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Mini-review

Biological effects of conjugated linoleic acid on obesity-related cancers

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ABSTRACT

Considerable evidence suggests that obesity and overweight play an important role in cancers i.e., breast, colon, endometrial, kidney, pancreatic, and liver. In fact, overweight and obesity are now established risk factors for cancer and cancer-related mortality. Conjugated linoleic acid (CLA) consists of a group of positional and geometric fatty acid (FA) isomers that are derived from linoleic acid (LA) [18:2(*n*-6)], which occurs naturally in food with a high concentration in products from ruminant animals. Studies in both *in vitro* cell and *in vivo* animal models have shown that CLA, specifically cis 9-trans 11 and trans 10-cis 12 CLA isomer, inhibits the initiation and promotion stages of carcinogenesis, suggesting that CLA has received considerable attention as a chemopreventive agent. In this review, the biological activities and multiple mechanisms of CLA in obesity-related cancers including cell lines, animal models and clinical observations are explained.

Contents

1. Introduction

During the past several decades, the percentage of overweight and obese adults and children has increased markedly [1]. Obesity is associated with increased risks of cancers of the breast, colon, endometrial, kidney, pancreatic, and liver cancer [2–7]. One study, using NCI Surveillance, Epidemiology, and End Results (SEER) data, estimated that, in 2007 in the United States, about 34,000 new cases of cancer in men (4 percent) and 50,500 in women (7 percent) were due to obesity [8]. The percentage of cases attributed to obesity varied widely for different cancer types but was as high as 40 percent for some cancers, particularly endometrial cancer

Abbreviations: AEH, atypical endometrial hyperplasia; CLA, conjugated linoleic acid; ERα, estrogen receptor alpha; GRAS, Generally Regarded as Safe; LA, linoleic acid; LXR, Liver X Receptor; PE, polyethyleneimine; ROS, reactive oxygen species; RCC, renal cell carcinoma; SCD, stearoyl-CoA desaturase; SEER, Surveillance, Epidemiology, and End Results; UCC, urothelial cell carcinoma.

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and esophageal adenocarcinoma [9]. Also, several studies have explored why being overweight or obese may increase cancer risk and growth, suggesting that people who are obese have more fat tissue that can produce hormones, such as insulin or estrogen, which may cause cancer cells to grow [10–12].

Conjugated linoleic acid (CLA) is a family of at least 28 isomers of linoleic acid found especially in the meat and dairy products derived from ruminants [13]. As the name implies, the double bonds of CLA are conjugated [13,14]. CLA was discovered accidentally by researchers looking for mutagens in beef [15]. In 1979, researchers from the University of Wisconsin applied a beef extract to mice skin [16]. The mice were then exposed to a strong carcinogen and when the researchers counted the number of tumors developed by the mice 16 weeks later, they found that the mice exposed to the beef extract had 20% fewer tumors [16]. The identity of this anti-carcinogen was not discovered till almost a decade later in 1987 [16]. Micheal Pariza, the scientist who discovered CLA, later remarked that "few anti-carcinogens, and certainly no other known fatty acids, are as effective as CLA in inhibiting carcinogenesis in these models" [17,18]. Although CLA is best known for its anti-cancer properties, researchers have also found that the cis-9, trans-11 form of CLA can reduce the risk for cardiovascular disease and help fight inflammation [19,20]. CLA is also known for its body weight management properties, which include reducing body fat and increasing lean muscle mass [21]. Over 30 clinical studies have been published investigating the effect of CLA on weight management [22]. The trials have quite variable designs, which lead to inconsistency [22]. However a meta-analysis conducted in 2007 clearly shows that CLA does indeed have a small impact on fat mass [23]. In July 2008, CLA received a no objection letter from the FDA on it Generally Regarded as Safe (GRAS) status for certain food categories including fluid milk, yogurt, meal replacement shakes, nutritional bars, fruit juices and soy milk [24]. With GRAS status, food companies are now able to add CLA to products in these food categories [24].

This review primarily focuses on current CLA publications along with a number of beneficial effects of CLA on obesity-related cancers (Fig. 1). Although scientific studies mainly investigated the effects of individual CLA isomers on cancer prevention *in vitro*, this review summarizes the effects of both individual and mixture of CLA isomers on the development and progression of cancer in animal *in vitro* and *in vivo*. Also, this review provides the biological activities and multiple mechanisms of CLA in clinical observations.

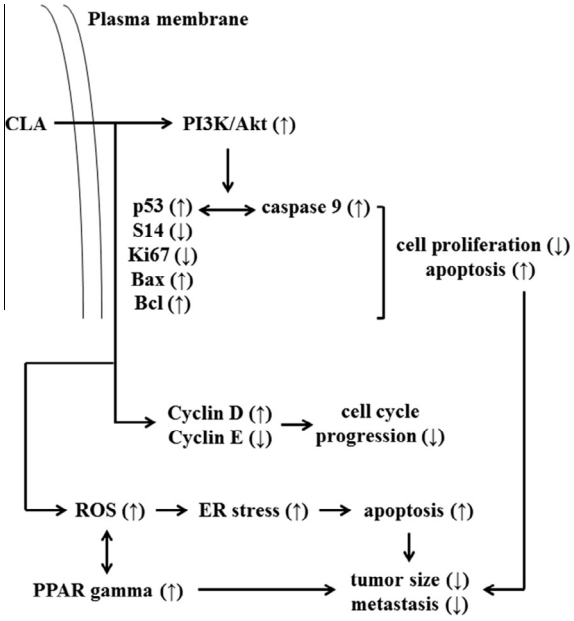

Fig. 1. Proposed mechanism of CLA on obesity-related cancers animal *in vitro*, animal *in vivo* and human *in vivo*. CLA activates PI3K/Akt signaling and stimulates tumor suppressor gene, p53, which up-regulates caspapse 9 in animal *in vitro*. Also, CLA down-regulates S14 and Ki67 in human *in vivo* but up-regulates Bax and Bcl in animal *in vivo*. These pathways decrease cancer cell proliferation, increase cancer cell apoptosis, and inhibit tumor growth. CLA also participates in cell cycle progression by modulating cyclin D and E expression in animal *in vitro*. CLA generates ROS and ER stress in animal *in vitro* and this pathways increases cancer cell apoptosis. Also, CLA increases expression level of PPAR gamma in animal *in vitro*, animal *in vivo* and human *in vivo*, suggesting that CLA decreases tumor size and metastasis. This figure was modified according to the signaling pathways previously described by other groups.

2. CLA and breast cancer

Breast cancer is the malignancy most frequently diagnosed and is the second most common cause of cancer deaths among women in worldwide [25]. Also, approximately 230,000 women are predicted to be diagnosed in the USA with invasive breast cancer in 2012 and 39,500 deaths are expected, suggesting a need for new therapeutic approaches [25,26]. CLA has been shown to down-regulate cell proliferation in breast cancer. Specifically, it has been shown that trans 9-trans 11 CLA isomer suppresses cell proliferation and induces apoptosis via Liver X Receptor (LXR) in MCF-7 breast cancer cell lines [27]. Trans 10-cis 12 CLA isomer has also been shown to inhibit cell growth and invasion through PI3K/Akt signaling pathway in MCF-7 breast cancer cell lines [28]. Moreover, it has been demonstrated that treatment of the cells with trans 9-trans 11 and trans 10-cis 12 CLA isomer significantly decrease stearoyl-CoA desaturase (SCD) protein levels in both MDA-MB-231 and MCF-7 breast cancer cell lines [18]. Previously, I have also demonstrated that CLA mixture stimulates apoptosis via p53-mediated signaling pathway in MCF-7 breast cancer cell lines [29]. Recently, the anti-cancer activity of CLA was investigated on nude mice xenografted human breast MCF-7 tumors, following intravenous injections of CLA, showing that CLA displays a significantly enhanced tumor growth inhibition effect, which is consistent with the observations in *in vitro* cytotoxicity tests [30]. Also, this report observed that coupling of gemcitabine (GEM), a nucleoside analog agent, with CLA has a longer plasma half-life, a higher bioavailability and a stronger anti-tumor activity compared to that of unmodified-GEM and/or -CLA in MCF-7 cells-injected female BALB/c nude mice [30]. These results suggest that the novel CLA–GEM coupling prepared would be a promising prodrug of CLA for future clinical use of breast cancer treatment. The major finding in a proof of principle study is that preoperative administration of at least a 10 day course of treatment with of 7.5 g/day CLA significantly reduced expression of S14 and reduced the proliferation marker Ki-67 in primary invasive breast cancer tissue [31]. This report demonstrated, clinical study (Women with Stage I-III- breast cancer) that breast cancer tissue expression of S14, but not fatty acid synthase and lipoprotein lipase, was decreased after a short course of treatment with 7.5 g/day CLA [31]. This metabolic dependency should be explored as it opens up the possibility of a future line of novel investigate drugs for breast cancer management. The limitations of these two studies above are relatively small sample size and short duration of CLA treatment, suggesting that further exploitation of this suppression *in vivo* may require an escalating dosing/timing/sampling study design. Despite these limitations, CLA consumption has been shown to be safe and well-tolerated, 7.5 g/day for up to 20 days at least. Hence, CLA may represent a prototype compound to target dependence of breast tumors.

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3. CLA and colon cancer

Colorectal cancer (also known as colon cancer) is a cancer from uncontrolled cell growth in the colon or rectum [32]. Symptoms of colorectal cancer typically include rectal bleeding and anemia which are associated with weight loss and changes in bowel habits, and most colorectal cancer occurs due to lifestyle and increasing age with only a minority of cases associated with underlying genetic disorders [32,33]. Colorectal cancer is the third most commonly diagnosed cancer in the world, but it is more common in developed countries [34]. Around 60% of cases were diagnosed in the developed world. It is estimated that worldwide, in 2008, 1.23 million new cases of colorectal cancer were clinically diagnosed, and that it killed 608,000 people [34]. CLA has been shown to have an anti-proliferative effect on colon cancer. It has been shown that trans 10-cis 12 CLA isomer induces cell death through reactive oxygen species (ROS)-mediated endoplasmic reticulum (ER) stress in human colon cell lines [35]. Anti-proliferative effect of CLA has also been demonstrated in Caco-2 cell lines, showing that CLA induces cell cytotoxicity via both PPARgamma and APC/beta-catenin signaling pathways [36]. Moreover, trans 10-cis 12 and cis 9-trans 11 CLA isomers inhibit G1 to S cell cycle progression and decrease ErbB3 expression in HT29 human colon cell lines [37]. These reports suggested that CLA inhibits cell proliferation through a p53-dependent mechanism and regulates the expression of G1-restriction point in colon cancer cells. Metabolic and growth inhibitory effects of CLA have also been demonstrated in human HT29 colon cancer cell lines with special regard to the conversion of trans 11-trans 13 CLA isomer [38]. In animal *in vivo* study, CLA mixture has been shown to suppress colon carcinogenesis in azoxymethane-pretreated rats with long-term feeding of diet containing beef tallow [39]. Also, it has been demonstrated that CLA mixture ameliorates inflammation-induced colorectal cancer in mice through activation of PPAR gamma signaling pathway and differentially alters polyp number and diameter in the Apc (min/+) mouse model of intestinal cancer [40]. Moreover, diet containing cis 9-trans 11 and trans 10-cis 12 CLA isomers were equally effective in inhibiting colon cancer cell metastasis in BALB/c mice [41]. One of study was designed to investigate possible additive or synergistic action among sphingomyelin SPH), cis 9-trans 11 CLA, and butyrate (BTY) against colon cancer and modulation of immune function *in vivo* in male Sprague–Dawley rats [42]. The results showed that three compounds may not act additively or synergistically either to inhibit the development of aberrant crypts or to enhance immune functions. By contrast, the CLA group (0.12% of the diet) had significantly higher natural killer cell (NK) activity than the control group. Previously, it has been suggested that the minimum effective dose of CLA was 0.5% of the diet [15]. Hence, CLA provided at this low level, 0.12% of the diet, to accentuate its synergism with other compounds might not be able to prevent colon cancer cell proliferation *in vivo*. A large population-based cohort of women with repeated diet assessment study has been performed and suggested that high consumption of high-fat dairy foods may lower the risk of colorectal cancer, particularly of cancer of the distal colon [43]. This report emphasized that the observed inverse association might, in part, be related to CLA intake. However, this observational study did not prove a cause-effect relation and the potential public health implications, more studies of the relation between the risk of colon cancer and CLA and high-fat dairy food intakes are needed. Also, additional work is needed to elucidate the mechanisms underlying the ability of dietary fat to protect against colon cancer. Since several minor isomers including trans 9-trans 11, cis 11-trans 13, cis 9-cis 11, and trans 7-cis 11 CLA isomers have not yet been studied, additional studies with purified isomers are also needed to establish the health benefit and risk ratios of each isomer in humans.

4. CLA and endometrial cancer

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world, particularly among postmenopausal women [44]. In fact, a significant number of women diagnosed with atypical endometrial hyperplasia (AEH) on endometrial biopsy will be diagnosed with endometrial cancer (EC) on the hysterectomy specimen at permanent section [45]. The most common subtype, endometrioid adenocarcinoma, typically occurs within a few decades of menopause, is associated with obesity, excessive estrogen exposure, and often develops in the setting of endometrial hyperplasia [45]. It has been reported that the expression of caspase-3 and the ratio of Bax/Bcl-2 were significant increased, but no obvious change was observed about Akt and p-Akt in cis 9-trans 11 CLA isomer-treated RL 95-2 endometrial cancer cell lines [46]. However, this paper showed that the expression of total ERα level in RL 95–2 cells-treated with cis 9-trans 11 CLA isomer was unchanged, while in the concentration of 80 mM, cis 9-trans 11 CLA isomer down-regulated the protein expression level of p-ERα. This result indicates that cis 9-trans 11 CLA isomer induces apoptosis via estrogen receptor alpha (ERα)-mediated signaling pathway in RL 95-2 endometrial cancer cell lines. Since there is only one publication paper regarding the effects of CLA on endometrial cancer, much more work needs to be done in the future. Specifically, there are no published reports to my knowledge whether CLA may regulate malignant potential i.e., cell adhesion, invasion, colony formation and migration in endometrial cancer *in vitro* and *in vivo*. Despite this limitation, the previous study above, followed by future *in vitro* and/or *in vivo* CLA studies involving additional signaling pathways and each CLA isomer, will eventually allow the full mapping and characterization of signaling pathways downstream of CLA in endometrial cancer.

5. CLA and kidney cancer

Kidney cancer is a type of cancer that starts in the cells in the kidney [47]. The two most common types of kidney cancer are renal cell carcinoma (RCC) and urothelial cell carcinoma (UCC) of the renal pelvis [48,49]. These names reflect the type of cell from which the cancer developed [49]. The different types of kidney cancer (such as RCC and UCC) develop in different ways, meaning that the diseases have different long term outcomes, and need to be staged and treated in different ways [49,50]. Hoffmann et al. has performed lipid class distribution study using healthy and cancerous parts of human kidneys, showing that CLA was preferentially incorporated into neutral lipid compared with phospholipid classes [51]. This report demonstrated that, comparing RCC and healthy kidney, the total CLA content was significantly lower in the cholesterylester fraction and significantly higher in the polyethyleneimine (PE) fractions from RCC. Also, this paper found that the most significant differences between healthy and cancerous renal tissue were in the content of trans 10-cis 12 CLA isomer, suggesting that this isomer may have an anti-proliferative effect on kidney cancer. Since there are no mechanistic studies regarding the effects of CLA on kidney cancer, much more work needs to be done in the future.

6. CLA and pancreatic cancer

Pancreatic cancer is when cancer cells form within the pancreas, a glandular organ located behind the stomach [52]. Signs

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and symptoms of pancreatic cancer may include abdominal or back pain, yellow skin, unexplained weight loss, light colored stools, dark urine and loss of hunger [53]. Ductal pancreatic adenocarcinoma, the most common primary pancreatic malignancy, represents the 5th leading cause of cancer death in Western industrialized nations [53]. Despite of diagnostic and therapeutic progress prognosis of pancreatic cancer remain poor [53,54]. Several authors observed an impact of dietary fat intake on experimental pancreatic cancer and assuming a causality between dietary content of *n*-6 PUFAs and carcinogenesis [55,56]. Thus an increased incidence of pancreatic cancer and liver metastasis was achieved by a dietary modification [55]. While CLA is regarded as an essential fatty acid with anti-carcinogenic effects, conventional LA is reported to promote tumor growth in various experimental studies probably caused by high sensitivity to non-enzymatic lipid peroxidation [56]. Hence, in order to investigate the impact of dietary LA and CLA on liver metastasis and lipidperoxidation (LPO), Kilian et al. has evaluated the impact of dietary LA and CLA on liver metastasis and LPO in N-nitrosobis-2-oxopropylamine (BOP)-injected Syrian hamsters for 12 weeks [57]. The results showed that number and size of liver metastases did not differ between the tumor groups. By contrast, anti-oxidative enzyme activity of GSH-Px was higher in non-metastatic liver, while SOD activity and lipidperoxidation were increased in liver metastases. These results suggest that there was no difference between the groups fed with LA and CLA according to the impact on liver metastasis in ductal pancreatic cancer. In 2003, Kilian et al. has also investigated whether dietary fat intake with high content of CLA decreases the incidence of pancreatic cancer, showing that CLA increased weight of pancreas in the tumor and non-tumor group compared to LA [58]. However, pancreas weight was fewer in cancer groups (LA/CLA) than in the corresponding healthy control group. Furthermore LA and CLA did not influence pancreatic lipid peroxidation or activity of anti-oxidative enzymes GSH-Px and SOD in tumor-free control groups. Moreover this paper did not observe any difference between the LA- and CLA-group concerning the activity of GSH-Px and SOD and the concentration of TBARS in tumor-free pancreatic tissue. However, in pancreatic cancer tissue the activity of GSH-Px was decreased compared to tumor-free pancreatic tissue while the concentration of lipid peroxidation was increased. This paper suggested that the content of CLA in dietary did not influence pancreatic tumor growth in a solid model of pancreatic adenocarcinoma in Syrian hamsters. Since this paper has used single dose of CLA, the impact of a higher content of CLA on oxidative stress, lipid peroxidation and the activities of lipid peroxidation protective enzymes needs to be performed in the future.

7. CLA and liver cancer

Liver cancer or hepatic cancer is a cancer that originates in the liver [54]. Liver cancer is the third leading cause of cancer-related cell death in human and the fifth in women worldwide [59,60]. Liver cancers are discovered on medical imaging equipment (often by accident) or present themselves symptomatically as an abdominal mass, abdominal pain, yellow skin, nausea or liver dysfunction [61]. Also, liver is one of the most common sites for metastatic disease, and optimal management of hepatic metastases often requires a multidisciplinary approach [62]. Most commonly, liver metastases are derived from a colorectal or neuroendocrine primary tumor [63]. It has been shown that CLA inhibits hypoxia inducible factor (HIF) 1 alpha stabilization under hypoxic condition in human hepatocellular carcinoma cell lines [64]. Also, CLA has been shown to have a pro-apoptotic effect via PPAR alpha and PP2A signaling pathways in SK-HEP-1human hepatoma cell lines [65]. Moreover, it has been demonstrated that trans 10-cis 12 CLA isomer induces mitochondria-related apoptosis and lysosomal destabilization in rat primary hepatoma cells [66]. Furthermore, it has been shown that trans 10-cis 12, but not cis 9-trans 11, CLA isomer has a strong cytotoxic effect on dRLh-84 rat hepatoma cells via activation of caspase 9 followed by cytochrome C release from mitochondria [67,66]. In animal *in vivo* study, dietary seed oil rich in CLA from bitter melon inhibits azoxymethane-induced rat colon carcinogenesis through elevation of colonic PPAR gamma expression and alteration of lipid composition [68]. Pomegranate seed oil rich in CLA has also been shown to suppress chemically induced colon carcinogenesis in rats [69]. Moreover, it has been shown that trans 10-cis 12 CLA isomer has a cytotoxic effect on rat hepatoma and this effect was modulated by other fatty acids, tocopherol, and tocotrienol [67]. Interestingly, it has been demonstrated that tumor weight was significantly higher in the 2% CLA group than 0% CLA group throughout the feeding period after the injection in hepatoma dRLh-84 cell-injected Donryu rats [70]. The different response between *in vitro* and *in vivo* could have derived from the differences in the duration and isomer of CLA infusion. In fact, most *in vitro* studies focused on trans 10-cis 12 CLA isomer but *in vivo* study used CLA mixture. Also, *in vitro* treatment time is totally different from *in vivo* administration period. Hence, additional studies with purified isomers, especially trans 10-cis 12 CLA in *in vivo* animal study need to be performed in the future.

8. Implications

When a person is overweight or obese, it means that they have too much body fat in relation to lean body tissue, such as muscle [1–3]. Many factors cause people to become overweight or obese, including genetic, hormonal, environmental, emotional, and cultural factors [1,2]. People who are overweight or obese have a higher risk of many serious health conditions, including type II diabetes, high blood pressure, and heart disease [1]. Also, being overweight or obese is strongly associated with an increased risk of cancer (obesity-related cancers) [2–5]. Several studies have explored why being overweight or obese may increase cancer risk, and many studies have investigated to find anti-cancer agents [2–12]. Among them, CLA has been shown to have anti-carcinogenic effects which have been demonstrated at different sites in several experimental *in vitro* cell culture, *in vivo* animal models and clinical studies [16,18,19,23,24] (Table 1). Hence, based on scientific evidences so far, CLA might be useful agents in the management or chemoprevention of obesity-related cancers. In fact, CLA has drawn significant attention in the last two decades for its variety of biologically beneficial effects. CLA reduces body fat [71], cardiovascular diseases [72] and cancer [16,18,19,23,24], and modulates immune and inflammatory responses [73] as well as improves bone mass [74]. It has been suggested that the overall effects of CLA are the results of interactions between two major isomers, cis 9-trans 11 and trans 10-cis 12, mainly in *in vitro* cell culture studies. However, most *in vivo* animal model studies have used CLA mixture. Hence, some results are controversial between *in vitro* and *in vivo*, and the effect of CLA on cancer cell proliferation and its underlying molecular mechanism have not been fully elucidated. Also, performing a cancer study with CLA is really difficult, and the clinical application of CLA is limited for cancer patients due to low bioavailability i.e., poor water solubility and short-half life [75]. In order to overcome these limitations, many studies have tried to synthesize and/or couple CLA and other fatty acids with biodegradable polymer, especially poly (ethylene glycol) (PEG) [29,76–78]. In fact, PEGylation is a well-established method for the modification of anti-cancer drugs, therapeutic peptides, and proteins [79]. Also, the advantages of PEGylation include improved circulation time *in vivo*, reduced antigenicity and immunogenicity, improved solubility and bioavailability [80,81]. Also, the FDA has

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Table 1
Main signaling pathways, main sites of action, and main effects of activation by CLA in obesity-related cancers.

Primary site of action	Sort by target	Signaling pathways	Effect	References
Breast cancer	Animal *in vitro*	LXR(↑), PI3K/Akt(↑), SCD(↓), p53(↑)	Suppresses cell proliferation, induces apoptosis	[27–29]
	Animal *in vivo*	Unknown	Inhibits tumor growth	[30]
	Human	S14(↓), Ki67(↓)	Reduces cell proliferation	[31]
Colon cancer	Animal *in vitro*	PPAR gamma(↑), p53(↑), APC beta (↑)	Induces cell death, activates ROS-mediated ER stress, inhibits G1 to S cell cycle progression	[34–38]
	Animal *in vivo*	PPAR gamma(↑)	Inhibit tumor growth, inhibits metastasis, induces NK activity	[39–43,15]
	Human	Unknown	Lowers risk of colon cancer	[43]
Endometrial cancer	Animal *in vitro*	Akt(↑), ER alpha(↓), Bax(↑), Bcl(↑)	Induces apoptosis	[46]
	Animal *in vivo*	Unknown	Unknown	–
	Human	Unknown	Unknown	–
Kidney cancer	Animal *in vitro*	Unknown	Decreases cholesterylester fraction, increases polyethyleneimine fraction	[51]
	Animal *in vivo*	Unknown	Unknown	–
	Human	Unknown	Unknown	–
Pancreatic cancer	Animal *in vitro*	Unknown	Unknown	–
	Animal *in vivo*	Unknown	Decreases tumor weight, dose not influence GSH-Px and SOD level	[57]
	Human	Unknown	Unknown	–
Liver cancer	Animal *in vitro*	HIF1 alpha(↓), PPAR gamma(↑), PP2A(↑), caspase 9(↑)	Increases apoptosis, induces cytotoxicity	[64–67]
	Animal *in vivo*	PPAR gamma(↑)	Decreases tumor size, induces cytotoxicity	[68,69,67]
	Human	Unknown	Unknown	–

approved PEG for human intravenous, oral, and dermal applications [79]. Hence, PEGylation of CLA may prove to be a stable drug to control the cancer cell proliferation, and this effect will offer a challenging approach for anti-cancer. Overall, CLA elicits a wide range of beneficial effects in various cell culture and animal models of disease. However, a minority of studies have reported ambiguous or deleterious effects of CLA supplementation. These observations must be carefully considered and warrant further investigation, before the widespread use of CLA for general purposes, should be promoted. In fact, the use of CLA as a weight loss supplement presents a particularly complex safety concern, since overweight or obese individuals may be predisposed to develop other conditions, such as atherosclerosis and diabetes, in which CLA appears to play a modulatory role. Thus, special attention should be paid to explaining the observations of negative health effects such as insulin resistance and increased LDL:HDL cholesterol ratios in the continuing evaluation of CLA as a dietary supplement. Also, a limited number of studies do not allow us to establish whether CLA can provide any protection in humans against cancer of any site. Moreover, studies with mixtures of CLA isomers in animal *in vivo* seem to lack a scientific basis, because the results reviewed here indicate that different CLA isomers act through different mechanisms and have potentially opposing effects on several metabolic pathways. Hence, the direct extrapolation of the results above to animals and humans needs to be more studied, and further investigations are needed to demonstrate both the short- and long-term effects of CLA in clinical trials, determine the effects of each isomer of CLA, and investigate its safety for applications to human.

Author contributions

Hyun-Seuk Moon wrote the manuscript, participated in the study design, performance and coordination, and conceived the study.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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