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Review

An overview on conjugated linolic acid (CLA): A dairy product derivative

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Conjugated linoleic acid (CLA) is an octadecadienoic fatty acid with conjugated double bonds, potent component in dairy product such as milk, meat and cheese etc. The increased functional dairy products would explain the possible use of CLA in daily life. Research has been enhanced after the novel findings towards its anticarcinogenic property and vast application in health. CLA formed as an intermediate in the biohydrogenation pathway of linoleic acid and acetate can also act as a substrate for CLA synthesis in a critical condition. Rumen microbes especially ciliated protozoa take an active part in synthesis. The concentration of CLA depends on the diet of the ruminants. The main theme of this review is to summarize the current knowledge of CLA, formation of CLA in ruminants, diet influence on CLA formation and the aspects concerning health.

Keywords: Cis-9, trans-11 conjugated linoleic acid (CLA), fatty acid, health.

INTRODUCTION

Conjugated linoleic acids (CLA) are a group of fatty acids that are micro components of ruminant fat. It is a mixture of positional and geometric isomers of octadecadienoic fatty acid with conjugated double bonds (C.W. Lin, Y.J. Wang 2002). These conjugated dienes were found to be responsible for many biological properties that relate to health, including anticarcinogenic (Parodi 1996; Belury 1995;), antiatherogenic (Nicolosi and others 1997; Lee and others 1994), anti-diabetic (Houseknecht 1998), antiobese (Park and others 1999; West and others 1998), antioxidative (Decker 1995), immunomodulative (Hayek and others 1999), antibacterial (Sugano and others 1997), cholesterol depressing (Huang and others 1994), and growth promoting (Chin and others 1994) properties. Those are the reasons for the intense recent interest in CLA concentration, distribution, and synthesis. Oral administration of a *Bifidobacterium breve* strain, with ability to form cis-9, trans-11 conjugated linoleic acid (CLA), resulted in modulation of the fatty acid composition of the host, including significantly elevated concentrations of c9, t11 CLA and omega-3 (n-3) fatty acids in liver and adipose tissue (Catherine Stanton 2011).

Food products from ruminants, particularly dairy products, are the major dietary source of CLA for humans. CLAs are intermediates in the biohydrogenation of linoleic acid, and it is generally accepted that CLAs in ruminants originate from the incomplete biohydrogenation of unsaturated fatty acid by rumen bacteria (M.L. Kelly, J.R 1998). However, it has been demonstrated that cows can also synthesize CLA from trans-11-octadeceno acid, another intermediate in the rumen biohydrogenation process (Y.J. Kim 2000). Dietary sources of CLA include milk fat, natural and processed cheeses, meat products, and plant oil (Y.L. Ha et al 1989, N.C. Shanta et al., 1991). Animal sources are richer in CLA than plant sources, and, in general, foods from ruminants contain more CLA than foods from non-ruminants and considerable research has been conducted on the CLA content and isomer distribution in cow's milk. A number of factors

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have been shown to influence CLA concentration in bovine milk fat, including lactation number (C.F. Stanton et al. 1997), dietary restriction (C. Ip, 1991), and feed allowance (C. Ip, 1991, F. Lawless 1998). Dairy products are one of the major dietary sources of CLA. Among the different isomers of CLA, c9t11-octadecadienoic represents more than 90% of the total CLA in milk fat. Dairy products from ruminants are very rich sources of CLA, among which 18:2 cis 9, trans 11, is the main isomer (Chin, Liu, Storkson, Ha, & Pariza, 1992). The presence of these compounds in dairy products is partly due to the isomerization and biohydrogenation of linoleic and linolenic acids that take place in the rumen; these processes are performed by ruminal bacteria, such as Butyrivibrio fibrisolvens and Megasphaera elsdenni (Bauman & Griinari, 2003; Jouany et al 2007; Sieber et al., 2004).

However only short-term clinical studies with small numbers of subjects have been conducted with CLA (24) in humans. Some CLA studies performed with a mixture of the bioactive isomers cis-9, trans-11 and trans-10, cis-12, showed reductions in BFM (Body Fat Mass) and in some cases increases in LBM (Lean Body Mass) (25-27). Other short-term studies performed with the use of different methods and technology, such as body-composition measurements, daily dosage, CLA composition, and study design, did not show any effects on body composition (28 -32), which raises questions about the consistency of the effects of CLA on BFM and LBM in humans. After correction for differences in metabolic rate, similar effects are observed in humans and in mice, which suggests that the mechanisms for reducing BFM in animals and humans may be similar.

Chemical structure of CLA

CLA metabolism

CLA isomers are metabolized through different pathways. In the liver and mammary glands of rats, as well as in the adipose tissue of humans, CLA metabolites which maintain the conjugated diene (CD) chemical structure, such as conjugated octadecetrienoic acid (CD 18:3), conjugated eicosatrienoic acid (CD 20:3), and conjugated eicosatetraenoic acid (CD 20:4) have been detected (Muller, A et al., .2005). These metabolites are formed by CLA isomer elongation and desaturation processes due to the action of D6 and D5 desaturases and an elongase (Banni, S et al., 2001). These conjugated dienes are different depending on their double bond configuration (cis/trans, trans/cis, or trans/trans) (Muller, A et al., 2005). As far as these metabolic processes are concerned, there are differences between the two main CLA isomers which are interesting from a physiological point of view. Thus, whereas the cis-9,trans-11 is easily metabolized to CD 20:4, the trans-10,cis-12 isomer appears to show a certain resistance to being transformed into CD 20:3 and CD 20:4 (Se´be´dio, J. L et al., 2001). At the moment, there is no clear explanation for this difference. It seems that the CD 18:3 derived from the trans-10, cis-12 CLA presents a greater resistance to elongation processes.

Beta-oxidation, both mitochondrial and peroxisomal, is the major metabolic pathway for fatty acid degradation. Initially, the fatty acids may experience a partial oxidation in peroxisome. Then they can be incorporated into the mitochondria where they will be further metabolized or incorporated into different lipid species. In addition, there are different oxidative routes for the fatty acids. In fact, CLA mitochondrial oxidation is lower than that experienced by linoleic acid and palmitic acid, with no differences in the peroxisomal oxidation (Demizieux, L., 2002). The behavior of the two main CLA isomers in the oxidation process is different. It seems that trans-10, cis-12 isomer is oxidized more readily than cis-9, trans-11 CLA. This fact is due to the positioning of their double bonds. Although trans-10, cis-12 CLA skips four potentially limiting enzymatic steps of beta-oxidation: those catalyzed by enoyl-CoA isomerase, 2-trans enoyl-CoA hidratase, beta-hidroxiacil-CoA dehydrogenase, and acyl-CoA dehydrogenase, cis-9, trans-11 CLA avoids only two steps, that catalyzed by acyl-CoA dehydrogenase and one by 2, 4-dienoil-CoA reductase (Martin, J. C., et al., 2002).

It is important to emphasize that there is a clear difference between the incorporation of CLA isomers and their derived metabolites, and linoleic acid and its metabolites. Thus, while CLA and its derivatives, with the exception of CD 20:4 are incorporated into neutral lipids, linoleic acid, and its metabolites are incorporated primarily into phospholipids (Belury, M. A. 2002). Apparently, the double bonds in cis configuration increase the possibility of incorporation of a fatty acid into phospholipids. As a result, the wider incorporation of linoleic acid into this lipid species could be due to the presence of a greater number of double bonds in cis configuration.

CLA invention as a potential component

CLA occur naturally in foods, such as meat, poultry, seafood, cheese, butter, milk, and vegetable oils (Ip 1994), but ruminant fats are the richest natural sources of CLA (Chin and others 1992; Chin and others 1991; Ha and others 1987; Shantha and others 1994). The conversion of linoleic acid into CLA catalyzed by those bacteria in rumen was first reported by Bartlet and Chapman (1961). Shorland and others (1995) also observed CLA formation through ruminal bacteria in their study of the ruminal effect on dietary fat. *Butyrivibrio fibrisolvens*, the most widely known organism in rumen (Jenkins 1993; Lal and Narayanan 1984), was identified capable of CLA formation in the ruminal biohydrogenation of linoleic acid (Kepler and others, 1966).

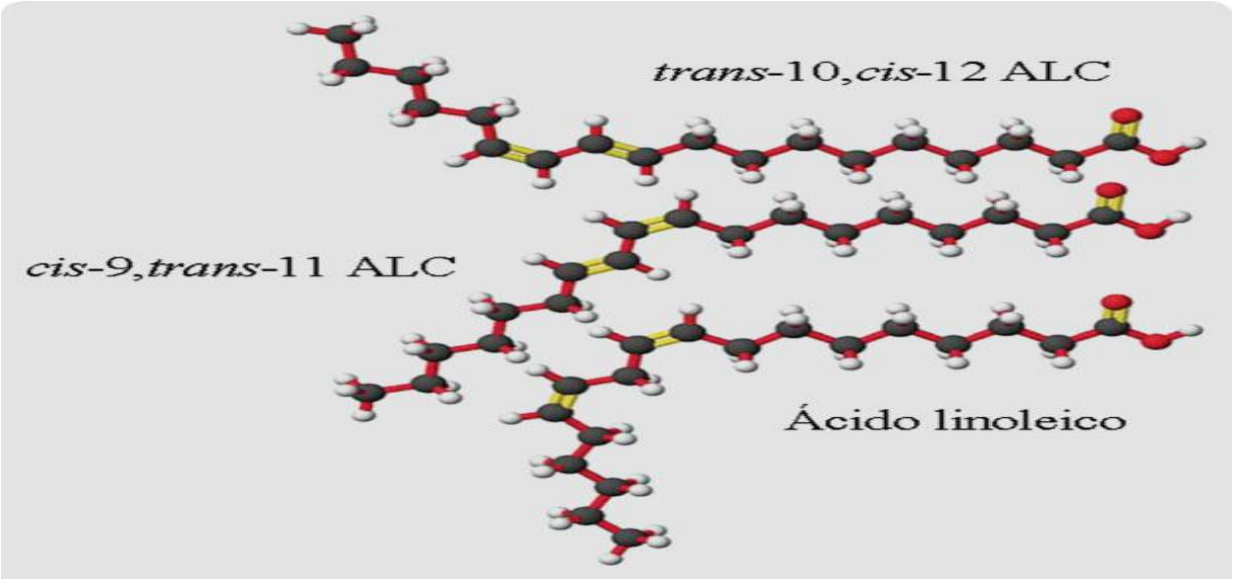

Fig 1. Structures of cis-9,trans-11 and trans-10,cis-12 CLA isomers (Pariza et al. 2001). Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.

Conversion of polyunsaturated fatty acids in a potent CLA in ruminants

Rumen is a favorable environment for intense microbial lipid metabolism. Conjugated dienoic acids content in milk (Bartlet & Chapman, 1961) and butter (Parodi, 1977) is balanced with dietary intake of linolic acid, hence the CLA is also incorporated in to milkfat (Bartlet & Chapman, 1961; Parodi, 1977) and *cis*-9, *trans*-11-CLA isomer found as an intermediate in biohydrogenation of linoleic acid Kepler *et al*. (1966).

CLA as an intermediate in Biohydrogenation

CLA was also formed as an intermediate in the biohydrogenation pathway of linoleic acid. However, in the biohydrogenation studies linolenic acid (*cis*-9, *cis*-12, *cis*-15-octadecatrienoic acid) converted to *cis*-9, *trans*-11, *cis*-15-conjugated triene, then to *trans*-11, *cis*-15-18:2, and finally to an octadecenoic acid which is either *trans*-11, *trans*-15, or *cis*-15 (Harfoot & Hazlewood, 1988). Therefore, the pathways from linolenic acid do not involve CLA as an intermediate. Harfoot & Hazlewood (1988) and Vivani (1970) studied that biohydrogenation pathway of linoleic acid. Although linoleate isomerase and CLA reductase have been purified from the bacteria *Butyrivibrio fibrisolvens* (Kepler & Tove, 1967; Hughes *et al*. 1982), in general, no one species of micro-organism carries out the full sequence of biohydrogenation (Harfoot & Hazelwood, 1988). R.E. Lawson *et al.* The enhancement of rumen biohydrogenation mainly depends on the diet. This has been shown to be due to a drop in pH, limiting at first lipolysis, and thus hydrogenation, which occurs only on free fatty acids (Van Nevel & Demeyer, 1996). A large amount of dietary linoleic acid and a decrease in the rate of hydrogenation are the two main factors that contribute to an increase in the concentration of the intermediate compounds CLA and *trans*monounsaturated fatty acids.

Denovo synthesis of CLA

(Ruth E. Lawson 2001) In critical conditions, acetate can act as a raw source for the *denova* fatty acid synthesis and adipose tissue serves as a major site in ruminants and mammary glands in lactating ruminants. In the cytoplasm palmitic acid synthesized from acetyl-CoA and hydroxybutyrate derivatives from mitochondria. Now, Mitochondria elongate palmitic acid to longer-chain fatty acids up to C22, whereas microsomes are capable of elongation as well as desaturation of fatty acids C18. Griinari & Bauman (1999) suggested that the ruminant mammary glands and the adipose cells are able to synthesise *cis*-9, *trans*-11-CLA from *trans*-11-18:1 and other CLA isomers from other *trans*- 18:1 isomers by action of the _9-desaturase on *trans*-18:1. Ward *et al*. (1998) showed in sheep that the _9-desaturase expression decreased in adipose tissue and increased in mammary tissue with the onset of lactation. Griinari & Bauman (1999) suggested that about 33 g/100 g *trans*- 11-18:1 taken up by the mammary gland is desaturated to *cis*-9, *trans*-11-CLA.

Microorganisms involved in CLA production

The ciliate protozoa are central group of microbes influence on rumen fatty acid metabolism, which effectively accumulate unsaturated fatty acids (R. John Wallace., 2010, Devillard et al., 2006), *Butyrivibrio fibrisolvens*is a diverse bacteria, it can metabolise

linoleic acid actively than other ruminal species (Polan et al., 1964; Maia et al., 2007), but a small subgroup of *B. fibrisolvens* carries out the reduction of 18 : 1 fatty acids, particularly trans-11-18 : 1 to 18 : 0(Wallace et al., 2006), known as Butyrivibrio proteoclasticus (Moon et al., 2008), Metabolism of linoleic acid by Butyrivibrio results in the formation of trans-11-18 : 1 and cis-9,trans-11-18 : 2 as major intermediates. The same is usually true in the mixed ruminal ecosystem, but under certain conditions trans-10-18: 1 isformed via the reduction of trans-10, cis-12-18: 2 or from the isomerization of cis-9-18: 1 and represents the major biohydrogenation intermediate of the mixed ruminal ecosystem in vivo (Shingfield & Griinari, 2007). Post-ruminal infusion experiments have established that trans-10,cis-12-18: 2 exerts anti-lipogenic effects in the lactating cow (Baumgard et al., 2000; Sæbø et al., 2005; Lock et al., 2006), Propioni bacterium acnes may be responsible for the formation of trans-10,cis-12-18 : 2 (Wallace et al., 2006).

Many strains of lactobacilli, lactococci and streptococci are able to produce CLA from linoleic acid in a special growth medium or in skim or whole milk; however, many others show no such activity (Jianget al.1998). The strains belonging to the genera Lactobacillus, Propionibacterium, Enterococcus and Pediococcus produced more than 70 micrograms total CLAper ml reaction mixture. In the produced CLA mixture the two c9, t11 or t9, c11 and t9, t11 isomers are more abundant (Kishino et al. (2002b). According to Propionibacterium strains were able to form CLA in the MRS medium, with the CLA mainly found in the extracellular phase (Jiang et al. 1998). Enhanced molecular biology tools revealed the expression strategies of CLA in mammary glands (Kramer et al.,2013).

Effect of Diet on CLA concentration in ruminants

Concentrations of CLA concentration in milk fat can be enhanced by changes in the diet, the diets contain high levels of other polyunsaturated fatty acids (PUFA) that do not yield CLA as an intermediate in rumen biohydrogenation (Griinari and Bauman 199). This raises the possibility of alternative sources of milk fat CLA (Griinari et al 2000) The CLA content of milk and milk products can be altered by affecting rumen production of CLA or *trans*-11-18:1, or by dietary supplementation with these fatty acids (Chouinard *et al*. 1999).Oils rich in linolic or linolenic acid diet increased the CLA content of the milk Dhiman *et al*. (1997), but oils inhibits the microbial population (Jenkins, 1993)., hence dietary oil seed does not change milk CLA (Dhiman *et al*. 1997). The supplementation of full-fat rapeseed (high in oleic acid) caused a greater increase in CLA content of milk than did soybean oil (high in linoleic acid), rapeseed supplementation resulted in an increase of 650 g CLA/kg milk over non-supplemented control, but the total fat concentration was not reported Stanton *et al*. (1997).By feeding sunflower oil (high in linoleic acid) increased CLA concentrations to 24·4 g/kg milk fat compared with values of 13·3 and 16·7 g/kg fat for high-oleic (peanut oil) and high-linolenic acid oils (linseed oil), respectively (Kelly *et al*. 1998*a*).Seasonal variations in the CLA content of milk are very marked, with values during the summeroften up to two or three times higher than during the winter (Jahreis *et al*. 1997; Parodi., 1999).Certain breeds of cattle and some individual cows appear to be more efficient at incorporating CLA into milk, with a range of 3-25 g/kg milk fat, when offered grazed grass. Older cows (>4 years old) tended to produce milk with more CLA, as did those fed a higher grass allowance Stanton *et al*. (1997).

Effective aspects of CLA in human and animal health

Active forms of CLA

The two most active forms of CLA are the cis-9, trans-11 isomer and the trans-10, cis-12 isomer.

Absorption

Since CLA is a fat-soluble nutrient, CLA supplements will be better absorbed from the gastrointestinal tract if they are taken with meals that contain some fat in the food that is being eaten.

Antioxidant Mechanisms

According to the discoverer of conjugated linoleic acid, CLA provides a previously unrecognized form of antioxidant defense against membrane attack by oxygen free radicals (Pariza MW et al.,1990) Studies using electron spin resonance (ESR) spectrometry have confirmed that CLA has free radical scavenging attributes whereas it's structural cousin linoleic acid (LA) (Yu L. 2001).

Lipid and Insulin Metabolism

CLA seems to help normalize impaired glucose tolerance and improve hyperinsulinemia due to its influence on hormone receptors that regulate genes involved in lipid and insulin metabolism (Lee KN,.1994)

Improves Blood Lipids transport

Dietary CLA decreases adiposity in various animal models and in humans. For example, rodents fed 1-1.5% CLA (w/w) as a crude mixture of cis-9, trans-11 and trans-10, cis-12 isomers had less body fat and greater lean body mass than control animals (K. Houseknecht.,1998. D. West., 1998. J. DeLany., 1999)

CLA improves blood lipids by lowering triglycerides and cholesterol levels. Studies in hamsters and rabbits indicate that this slows the onset of atherosclerosis compared to control animals (Yu L. 2001, Nicolosi R, et al., 1997)

Reductions in Body Fat

Conjugated linoleic acid inhibits the activity of the enzyme lipoprotein lipase. This is an enzyme that breaks down fat particles in the blood so that they can be taken up by fat cells called adipocytes for storage. Thus, CLA helps to prevent the deposition and buildup of fat in the body. In animal studies, CLA resulted in a 66% reduction in lipoprotein lipase activity, which resulted in substantial reductions in body fat coupled with 5% to 14% increases in lean body mass (Houseknecht KL, et al., 1998). Results of a study indicated that CLA reduced body fat mass and increased lean body mass in healthy overweight adults (Park Y, et al., 1997, Gaullier JM et al., 2004).

Fortifying foods with CLA

With an obesity epidemic sweeping the globe and an increasing the risk of adverse health outcomes, such as heart disease, diabetes and cancer, there has been increasing interest in determining whether various bioactive food components can influence health ailments. When fortifying new products, there are many challenges we're faced with every day - factors that impact the stability of nutrients and their retention, such as temperature, moisture, pH and oxygen, bioavailability and interactions

Anti carcinogenic properties of CLA

CLA has been reported to prevent carcinogenesis (Pariza and Hargraves, 1985), atherosclerosis (Nicolosi et al., 1997), and tumor genesis (Ha et al., 1990; Ip et al., 1991), to improve hyperinsulinemia (Houseknecht et al., 1998), and to modulate immune activity (Cook et al., 1993; Miller et al., 1994). Furthermore, CLA has been shown to reduce body fat to muscle mass ratio (Chin et al., 1992) and alter the ratio of low density lipoprotein to high-density lipoprotein cholesterol (Lee et al., 1994).
CLA inhibits both dimethylbenz[*a*]anthracene and *N*-nitroso-*N*-methylurea induced rat mammary carcinogenesis, and its antitumor efficacy is similar whether it is fed only during puberty, or continuously during promotion. Pubertal feeding is associated with a reduced proliferation of the epithelial cells within the terminal end buds (TEBs) and lobular epithelium, and results in a decrease in the epithelial density, suggesting a reduction in the carcinogen-sensitive target population. During promotion, CLA feeding induces apoptosis of preneoplastic lesions. The effects of CLA are mediated by a direct action on the epithelium, as well as by an indirect effect through the stroma. CLA is incorporated into the neutral lipids of mammary adipocytes, where it can serve as a local reservoir of CLA. Additionally, CLA induces the adipogenic differentiation of multipotent mammary stromal cells in vitro, and inhibits their development into three-dimensional capillary networks. This suggested that CLA might inhibit angiogenesis in vivo, a hypothesis that was subsequently confirmed. The antiangiogenic effect is mediated, in part, through a CLA-induced decrease in serum VEGF (vascular endothelial growth factor) and mammary gland VEGF and flk-1. Together, the data suggest that CLA may be an excellent candidate for prevention of breast cancer (Margot M. Ip 2003).

CLA and the immune system

CLA can directly alter immune functions. However, it is not clear whether individual isomers of CLA could act similarly or differently on components of the immune system. With regard to acute phase or inflammatory immune responses, CLA isomers are reported to decrease the production of eicosanoids both in vivo and in cell cultures and to suppress the release of pro-inflammatory cytokines, particularly TNF-a, in animals (Wahle, K. W. J., 2004). Concerning adaptive or specific immune responses, there is some evidence that CLA isomers can enhance some specific immune functions. For example, whereas splenic levels of immunoglobulin A (IgA), IgG and IgM increase in rats, IgE significantly decreases in animals fed a CLA mixture (Sugano, M., 1998). In another study a significant increase in the IgA, IgG and IgM production in rat spleen lymphocytes was recognized after CLA supplementation (Yamasaki, M., 2000).
It has also been reported that CLA isomers can increase the proliferation of CD8þ T-cells in pigs (Bassaganya-Riera, J., 2003). In a human study Albers et al. (Albers, R., 2003) suggested that CLA may beneficially affect the initiation of a specific response to a hepatitis B vaccination. Healthy males received a mixture of 50% cis-9,trans-11 CLA and 50% trans-10,cis-12 CLA isomers (CLA 50:50) or a mixture of 80% cis-9,trans-11 CLA and 20% trans-10,cis-12 CLA isomers (CLA 80:20) and almost twice as many subjects reached protective antibody levels to hepatitis B when consuming CLA 50:50 mixture (62%) compared with subjects consuming CLA 80:20 mixture (36%). Other aspects of immune function were not affected. Kelley et al. observed that CLA supplementation had no impact on immune system parameters in healthy women (Kelley, D. S., 2000) and were not able to show any effect of CLAs on a wide variety of cytokines ex vivo (Kelley, D.S.,2001). This indicates that the actions of CLAs on the human immune system are limited, and that the effects on gross outcomes, such as increased protective antibody levels,

may not be related to effects on cytokines. Nevertheless, it is not known whether identical results would be found in individuals with autoimmune conditions. Whether CLA would have any benefit or detriment to immune performance in elderly, immune compromised, or individuals with autoimmune processes, requires clarification.

CONCLUSION

Conjugated linoleic acid (CLA) is an octadecadienoic fatty acid with conjugated double bonds, it has divers applications as a functional dairy food. Though it can direct immune function, but it is not clear that all individual isomers are effecting similarly or differently. By administrating the microbes which can synthesize CLA in ruminants feed, the concentration of CLA in dairy product can increase. Developed technical tools and potent applications of CLA enhanced the focus of R&D towards its metabolic pathways and effect in human health. So far work has been done on the improvement of CLA and its effect on health in animals and human, but the keen research has to be done on the mechanism of its action and its molecular characterization, hence we can use in a divers application.

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