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The role of conjugated linoleic acid in farm animal

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Abstract

The many functions of conjugated linoleic acids (CLAs) in animal metabolism and their possible advantages for human and animal health are the main topics of this review. The rumen microbiota of ruminants produces CLAs, a class of geometric isomers of octadecadienoic acids, as an intermediate. Due to their distinct roles as antioxidants, anti-carcinogens, anti-atherosclerotics, anti-obesity agents, anti-diabetics, and immune system enhancers, two major isomers of CLA, cis-9, trans-11 CLA (CLA-9) and trans-10, cis-12 CLA (CLA-10), have been thoroughly examined in recent decades. Due to its structure, CLA is an effective antioxidant. Because it possesses the conjugated diene orientation necessary for the lipid peroxidation process, it contributes to the scavenging of free radicals. The anticarcinogenic action of CLA may be partially attributed to its antioxidant properties. CLAs are also associated with enhancing immune system properties by mediating the synthesis of inflammation markers. Nevertheless, little is known about the precise health benefits of CLAs and the mechanisms behind their action. CLA is also linked to the metabolism of fats in animal products, such as meat and milk. The supplementation of CLA potently reduces milk fat, involving different pathways that inhibit gene expression of lipogenic enzymes, resulting in milk fat depression in ruminant animals. In addition, supplementation of CLA to non-ruminant animals could shift the lipid composition to more saturated fatty acids in place of monounsaturated fatty acids in their meat.

Keywords: CLA, antioxidant, anti-carcinogenic, lipid metabolism

Introduction

The term 'functional food' is often used as a generic description for the beneficial health effects of ingested foods that go beyond their traditional nutritive values (Benjamin & Spener, 2009) [13]. Ha *et al.* originally identified the alleged health benefits of conjugated linoleic acids (CLAs) in 1987 when they observed that ground beef included a number of conjugated dienoic isomers of LA that showed anti-carcinogenic properties. When linoleic acid (LA) and α-linolenic acid (ALA) are biohydrogenated into saturated stearic acid (C18:0), the rumen microbiota of the ruminants synthesizes conjugated linoleic acids, a group of geometric isomers of octadecadienoic acids (18:2) with cis and trans orientation, as an intermediate (Bauman *et al.*, 1999; 2003) [5, 6]. Since these CLA isomers are natural food ingredients with significant health advantages, they have drawn increased attention in the last ten years. Anticarcinogenic, anti-atherosclerotic, anti-obesity, anti-diabetic, and immune-boosting are some of the positive effects (McGuire & McGuire, 2000) [42].

Numerous biological investigations, including CLA, were developed following the initial discovery, and the results demonstrated a variety of beneficial health effects of CLA in experimental animal models (Benjamin *et al.*, 2015) [14]. For example, CLA was supposed to have beneficial health effects, such as suppressing cancer, reducing atherosclerosis development and cardiovascular diseases (CVD), delaying the onset of type II diabetes, and improving the mineralization of bone and modulating the immune system (McGuire & McGuire, 2000; Whigham *et al.*, 2000; Pariza *et al.*, 2001) [42, 58, 44]. Therefore, CLA-rich foods may be considered as functional foods; and that CLAs per se are neither a food nor a functional food but a FA class with some bioactive properties (Benjamin *et al.*, 2015) [14]. However, there are certain similarities in the methods by which CLA worked in animals.

Corresponding Author: Rawad Sweidan Livestock research directorate, National Agricultural Research Center, PO Box 639, Baqa'a 19381, Jordan These mechanisms and the health benefits of CLA supplementation have been extensively studied in humans using animal models most of these studies have utilized mice or murine tissues to investigate the beneficial effects of CLA on human nutrition. However, little research has been conducted to examine the potential health benefits of supplementing animals with CLA. Numerous nutritional studies have examined the effects of adding CLA to an animal's diet on lipid metabolism and milk fat depression (Bauman & Griinari, 2003; Griinari & Bauman, 2006; Conte *et al.*, 2018; Dewanckele *et al.*, 2020) [8, 40, 19].

The aim of this review is to focus on the mechanism by which CLA play a role as anti-oxidant reagent, anti-carcinogenic, anti-atherosclerotic, insulin resistance, immune system and inflammation, oxidative stress and lipid metabolism. It also focuses on the role of CLA in both human and animal health and their role in animal production.

The Role of CLA in Oxidative Stress

According to Halliwell (2007) ^[25], oxidative stress is the outcome of an imbalance between the body's capacity to quickly detoxify reactive oxygen species (ROS) or repair the harm they cause to cell components, such as proteins, lipids, and nucleic acids, and the systemic manifestation of these ROS (Subedi *et al.*, 2014) ^[55].

The two main sources of intracellular ROS generation are mitochondria and NADPH oxidases (NOXs) (Di Cristofano *et al.*, 2021) [20]. Apart from their metabolic function in the Krebs cycle, the metabolism of fatty acids and amino acids generates the majority of cellular energy through mitochondrial respiration, which includes the oxidative phosphorylation system and electron transport chain (Friedman & Nunnari, 2014) [22]. These organelles are the site of O2•- free radical production due to electron leak from the ETC and one-electron reduction of oxygen (Handy & Loscalzo, 2012) [26]. NOXs are another important cellular source of ROS, including hydrogen peroxide (H₂O₂) and the superoxide anion radical (O2•-) (Bedard & Krause, 2007; Sies & Jones, 2020) [10,53].

It is generally recognized that free radicals, including reactive oxygen produced by lipid peroxidation, can damage cells by "stealing" electrons from the lipids in cell membranes (Halliwell, 2007) [25]. Since CLA already contains the conjugated diene orientation needed for the lipid peroxidation process, it may be able to scavenge a free radical. The formation of a conjugated diene by the rearrangement of fatty acids is a crucial step in stabilizing the free radical (Ayala *et al.*, 2014) [4].

The earliest evidence of CLA's antioxidant activity came from in vitro tests conducted in 1987 (Ha *et al.*, 1987). According to their findings, CLA is a powerful antioxidant that is nearly as efficient as butylated hydroxytoluene (BHT) and more potent than vitamin E. IP *et al.* (1991) [29] proposed that the antioxidant effect of CLA may be partly responsible for its anti-carcinogenic properties.

The free radical scavenging capabilities of CLA-9 (cis-9, trans-11) and CLA-10 (trans-10, cis-12) isomers against the stable 2, 2-diphenyl-1-picryhydrazyl radical (DPPH) in ethanol were examined in a study by Ali *et al.* (2009) ^[2]. Their findings demonstrated that CLA directly responded and quenched free DPPH radicals in a dose and time manner without any lag phase, using an ELISA reader approach. Furthermore, under the same experimental conditions, trans-10, cis-12 had a higher Total Antioxidant Capacity (TAC) than cis-9, trans-11.

The antioxidant ability of two CLAs (trans-10, cis-12/cis-9, and trans-11) mixed at two ratios (1:6 and 1:13, respectively) was also investigated by the same group of researchers (Ali et al., 2012) in comparison to vitamin E. At low concentrations (2.5 and 5 mg/ml) in the system, they discovered that cis-9, trans-11 CLA was the most effective isomer to directly react and quench free radicals, while trans-10, cis-12 CLA had higher maximal efficacy than other tested CLAs as free radical scavenger TAC at high doses (20, 40, and 80 mg/ml). Studies including CLA supplementation for one to two years have shown that it is well-tolerated; nonetheless, there was a rise in inflammatory markers in the blood, including TNF, ILs, and CRP (Tholstrup et al., 2008) [56]. The rise in insulin resistance linked to the risk of cardiovascular disease may be connected to alterations in oxidative stress and inflammatory indicators (Lamarche & Desroches, 2004) [34].

The Role of CLA as Anti-Carcinogenic

In several animal models, dietary supplementation with CLA has been shown to prevent chemically induced cancers of the epidermis, colon, mammary gland, and fore stomach (Kelley et al., 2007) [33]. Research on the effects of CLA on tumors generated in the mouse forestomach (Chen et al., 2003) [16] and rat mammary gland (Ip et al., 2002) [30] indicates that CLA inhibits tumor production or incidence. According to reports, the mechanisms underlying CLA's inhibitory effects on various cancer types include changes in tissue fatty acid composition, lipid peroxidation, eicosanoid metabolism, and the expression of genes that regulate cell growth and apoptosis (Kellev et al., 2007) [33]. Different cancer types would likely respond differently to CLA therapies in different organs since the mechanisms of action linked to the carcinogenic effects of CLA vary depending on the kind of tumor and the stage of tumor progression (Belury, 2002a) [11]. A CLA supplement was linked to a nearly 30% lower risk of colorectal cancer, according to research by Larsson et al. (2005) [35]. In their 2009 study, the same researchers found no indication that CLA consumption protected Swedish women from developing breast cancer (Larsson et al., 2009) [36]. CLA-9 was shown to have a preventive effect on breast

CLA-9 was shown to have a preventive effect on breast cancer patients by McCann *et al.* (2004) [41]. Higher consumption of CLA was observed to reduce the proportion of ER-negative to ER-positive epithelial cells in these women. Since premenopausal women with breast cancer frequently have ER-negative epithelial cells, CLA intakes did not demonstrate an anti-carcinogenic impact on breast cancer (McCann *et al.*, 2004) [41]. The anti-carcinogenic properties of CLA in humans with breast cancer incidence were not confirmed by another epidemiological investigation with 6.4 years of follow-up (Brown, 2008) [15].

The Role of CLA in Immunity and Inflammation Reactions

CLA mediates inflammatory responses and contributes to the immune system. According to a study by Risérus *et al.* (2002), when 60 men with metabolic syndrome were given CLA-10 for 12 weeks, their levels of PGF2 α increased sixfold, and their levels of C-reactive protein (CRP), a marker of circulatory inflammation that aids in the prediction of CVD (Ridker *et al.*, 2003) [48], increased by 10%. This was in contrast to the placebo group. The body's levels of PGF2 α , an indicator of inflammation, and PGF2 α , an indicator of oxidative stress, increased when CLA-9 (3g/d) was supplemented (Risérus *et al.*, 2004) [50].

The body uses peripheral blood mononuclear cells (PBMCs) to secrete TNF α , IL-1 β , leukotriene B4, and PGE2 (Kelley *et al.*, 2001) ^[32]. According to Albers *et al.* (2003), CLA supplementation with both CLA-9 and CLA-10 in the ratios of 50:50 or 80:20, respectively, increased the concentration of CLA in the lipid portion of PBMC by 35%.

Cytokines are hormone-like mediators of immunity and inflammation that are produced by macrophages and other immune cells in response to stimulation (Pariza *et al.*, 2000) ^[45]. Tumor necrosis factor-α (TNF-α), along with interleukin-1 (IL-1), induces various effects in immune cells, including the inflammatory response. Eicosanoids, especially prostaglandin (PGE2), control the production and function of TNF-α and IL-1 (Lewis, 1983) ^[37]. Li and Watkins (1998) ^[38] suggested that CLA affects the formation of prostaglandins, specifically PGE2, based on several laboratory studies. According to research by Sebedio *et al.* (1997) ^[51], CLA-9 and CLA-10 are both elongated and desaturated in ways similar to those of linoleic acid, which provides precursors for probable eicosanoids generated from CLA.

Although the mechanisms of the physiological actions of CLA are not yet fully clear, a possible mechanism has been suggested by Pariza *et al.* (2000) ^[45], who proposed that CLA can reduce the production of eicosanoids by decreasing the amount of arachidonic acid (C20:4 n-6). CLA is regarded as an anti-inflammatory and anti-cancer drug because eicosanoids contribute to the synthesis of cytokines, which in turn have an impact on inflammation (Pariza *et al.*, 2000; Belury, 2002b) ^[45, 11].

The Role of CLA in Lipid Metabolism

It is commonly known that providing dairy ruminants with dietary supplements of CLA can increase the amount of CLA in their milk (Shingfield & Griinari, 2007) ^[52]. However, CLA supplementation reduces milk fat in dairy ruminants, particularly in sheep and cows (Baumgard *et al.*, 2001; Bauman *et al.*, 2008) ^[9, 39]. This is mostly because it reduces lipid production.

According to a study by Vyas *et al.* (2013), the de novo fatty acid synthesis of dairy cows was decreased by CLA infusion into the abomasum. According to Perfield *et al.* (2007) [46], who investigated the effect of CLA on cows' milk fat, a rise in CLA-9 was associated with a decrease in milk fat yield. The supplementation of CLA-10 also decreased the de novo synthesis of fatty acids and the desaturation of 18:0 via Δ 9-desaturase (Perfield *et al.*, 2007) [46].

Bauman *et al.* (2008) ^[39], reported that CLA-10 has also been shown to reduce milk fat in both ruminants and nonruminants. Research conducted on nursing sheep (Lock *et al.*, 2006; Sinclair *et al.*, 2007; Lock *et al.*, 2008) ^[40, 54, 39] revealed that CLA-10 supplementation decreased the generation of milk fat similar to that seen in dairy cows. Hussein *et al.* (2013) ^[27] also found that lower expression of mammary genes involved in lipid production in dairy sheep is linked to the effect of CLA on milk fat depression. CLA decreased the milk fat output and percentage by almost 23% in their study. Lactating goats' milk fat is decreased when lipid-encapsulated CLA-10 is supplemented (Lock *et al.*, 2008) ^[39].

According to a study on the adipose and mammary tissues of mice (Kadegowda *et al.*, 2013) [31], supplementing nonruminant animals with CLA-10 also lowers their milk fat. According to their findings, mice given 37 mg/day of CLA-10 supplementation had a 44% lower milk fat concentration on day 10 postpartum than on day 6 postpartum. They also concluded that CLA primarily affects the mammary tissues

through changes in phospholipid biosynthesis and cellular signaling pathways (Kadegowda *et al.*, 2013) [31]. However, the fatty acid content of meat is also influenced by dietary CLA

Dietary CLA is reported to reduce the amount of unsaturated fatty acids in poultry meat, according to Du *et al.* (2001). They discovered that dietary CLA alters the composition of fatty acids, increasing the proportion of saturated fatty acids while reducing the levels of arachidonic, linoleic, and oleic acids in fat. The primary causes of meat's elevated saturated fatty acid (SFA) and decreased monounsaturated fatty acid (MUFA) content are these alterations in fatty acid composition.

Stearoyl-CoA desaturase-1 (SCD-1), a crucial enzyme involved in lipogenesis, has its gene expression inhibited by supplementing with mixed isomers of CLA (Choi *et al.*, 2000) ^[17]. In order to provide MUFA that is required for incorporation into the sn-2 position of triglycerides, SCD-1 catalyzes the $\Delta 9$ -cis desaturation of several fatty acid substrates, such as palmitoyl and stearoyl-CoA (Park *et al.*, 2000) ^[45].

Conclusion

This paper reviewed several potential health benefits of conjugated linoleic acids (CLAs) supplementation. These potential health benefits have been studied primarily in animal models, to help our understanding the metabolic pathways of CLAs and their role in human health and consequently in farm animal. CLA isomers have been found to possess antioxidant properties, scavenging free radicals and protecting against oxidative stress. It also shows anti-carcinogenic effects on chemically induced tumors in various animal models, including the mammary gland, skin, and colon. CLAs have a positive impact on cardiovascular health by reducing the participation of lipids that develop atherosclerosis. CLA supplementation has been shown to increase the levels of PGF2α and cause a 10% increase in the levels of C-reactive protein (CRP), a circulatory inflammation marker that helps in predicting CVD.

Additionally, CLAs have been found potentially modulating immune function and inflammation response properties by reducing the production of eicosanoids and decreasing inflammation. CLA is also associated with enhancing insulin sensitivity, which can help in the prevention and management of type II diabetes. CLA plays a key role in gene expression of lipogeneses enzymes in both ruminants and non-ruminants, supplementation of CLA is associate with milk fat depression in dairy cows, sheep and goat, and increase saturated fatty acid in poultry meat by influencing the mechanism by which these lipids metabolized in farm animals.

In conclusion, this review paper report several research results that support the potential health benefits of CLA in both animal and humans. It also provides evidence on the significant role of CLAs as an antioxidant reagent, anticarcinogenic, immune system and inflammation, oxidative stress, and lipid metabolism

Conflict of Interest

Not available

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Reference

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