Inhibitory effects of d-limonene on the development of colonic aberrant crypt foci induced by azoxymethane in F344 rats. Carcinogenesis 17: 369–372, 1996.

[46] Jia SS, Xi GP, Zhang M, Chen YB, Lei B, Dong XS, and Yang YM. Induction of apoptosis by D-limonene is mediated by inactivation of Akt in LS174T human colon cancer cells. Oncol Rep 29: 349–354, 2013.

[47] Vigushin DM, Poon GK, Boddy A, et al. Phase I and pharmacokinetic study of d-limonene in patients with advanced cancer. Cancer Research Campaign Phase I/II Clinical Trials Committee. Cancer Chemother Pharmacol 42: 111–117, 1998.

[48] Sun J. D-Limonene: safety and clinical applications. Altern Med Rev 12: 259–264, 2007.
Crowell PL, Ren Z, Lin S, Vedejs E, and Gould MN. Structure-activity relationships among monoterpene inhibitors of protein isoprenylation and cell proliferation. Biochem Pharmacol 47: 1405–1415, 1994.

Reddy BS, Wang CX, Samaha H, Lubet R, Steele VE, Kelloff GJ, and Rao CV. Chemoprevention of colon carcinogenesis by dietary perillyl alcohol. Cancer Res 57: 420–425, 1997.

Bardon S, Foussard V, Fournel S, and Loubat A. Monoterpenes inhibit proliferation of human colon cancer cells by modulating cell cycle-related protein expression. Cancer Lett 181: 187–194, 2002.

Ripple GH, Gould MN, Stewart JA, et al. Phase I clinical trial of perillyl alcohol administered daily. Clin Cancer Res 4: 1159–1164, 1998.

Ripple GH, Gould MN, Arzoomanian RZ, et al. Phase I clinical and pharmacokinetic study of perillyl alcohol administered four times a day. Clin Cancer Res 6: 390–396, 2000.

Azzoli CG, Miller VA, Kenneth KNG, et al. A phase I trial of perillyl alcohol in patients with advanced solid tumors. Cancer Chemotherap Pharmacol 51: 493–498, 2003.

Hudes GR, Szarka CE, Adams A, et al. Phase I pharmacokinetic trial of perillyl alcohol (NSC 641066) in patients with refractory solid malignancies. Clin Cancer Res 6: 3071–3080, 2000.

Meadows SM, Mulkerin D, Berlin J, et al. Phase II trial of perillyl alcohol in patients with metastatic colorectal cancer. Int J Gastrointest Cancer 32: 125–128, 2002.

da Fonseca CO, Simao M, Lins IR, Caetano RO, Futuro D, and Quirico-Santos T. Efficacy of monoterpene perillyl alcohol upon survival rate of patients with recurrent glioblastoma. J Cancer Res Clin Oncol 137: 287–293, 2011.

Da Fonseca CO, Teixeira RM, Silva JC, De Saldanha DA, Gama Fischer J, Meirelles OC, Landeiro JA, and Quirico-Santos T. Long-term outcome in patients with recurrent malignant glioma treated with perillyl alcohol inhalation. Anticancer Res 33: 5625–5631, 2013.

Hayes AJ, Leach DN, Markham JL, and Markovic B. In vitro cytotoxicity of Australian tea tree oil using human cell lines. J Essential Oil Res 9: 575–582, 1997.

Asanova ZK, Suleimenov EM, Atazhanova GA, et al. Biological activity of 1,8-cineole fromlevant wormwood. Pharma Chem J 37: 28–30, 2003.

Battacharjee B, and Chatterjee J. Identification of proapoptotic, anti-inflammatory, anti-proliferative, anti-invasive and anti-angiogenic targets of essential oils in cardamom by dual reverse virtual screening and binding pose analysis. Asian Pacific J Cancer Prev 14: 3735–3742, 2013.
[62] Chen W, Liu Y, Li M, Mao J, Zhang L, Huang R, Jin X, and Ye L. Anti-tumor effect of α-pinene on human hepatoma cell lines through inducing G2/M cell cycle arrest. J Pharmacol Sci 127: 332–338, 2015.

[63] Wu X, Qin L, Fako V, and Zhang JT. Molecular mechanisms of fatty acid synthase (FASN)-mediated resistance to anti-cancer treatments. Adv Biol Regul 54: 214–221, 2014.

[64] Furuta E, Okuda H, Kobayashi A, and Watabe K. Metabolic genes in cancer: their roles in tumor progression and clinical implications. Biochim Biophys Acta 1805: 141–152, 2010.

[65] Kusakabe T, Maeda M, Hoshi N, et al. Fatty acid synthase is expressed mainly in adult hormone-sensitive cells or cells with high lipid metabolism and in proliferating fetal cells. J Histochem Cytochem 48: 613–622, 2000.

[66] Weiss L, Hoffmann GE, Schreiber R, et al. Fatty-acid biosynthesis in man, a pathway of minor importance. Purification, optimal assay conditions, and organ distribution of fatty-acid synthase. Biol Chem Hoppe-Seyler 367: 905–912, 1986.

[67] Smith S, Witkowski A, and Joshi AK. Structural and functional organization of the animal fatty acid synthase. Prog Lipid Res 42: 289–317, 2003.

[68] Nguyen PL, Ma J, Chavarro JE, et al. Fatty acid synthase polymorphisms, tumor expression, body mass index, prostate cancer risk, and survival. J Clin Oncol 28: 3958–3964, 2010.

[69] Zhou Y, Niu C, Li Y, et al. Fatty acid synthase expression and esophageal cancer. Mol Biol Rep 39: 9733–9739, 2012.

[70] Long QQ, Yi YX, Qiu J, Xu CJ, and Huang PL. Fatty acid synthase (FASN) levels in serum of colorectal cancer patients: correlation with clinical outcomes. Tumour Biol 35: 3855–3859, 2014.

[71] Kearney KE, Pretlow TG, and Pretlow TP. Increased expression of fatty acid synthase in human aberrant crypt foci: possible target for colorectal cancer prevention. Int J Cancer 125: 249–252, 2009.

[72] Ong ES, Zou L, Li S, Cheah PY, Eu KW, and Ong CN. Metabolic profiling in colorectal cancer reveals signature metabolic shifts during tumorigenesis. Mol Cell Proteomics 2010 Feb 10 Epub.

[73] Luque-García JL, Martínez-Torrecuadrada JL, Epifano C, Cañamero M, Babel I, and Casal JL. Differential protein expression on the cell surface of colorectal cancer cells associated to tumor metastasis. Proteomics 10: 940–952, 2010.

[74] Kuhajda FP. Fatty-acid synthase and human cancer: new perspectives on its role in tumor biology. Nutrition 16: 202–208, 2000.
[75] Kuhajda FP. Fatty acid synthase and cancer: new application of an old pathway. Cancer Res 66: 5977–5980, 2006.

[76] Yoshii Y, Furukawa T, Oyama N, et al. Fatty acid synthase is a key target in multiple essential tumor functions of prostate cancer: uptake of radiolabeled acetate as a predictor of the targeted therapy outcome. PLoS One 8: e64570, 2013.

[77] Sadowski MC, Pouwer RH, Gunter JH, Lubik AA, Quinn RJ, and Nelson CC. The fatty acid synthase inhibitor triclosan: repurposing an anti-microbial agent for targeting prostate cancer. Oncotarget 5: 9362–9381, 2014.

[78] Impheng H, Pongcharoen S, Richert L, Pekthong D, and Srisawang P. The selective target of capsaicin on FASN expression and de novo fatty acid synthesis mediated through ROS generation triggers apoptosis in HepG2 cells. PLoS One 9: e107842, 2014.

[79] Fan H, Tian W, and Ma X. Curcumin induces apoptosis of HepG2 cells via inhibiting fatty acid synthase. Target Oncol 9: 279–286, 2014.

[80] Benjamin DI, Li DS, Lowe W, Heuer T, Kemble G, and Nomura DK. Diacylglycerol metabolism and signaling is a driving force underlying FASN inhibitor sensitivity in cancer cells. ACS Chem Biol 10: 1616–1623, 2015.

[81] Ventura R, Mordec K, Waszczuk J, Wang Z, Lai J, Fridlib M, Buckley D, Kemble G, and Heuer TS. Inhibition of de novo palmitate synthesis by fatty acid synthase induces apoptosis in tumor cells by remodeling cell membranes, inhibiting signaling pathways, and reprogramming gene expression. EBio Med 2: 806–822, 2015.

[82] Hardwicke MA, Rendina AR, Williams SP, Moore ML, Wang L, Krueger JA, Plant RN, Totoritis RD, Zhang G, Briand J, Burkhart WA, Brown KK, and Parrish CA. A human fatty acid synthase inhibitor binds β-ketoacyl reductase in the keto-substrate site. Nat Chem Biol 10: 774–779, 2014.

[83] Nomura S, Horiuchi T, Hata T, and Omura S. Inhibition of sterol and fatty acid biosyntheses by cerulenin in cell-free systems of yeast. J Antibiot (Tokyo) 25: 365–368, 1972.

[84] Nomura S, Horiuchi T, Omura S, and Hata T. The action mechanism of cerulenin. I. Effect of cerulenin on sterol and fatty acid biosynthesis in yeast. J Biochem 71: 783–796, 1972.

[85] Vance D, Goldberg I, Mitsuhashi O, and Bloch K. Inhibition of fatty acid synthetases by the antibiotic cerulenin. Biochem Biophys Res Commun 48: 649–656, 1972.

[86] D’Agnolo G, Rosenfeld IS, Awaya J, Omura S, and Vagelos PR. Inhibition of fatty acid synthesis by the antibiotic cerulenin. Specific inactivation of beta-ketoacyl-acyl carrier protein synthetase. Biochim Biophys Acta 326: 155–156, 1973.

[87] Goldberg I, Walker JR, and Bloch K. Inhibition of lipid synthesis in Escherichia coli cells by the antibiotic cerulenin. Antimicrob Agents Chemother 3: 549–554, 1973.
[88] Omura S. The antibiotic cerulenin, a novel tool for biochemistry as an inhibitor of fatty acid synthesis. Bacteriol Rev 40: 681–697, 1976.

[89] Omura S. Cerulenin. Methods Enzymol 72: 520–532, 1981.

[90] Jeong NY, Lee JS, Yoo KS, et al. Fatty acid synthase inhibitor cerulenin inhibits topoisomerase I catalytic activity and augments SN-38-induced apoptosis. Apoptosis 18: 226–237, 2013.

[91] Chen HW, Chang YF, Chuang HY, Tai WT, and Hwang JJ. Targeted therapy with fatty acid synthase inhibitors in a human prostate carcinoma LNCaP/tk-luc-bearing animal model. Prostate Cancer Prostatic Dis 15: 260–264, 2012.

[92] Zhao W, Kridel S, Thorburn A, et al. Fatty acid synthase: a novel target for antiglioma therapy. Br J Cancer 95: 869–878, 2006.

[93] Murata S, Yanagisawa K, Fukunaga K, et al. Fatty acid synthase inhibitor cerulenin suppresses liver metastasis of colon cancer in mice. Cancer Sci 101: 1861–1865, 2010.

[94] Shiragami R, Murata S, Kosugi C, et al. Enhanced antitumor activity of cerulenin combined with oxaliplatin in human colon cancer cells. Int J Oncol 43: 431–438, 2013.

[95] Denley A, Gymnopoulos M, Kang S, Mitchell C, and Vogt PK. Requirement of phosphatidylinositol-(3,4,5) trisphosphate in phosphatidylinositol 3-kinase-induced oncogenic transformation. Mol Cancer Res 7: 1132–1138, 2009.

[96] Chang L, Wu P, Senthilkumar R, Tian X, Liu H, Shen X, Tao Z, and Huang P. Loss of fatty acid synthase suppresses the malignant phenotype of colorectal cancer cells by down-regulating energy metabolism and mTOR signaling pathway. J Cancer Res Clin Oncol 142: 59–72, 2016.

[97] Bauerschlag DO, Maass N, Leonhardt P, Verburg FA, Pecks U, Zeppernick F, Morgenroth A, Mottaghy FM, Tolba R, Meinhold-Heerlein I, and Bräutigam K. Fatty acid synthase overexpression: target for therapy and reversal of chemoresistance in ovarian cancer. J Transl Med 13: 146, 2015.

[98] Kuhajda FP, Pizer ES, Li JN, Mani NS, Frehywot GL, and Townsend CA. Synthesis and antitumor activity of an inhibitor of fatty acid synthase. Proc Natl Acad Sci U S A 97: 3450–3454, 2000.

[99] Rahman MT, Nakayama K, Rahman M, et al. Fatty acid synthase expression associated with NAC1 is a potential therapeutic target in ovarian clear cell carcinomas. Br J Cancer 107: 300–307, 2012.

[100] Horiguchi A, Asano T, Asano T, Ito K, Sumitomo M, and Hayakawa M. Pharmacological inhibitor of fatty acid synthase suppresses growth and invasiveness of renal cancer cells. J Urol 180: 729–736, 2008.
[101] Li JN, Gorospe M, Chrest FJ, Kumaravel TS, Evans MK, Han WF, and Pizer ES. Pharmacological inhibition of fatty acid synthase activity produces both cytostatic and cytotoxic effects modulated by p53. Cancer Res 61:1493–1499, 2001.

[102] Thupari JN, Landree LE, Ronnett GV, and Kuhajda FP. C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity. Proc Natl Acad Sci U S A 99: 9498–9502, 2002.

[103] Loftus TM, Jaworsky DE, Frehywot GL, et al. Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. Science 288: 2379–2381, 2000.

[104] McFadden JM, Medghalchi SM, Thupari JN, et al. Application of a flexible synthesis of (5R)-thiolactomycin to develop new inhibitors of type I fatty acid synthase. J Med Chem 48: 946–961, 2005.

[105] Orita H, Coulter J, Lemmon C, Tully E, Vadlamudi A, Medghalchi SM, Kuhajda FP, and Gabrielson E. Selective inhibition of fatty acid synthase for lung cancer treatment. Clin Cancer Res 13: 7139–7145, 2007.

[106] Orita H, Coulter J, Tully E, Abe M, Montgomery E, Alvarez H, Sato K, Hino O, Kajiyama Y, Tsurumaru M, and Gabrielson E. High levels of fatty acid synthase expression in esophageal cancers represent a potential target for therapy. Cancer Biol Ther 10: 549–554, 2010.

[107] Kridel SJ, Axelrod F, Rozenkrantz N, and Smith JW. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. Cancer Res 64: 2070–2075, 2004.

[108] Halpern B, and Halpern A. Safety assessment of FDA-approved (orlistat and lorcaserin) anti-obesity medications. Expert Opin Drug Saf 14: 305–315, 2015.

[109] Borgström B. Mode of action of tetrahydrolipstatin: a derivative of the naturally occurring lipase inhibitor lipstatin. Bioch Biophys Acta 962: 308–316, 1988.

[110] Zhi J, Melia AT, Eggers H, et al. Review of limited systemic absorption of orlistat, a lipase inhibitor, in healthy human volunteers. J Clin Pharmacol 35: 1103–1108, 1995.

[111] Ballinger A, and Peikin SR. Orlistat: its current status as an anti-obesity drug. Eur J Pharmacol 440: 109–117, 2002.

[112] Mancini MC, and Halpern A. Orlistat in the prevention of diabetes in the obese patient. Vasc Health Risk Manag 4: 325–336, 2008.

[113] Menendez JA, Vellon L, and Lupu R. Anti-tumoral actions of the anti-obesity drug orlistat (Xenical TM) in breast cancer cells: blockade of cell cycle progression, promotion of apoptotic cell death and PEA3-mediated transcriptional repression of Her2/neu (erbB-2) oncogene. Ann Oncol 16: 1253–1267, 2005.

[114] Little JL, Wheeler FB, Fels DR, Koumenis C, and Kridel SJ. Inhibition of fatty acid synthase induces endoplasmic reticulum stress in tumor cells. Cancer Res 2007; 67: 1262–1269.
[115] Carvalho MA, Zecchin KG, Seguin F, et al. Fatty acid synthase inhibition with Orlistat promotes apoptosis and reduces cell growth and lymph node metastasis in a mouse melanoma model. Int J Cancer 123: 2557–2565, 2008.

[116] Yang CS, Matsuura K, Huang NJ, Robeson AC, Huang B, Zhang L, and Kornbluth S. Fatty acid synthase inhibition engages a novel caspase-2 regulatory mechanism to induce ovarian cancer cell death. Oncogene 34: 3264–3272, 2015.

[117] Agostini M, Almeida LY, Bastos DC, Ortega RM, Moreira FS, Seguin F, Zecchin KG, Raposo HF, Oliveira HC, Amoêdo ND, Salo T, Coletta RD, and Graner E. The fatty acid synthase inhibitor orlistat reduces the growth and metastasis of orthotopic tongue oral squamous cell carcinomas. Mol Cancer Ther 13: 585–595, 2014.

[118] Lin Y, Shi R, Wang X, and Shen HM. Luteolin, a flavanoid with potential for cancer prevention and therapy. Curr Cancer Drug Target 8: 634–646, 2008.

[119] Chang J, Hsu Y, Kuo P, Kuo Y, Chiang L, and Lin C. Increase of Bax/Bcl-XL ratio and arrest of cell cycle by luteolin in immortalized human hepatoma cell line. Life Sci 76: 1883–1893, 2005.

[120] Leung HW, Wu CH, Lin CH, and Lee HZ. Luteolin induced DNA damage leading to human lung squamous carcinoma CH27 cell apoptosis. Eur J Pharmacol 508: 77–83, 2005.

[121] Lim do Y, Jeong Y, Tyner AL, and Park JH. Induction of cell cycle arrest and apoptosis in HT-29 human colon cancer cells by the dietary compound luteolin. Am J Physiol Gastrointest Liver Physiol 292: G66–G75, 2007.

[122] Abdel Hadi L, Di Vito C, Marfia G, Ferraretto A, Tringali C, Viani P, and Riboni L. Sphingosine kinase 2 and ceramide transport as key targets of the natural flavonoid luteolin to induce apoptosis in colon cancer cells. PLoS One 10: e0143384, 2015.

[123] Osman NH, Said UZ, El-Waseef AM, and Ahmed ES. Luteolin supplementation adjacent to aspirin treatment reduced dimethylhydrazine-induced experimental colon carcinogenesis in rats. Tumour Biol 36: 1179–1190, 2015.

[124] Pandurangan AK, Kumar SA, Dharmalingam P, and Ganapasam S. Luteolin, a bioflavonoid inhibits azoxymethane-induced colon carcinogenesis: Involvement of iNOS and COX-2. Pharmacogn Mag 10(Suppl. 2): S306–S310, 2014.

[125] Pandurangan AK, Dharmalingam P, Sadagopan SK, Ramar M, Munusamy A, and Ganapasam S. Luteolin induces growth arrest in colon cancer cells through involvement of Wnt/β-catenin/GSK-3β signaling. J Environ Pathol Toxicol Oncol 32: 131–139, 2013.

[126] Wang X, and Tian W. Green tea epigallocatechin gallate: a natural inhibitor of fatty-acid synthase. Biochem Biophys Res Commun 288: 1200–1206, 2001.
[127] Wang X, Song KS, Guo QX, and Tian WX. The galloyl moiety of green tea catechins is the critical structural feature to inhibit fatty-acid synthase. Biochem Pharmacol 66: 2039–2047, 2003.

[128] Vergote D, Cren-Olivé C, Chopin V, et al. (−)-Epigallocatechin (EGC) of green tea induces apoptosis of human breast cancer cells but not of their normal counterparts. Breast Cancer Res Treat 76: 195–201, 2002.

[129] Khan N, Bharali DJ, Adhami VM, et al. Oral administration of naturally occurring chitosan-based nanoformulated green tea polyphenol EGCG effectively inhibits prostate cancer cell growth in a xenograft model. Carcinogenesis 35: 415–423, 2014.

[130] Yeh CW, Chen WJ, Chiang CT, Lin-Shiau SY, and Lin JK. Suppression of fatty acid synthase in MCF-7 breast cancer cells by tea and tea polyphenols: a possible mechanism for their hypolipidemic effects. Pharmacogenom J 3: 267–276, 2003.

[131] Du GJ, Zhang Z, Wen XD, Yu C, Calway T, Yuan CS, and Wang CZ. Epigallocatechin gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. Nutrients 4: 1679–1691, 2012.

[132] Pan MH, Lin CC, Lin JK, and Chen WJ. Tea polyphenol (−)-epigallocatechin 3-gallate suppresses heregulin-beta1-induced fatty acid synthase expression in human breast cancer cells by inhibiting phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase cascade signaling. J Agricult Food Chem 55: 5030–5037, 2007.

[133] Shimizu M, Shirakami Y, Sakai H, et al. (−)-Epigallocatechin gallate inhibits growth and activation of the VEGF/VEGFR axis in human colorectal cancer cells. Chem Biol Interact 185: 247–252, 2010.

[134] Tran PL, Kim SA, Choi HS, Yoon JH, and Ahn SG. Epigallocatechin-3-gallate suppresses the expression of HSP70 and HSP90 and exhibits anti-tumor activity in vitro and in vivo. BMC Cancer 10: 276, 2010.

[135] Jin H, Gong W, Zhang C, and Wang S. Epigallocatechin gallate inhibits the proliferation of colorectal cancer cells by regulating Notch signaling. Onco Targets Ther 6: 145–153, 2013.

[136] Maruyama T, Murata S, Nakayama K, et al. (−)-Epigallocatechin-3-gallate suppresses liver metastasis of human colorectal cancer. Oncol Rep 31: 625–633, 2014.

[137] Shimizu M, Fukutomi Y, Ninomiya M, Nagura K, Kato T, Araki H, Suganuma M, Fujiki H, and Moriwaki H. Green tea extracts for the prevention of metachronous colorectal adenomas: a pilot study. Cancer Epidemiol Biomark Prev 17: 3020–3025, 2008.

[138] Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, and Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. Cancer Res 66: 1234–1240, 2006.
[139] Stingl JC, Ettrich T, Muche R, Wiedom M, Brockmüller J, Seeringer A, and Seufferlein T. Protocol for minimizing the risk of metachronous adenomas of the colorectum with green tea extract (MIRACLE): a randomised controlled trial of green tea extract versus placebo for nutriprevention of metachronous colon adenomas in the elderly population. BMC Cancer 11: 360, 2011.

[140] Rodricks JV, Swenberg JA, Borzelleca JF, Maronpot RR, and Shipp AM. Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. Crit Rev Toxicol 40: 422–484, 2010.

[141] Liu B, Wang Y, Fillgrove KL, and Anderson VE. Triclosan inhibits enoyl-reductase of type I fatty acid synthase in vitro and is cytotoxic to MCF-7 and SKBr-3 breast cancer cells. Cancer Chemother Pharmacol 49: 187–193, 2002.

[142] Lu S, and Archer MC. Fatty acid synthase is a potential molecular target for the chemoprevention of breast cancer. Carcinogenesis 26: 153–157, 2005.

[143] Kumar V, Chakraborty A, Kural MR, and Roy P. Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. Reprod Toxicol 27: 177–185, 2009.

[144] Pandey PR, Liu W, Xing F, Fukuda K, and Watabe K. Anti-cancer drugs targeting fatty acid synthase (FAS). Recent Pat Anticancer Drug Discov 7: 185–197, 2012.

[145] Aza-Gonzalez C, Nunez-Palenius HG, and Ochoa-Alejo N. Molecular biology of capsaicinoid biosynthesis in chili pepper (Capsicum spp.). Plant Cell Rep 30: 695–706, 2011.

[146] Reilly CA, Ehlhardt WJ, Jackson DA, et al. Metabolism of capsaicin by cytochrome P450 produces novel dehydrogenated metabolites and decreases cytotoxicity to lung and liver cells. Chem Res Toxicol 16: 336–349, 2003.

[147] Huang SP, Chen JC, Wu CC, et al. Capsaicin induced apoptosis in human hepatoma HepG2 cells. Anticancer Res 29: 165–174, 2009.

[148] Skrzypski M, Sassek M, Abdelmessih S, et al. Capsaicin induces cytotoxicity in pancreatic neuroendocrine tumor cells via mitochondrial action. Cell Signal 26: 41–48, 2014.

[149] Lau JK, Brown KC, Dom AM, et al. Capsaicin induces apoptosis in human small cell lung cancer via the TRPV6 receptor and the calpain pathway. Apoptosis 19: 1190–1201, 2014.

[150] Pramanik KC, Boreddy SR, and Srivastava SK. Role of mitochondrial electron transport chain complexes in capsaicin mediated oxidative stress leading to apoptosis in pancreatic cancer cells. PLoS One 6: e20151, 2011.
[151] Zhang JH, Lai FJ, Chen H, et al. Involvement of the phosphoinositide 3-kinase/Akt pathway in apoptosis induced by capsaicin in the human pancreatic cancer cell line PANC-1. Oncol Lett 5: 43–48, 2013.

[152] Braga ME, Leal PF, Carvalho JE, et al. Comparison of yield, composition, and antioxidant activity of turmeric (Curcuma longa L.) extracts obtained using various techniques. J Agric Food Chem 51: 6604–6611, 2002.

[153] Khor TO, Keum YS, Lin W, et al. Combined inhibitory effects of curcumin and phenethyl isothiocyanate on the growth of human PC-3 prostate xenografts in immune deficient mice. Cancer Res 66: 613–621, 2006.

[154] Kunnumakkara AB, Anand P, and Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett 269: 199–225, 2008.

[155] Kunnumakkara AB, Guha S, Krishnan S, et al. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB regulated gene products. Cancer Res 67: 3853–3861, 2007.

[156] Ravindran J, Prasad S, and Aggarwal BB. Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? AAPS J 11: 495–510, 2009.

[157] Wu SH, Hang LW, Yang JS, et al. Curcumin induces apoptosis in human non-small cell lung cancer NCI-H460 cells through ER stress and caspase cascade and mitochondria-dependent pathways. Anticancer Res 30: 2125–233, 2010.

[158] Xu Y, Zhang J, Han J, et al. Curcumin inhibits tumor proliferation induced by neutrophil elastase through the upregulation of α1-antitrypsin in lung cancer. Mol Oncol 6: 405–417, 2012.

[159] Ruby AJ, Kuttan G, Babu KD, et al. Anti-tumour and antioxidant activity of natural curcuminoids. Cancer Lett 94: 79–83, 1995.

[160] Zhao J, Sun X, Ye F, et al. Suppression of fatty acid synthase, differentiation and lipid accumulation in adipocytes by curcumin. Mol Cell Biochem 351: 19–28, 2011.