Systematic evaluation on the effectiveness of conjugated linoleic acid in human health

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Abstract

The term CLA (conjugated linoleic acid) corresponds to a mixture of positional and geometric isomers of linoleic acid. Two of these isomers (9c, 11t and 10t, 12c) have biological activity. The milk and dairy products are the most abundant source of conjugated linoleic acid, which refers to a group of positional and geometric isomers of CLA (CLA 18:2 cis-9, cis-12). The following research aims to approach aspects regarding the CLA, as well as its relationship with diseases. Conjugated linoleic acids have been studied for their beneficial effects in the prevention and treatment of many diseases, including obesity, cancer, diabetes, and cardiovascular diseases. Scientific information put together the physiological properties of CLA, which serve as inputs to claim their potential as functional ingredients to be used in the prevention and control of several chronic metabolic disorders.

Key-words

conjugated linoleic acid, benefit, dairy, health

Introduction

Due to changes in consumer demand for healthier foods with more beneficial health effects, more importance has been given to the characteristics related to food security, health, and nutritional value. Animal products have played an important role due to the composition of fatty acids that can influence human health. Recently, research has focused on conjugated linoleic acid (CLA),

Conjugated linoleic acids (CLA) are fatty acids found naturally in foods from ruminant animals such as meat, milk, and dairy products due to the process of bacterial biohydrogenation in the rumen (Bhattacharya et al., 2006).

CLA has been reported to have beneficial effects on health, being related to diseases using animal models and cultured cells derived from humans and animals. CLA has shown beneficial health effects such as an anticarcinogenic (Kelly et al., 2007), reduction in body fat deposition, reduced development of atherosclerosis (Serra et al., 2009), stimulation of immune function (Bhattacharya et al., 2006) and blood glucose lowering (Belury et al., 2002).

Currently, the discussion on CLA has been explored regarding the results found by many research groups. Although the physiological effects of CLA have been studied, its mechanisms of action are still controversial and appear to be dependent on animal species, dose and duration of the experiments. Thus, it is clear the need for further investigation.

Discovery of conjugated linoleic acid

In the late 70s, Pariza and colleagues suggested that grilled beef had a carcinogenic component (Pariza et al., 1979). Some years later, these researchers observed the presence of compounds with antimutagenic activity in extracts of meat. Such compounds, unlike the mutagenic factors, which are formed during cooking, were present regardless of the cooking process (Hargraves and Pariza, 1983).

In 1985, Hargraves and Pariza demonstrated that these components in the extract from beef could inhibit tumor progression in epithelial cells of mice. Only in 87 Ha et al. using spectrophotometry and chromatography techniques, managed to isolate and characterize these unknown antimutagenic components of the lipid fraction of meat. The authors then discovered the existence of four isomers of linoleic acid derivatives, and each contained a conjugated double bond system, being named conjugated linoleic acids (CLAs).

Characterization of the molecule of CLA

Conjugated linoleic acid (CLA) is a mixture of position and geometrical isomers of linoleic acid with conjugated double bonds, separated only by a single carbon-carbon (Chouinard et al., 1999) (Figure 1).

This compound is found in small quantities in a variety of food and it is estimated that there are 56 possible isomers (Yurawez et al., 1999). Amongst these isomers, two already have already had their activity identified: cis-9, trans-11 isomer is a potent

natural anticarcinogen (Ip et al., 1991), while the trans-10, cis-12 is an effective nutrients splitter (Park et al., 1997). Many studies applying different experimental models, relate to other CLA positive effects which could improve human health, including a reduction of arteriosclerosis, prevention and treatment of diabetes mellitus, noninsulin dependent modulation of potentiation of the immune system and bone mineralization (Sebedio et al., 1999).

Production of CLA

CLA might be originated from rumen by biohydrogenation incomplete polyunsaturated fatty acids deriving from the diet and also for the desaturation of fatty acid C18:1 trans-11 by action of stearoyl - CoA desaturase (SCD) (Corl et al., 2001).

Biohydrogenation

In ruminants, throughout the process of biohydrogenation of linoleic acid, the cis-9, trans-11 C18:2 isomer is the first intermediate formed by ruminal bacteria. Among the existing bacteria, *Butyrivibrio fibrosolvens* is the best known (Martin and Jenkins, 2002). Although several other species have lipases capable of hydrolyzing the ester linkages of fatty acids, and thus produce CLA, among them are the *Lactobacillus casei* and *Lactobacillus acidophilus* (Alonso et al., 2003). The isomerization is catalyzed by the initial Δ^{12} cis, Δ^{11} trans isomerase which is most frequently from the rumen bacterium *Butyrivibrio fibrosolvens* originating cis-9, trans-11, which after saturation of the binding medulla cis-9 by the action of a reductase forms the vaccenic acid (C18:1 trans-11) (Martin and Jenkins, 2002). Sequentially, there is a reduction, resulting in the formation

of stearic acid (C18:0) (Chouinard et al., 1999). Usually the biohydrogenation occurs in a complete way, but some intermediate products such as cis-9, trans-11 C18: 2, can cross the rumen pass into the bloodstream, be absorbed by the mammary gland and incorporated into milk fat. There are several factors that may influence biohydrogenation in the rumen, and thereby change the amount and composition of unsaturated fatty acids available for deposition in adipose tissue or milk fat secretion. The power supply conditions and the type and concentration of fatty acids present, which determine rumen bacteria are prevalent and hence the pH, which promote for the production of CLA must be greater than 6.0 (Alonso et al., 2003; Martin and Jenkins, 2002).

Synthesis via Δ^9 desaturase

Fatty acid C18:1 suffers desaturation by enzyme Δ^9 desaturase present in the mammary gland and adipose tissue. To support the hypothesis that the C18:1 trans-11 produced in the rumen can be converted to CLA in the mammary gland by the action of Δ^9 desaturase. Griinari et al. (2000) infused a mixture of C18:1 trans-11 and C18:1 trans-12 (50% - 50%) in the abomasum in dairy cows. These authors noted a 31% increase in the content of CLA to cis-9, trans-11 secreted into milk fat, indicating that the animals are capable of synthesizing CLA endogenously. In order to ascertain the importance of endogenous synthesis of CLA via Δ^9 desaturase, a second experiment has been conducted in which esterculina oil was infused, a potent inhibitor of Δ^9 desaturase in the abomasum of cows. There was a 45% reduction in the concentration of milk fat and other products of the action of Δ9 desaturase, which were identified by

increased two to three times the ratio of the proportion of fatty acids 14:0 / 14:1, 16:0 / 16:1, and 18:0 / 18:1.

Using the change in the ratio 14:0 / 14:1 as an indication of the extent of inhibition of Δ^9 desaturase, the authors estimated that 64% of CLA in milk fat of ruminants is endogenously produced, suggesting that this pathway is responsible for most of CLA in milk (Griinari et al., 2000).

Contributing to these results, Corl et al (2001) demonstrated a significant reduction of 60-65% in the CLA cis-9, trans-11 when cows were fed a diet supplemented with esterculina oil. Reductions of 84%, 59% and 46% for C14: 1 cis-9, C16: 1 cis-9 and C 18: 1cis-9, respectively were also observed.

Food sources and human consumption of CLA

The consumption of meat and milk will increase globally in the next twenty years, due to the growing world population, a higher yield potential and availability of these foods to meet nutrient needs as part of a daily diet. More recently in Britain, a national survey on nutrition and diet as meat, milk and milk products were responsible for supplying 25% of the total caloric content of the diet (Woods and Fearon, 2009).

Milk fat is probably the most complex of all fats. More than 400 different fatty acids were detected in milk fat by now, from C2 to C28, including odd, saturated, monounsaturated and polyunsaturated, cis and trans, branched and linear (Collomb et al., 2000).

CLA is found in many foods, in larger proportions in the dairy products, beef, and in smaller quantities in swine, poultry, and vegetable oil (Hur et al., 2007). The milk and dairy products are the most abundant source of conjugated linoleic acid, which refers to a group of positional and geometric isomers of CLA (CLA 18:2 cis-9, cis-12). The presence of CLA in milk fat has been known for years, but its exact composition was unknown until they were recognized as bioactive in human biochemistry and different disease processes, such as cancer (Ledoux et al., 2005).

The concentration of CLA in milk products range from 2.9 to 8.2 mg/g fat, and the cis-9, trans-11 is between 73-93% of the total CLA (Kelly, 2001). Khanal et al. (2005) found values of 5.2 mg CLA in milk, 4.7 mg for cheddar cheese. Rainer and Heis (2004) found that levels of CLA in yoghurt vary from 2.8 to 4.8 mg/g, Parodi (1999) observed 6.1 mg of CLA present in butter and Ledoux et al. (2005) 4.5 mg/g for butter winter, 5.8 mg/g spring, and 8 mg/g in summer (Collomb et al., 2006; Park, 2009).

The content of CLA in milk and dairy and beef is about 4 to 5 mg/g fat, respectively, the cis-9, trans-11 responsible for more than 80% of that content, as can be seen in Table 1 (Funck et al., 2007). Chouinard et al. (2001) suggested that the content of CLA in milk can be substantially increased by modifying the diet. Bauman et al. (2000) suggests that by feeding cows with sunflower oil, the content of CLA in the butter would be increased by more than seven times.

CLA in human diets

Consumption of CLA by the population is hard to be estimated, but some research has been conducted to this end (Ritzenthaler et al., 2001). It is difficult to quantify the intake of CLA from the diet, since there is insufficient data on the content of isomers in foods and the factors that condition it. Despite these shortcomings, the data have been published in different countries, the U.S. estimated an intake between 52 and 137 mg/day, England and Australia are much higher, between 600-800 mg/day and 1500mg/day, respectively (Pariza et al., 2001). Ritzenthaler et al. (2001) studied 51 men and 51 women for 12 months and their dietary intakes measured by food weighing; total consumption of CLA was 212 and 151mg/day, respectively.

Medeiros (2002) conducted a study in University Cafeteria in the city of São Paulo, using 6 samples of full meals (lunch), which were selected in the desired quantities as a regular user of the restaurant (man, 33 years old, 75 kg of weight). It was observed that the concentration of CLA in the diet varied from 0.9 to 4.9 mg/g. Although there is no established recommendation for daily intake of CLA to protect

the consumer, the results of the study suggest that to achieve the proposed 350mg/day consumption would require a richer diet with CLA.

Higher values are reported by Gómez-Candela (2004) estimating an intake of around 1.5-2g/day. The only ways to ensure a beneficial intake of CLA is about 3-6g/d, which seems to be the level where health benefits can be expected. This can be achieved by increasing the level of milk in dairy products by manipulating the feeding of

cows or intake of CLA in the form of capsules oil enriched or fortified foods. This approach is considered as the use of natural compounds in pharmaceutical doses for a particular health benefit. (Whale et al., 2004; Tricon et al., 2005).

Most studies in animals and humans came to very different values in relation to consumption, it is important to note that studies in humans have used a mixture of cis-9, trans-11 and trans-10, cis-12.

Effects of CLA on body composition

Obesity represents a major public health problem due to the increasing prevalence and association of it with a variety of diseases, deserving greater attention of physicians and other health professionals. Based on a representative sample of England, in 2004, 22.9% of the population was obese and 43.9% of men and 33.9% of women were overweight, suggesting that more than half of adults were overweight or obese (Sharma et al., 2009).

Supplementation with conjugated linoleic acid has been studied with the aim of reducing the percentage of body fat (Gaze et al., 2007). The ability of CLA to reduce body fat in animals, first reported in 1995 (Park et al., 1995), confirming that the isomer trans-10, cis-12 is responsible for this activity (Park et al., 1998).

Park et al. (1997) studied mice supplemented with 0.5% CLA, observing a 60% reduction on body fat. Ostrowska et al. (1999) researching hamsters and pigs, observed a reduction both in weight and body fat after CLA supplementation. A study in obese

and diabetic mice, the ingestion of 1.5% CLA (47% + 47.9% c9t11 t10c12) decreased weight gain and fat (Ryder et al., 2001). Despite the evidence that the CLA can reduce the fat of animals, surprisingly few studies have been conducted to verify that the same applies in humans (Whale et al., 2004).

Norway was the first country to investigate the effect of CLA supplementation on body composition in humans (Thom et al., 2001). In a study of physically active people who received 1.8 g/d of a CLA mixture and a control group that received olive oil for 12 weeks, did not observe changes in body weight, but the CLA group reported a 4% decrease in body fat compared to placebo. In Wisconsin, Madison University evaluated the effect of an intake of 2.7 g/d of CLA in the loss of weight and body fat in obese individuals, observing a reduction of 2.5 to 1 kg, respectively, in the control obese group and the (Atkinson et al., 1999).

Blankson et al. (2000) analyzed 47 obese and overweight supplemented with 1.7, 3.4, 5.1, or 6.8 g/day of CLA or 9 g/day olive oil for 12 weeks. After treatment, a reduction in body fat not dependent on the dose groups supplemented with 3.4 and 6.8 g/d CLA. Importantly, most human studies, the objective of reducing the fat deposits already formed (Pariza et al., 2000).

There are several mechanisms proposed to explain this change in body composition, among them are the reduction of proliferation and differentiation of preadipocytes, decreased esterification of fatty acids in triacylglycerols, increased energy expenditure, increased lipolysis, alteration of the enzymes carnitine

palmitoyltransferase and lipoprotein lipase and the concentration of leptin, among others (Wang and Jones, 2004).

CLA and Cancer

In the last thirty years, many epidemiological studies have examined the relationship between dietary fat intake and risk of developing several types of cancer. The limitations and difficulties in conducting such studies, especially the food recall is well known. Perhaps not surprisingly, conflicting results have been reported, which led to some confusion about the role of fat in the etiology of cancer (Whale et al., 2004).

The CLA may influence cancer progression in three ways: directly affecting the process of carcinogenesis by reducing the excessive accumulation of body fat that indirectly increases the risk of cancer, and reducing cachexia that is associated with advanced stages of cancer (Pariza et al., 2001).

The first studies investigating the anticarcinogenic properties of CLA are from the early 90s. Ha et al. (1990) studied the anticarcinogenic action of this compound in mice subjected to induction of stomach cancer by benzopyrene, and observed that animals treated with CLA showed half the number of neoplasms, compared to control. Only the cis-9, trans-11 was found in the phospholipids of the stomach of mice, demonstrating that this is the isomer responsible for the anticarcinogenic action.

The mechanism of action could be related to antioxidant property of the compound, in particular cis-9, trans-11. This isomer inhibit Fenton type reactions and,

consequently, the damage caused by hydroxyl radicals in cell membranes, directly related to the development of various pathological processes, including those of initiation and promotion of some types of cancer.

First study of CLA and cancer was by Knekt et al. (1996), although indirect evidence were, an inverse relationship between milk consumption and incidence of breast cancer was observed, suggesting that CLA, a component of milk has potential assets. Ip et al. (1995) found that the supply of 1% CLA in the diet of rats, the post-weaning until puberty, was sufficient to inhibit the growth of mammary tumor. Ip & Scimeca (1997) described the effect of CLA in inhibiting mammary tumor is independent of the dose of dietary linoleic acid. These authors rodent diet supplemented with doses of 0.5% to 2% of CLA, and the anticarcinogenic activity of CLA was maximal at a dose of 1% CLA. The mechanisms of action of CLA are not fully clear; some studies attribute these effects to a reduction of cell proliferation (Pariza et al., 2001).

Aro et al. (2000) observed a preventive effect with foods rich in CLA in postmenopausal women, while others found no correlation between CLA and the risk of breast cancer (Aro et al., 2000; Chajes et al., 2003, Rissanen et al., 2003; Voorrips et al., 2002). Besides breast cancer, Larsson et al. (2005) reported an inverse correlation between CLA and the incidence of colorectal cancer in a 15-year study involving women.

Research on the protective effect of CLA against colon cancer has been going steadily, and molecular mechanisms of action have been identified. In 2004, Park et al. studying

cancer of the colon induced by dimethylhydrazine in rats have shown that reducing the incidence of cancer is related to the increase of apoptotic cells and the consumption of 1% CLA. Subsequently, the same group showed that the increase in apoptotic cells is related in part to the reduction of prostaglandin E2, accompanied by an increase of the ratio of pro-apoptotic proteins Bax/Bcl-2, as noted by the authors (Park et al., 2004). Lim et al. (2005) demonstrated that the administration of physiological concentrations of CLA interrupt the growth of colon cancer cells, since there was a significant increase of cells in the G1 phase of cell cycle. This increase was accompanied by the induction of p21, protein that negatively regulates cell growth promoters such as proliferating cell nuclear antigen (PCNA), and cyclins A, D1, and E, which were reduced after treatment with CLA.

Another mechanism that may be attributed to the effect of CLA is the reduction in cellular proliferation has been observed in cell culture and animal models. A possible explanation for this effect can be increased apoptosis mediated by the CLA. Bergamo et al. (2004) attributed to CLA a mechanism of anticancer activity, involving production of reactive oxygen species, leading to activation of an enzyme called caspase-3, considered a key enzyme in apoptosis. Other authors also reported an increase in apoptosis in the mammary tissue, liver and adipose tissue (Haugen et al., 2003; Hargrave et al., 2004).

Food with higher amounts of CLA has also large quantities of fat, which qualitative and quantitative profile of fatty acids may interfere with its activity.

CLA and insulin resistance

The incidence of diabetes and glucose tolerance is increasing worldwide and is starting to affect younger populations (Belury et al., 2003). Central to this disease is obesity and changes in lifestyle, resulting in a small reduction in body weight (approximately 7%) which is associated with a significant reduction in risk of developing diabetes in individuals at a known risk.

The insulin resistance found in obesity is accompanied by effects on other systems. Thus, an increased accumulation of fat can lead to changes in glucose and lipid metabolism as well as in other systems including blood pressure. However, deficiency of adipose tissue is also followed by insulin resistance and high incidence of type 2 diabetes mellitus (Ganda, 2000).

Studies by Belury et al. (2002) in patients with type 2 diabetes suggest that supplementation of CLA (6 g/day) for 8 weeks is associated with a significant decrease in blood glucose. However, do not observe the effects on concentrations of fasting insulin, glycosylated hemoglobin, triglycerides, total cholesterol and HDL cholesterol in obese subjects with high cardiovascular risk. Belury et al. (2003) demonstrated that 81% of individuals with non-insulin dependent diabetes mellitus (n = 11) who received 6.0 g CLA/day for 8 weeks showed significant reduction in blood glucose and fasting when compared to the control group. Risérus et al. (2004) have shown that supplementation of cis-9, trans-11 CLA (3 g / day) is related to increased insulin resistance and increased lipid peroxidation.

Obese men and non-diabetic (n = 25) received 3 g / day of olive oil control) or a mixture composed predominantly of cis-9, trans-11 CLA. After a period of 12 weeks of supplementation, the group receiving CLA showed a higher resistance ($p<0.05$) insulin activity (Risérus et al., 2004).

Amongst the mechanisms that explain the improvement in insulin resistance, particularly the cis-9, trans-11, increased fatty acid oxidation in muscle and liver and increased energy expenditure are among the most discussed by the authors (Medina et al., 2000).

The effect of CLA in diabetes seems to be dependent on the dose, isomer, species, gender, and especially of the prior existence of obesity and insulin sensitivity. Thus, more comprehensive research should be done seeking to elucidate the effect of this compound on the benefit to the disease (Hargrave et al., 2004).

Effects of CLA on lipid profile

Cardiovascular diseases are the main causes of morbidity and mortality in developed countries and in most developing countries. Among these diseases, atherosclerosis is the primary, accounting for 50% of deaths in the West (Tomey et al., 2003). Atherosclerosis is a progressive disease characterized by accumulation of lipids in the arteries that involve a complex inflammatory process, and hypercholesterolemia is an important factor for its appearance (Libby, 2002).

The administration of CLA under the most diverse ways and concentrations seem to be responsible for the improved blood lipid profile, reduction of atherosclerosis by mechanisms distinct and differently in animals and humans (Santos-Zago et al., 2008).

Food or a mixture of CLA individual isomers showed a reduction in severity of cholesterol induced atherosclerotic lesions in the thoracic aorta and aortic arch into hamsters and rabbits (Yucawecz et al., 1999). Even when rats fed at levels as low as 0.1% of the diet, atherosclerosis was reduced by 28% and 41% respectively. This was increased with the increasing of the dose of CLA, such that 0.5% of CLA aortic atherosclerosis severely reduced by 60% and 56% in the arc and the thorax respectively (Kritchevsky et al., 2002).

Animal studies indicate that CLA has positive effects on risk factors related to cardiovascular disease by reducing serum cholesterol levels and triglycerols (Roche et al., 2001). Wilson et al. (2000) in a study with hamsters fed for 12 weeks with a hypercholesterolemic diet supplemented with 1% CLA in the diet indicated that the groups fed CLA had lower total cholesterol levels compared to that received hypercholesterolemic diet.

Other important results were found in studies with mice. Toomey et al. (2003) found positive results when supplemented knockout mice with 1% cis-9, trans-11 CLA. These animals, characterized by having predetermined atherosclerosis showed a delay in development of new lesions, as well as regression in the size of existing lesions.

Compared to studies in animal models, there have been few human studies that evaluated the effects of CLA on the risk factors for cardiovascular disease. Furthermore, there was considerable variation between different studies.

Studies in humans are also contradictory and difficult to extrapolate the results. Blankson et al. (2000) reported a reduction in LDL, HDL and total cholesterol in humans with body mass index of 25-35 kg/m², fed CLA (1.7, 3.4, 5.1, or 6.8 g/day for 12 weeks), although statistically significant, the reduction was not considered statistically significant. Tricon et al. (2004) have shown that supplementation with 750mg of cis-9, trans-11 CLA in the form of capsules is related to a reduction of total cholesterol and LDL could therefore have beneficial effects.

The antiatherogenic effect of CLA supplementation can be explained by the decline in the production of cholesterol, as well as its secretion by the liver, by reducing the synthesis of triacylglycerols, associated with increased oxidation and increased activation of PPAR gamma (perxissoma proliferator γ) (Toomey et al., 2003) and also by inhibition of thromboxane production and consequently a decrease of platelet aggregation (Stangl, 2000). Because the show CLA to be effective on the changes in lipid profile in some experimental models, further work needs to be done in order to elucidate the mechanisms of action of CLA in the prevention of atherosclerosis and thus ensure their use in reducing cardiovascular disease in humans (Belury et al., 2002). More long-term studies are urgently needed in different populations with the intake of CLA, and this can be recommended to improve cardiovascular health in humans.

CLA and the immune system

Some studies have shown that the immune system may also be benefits by CLA. The dietary intake of CLA could enhance immune responses, as well as reduce the adverse effects mediated catabolism (Pariza et al., 2001).

Anti-inflammatory properties of CLA have been reported in: reducing the inflammation of the colon, decrease antigen-induced cytokine production in immune competent cells, and modulating cytokine production (Bhattacharya et al., 2006). However, Poirier et al. (2006) reported that the isomer trans-10, cis-12 induced inflammatory responses in adipose tissue. CLA has been shown to enhance immune responses related to tumor necrosis factor, cytokines, prostaglandins, nitric oxide or reducing the type immune responses (Bhattacharya et al., 2006). Cis-9, trans-11 is related to inhibition of tumor growth and modulation of immune response (Pariza et al. 2001)

Yamasaki et al. (2000) showed that when rats were supplemented with different amounts of CLA (0, 0.05, 0.10, 0.25, and 0.50%) for 3 weeks, there was an increase in antibody production by spleen of these animals. Turpeinen et al. (2008) found that CLA supplementation relieved some allergic responses, such as pollen allergy.

Model studies on cultured animal cells show that the CLA acts as a modulator of immune function. In humans, recent studies indicate that the main isomers of CLA may alter the production of prostaglandins, cytokines, immunoglobulins, despite the possible mechanisms of action is very complex and not well known (O'shea et al., 2004). Nugent

et al. (2005) have shown that supplementation with the two main isomers of CLA exerts minimal effects on the most important immune functions.

In humans, the activity of CLA seems to be different from that found in animal models. Seventeen healthy women were confined in a metabolic unit for 93 days, receiving the first 30 days of sunflower oil capsules (6g/day) to adapt. Then they were divided into two groups, with 10 of them have received capsules with CLA (3.9 g / day) and the other continued to receive sunflower oil. After that time the immune status of these women were compared and found no increase in the number of lymphocytes, granulocytes and monocytes in both groups (Kelly et al., 2000).

Considering such conflicting results, the consumption of CLA in order to promote human health, especially preventing weight loss in diseases such as cancer, AIDS, and lupus deserve further investigation (Whigham et al., 2000).

Conclusion

This study brings together scientific information which put together the physiological properties of CLA, serving as inputs to claim their potential as functional ingredients to be used in the prevention and control of several chronic metabolic disorders.

Recently, the available literature, mainly from the cell line and animal studies indicate that the individual isomers of CLA (c9, t11 and t10, c12) might bring numerous health benefits. Comparatively, the literature is very limited on the effects of CLA in

humans. Furthermore, there are considerable variations in the studies and the beneficial effects observed in some animal models which have not been reflected from studies in humans. It can be attributed to differences in the dose of CLA used in animals and clinical studies and source differences of CLA (CLA is in the form of capsules obtained from the diet).

Research carried out in experimental animals and cell culture is intense, with very promising results, although in humans being scarce and sometimes contradictory. This divergence may be associated with specific characteristics of the study population (body composition, age, lifestyle), in addition, intake and duration of studies are very variable and not always specified the major isomers ingested. For more reliable conclusions, it is necessary to consider these factors to strengthen the mechanisms of action to establish possible adverse effects of certain isomers and determine the effective, safe and easy dose to reach with the consumption of a balanced diet and healthy habits. Future research can provide crucial information about the potential of CLA.

Safety and concern regarding the use of CLA in humans persist and require further investigation, not only for the CLA as a mixture, but also as individual isomers, with better experimental designs which will clarify the mechanisms of the activities of CLA.

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