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REVIEW

# Health benefits of Conjugated linoleic acid: A Review

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## Introduction

## Conjugated linoleic acid

Conjugated linoleic acid (CLA) is a generic name for a mixture of isomers of linoleic acid with conjugated double bonds. The double bonds can be in several possible positions either as *cis* or *trans* isomers. Double bonds of CLA are mainly found at positions 9 and 11, or 10 and 12 (Ha *et al*., 1987), while isomers having double bonds at other positions also have been reported (Christie *et al*., 1997). Several scientists, based on studies primarily in animal models, have suggested that CLA has potential health or nutritional effects, including anti carcinogenic activity (Ha *et al*., 1990), anti atherogenic activity (Lee *et al*., 1994; Pariza *et al*.,1996), the ability to reduce the catabolic effects of immune stimulation (Cook *et al*., 1993), and the ability to reduce body fat (Pariza *et al*., 1996) Of the individual isomers of CLA, *cis*-9, *trans*-11-octadecadienoic acid has been implicated as the most biologically active because it is the predominant isomer incorporated into the phospholipids of cell membranes (Ip *et al*., 1994). The *cis*-9, *trans*-11 CLA isomer also is the predominant isomer found in the diet. On the other hand probiotics (*lactic acid bacillus*) have been reported with many health benefits. The Health impact with the consumption of microflora consisting of probioics is reported in humans (Isolauri, 2001; Kumar *et al*., 2002; Liu *et al*., 2007; Maassen and Claassen 2008) and in animals (Gill *et al*., 2000; Wollowski *et al*., 2001; Peng *et al*., 2007; Yadav *et al*., 2007). Different bacteria have different actions in different disease states, taking into account that some disease states are better treated with combination of bacteria.

## Various Health Effects Of Probiotics Are :

Reduction in Serum Cholesterol, Improvement in lactose Intolerance and Calcium malabsorption, Anti-mutagenic properties, Effectiveness against Diarrhoea, *Helicobacter pylori* infection, Inflammatory Bowel Disease (IBD), Genitourinary Tract infection (GTI), Calcium Oxalate Stone disease (COSD), Allergies/Eczema, Inflammation/Arthritis, HIV/Compromised Immunity.

## Source of CLA

Food products from ruminants, particularly dairy products, are the major dietary source of CLA for humans. They are intermediates in the bio-hydrogenation of linoleic acid, and it is generally accepted that CLA in ruminants originate from the incomplete bio-hydrogenation of the unsaturated fatty acid linoleic acid by rumen bacteria (Kelly *et al*.,

1998). However, it has been demonstrated that cows also can synthesize CLA from *trans*-11-octadecenoic acid, another intermediate in the rumen bio-hydrogenation process (Kim and Liu, 2000).

Information is lacking on CLA levels required by humans, but it is estimated from animal studies that a daily intake of 3 g/d may be effective for cancer prevention (Ip *et al*., 1994). Dietary sources of CLA include milk fat, natural and processed cheeses, meat products, and plant oil (Ha *et al*., 1989; Shanta *et al*., 1992). Animal sources are richer in CLA than plant sources, and in general, foods from ruminants contain more CLA than foods from non ruminants. Considerable research has been conducted on the CLA content and isomer distribution in cow's milk. The wide variation of CLA content in dairy products also may be due to processing parameters such as different heat treatment procedures during pasteurization. The CLA content in yogurt or cheese can be increased by action of the starter cultures (Lin *et al*., 1999).

Jiang *et al*. (1998) reported the formation of CLA from linoleic acid by *Propionibacterium freudenreichii*. Their study also included seven cultures of lactobacilli, none of which were found to form CLA. Lin *et al*. (1999), Lin (2000), and Ogawa *et al*. (2001) reported the production of CLA from free linoleic acid by *Lactobacillus acidophilus*. Each study included one strain, and in all cases the entire culture (i.e., growth medium plus cells) was assayed for CLA. Kishino *et al*. (2002) found that washed cells of *Lactobacillus plantarum* formed high levels of CLA from free linoleic acid upon extended incubation. They indicated most of the CLA for this culture was associated with the bacterial cells.

## Conjugated Linoleic Acid Also Have Many Health Benefits. Which are described as follows:

Human Tissue.
Anti-Carcinogenic.
Anti-Atherogenic.
Anti-Diabetic.
Bone formation.
Immuno modulatory properties.
Gene Expression.
Anti Oxidant activity.

## CLA in Human Tissue:

Cawood et *al*. (1983) studied low concentrations of CLA are found in human blood and tissues. The author suggested that CLA may be produced *in vivo* from free radical-mediated oxidation of linoleic acid.

Harrison *et al*.(1985) investigated the free radical species and subsequent diene conjugation produces an linoleic acid (LA) lipid radical with conjugated diene structure. In the presence of protein, the LA radical may react with protein instead of molecular oxygen, giving rise to a CLA molecule and a protein radical. CLA in human tissues may be derived from dietary sources, such as fried ground beef and dairy products. Blood CLA levels have been increased in human subjects by feeding CLA-rich diets.
Huang *et al*. (1994) studied on nine men, plasma CLA increased 19% to 27% feeding four weeks of cheddar cheese, but no appreciable changes in linoleic and arachidonic acids, cholesterol or phospholipids levels were observed. This finding may be of importance in changing the levels of CLA in biological fluids by altering specific dietary foods and fatty acids as sources of CLA and, thereby, protecting against cancer.

## Effect Of CLA On Cancer:

The anticancer potential of CLA has received a great deal of research attention in both *in vitro* and animal models. Pariza and Hargraves *et al.* (1985) first reported that topical applications of a partially purified extract from grilled ground beef (enriched with mutagenesis modulator) five minutes prior to DMBA (7,12 dimethylbenz anthracene) treatment reduced the number of papillomas per mouse as well as the number of mice with papillomas. The anti

carcinogenic factor was then isolated and identified as a mixture of dienoic derivatives of linoleic acid.

Ha *et al.* (1987) investigated that CLA had inhibited the development of mouse epidermal tumours.

Ha *et al.* (1989) found that Dietary sources of CLA included milk fat, natural and processed cheeses, meat products, and plant oil. Animal sources are richer in CLA than plant sources, and in general, foods from ruminants contain more CLA than foods from non ruminants.

Ha *et al.* (1990) reported Inhibition of benz(a) pyrene-induced mouse fore stomach neoplasia by conjugated dienoic derivatives of linoleic acid.

Schonberg *et al* (1995) Observed inhibition of proliferation of estrogen receptor-positive MCF-7 cells by CLA. The author found that Bovine milk fat enriched with CLA was more effective in inhibiting human MCF-7 breast cancer cells.

Durgam *et al.* (1997) investigated that CLA in the form of free fatty acids exerts an anti proliferate effect, Milk fat enriched with CLA appears to have even greater *in vitro* activity. Bovine milk fat enriched with CLA was more effective in inhibiting human MCF-7 breast cancer cells than were isolated CLA isomers. Incubation of cells with bovine milk fat enriched with CLA decreased viable cell numbers by up to 90% . Incubation with a mixture of CLA isomers or with the c-9, t-11 CLA isomer resulted in a 60% decrease. Incubation with the t-10, c-12 CLA isomer caused only a 15% decrease in cell numbers under similar conditions. In contrast to the results obtained with the various forms of CLA, incubation with linoleic acid resulted in a 25% increase in cell proliferation. *In vitro* evidence suggests a higher percentage of estrogen receptor-positive MCF-7 cells treated with CLA remained in the G0/G1 phase as compared to controls and those treated with linoleic acid. The effect of CLA on these cells was only temporary and was reversed when CLA was withdrawn from the media.

Ip *et al*. (1999) found greater *in vitro* antiproliferative ability of *c-9, t-11* isomer and owed it due to its accumulation to a greater degree in rat mammary tissue thus author suggested that *c-9, t-11* isomer might be the most important for anticancer effects.

Thomas Yeung *et al.* (2000) investigated *in vitro* anticancer activity for CLA. And inhibition the proliferation of human hepatoma cell lines by it.

Igarashi *et al*. (2001) observed inhibitory effects of CLA on lung adenocarcinoma cell lines and human glioblastoma cell line.

Shultz *et al*. (1992) observed Inhibitory effect of conjugated dienoic derivatives of linoleic acid and beta-carotene on the in vitro growth of human cancer cells.
Ip *et al.* (1995) Studied the effect of timing and duration of dietary conjugated linoleic acid (CLA) on mammary cancer prevention. female rats were fed a diet containing one-percent CLA between early post weaning and a period analogous to puberty (from 21 to 42 days of age) tumour formation as a result of methyl nitrosourea (MNU) administration at 56 days of age was substantially reduced.

Liew *et al.* (1995) Studied the anticancer effects of CLA in colon cancer in rats which were exposed to the carcinogen 2-amino-3-methylimidazol[4,5-f] quinolone to induce colon carcinogenesis. Controls (normal diet) and CLA (0.5% ) treated rats were exposed to the carcinogen during weeks 3 and 4 of the study period. After week 16 the rats were killed in order to quantify aberrant crypt foci (ACF). While CLA administration had no impact on the size of ACF the number of ACF was significantly reduced in the CLA treated group when compared with the controls.

Ip *et al.* (1996) studied the efficacy of conjugated linoleic acid in mammary cancer The author stated that prevention is independent of the level or type of fat in the diet. *In vivo* evidence has also indicated that adding CLA to the diet of female rats exposed to carcinogens results in lower levels of mammary tissue malondialdehyde (an end product of lipid peroxidation), suggesting the potential for some degree of antioxidant activity.

Banni *et al.* (1997) investigated that CLA exert a profound effect on protection against induced dimethylbenz[a]anthracene (DMBA) mammary tumour in mice and rats.

Ip *et al.* (1997a and 1997b) reported significant cancer protection was found only in the rats receiving CLA for the entire 20 weeks. As soon as CLA feeding was discontinued, protection against carcinogen-induced cancer formation was lost. The authors stated that Conjugated linoleic acid and linoleic acid as distinctive modulators of mammary carcinogenesis.

Belury *et al*. (1997) reported modulation of hepatic lipid composition in mice by Conjugated linoleic acid.

Wong *et al.* (1997) investigated the effects of dietary conjugated linoleic acid on lymphocyte function and growth of mammary tumours in mice.

Visonneau *et al.* (1997) found that Conjugated linoleic acid suppresses the growth of human breast adenocarcinoma cells in SCID mice. Feeding CLA to SCID mice resulted in protection against cancer formation and metastasis via mechanisms independent of the host immune system. The author stated that it was unlikely that CLA ability to protect rats and mice against cancer is directly related to immune system activation.

Cesano *et al.*(1998) investigated the anticancer activity and antimetastatic activity in animal models of prostate cancer by dietary CLA *In vitro.* The authors suggested CLA's anticancer activity might be partially a result of CLA-inducing lipid peroxidation. However lipid peroxidation as the role mechanism of action *in vitro*.

Banni *et al.* (1999) investigated the decrease in linoleic acid metabolites as a potential mechanism in cancer risk reduction by conjugated linoleic acid. Evidence of the study suggested that degree of CLA's activity might be a result of modifying eicosanoid production. Feeding CLA to mice resulted in a decrease in arachidonic acid production.

Kavanaugh *et al*.(1999) observed Effect of dietary conjugated linoleic acid on phorbol ester-induced PGE2 production and hyperplasia in mouse epidermis. Dietary CLA also reduced PGE2 synthesis approximately twofold in mice treated topically with the tumour promoter 12-O-tetradecanoylphorbol-13-acetate.

Ip *et al.* (2000) reported the induction of apoptosis by conjugated linoleic acid in cultured mammary tumour cells and pre malignant lesions of the rat mammary gland. *In vivo* evidence suggests an ability of CLA to induce apoptosis, suggested that some of CLA ability to decrease tumour mass might be a result of inducing programmed cell death.

Hubbard *et al.* (2000) studied reduction of murine mammary tumour metastasis by conjugated linoleic acid.

Anee *et al.* (2006) reported reduction in human cancer Cell growth by Beef Conjugated linoleic acid (CLA) isomers

## Effect of CLA On Atherosclerosis

Briggs *et al*. (1993) studied that CLA isomers could modulate atherogenesis is regulating the production of lipoproteins in the liver. Sterol element binding proteins (SREBP) are a group of membrane-bound transcription factors that bind to their specific DNA binding sites (SRE-1) to activate the expression of target genes that

encode enzymes necessary for lipid synthesis, including the LDL receptor (LDLR) gene in sterol-depleted cells.

Lee *et al*. (1994) observed that Lipid levels among the CLA-supplemented rabbits consisted of lower triglycerides and low density lipoprotein (LDL) cholesterol levels. Further examination of the aortas of CLA-fed rabbits showed less atherosclerosis.

Nicolosi *et al*.(1997) investigated reduction in early atherosclerosis in the CLA-supplemented animals.

Brashears *et al.*(1998) founded the bile salt de conjugation of CLA and cholesterol removal from media by *Lactobacillus casei.*

Stangl *et al.* (1999) found that HDL cholesterol ratio was significantly increased by feeding CLA to the animals.

Munday *et al.* (1999) substituted CLA (0.5% of the diet) in diet for linoleic acid for C57BL/6 mice. This strain of mice is genetically susceptible to the development of fatty streaks in the intima of the aortic sinus when placed on a diet similar to the control diet used in the study. In these mice, CLA addition to the diet resulted in a lipid profile considered less atherogenic (lower triglycerides, and a higher serum HDL total cholesterol ratio)

Kritchevsky *et al.* (2000) found one percent CLA to the diet for 90 days resulted in an average regression of established atherosclerosis of 30%. CLA supplementation in conjunction with an atherosclerotic diet fed to rabbits showed similar beneficial effect in retarding atherosclerosis in his second study.

Blankson *et al.* (2000) did a clinical studied in human subjects with BMIs between 25-35 kg/m2, The author noticed statistically significant reductions in LDL. HDL and total cholesterol in all groups receiving CLA. However these changes were not large enough to be clinically significant. An increase in lipoprotein(a)was found in the groups receiving 3.4 grams or more of CLA per day.

Kritchevsky *et al.* (2004) investigated that Conjugated linoleic acid isomer effects in regression of lesions in atherosclerosis.

Nicholson *et al*.(2004) reported that CD36 oxidized LDL and PPAR gamma Pathological interactions in macrophages and atherosclerosis. LDL oxidation also results in changes in apolipoprotein B -epitope. The oxidized apo lipoprotein portion of LDL is subsequently recognized and internalized by SR-A where as the oxidized lipid moiety of LDL is bound to CD36 on macrophages.

Antonius *et al*. (2004) observed the effect of conjugated linoleic acid reduces body composition and plasma lipids in humans.

Desroches *et al.* (2004) investigated the Metabolic syndrome and effect of Conjugated linoleic acid on obesity and lipoprotein disorders.

## Effect Of CLA On Insulin

Houseknecht *et al*. (1998) and Banni *et al*. (1999) reported that CLA isomers are potent modulators of Peroxisome proliferators-activated receptors (PPARs). PPARs bind to target gene and resultant change in gene expression accounts for effects on Glucose metabolism, lipid metabolism, atherosclerosis and carcinogenic activity.

Houseknecht *et al*. (1998) investigated the effect of CLA on insulin levels, glucose tolerance, and glucose homeostasis was investigated in male Zucker diabetic rats (an animal model of type 2 diabetes). An improvement in glucose disposal and a more rapid return to baseline glucose levels subsequent to a glucose infusion was also observed in the CLA-fed rats.

West *et al.* (2000) observed in AKR/J mice (a strain susceptible to dietary obesity),

adding CLA as one percent of dietary calories resulted in a nearly two-fold increase in plasma insulin levels. In these mice there was also a trend toward higher blood glucose levels.

Belury *et al.* (2003) studied that conjugated linoleic acid (CLA) isomer, t-10, c-12-CLA is inversely associated with changes in body weight and serum leptin in subjects with type 2 diabetes mellitus.

Moloney *et al.* (2004) observed conjugated linoleic acid (CLA) supplementation in some animals may have therapeutic potential with respect to insulin sensitivity and lipid metabolism, which is important cardiovascular disease (CVD) risk factors associated with type 2 diabetes mellitus.

## CLA and Bone Formation

Jameela Banu *et al.* (2006) observed the Effects of conjugated linoleic acid and exercise on bone mass in young male Balb/C mice.

Hur *et al*. (2007) investigated that Dietary CLA inhibits endosteal bone resorption, increases endocortical bone formation, and modulates the action and expression of cyclo oxygenase (COX) enzyme, thereby decreasing prostaglandin-dependent bone resorption. CLA also enhances calcium absorption and may improve bone formation in animals, although results are not consistent. Since CLA can also affect inflammatory cytokines, it is hypothesized that CLA may be a good tool for prevention or reduction of rheumatoid arthritis symptoms. The possible mechanisms by which CLA prevents rheumatoid arthritis as well as other inflammatory diseases.

Ilana Platt *et al.*(2007) investigated Isomer-Specific Effects of Conjugated Linoleic Acid on Mineralized Bone Nodule Formation from Human Osteoblast-Like Cells. The *cis-9*,*trans-11* isomer increased the number and size of mineralized bone nodules from 25 to 100 μM, but the 10*trans*,12*cis* isomer did not. The increase in mineralized bone nodule formation by *cis-9*, *trans-11* CLA was accompanied by a variable increase in ALP activity. These results show that the *cis-9*, *trans-11* isomer of CLA increases the formation of mineralized bone nodules using bone cells of human origin, and provide evidence for isomer-specific effects of CLA on bone health.

## CLA Modulation Of Immune Response

The immune system of body is central defence against cancer, it is possible that the anticancer activity of CLA may be mediated through enhanced immune function. The physiological role of CLA in normal and immune-stimulated animals has been studied. Most of the studies show the relation of body growth and immune stimulation by conjugated linoleic acid.

Klasing *et al.* (1987) investigated the ability of CLA to influence growth in baby chicks following immune stimulation with bacterial lipo-polysaccharide (LPS, otherwise known as endotoxin). Typically chicks lose body weight for 24 hours after being injected with LPS, a loss as a result of cytokines released by immune cells. These cytokines (primarily interleukin-1 and tumour necrosis factor, TNF) induce skeletal muscle catabolism.
Cook (1991) conducted studies that how nutritional methods could prevent growth suppression that is usually observed with immune stimulation in animals, e.g. vaccination.

Cook *et al*. (1993) documented antioxidant properties of CLA and hypothesized that this LA isomer may have an impact on the immune response in aging mammalian species. Chicks fed CLA and injected with the endotoxin lipo-polysaccharide (LPS) continued to grow, whereas those not fed CLA either failed to grow or lost weight following LPS injection. In addition, dietary CLA enhanced the phytohemagglutinin response and alleviated the catabolic effect of immune stimulation in rats.

Hotamisligil and Spiegelman *et al*. (1993) concluded that the cytokine produced biochemical changes in a wide variety of cells attributable to its capacity for using multiple signaling pathways through its cell surface receptors. Hence TNF-$\alpha$, like CLA, is multifunctional. Mice were fed control diet or diet supplemented with 0.5% CLA for 32 days, then injected with TNF-$\alpha$ as indicated. The CLA-fed mice experienced less weight loss indicating that they were partially protected against the cachexia that was induced by the cytokine. These results provide evidence indicating that CLA may modulate a cellular response to TNF-$\alpha$, possibly through the regulation of eicosanoid and CLA.

Miller *et al.* (1994) observed the ability of conjugated linoleic acid to prevent endotoxin-induced growth suppression. Conjugated linoleic acid prevented anorexia from endotoxin injection. Splenocyte blastogenesis was increased by conjugated linoleic acid. Based on the observation that CLA feeding decreased tissue arachidonic acid content, the authors concluded that CLA may be preventing the catabolism of tissue by removing eicosanoid precursors.

Suganuma *et al.* (1996) Studied the process of cancer prevention mediated through inhibition of tumour necrosis factor- $\alpha$ expression. TNF-$\alpha$ appears to be a key mediator in many chronic pathologies including cachexia, atherosclerosis, carcinogenesis .

Wong *et al.* (1997 ) studied the effects of conjugated linoleic acid on lymphocyte function and growth of a transplantable murine mammary tumor. In one experiment Female Balb/c mice eight-week-old were fed 0.1%, 0.3% or 0.9% CLA for three or six weeks. Lymphocyte proliferation, interleukin-2 production and lymphocyte cytotoxicity were assessed using splenic lymphocytes. Plasma CLA concentrations increased in a dose-dependent manner with CLA feeding. Lymphocyte proliferation in mice and phytohemagglutinin and production of IL-2 also was stimulated by CLA. Therefore, dietary CLA modulated certain aspects of the immune defense but had no obvious effect on the growth of an established, aggressive mammary tumor.

Moya *et al*.(1999) investigated that CLA is potent naturally occurring ligand and activator of PPARs. The author observed that PPARs involved in regulating expression of various gene involved in proliferation of lymphocytes monocytes and macrophages, apoptosis and inflammation.

Hayek *et al*. (1999) found that young and old C57BL / 6NCrlBR mice fed 1% CLA had greater splenocytes proliferation in response to concanavalin A and phytohemagglutinin-A (PHA) than mice fed the control diet. CLA-supplemented young mice had significantly higher splenocyte interleukin-2 production than those fed the control diet. These findings suggest that CLA is effective in preventing the catabolic effect of immune stimulation, and possesses a potent immuno stimulatory effect in mammalian species. The potential of preventing the catabolic losses without affecting the generation of adaptive immunity could provide benefit to growth and development.

Bassaganya *et al*. (2002) reported that CLA interacts with peroxisome proliferator-activated receptors (PPARs). Which are the fatty acid receptor that regulates the expression of genes involved in immune functions and energy homeostasis.

Iwakiri *et al.* (2002) investigated the Suppression of cyclooxygenase-2 and inducible nitric oxide synthase expression by conjugated linoleic acid (CLA) in murine macrophages.

Alber *et al.* (2003) studied that CLA supplementation beneficial for immunocompromised individuals which are slow or low responders to vaccination.

Torres *et al.* (2003) observed that Conjugated linoleic acid exhibits stimulatory and inhibitory effects on

prostanoid production in human endothelial cells and platelet.

Yang *et al.* (2003) reported that Dietary conjugated linoleic acid decreased cachexia, Macrophages and production of cytokines. CLA was shown to inhibit lipopolysccharide (LPS)-stimulated tumour necrosis factor-α (TNF-α). The authors observed decrease in interleukin-4 (IL-4) in CLA fed mice when splenocytes were stimulated with concanavalin-A (con-A) for 44 hours.
Yamasaki *et al.* (2003) reported the Immunoglobulin and Cytokine production from spleen lymphocytes is modulated in C57BL/6J mice by dietary *cis-9, trans-11 and trans-10, cis-12* conjugated linoleic acid. The author observed that spleen lymphocytes isolated from the mice fed with *trans-10, cis-12-* CLA produced more immunoglobulin (Ig)A and (Ig)M but (Ig)G. (Ig)A production was greater in *t-10, c-12*-CLA treated group than controls. Conversely, *C-9, t-11*-CLA did not affect the production of any Ig subclasses. Lymphocytes isolated from *C-9, t-11*-CLA fed mice produced more tumour necrosis factor- α than control group. The proportion of B-cells in the spleen lymphocytes was significantly lower in *C-9, t-11*-CLA group than and higher in t-10, c-12- CLA group than in controls. Moreover the percentage of $CD4^+$ T cells lower in the *t-10, c-12*-CLA and percentage of $CD8^+$ T was higher in *C-9, t-11*-CLA. The ratio of $CD4^+$ T/ $CD8^+$ T was lower in control groups.

Marianne *et al.* (2004) demonstrated that conjugated linoleic acid modulates immune function. The author observed both the innate and adaptive immune response are affected by dietary CLA supplementation. CLA decrease tumour necrosis factor-α (TNF- α) and interleukin 6 (IL-6) and isomers of CLA *cis-9, trans-11 and trans-10, cis-12* exerts distinct effects on T-cells population and immunoglobulin subclasses in rats models.

Li *et al.* (2006) studied that conjugated linoleic acid suppresses NF-kB activation and lipo polysaccharide (LPS)-induced IL-12 by a conjugated linoleic acid. The author observed that *cis-9, trans-11* suppresses IL-12 production by LPS- stimulated dendritic cells by ERK mediated IL-10 induction. The IL-10 mediated effects are inhibition of NF-kB activation indicated that *cis-9, trans-11* can enhance transcription and production of anti-inflammatory cytokine IL-10.

Mullen *et al.* (2007) investigated that Conjugated linoleic acid supplementation reduces peripheral blood mononuclear cell interleukin-2 production in healthy middle-aged males.

## CLA mediated Gene Expression:

Yu *et al.* (2004) demonstrated that a CLA isomer mixture (50:50, 400 μmol/L final concentration) up-regulated LDL receptor (LDLR) mRNA and protein expression at three- to five-fold in HepG2 cells. The results of the study suggest the up regulation of the LDLR gene by CLA through a mechanism that is independent of SREBP-1 and acyl CoA cholesterol acyl- transferase (ACAT).
Ringseis *et al.* (2006) reported that the *trans*-10, *cis*-12 CLA isomer, not the *cis*-9, *trans*-11 CLA isomer, induced LDLR gene expression via SREBP-2 in human hepatoma cells (HepG2). They concluded that the enhanced uptake of VLDL and LDL cholesterols by hepatic LDLR may account for the decreased plasma cholesterol levels in response to CLA isomer.

Alibin *et al.* (2008) observed the Suppression of cardiac myocyte hypertrophy by conjugated linoleic acid and role of peroxisome proliferator-activated receptors (PPARs).

## CLA and Antioxidant Activity

CLA has been investigated for antioxidant activity by several researches since it was considered as a possible explanation for some of its health effects such as carcinogenesis and atherosclerosis. However it is clear that the conjugated double bonds

made contribution to the radical scavenging capacity of CLA. The difference in the reaction kinetics between CLA-radicals and linoleic acid- radical perhaps provide a reasonable explanation for CLA have anticarciongenic. While increase linoleic acid was observed to promote tumour formation (MacDonald, 2000).

Ha *et al*. (1987) reported that CLA was more effective in preventing linoleic acid oxidation than α- tocopherols.

Wu *et al*. (1994) and Beharka et al. (1997) investigated that antioxidant nutrients (e;g Vitamin E, p-carotene and glutathione) can enhance the immune response in rodents and humans.

Yurawecz *et al.* (1995) found that CLA could be converted to furan fatty acid by air oxidation in methanol and should be consider as a source of furan fatty acids in biological systems. Formation of furan fatty acids may contribute to the antioxidant properties of CLA.

Cantwell *et al.* (1999) reported the effect of conjugated linoleic acid on the antioxidant enzymes defence system in rat hepatocytes.

O' Shea *et al*. (1999) investigated the antioxidant enzyme defence responses of human MCF-7 and SW480 cancer cells to conjugated linoleic acid.

Leung *et al*. (2000) reported that trans-10, cis-12 conjugated linoleic acid has strong oxy radical scavenging capacity. Their study also showed that t-10, c-12 CLA have high antioxidant activity than c-9, t-11 CLA.

Liangli Yu. (2001) investigated free radical scavenging properties against the stable 2,2-diphenyl-1- picry hydrazyl radical (DPPH). Kinetics of CLA- DPPH reactions was different to that linoleic acid (LA). The author observed CLA had reacted and quenched DPPH radicals while LA had showed no radical quenching activity indicating that CLA can provide immediate protection against free radicals.

Liangli Yu et *al.* (2002) reported the conjugated linoleic acid cis-9, trans-11 and cis-12, trans-10 isomers differ in free radical scavenging properties. The author concluded that individual CLA isomers differ in their biological actions and indicate that interaction between isomers contribute to their beneficial health effects.

## Bioconversion Of CLA

CLA can be formed from linoleic acid by the ruminal bacteria (*Butyrivibrio fibrisolvens)* and other prebiotics *Lactobacillus*. Free linoleic acid can be converted to CLA in rats but esterified linoleic acid cannot do so. However germ-free rats were not capable of converting linoleic acid to CLA, suggesting that the intestinal micro-flora of non-ruminants also has a limited ability to isomerise linoleic acid to CLA.

Kepler *et al.* (1966) studied the intermediates and products of the bio hydrogenation of linoleic acid by *Butyrivibrio fibrisolvens*. A rumen bacterium, *Butyrivibrio fibrisolvens* was able to convert linoleic acid to oleic acid via conjugated linoleic acid.

Chin *et al.* (1994) reported that Conjugated linoleic acid (9,11- and 10,12-octadecadienoic acid) is produced in conventional but not germ-free rats fed linoleic acid.

Buck *et al.* (1994) studied comparisons of freshly isolated strains of *Lactobacillus acidophilus* of human intestinal origin. Two strains of *L. acidophilus* (L1 and O16) and two of *L. casei* (E5 and E10) isolated from human intestinal sources were used to produced conjugated linoleic acid

Boyaval *et al.* (1995) observed CLA production in that .Less was produced in the presence of 0.05% than in 0.02% linoleic acid by propionic acid bacteria.

Lin *et al.* (1999,2000) reported that Conjugated linoleic acid concentration is affected by lactic cultures and added linoleic. Their study revealed that a culture of *L.acidophilus* produced *cis-9, trans-11* in sterilized skim milk supplemented with free linoleic acid after 24 h of incubation at 37°C.

Ogawa *et al.* (2001) investigated Conjugated linoleic acid accumulation via 10-hydroxy-12-octadecaenoic acid during micro aerobic transformation of linoleic acid by *Lactobacillus acidophilus*.

Kishino *et al*. (2002) reported Conjugated linoleic acid production from linoleic acid by *lactic acid* bacteria. The authors found that washed cells of *Lactobacillus plantarum* formed high levels of CLA from free linoleic acid upon extended incubation. They indicated most of the CLA of culture was associated with the bacterial cells.

Alonso *et al*. (2003) investigated the production of free conjugated linoleic acid by *Lactobacillus acidophilus* and *Lactobacillus casei* of Human intestinal Origin. Their study has shown that two cultures each of *Lactobacillus acidophilus* (016, L1) and *Lactobacillus casei* (E5, E10) were able to convert free linoleic acid to CLA. Of the possible isomers of CLA, cis-9 and trans-11, cis-12 and trans-10 formed. cis-9 trans-11 comprised more than 90% of the total CLA.

**John Wallace *et al.* (2007) reported that the i**somers of conjugated linoleic acids are synthesized via different mechanisms in ruminal digesta and bacteria. Digesta samples from the ovine rumen and pure ruminal bacteria were incubated with linoleic acid (LA) in deuterium oxide-containing buffer to investigate the mechanisms of the formation of conjugated linoleic acids (CLA)

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