Chapter 16

New Chemotherapeutic Agents: Monoterpenes and Fatty Acid Synthase Inhibitors

Soichiro Murata

Additional information is available at the end of the chapter

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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, monoterpene, colorectal cancer, chemotherapy, cerulenin

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].

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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 synergy	Caco-2	200 μM (Caco-2 IC30)	[26]
	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 reduction		53% tumor reduction	
Monocyclic				
Alpha terpineol	Cell cycle arrest, apoptosis	HCT-116 (p53+/+, −/−)	1 mM	[30]
Linalyl acetate			Alpha terpineol + linalyl acetate + camphor	
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]
	Anti-oxidant activity	DMH/DSS carcinogenesis rat	50 mg/kg	[35]
Thymol	Cytotoxic effect	Caco-2	700 μM (IC 50))	[34]
	Apoptosis	HL60	75 μM(12 h), 50 μM(24 h)	[36]
Thymoquinone (TQ)	Apoptosis, Wnt signal	Apc^{Min} 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)	[40]
		DLD-1	42 μM (IC50 24 h)	

Compound	Mechanism	Animal/cell line tested	IC50, etc	Reference
		HT-29	110 μM (IC50 48 h)	
	Nanoparticle with poly(sodium *N*-undecylenyl-valinate)	MDA-MB-231	viability 16.0 ± 5.6%(96 h)	[41]
	Protection from Doxorubicin	Mouse with DOX(20 mg/kg)	TQ (8 mg/kg p.o.) protect cardiotoxicity	[42]
	Synergistic with Doxorubicin	HT-29	46.8 μM to 39.0 μM (with DOX)	[43]
D-limonene	Blood orange volatile	SW480, HT-29	100 ppm, 74.2% reduction of SW480	[44]
	Ornithine decarboxylase (ODC)	Azoxymethane, F344 rat	0.5% d-limonene decreases ACF formation	[45]
	Apoptosis by Akt inactivation	colon cancer (LS174T)	3.2 mM viability 30% decrease	[46]
	Clinical trial phase I and II	CRC patients	0.5 mg/m^2/day	[47, 48]
Perillyl alcohol	Protein isoprenylation	HT-29	50 μM (IC50)	[49]
	Apoptosis	Azoxymethane	2 g/kg decrease cancer incidence to 1/3	[50]
	G1 arrest	HCT-116	0.5 mM (IC50)	[51]
	Clinical trial	CRC patients	1200–1600 mg/m^2/day	[52–56]
Bicyclic				
1,8-cineole	Akt inactivation	RKO	50 mg/kg reduced tumor weight as 1/3	[24]

Table 1. Monoterpene and colorectal cancer.

3.1. Geraniol

Geraniol is an acyclic monoterpenes. 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 monoterpenes, 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.

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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 monoterpene 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 monoterpene 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 monoterpene 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^{Min+} 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 monoterpene, 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/m^2 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/m^2/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/m^2/day for 12 months. Another patient with local retrovesical recurrence of colorectal adenocarcinoma remained stabilized on 1 g/m^2/day (2 g/day) for 7.5 months [47, 48].

3.7. Perillyl alcohol (POH)

POH is a monocyclic monoterpene, and it is derived from limonene. POH is a naturally occurring dietary monoterpene 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].

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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]
	S1P, ceramide, Akt inhibition	Caco-2	100 μM more than 50% decrease at 48 h	[122]
	Synergic effect with aspirin	DMH rat carcinogenesis	0.2 mg/kg/weekly for 15 weeks	[123]
	iNOS, COX2 inhibition	Mouse, azoxymethane administration	1.2 mg/kg orally	[124]
	β-catenin, GSK-3-β, cyclin D1 inhibition	HCT-15	100 μM (IC50)	[125]
EGCG	Cell proliferation, apoptosis	HCT-116	100 μM 98.4% decrease of survival at 48 h	[131]
	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.

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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 human CRC cell lines HCT-116 and RKO. The 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 weightloss 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-

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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 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 supplementations 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

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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 inhibitors14, C75 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.

Author details

Soichiro Murata

Address all correspondence to: soichiro@yokohama-cu.ac.jp

Department of Regenerative Medicine, Yokohama City University, Yokohama, Japan

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