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Dietary Conjugated Linoleic Acid Isomers Modify the Fatty Acid Composition of Liver and Adipose Tissues

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ABSTRACT

Background: Conjugated linoleic acids are a group of isomers derived from linoleic acid, naturally present in beef, lamb, and dairy products. CLA has been reported to exert therapeutic effects on cancer, obesity, and diabetes. This study evaluated the effects of a mixture containing equal proportions of CLA isomers (c9,t11 and t10,c12) on IR and their incorporation into the plasma membranes of adipocytes and hepatocytes in SHRs.

Methods: For eight weeks, one group of hypertensive rats received sunflower oil supplemented with CLA isomers, while the control group received only vegetable oil. Serum parameters were measured, and the fatty acid composition of plasma membranes was analyzed using gas chromatography.

Results: Rats treated with CLA isomers showed a reduction in BW, IR, and hypertension. Additionally, there was a significant incorporation of CLA into the plasma membranes of adipocytes and hepatocytes. In contrast, the control rats displayed higher levels of n-6 PUFA and AA in their membranes, which promote the synthesis of eicosanoids and hypertensive prostaglandins. These findings were further supported by data mining analysis, which linked the results to the expression levels of genes encoding enzymes involved in the synthesis of PGE2, D2, and F2α from AA.

Conclusion: The mixture of CLA isomers reduced BW, IR, and HTN in SHRs. These effects were associated with the incorporation of c9,t11 and t10,c12 isomers into the plasma membranes of adipocytes and hepatocytes.
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Keywords: Adipocytes, Conjugated linoleic acid, Hepatocytes, Hypertension, Insulin resistance

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List of Abbreviations:
AA: arachidonic acid; **AKR1C3:** aldo-keto reductase family 1 member C3; **BP:** blood pressure; **BW:** body weight; **CBR1:** carbonyl reductase 1; **CLA:** conjugated linoleic acid; **HOMA:** homeostatic model assessment; **HPGD:** 5-hydroxyprostaglandin dehydrogenase; **HPGDS:** hematopoietic prostaglandin D synthase; **HTN:** hypertension; **IR:** insulin resistance; **KW:** Kyoto Wistar; **MUFA:** monounsaturated fatty acid; **PGE2:** prostaglandin E2; **PPAR-γ:** peroxisome proliferator-activated receptor-gamma; **PTGES:** prostaglandin E synthase; **PTGS1:** Prostaglandin endoperoxide synthase 1; **PTGS2:** prostaglandin endoperoxide synthase isoform 2; **PUFA:** polyunsaturated fatty acid; **QUICKI:** Quantitative Insulin Sensitivity Check Index; **SBREBP 1c:** sterol regulatory element binding protein 1c; **SFA:** saturated fatty acid; **SHR:** spontaneously hypertensive rat

INTRODUCTION

CLA is a group of PUFAs characterized by conjugated double bonds with different cis and trans configurations[1]. To date, 16 natural CLA isomers have been identified[2]. CLA is naturally found in the human diet and is found in beef, lamb, dairy products, and hydrogenated vegetable oils[3,4]. Studies in both humans and animals have reported the beneficial effects of CLA supplementation, suggesting potential therapeutic applications for cancer[5], obesity[6], atherosclerosis[7], diabetes[8], and HTN[9]. These effects are primarily attributed to the role of CLA in improving IR, a common underlying mechanism in many of these conditions[8].

The biological response to dietary CLA varies according to the specific isomers consumed, the individual's health status, and inter-organ communication[10]. For instance, the trans-10,cis-12 isomer has been shown to promote weight loss in obesity; however, it can also induce hepatic steatosis due to the increased mobilization of fatty acids from adipose tissue to the liver[11]. Commercial CLA supplements often contain varying proportions of these isomers, which alleviate disease symptoms, though they can disrupt normal metabolic functions. Thus, evaluating the effects of different isomer ratios would be essential to avoid contradictory outcomes.

The underlying molecular mechanisms of CLA remain under investigation. Dietary fatty acids, including CLA, are incorporated into membrane lipids, where they act as both biomarkers of dietary changes and precursors for eicosanoid synthesis in insulin-sensitive tissues such as the liver and adipose tissue. Eicosanoids—including prostaglandins, thromboxanes, and leukotrienes—are derived from AA and have central roles in inflammation[12]. AA is synthesized from linoleic acid via delta-6-desaturase and elongase enzymes and incorporated into membrane phospholipids. Upon stimulation by lipopolysaccharides, cytokines, or hormones, phospholipase A2 releases AA, which is metabolized by cyclooxygenase and lipoxygenase into proinflammatory mediators such as PGE2 and leukotrienes[13]. In contrast, when CLA predominates in membranes, it leads to the formation of the conjugated arachidonate, which is not a substrate for these enzymes, thereby reducing the synthesis of PGE2 and leukotrienes. This mechanism highlights the potential of CLA to modulate inflammatory responses and regulate eicosanoid production[14]. In addition, dietary CLA alters the lipid composition of adipose and hepatic tissues, counteracting IR and hepatic steatosis—conditions frequently associated with obesity and fat accumulation[11]. Further investigation is needed to clarify the effects of CLA isomer mixtures on weight regulation, insulin sensitivity, and HTN, while minimizing adverse outcomes. These effects are believed to stem from modifications in membrane fatty acid composition, which influence eicosanoid production, receptor activity, and the expression of genes encoding proinflammatory and hypertensive prostaglandins[13].

Prostaglandins such as E2[12], D2[15], and F2α[16], synthesized from AA in adipocyte and hepatocyte membranes, play critical roles in inflammation and BP regulation. To extrapolate findings from animal models to humans, data mining approaches can be employed to analyze gene expression patterns associated with prostaglandin synthesis in human adipose and liver tissues. This strategy provides an integrated perspective to validate the therapeutic potential of CLA isomer mixtures when administered in appropriate proportions.

Adequate intake of CLA isomers may therefore serve as a complementary strategy to reduce BW, improve insulin sensitivity, and manage insulin resistance and hypertension. The present study aimed to evaluate the effects of a 50:50 mixture of cis-9,trans-11 and trans-10,cis-12 CLA isomers on lipid composition in adipose and hepatic tissues, as well as their impact on BW, IR, and HTN in SHRs. Additionally, changes in AA levels in adipocytes and hepatocytes, along with gene expression patterns related to proinflammatory and hypertensive prostaglandin synthesis, were examined in human tissues through data mining analysis.

MATERIALS AND METHODS

Materials

Analytical grade of chemicals and dietary components used in this study were purchased from JT Baker (México), Bayer (Mexico), and Envigo RMS Inc.-Harlan Teklad (Madison, WI).

Rodent diets

Rodent diets were formulated with defined amounts of essential nutrients and lipid sources. Each diet contained casein (440 mg), DL-methionine (3.1 mg), cellulose (40 mg), corn starch (658 mg), a vitamin mix (20 mg), a mineral mix (80 mg), and butylated hydroxytoluene (0.4 mg). Lipid components consisted of sunflower oil (100 mg) and CLA (20 mg). The fatty acid profile of sunflower oil comprised 13.5% saturated fatty acids, primarily myristic acid (14:0, 0.55%) and palmitic acid (16:0, 12.8%); 50.7% MUFA, represented exclusively by oleic acid (18:1); and 36.3% PUFA, including linoleic acid (18:2 n-6, 32.8%) and α-linolenic acid (18:3 n-3, 3.5%). When sunflower oil was combined with CLA, the lipid composition shifted to 10.68% SFA

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(14:0, 0.40% and 16:0, 10.28%), 40.54% MUFA (18:1), and 29.02% PUFA (18:2 n-6, 26.20% and 18:3 n-3, 2.82%). The CLA-enriched formulation included two major isomers: cis-9,trans-11 (9.96%) and trans-10,cis-12 (9.97%).

Model of IR and HTN in SHRs

SHR and KW rats, as controls, were subjected to two weeks of adaptation before being randomly assigned to treatment groups. All procedures followed the Mexican Official Standards (NOM-062-Z00-1999)[17] and the NIH Guide for the Care and Use of Laboratory Animals[18]. The animals were purchased from Envigo RMS Inc. (Mexico).

Experimental design

The study included three groups of rats (n = 5 each): (1) SHR + sunflower oil + CLA group, receiving 6.0% sunflower oil plus 1.5% CLA; (2) SHR + sunflower oil group, receiving 7.5% sunflower oil only; (3) KW control group, receiving 7.5% vegetable oil. The CLA mixture consisted of a 50:50 ratio of cis-9,trans-11, and trans-10,cis-12 isomers.

BP measurement

Systolic BP was measured in conscious rats using a non-invasive instrument (Life Science model 29, Woodland Hills, CA). Each measurement was performed five times, and mean values were calculated.

Measurement of serum parameters and organ preservation

Serum biochemical parameters were measured by enzymatic methods using a Selectra-E analyzer (ELITech Clinical Systems, France). Insulin concentrations were quantified using an ELISA assay (Invitrogen, USA). Blood samples were obtained after an 18-hour fasting period by lateral vein puncture and centrifuged at 1,086 ×g. Serum was stored at -20 °C until analysis. Following euthanasia, major organs and adipose tissues were excised and stored at -70 °C. A portion of the liver was fixed in formalin for histological analysis.

Evaluation of insulin resistance indicators

Insulin resistance was evaluated using three indices: HOMA-IR = [insulin (μU/mL) × glucose (mmol/L)]/22.5[19]; QUICKI = 1 / (log insulin + log glucose [mg/dL])[20]; Reciprocal of HOMA-IR = 1/HOMA-IR[21].

Lipid extraction and fatty acid determination

Liver and epididymal fat samples (1–2 g), preserved at -70 °C, were homogenized in Bouskella-Ringer buffer (pH 7.4) using a rotary homogenizer (Daigger Scientific, USA) equipped with a Teflon pestle, stirring motor, and electronic speed controller. Homogenates were centrifuged at 40,000 ×g at 4 °C for 40 min. Plasma membranes were isolated using a Percoll gradient[22]. Total lipids from diets and plasma membranes were extracted by the Folch method. Fatty acids were converted to methyl esters via acid-catalyzed transesterification with H_2SO_4[23]. Gas chromatography was performed on a Hewlett-Packard model 6890 (Andover, MA, USA) with a Supelcowax capillary column (60 m × 0.25 mm × 0.25 μm). A flame ionization detector was used at 250 °C for injector and detector temperatures. The oven was programmed from 100 °C to 210 °C at 2 °C/min, with nitrogen as carrier gas. Fatty acid methyl esters were identified using a Supelco® 37-component standard mixture (Sigma-Aldrich, USA; Fig.1).

Gene expression in humans

Gene expression data were obtained through data mining of the publicly available human datasets from Uhlén et al.[24] and Fagerberg et al.[25], including transcriptomic profiles from 44 and 95 individuals, respectively.

Statistical analysis

Data were analyzed with Minitab 17 software. ANOVA followed by Tukey's post hoc test was used for comparisons among groups. Homogeneity of variance and normality were tested before analysis. Student's *t*-test was applied for two-group comparisons. When assumptions for the parametric testing were not met, appropriate non-parametric tests were used. Statistical significance was defined as $p \leq 0.05$.

RESULTS

IR and metabolic syndrome in SHRs

After a two-week adaptation period, SHRs exhibited diagnostic features consistent with metabolic syndrome. BP reached 190 ± 9.0 mmHg, a 56% increase compared to controls (125 ± 7.5 mmHg, $p < 0.01$). Serum triglyceride levels increased by 42% ($p < 0.01$), insulin by 110% ($p < 0.01$), and BW by 63% ($p < 0.01$). No differences were observed in serum glucose or total cholesterol levels. Insulin resistance was evident, with a 110% decrease in 1/HOMA-IR and 108% increase in HOMA-IR ($p < 0.01$). No significant differences were detected in the QUICKI index among groups (Table 1).

Effect of mixed dietary CLA isomers on body weight

BW progression was monitored throughout an eight-week intervention. CLA-supplemented rats (sunflower oil + CLA/SHR group) gained only 9% in BW

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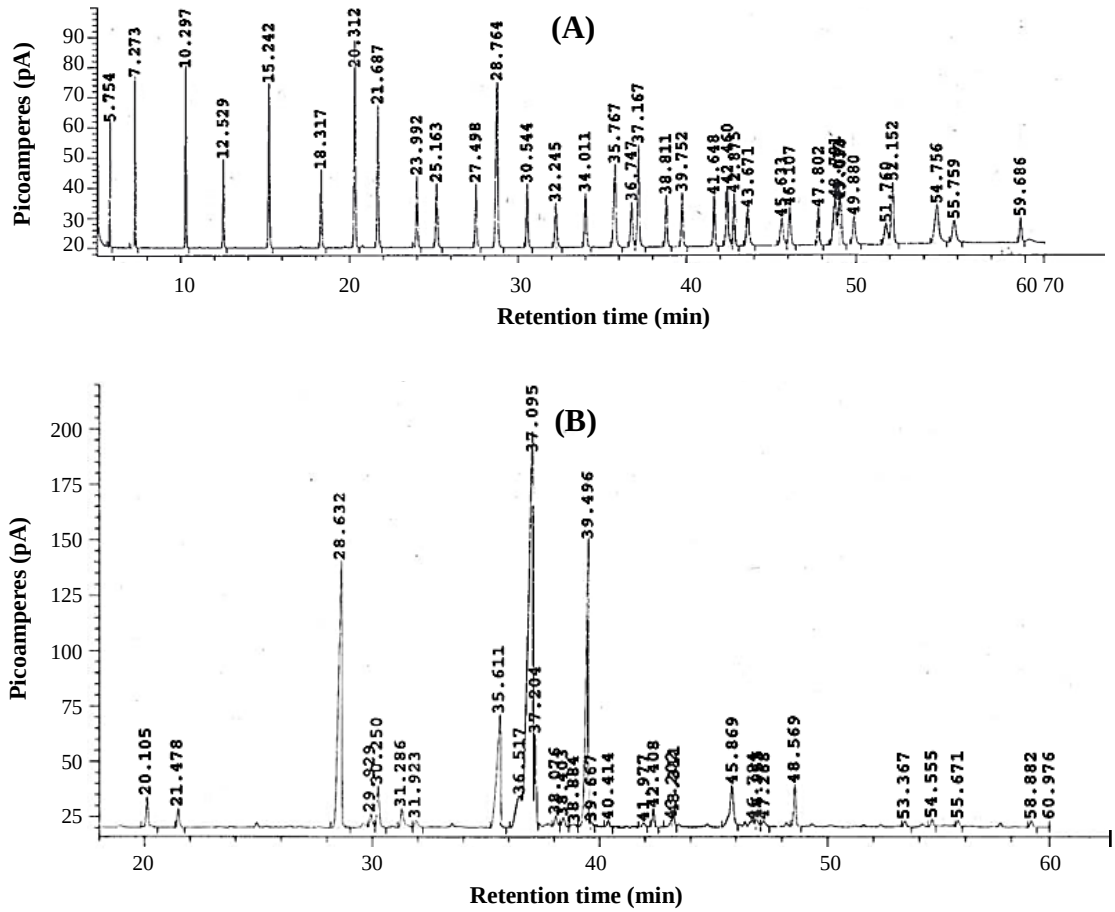

Fig. 1. (A) Chromatogram of the standard mixture of fatty acid methyl esters (Sigma-Aldrich); (B) Fatty acid composition of methyl esters extracted from the plasma membrane of adipocytes.

($p < 0.05$). In contrast, SHR rats fed Sf oil without CLA exhibited a 75% increase in BW by week eight, reflecting a sustained and significantly greater weight gain compared to the KW group (Table 2).

Anthropometry and calorie intake

Daily caloric intake is shown in Table 2. CLA-fed rats consumed calories comparable to KW controls, whereas SHR rats without CLA ingested significantly more calories than controls ($p < 0.05$). This overconsumption was associated with the marked increases in adiposity: epididymal fat (+46%), abdominal fat (+88%), and pericardial fat (+275%), resulting in an 81% increase in total body fat and a 28% rise in adiposity index ($p < 0.05$). In contrast, CLA-fed rats showed only modest fat deposition (epididymal +20%, abdominal +8%, pericardial +25%), yielding a 9% increase in total fat and <1% increase in adiposity index ($p < 0.05$). Rats without CLA exhibited significant increases in organ weights: heart (+161%), liver (+141%), and hepatosomatic index (+72%). CLA supplementation attenuated these effects, resulting in moderate increases of 63%, 15%, and 5%, respectively ($p < 0.05$).

BP and insulin resistance indicators

Table 3 summarizes the effects of CLA on BP and metabolic markers. SHR rats without CLA remained hypertensive, with BP elevated by 39% compared to the controls ($p < 0.01$). In contrast, CLA-fed rats displayed BP values similar to the normotensive KW controls. Glucose levels increased by 59% in SHR rats without CLA ($p < 0.05$), whereas CLA supplementation reduced glucose by 12% relative to the controls ($p < 0.05$). Insulin and HOMA-IR were enhanced dramatically in the CLA-free SHR group (+210% and +391%, respectively; $p < 0.05$), but remained within control levels in the CLA-fed rats. QUICKI values confirmed a preserved insulin sensitivity in the CLA-treated rats, while SHR rats without CLA showed a 26% decrease ($p < 0.01$). Lipid profiles were also affected: SHR rats

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Table 1. BP and diagnostic markers of IR and metabolic syndrome in SHRs following a two-week adaptation period

Paramentes	KW group (n = 10)	SHR group (n = 30)
BW (g)	151 ± 4	247 ± 3*
Glucose (mg/dL)	131 ± 4.50	129 ± 7
Insulin (µUI/mL)	3.70 ± 0.44	7.80 ± 0.98*
Cholesterol (mg/dL)	52.00 ± 2.10	47.03 ± 3.00
Triglycerides (mg/dL)	82.67 ± 1.53	118 ± 4.75*
HOMA-IR	1.19 ± 0.01	2.48 ± 0.05
1/HOMA-IR	0.84 ± 0.01	0.40 ± 0.05
QUICKI Index	0.32 ± 0.01	0.33 ± 0.06
BP (mmHg)	125 ± 7.5	190 ± 9.0*

Values are the mean ± SD. *$p < 0.05$

without CLA displayed elevated cholesterol (+21%) and triglycerides (+35%) ($p < 0.05$). CLA-fed rats exhibited marked reductions in both parameters (-31% and -51%, respectively; $p < 0.05$).

Fatty acid composition of adipocyte plasma membrane

As shown in Table 4, SHR rats without CLA exhibited significantly elevated levels of n-6 PUFA (35.97 ± 1.27%), primarily due to the increased AA (21.83 ± 0.05%). CLA-fed rats demonstrated reduced n-6 PUFA (27.88 ± 1.79%) and AA (14.11 ± 0.82%) levels compared to CLA-free SHR rats ($p < 0.05$). Total SFA and MUFA levels did not differ significantly across groups. CLA supplementation failed to restore n-3 PUFA levels, which remained markedly reduced relative to controls. Notably, CLA-fed rats incorporated CLA isomers into adipocyte membranes (9.69 ± 0.08% of total fatty acids), primarily cis-9,trans-11 (5.99 ± 0.03%) and trans-10,cis-12 (3.70 ± 0.05%).

Table 2. Caloric intake and anthropometric parameters in SHRs receiving a diet containing sunflower Oil with or without CLA for eight weeks

Serum parameters	Groups (n = 5 each)		
	KW	Sunflower oil/SHR	Sunflower oil + CLA/SHR
Dietary calories			
Liquid intake (mL/day)	47.81 ± 3.04^a	52.00 ± 2.00^a	53.63 ± 3.46^a
Food intake (g/day)	15.88 ± 0.60^a	34.00 ± 1.16^b	21.33 ± 0.98^c
Kcal/day/100 g BW	20.03 ± 2.89^a	38.77 ± 1.16^b	22.23 ± 1.32^a
Anthropometric parameters			
BW initial (g)	151 ± 7^a	160 ± 10^a	167 ± 10^a
Final weight (g)	304 ± 8^a	428 ± 8^b	335 ± 17^c
Weight gained(g)	153 ± 4^a	268 ± 6^b	168 ± 8^c
Heart weight (g)	1.16 ± 0.75^a	3.03 ± 0.50^b	1.90 ± 0.80^a
Liver weight (g)	3.16 ± 0.10^a	7.64 ± 0.16^b	3.64 ± 0.50^a
Hepatosomatic index (%)	1.03 ± 0.04^a	1.78 ± 1.00^b	1.08 ± 0.10^a
Epididymal fat (g)	5.00 ± 0.10^a	7.30 ± 0.05^b	6.00 ± 0.10^c
Abdominal fat (g)	6.50 ± 0.30^a	12.25 ± 1.00^b	7.00 ± 0.20^c
Pericardial fat (g)	0.40 ± 0.10^a	1.50 ± 0.01^b	0.50 ± 0.10^c
Total body fat (g)	11.90 ± 0.50^a	21.55 ± 1.06^b	13.00 ± 0.40^c
Adiposity index (%)	3.91 ± 0.30^a	5.03 ± 0.24^b	3.88 ± 0.11^a

Total fat weight = Σ (abdominal, epididymal, and pericardial fat); adiposity index (%) = (total fat weight/final BW) ×100; hepatosomatic index (%) = (liver weight/final BW) ×100. Different superscript letters (a, b, c) within the same row indicate statistically significant differences among groups ($p < 0.05$).

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Table 3. Blood pressure, IR markers, and dyslipidemia in SHRs receiving a diet containing sunflower oil with or without CLA for eight weeks

Serum parameters	Groups (n = 5 each)		
	KW	Sunflower oil/SHR	Sunflower oil + CLA/SHR
BP (mmHg)	140 ± 7[a]	195 ± 8[b]	155 ± 8[c]
Glucose (mg/dL)	105.00 ± 6.00[a]	166.86 ± 2.00[b]	93.00 ± 2.26[c]
Insulin (µUI/mL)	3.57 ± 0.85[a]	11.09 ± 1.14[b]	3.99 ± 0.24[a]
Cholesterol (mg/dL)	80.13 ± 5.00[a]	97.00 ± 2.00[b]	61.00 ± 2.00[c]
Triglyceride (mg/dL)	104.00 ± 4.00[a]	140.00 ± 2.00[b]	69.00 ± 2.00[c]
HOMA-IR	0.93 ± 0.03[a]	4.57 ± 0.05[b]	0.92 ± 0.04[a]
1/HOMA-IR	1.07 ± 0.03[a]	0.21 ± 0.01[b]	1.12 ± 0.01[a]
Quicky index	0.38 ± 0.01[a]	0.30 ± 0.01[b]	0.39 ± 0.01[a]

Values are the mean ± SD; sunflower oil diet (KW group, n = 5 and sunflower oil/SHR group, n = 5) and sunflower oil + CLA diet (sunflower Oil + CLA/SHR group, n = 5). Different superscript letters (a, b, c) within the same row indicate statistically significant differences among groups ($p < 0.05$).

Hepatocyte plasma membrane fatty acid composition

Hepatocyte membrane fatty acids are summarized in Table 5. No major differences were detected in SFA, MUFA, or n-6 PUFA content across the study groups. However, CLA-supplemented rats incorporated CLA isomers into hepatocyte membranes (3.75 ± 0.02% of total fatty acids), with cis-9,trans-11 and trans-10,cis-12 present in nearly equivalent proportions.

Gene expression and prostaglandin synthesis

Figure 2 shows basal expression of genes encoding enzymes involved in prostaglandin synthesis from AA in human adipose and liver tissues. *PTGS1* was more highly expressed in adipose tissue than liver ($p < 0.01$), while *PTGS2* showed the opposite pattern ($p < 0.001$). *PTGES*, *PTGDS*, *HPGDS*, and *AKR1C3* were all highly expressed in adipose tissue ($p < 0.001$), whereas *CBR1* and *HPGD* were predominantly expressed in the liver

Table 4. Fatty acid composition of adipocyte plasma membranes in SHRs receiving a diet containing sunflower oil with or without CLA for eight weeks

Fatty acids	Groups (n = 5 each)		
	KW	Sunflower oil/SHR	Sunflower oil + CLA/SHR
14:0	0.79 ± 0.03[a]	0.74 ± 0.23[b]	0.64 ± 0.09[a]
15:0	0.13 ± 0.04[a]	0.21 ± 0.03[a]	0.15 ± 0.05[a]
16:0	24.42 ± 1.63[a]	23.18 ± 1.03[a]	23.66 ± 0.47[a]
18:0	20.21 ± 1.52[a]	11.63 ± 1.74[b]	15.84 ± 1.35[a]
20:0	0.51 ± 0.12[a]	0.55 ± 0.23[a]	0.51 ± 0.21[a]
Total SFA	46.06 ± 3.34[a]	36.31 ± 3.26[a]	40.80 ± 2.17[a]
16:1	**1.34 ± 0.35[a]**	**1.42 ± 0.03[b]**	**1.28 ± 0.06[b]**
18:1	20.51 ± 4.31[a]	23.54 ± 1.23[a]	18.72 ± 1.13[b]
24:1	1.56 ± 0.22[a]	1.56 ± 0.12[b]	1.36 ± 0.23[b]
Total MUFA	23.41 ± 4.88[a]	26.52 ± 1.38[a]	21.36 ± 1.42[a]
18:2	8.33 ± 2.01[a]	11.90 ± 0.65[a]	11.09 ± 0.87[a]
18:3	1.22 ± 0.34[a]	2.24 ± 0.57[b]	2.68 ± 0.10[b]
20:4	19.98 ± 0.07[a]	21.83 ± 0.05[b]	14.11 ± 0.82[c]
Total n-6 PUFA	29.53 ± 2.42[a]	35.97 ± 1.27[b]	27.88 ± 1.79[a]
18:3	0.24 ± 0.02[a]	0.07 ± 0.02[b]	0.13 ± 0.04[c]
20:5	0.43 ± 0.12[a]	0.37 ± 0.06[b]	0.27 ± 0.06[c]
22:6	0.28 ± 0.07[a]	0.31 ± 0.03[b]	0.15 ± 0.04[c]
Total n-3 PUFA	0.95 ± 0.21[a]	0.75 ± 0.11[b]	0.55 ± 0.14[c]
CLA isomer (c9, t11)	nd	nd	0.13 ± 0.04[c]
CLA isomer (t10,c12)	nd	nd	0.27 ± 0.06[c]
Total CLA	nd	nd	0.15 ± 0.04[c]

Values are the mean ± SD. Different superscript letters (a, b, c) within the same row indicate statistically significant differences among groups ($p < 0.05$). nd: not detected.

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Table 5. Plasma membrane fatty acid composition of hepatocytes from SHRs receiving a diet containing sunflower oil with or without CLA for eight weeks

Fatty acids	Groups (n = 5 each)		
	KW	Sunflower oil/SHR	Sunflower oil + CLA/SHR
14:0	1.31 ± 0.01[a]	2.01 ± 0.01[b]	1.39 ± 0.01[a]
16:0	19.60 ± 2.00[a]	20.36 ± 1.00[a]	20.39 ± 2.59[a]
18:0	18.76 ± 1.00[a]	19.29 ± 2.00[b]	17.83 ± 1.50[a]
20:0	7.58 ± 0-50[a]	7.50 ± 1.50[b]	7.80 ± 1.00[a]
22:0	6.00 ± 2.00[a]	5.40 ± 1.50[a]	5.76 ± 1.00[a]
24:0	3.20 ± 0.20[a]	3.29 ± 0.10[a]	2.80 ± 0.20[a]
Total SFA	54.46 ± 5.21[a]	57.85 ± 4.61[a]	55.92 ± 5.13[a]
18:1 n-9	16.45 ± 1.15[a]	18.49 ± 1.16[a]	15.03 ± 2.20[a]
Total MUFA	16.45 ± 1.15[a]	18.49 ± 1.16[a]	15.03 ± 2.20[a]
18:2 n-6	14.18 ± 1.00[a]	9.66 ± 1.50[b]	13.84 ± 1.00[b]
20:4 n-6	13.00 ± 1.20[a]	14.00 ± 1.00[a]	12.00 ± 1.50[a]
Total n-6 PUFA	27.18 ± 2.20[a]	23.66 ± 2.50[b]	25.84 ± 2.50[a]
Total n-3 PUFA	nd	nd	nd
CLA isomer (c9,t11)	nd	nd	1.85 ± 0.01
CLA isomer (t10,c12)	nd	nd	1.90 ± 0.01
Total CLA	nd	nd	3.75 ± 0.02

Values are the mean ± SD. Different superscript letters (a, b, c) within the same row indicate statistically significant differences among groups ($p < 0.05$). nd: not detected.

($p < 0.001$). *PTGR2* levels were similar among the tissues. These results highlight tissue-specific regulation of prostaglandin biosynthetic pathways.

DISCUSSION

This study evaluated the effects of a 50:50 mixture of CLA isomers—cis-9,trans-11 and trans-10,cis-12—on BW, IR, HTN, and their incorporation into plasma membranes of adipocytes and hepatocytes in SHRs.

Our findings demonstrated that dietary CLA significantly reduced BW in SHRs to levels comparable to control rats. This reduction was accompanied by a marked decrease in adipose tissue, particularly in abdominal, epididymal, and pericardial depots, resulting in a lower adiposity index, which is consistent with previous reports by Wang and colleagues[26]. The physiological response to CLA varies with species, metabolic status, and dietary fat type[26,27]. Nonetheless, supplementation with commercial CLA mixtures containing both isomers generally decreases body fat, independent of dietary lipid type or quantity [26,28]. Proposed mechanisms underlying CLA-induced fat reduction in rodents include downregulation of mRNA expression of lipogenic enzymes in adipose tissue (fatty acid synthase, acyl-CoA synthetase) and altered expression of transcription factors, which regulate lipid metabolism, such as SREBP-1c and PPAR-γ. CLA may also upregulate tumor necrosis factor-α, promoting adipocyte apoptosis, and increase the expression of uncoupling protein-2, thereby enhancing energy expenditure[29]. Although these mechanisms could explain the BW reduction observed in SHRs, they were not directly assessed in this study.

While numerous animal studies support the anti-obesity effects of CLA, findings in humans remain inconsistent. A systematic review and meta-analysis by Asbaghi et al. (8,351 participants across 8,351 studies) reported modest but statistically significant improvements in some body composition parameters. However, high-quality studies have not substantiated significant fat-reducing effects, reporting only minimal weight loss that is unlikely to be clinically meaningful[30]. Beyond weight management, CLA has been associated with antidiabetic, anti-inflammatory[31], and antihypertensive properties in both animal models and humans, potentially through regulation of endothelial function, nitric oxide production, and eicosanoid synthesis[9,32-34]. Nevertheless, Engberink et al. observed no significant antihypertensive effects in their clinical study[35].

In our study, reduced BP values in CLA-fed SHRs may be partly attributed to the decreased BW, since obesity is a major risk factor for HTN. CLA-supplemented rats did not exhibit an increase in adiposity; conversely, SHR rats receiving sunflower oil without CLA developed a substantial fat accumulation.

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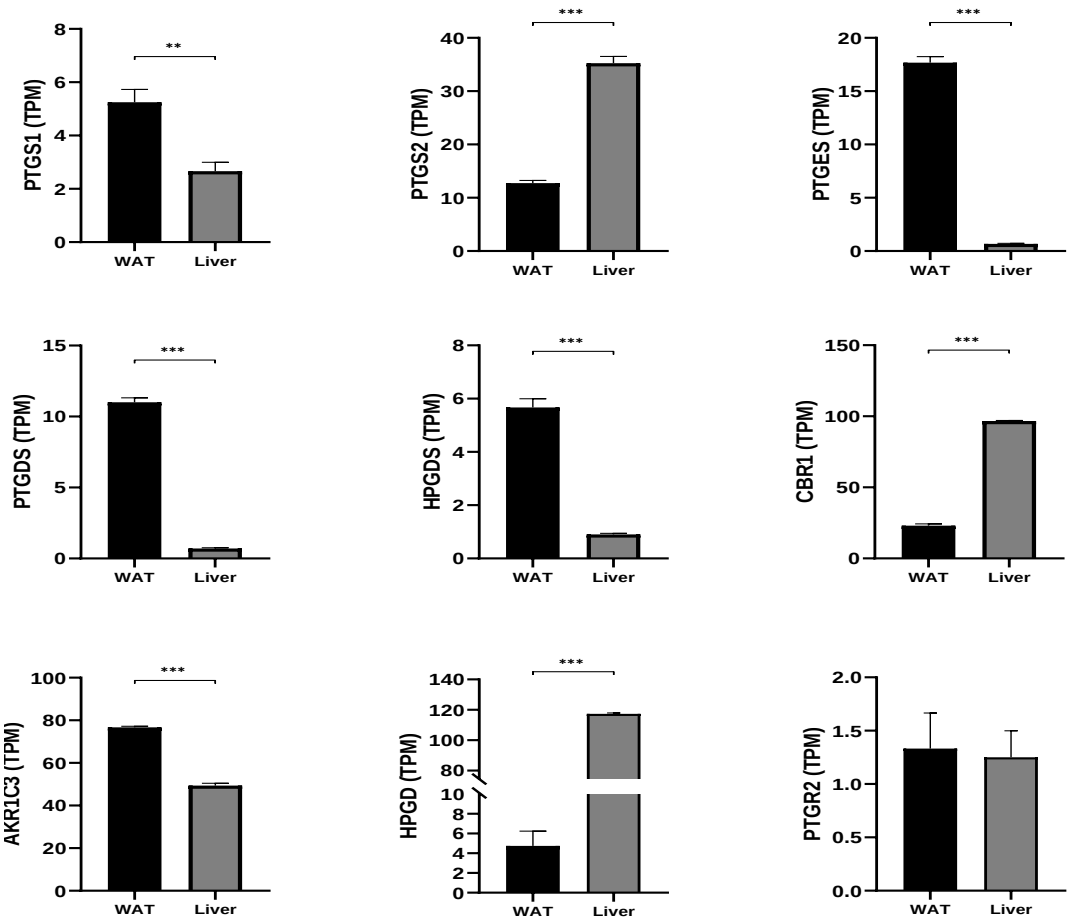

Fig. 2. Basal expression levels of the genes encoding key enzymes involved in prostaglandin synthesis from AA in human white adipose tissue and liver ($^{**}p < 0.01$; $^{***}p < 0.001$).

These findings suggest that reduced adiposity contributes to BP lowering, which brings SHR values closer to controls. Hypertrophic adipocytes are known to secrete adipocytokines such as angiotensinogen and adiponectin, both implicated in obesity-related HTN[36]. Increased angiotensinogen expression correlates with higher BP[37]. Notably, the trans-10,cis-12 CLA isomer has been shown to reduce angiotensinogen mRNA expression in adipose tissue[9,32,38], supporting the antihypertensive effects of CLA in young rats. In contrast, adiponectin levels typically decline with increasing adiposity[39,40], which contributes to obesity-induced HTN[41]. Importantly, supplementation with CLA mixtures has been reported to increase serum adiponectin and its mRNA expression in adipose tissue[42], suggesting a mechanism through which CLA may alleviate HTN. However, comparisons with human studies remain essential.

A meta-analysis by Yang et al., encompassing 318 randomized controlled trials, found no robust evidence supporting significant antihypertensive effects of CLA, although study duration and obesity status emerged as important moderating factors[43]. In the present study, CLA supplementation improved BW, IR, HTN, and HOMA-IR in SHRs, approaching values observed in the control group. In contrast, SHR rats without CLA supplementation displayed pronounced insulin resistance. These results suggest that weight reduction is a key contributor to normalization of BP, IR, and dyslipidemia. CLA-fed rats exhibited significantly lower serum triglyceride and cholesterol than their CLA-free counterparts, consistent with the lipid-lowering effects of CLA reported in animal studies. Isomer-specific effects of CLA have been well-documented; the trans-10,cis-12 isomer reduces serum lipid concentrations, whereas cis-9,trans-11 can exert opposite effects[39]. Although the underlying mechanisms remain unclear, CLA may reduce cholesterol absorption by modulating intestinal sterol O-acyltransferase activity or inhibiting apolipoprotein B synthesis[44,45]. However, findings across studies are not entirely consistent. Moloney et al. reported no reliable improvements in IR or serum lipids, and some human trials have even documented adverse effects. A double-

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blind, placebo-controlled trial administering 3.0 g/day of CLA (50:50 mixture) for eight weeks showed negative effects on IR and glucose metabolism, with no significant reductions in cholesterol or HDL[46].

Our study also showed that CLA supplementation led to incorporation of isomers into adipocyte and hepatocyte membranes, correlated with weight reduction, and improved IR. These results align with those of Park et al., who showed that a dietary CLA mixture reduced fat mass and increased lean mass in mice[47]. At the molecular level, CLA can downregulate lipogenic genes (fatty acid synthase, acyl-CoA synthetase) and transcription factors (SREBP-1c, PPAR-γ) in adipocytes[29]. In contrast with these data, SHR rats without CLA demonstrated an elevated incorporation of n-6 PUFAs, particularly AA, a precursor of proinflammatory and atherogenic eicosanoids. CLA-fed rats were protected from these increases, supporting membrane remodeling as a potential underlying mechanism.

In hepatocytes, CLA incorporation into membranes may be linked to upregulation of the genes involved in mitochondrial and peroxisomal fatty acid oxidation, such as carnitine palmitoyltransferase-1, facilitating transport of fatty acyl-CoA into mitochondria[48,49]. This mechanism may mitigate lipid accumulation by limiting the influx of fatty acids derived from adipose tissue lipolysis. In line with observations in adipocytes, hepatocytes from non-CLA rats incorporated higher levels of n-6 PUFAs, a profile associated with enhanced pro-inflammatory signaling.

Membrane lipid composition influences tissue-specific functions through mechanisms such as changes in microviscosity and fluidity. These mechanisms affect receptor expression, signaling pathways, and metabolite production, regulating gene expression[49]. AA and CLA-derived lipids play central roles in the biosynthesis of thromboxanes, leukotrienes, and prostaglandins—key regulators of cardiovascular and inflammatory physiology[27]. Incorporation of CLA into adipocyte and hepatocyte membranes has direct implications for arachidonic acid metabolism. Upon release from membrane phospholipids, this acid serves as a substrate for cyclooxygenase and lipoxygenase pathways, leading to the production of PGE_2 and leukotrienes[13]. In contrast, conjugated arachidonate derived from CLA isomers is not a substrate for these enzymes, reducing PGE2 and leukotriene synthesis. Since PGE2 promotes inflammation and suppresses anti-inflammatory cytokines, CLA-driven suppression of PGE2 synthesis may attenuate proinflammatory signaling[14]. To validate this mechanism, we analyzed the expression of prostaglandin-related genes in human adipose and liver tissues using public transcriptomic datasets[25,41]. Genes such as *PTGS1*, *PTGES*, *PTGDS*, *HPGDS*, and *AKR1C3* were more highly expressed in adipose tissue, whereas *PTGS2*, *CBR1*, and *HPGD* showed greater expression in liver tissue, which is consistent with their established roles in prostaglandin biosynthesis[50]. Given that AA is a key substrate for prostaglandin synthesis, reduced AA incorporation into adipocyte and hepatocyte membranes with CLA supplementation may attenuate prostaglandin biosynthesis, thereby reducing HTN and inflammation. In the liver, an increased expression of *PTGS2* and *CBR1* was observed, consistent with an enhanced capacity for prostaglandin synthesis. HPGD, a key enzyme in prostaglandin degradation, was also upregulated, highlighting its potential anti-inflammatory function in hepatic tissue. However, there was also an upregulation of HPGD, a key enzyme involved in prostaglandin degradation, underscoring its anti-inflammatory role.

Overall, CLA supplementation remodeled membrane lipid composition, reduced AA incorporation, and modulated gene expression, correlating with improvements in IR, HTN, BW, and adiposity in SHRs. In contrast, CLA-free rats exhibited an elevated AA level, potentially promoting the synthesis of proinflammatory prostaglandins and exacerbating hypertensive conditions.

CONCLUSION

Dietary CLA isomers, particularly cis-9,trans-11 and trans-10,cis-12 in a 50:50 ratio, modified the fatty acid composition of adipose and hepatic tissues in SHRs. These membrane alterations were associated with reduced body weight, improved insulin resistance indices, and lower blood pressure. Collectively, these findings suggest that CLA supplementation may exert beneficial effects on metabolic and cardiovascular health through membrane lipid remodeling.

DECLARATIONS

Acknowledgments

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Ethical approval

The entire protocol of this study, including both research and ethical aspects, was approved by the full faculty of UNIDA through several presentations and

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evaluations. This protocol, together with others from the same group, has been submitted to an independent ethics committee of the Cristobal Colon University in the city of Veracruz. México.

Consent to participate

Not applicable

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

GHD: investigation, formal analysis, and writing–original draft preparation; JCRN: supervision and project administration; IAM: formal analysis, data curation, and writing–review & editing; BAL: methodology and validation; NLCR: data curation and software; SHL: data curation and visualization; HSG: conceptualization, resources, project administration, and writing–review & editing; AAA: conceptualization, supervision, and writing–review & editing

Data availability

Data can be made available upon request.

Competing interests

The authors declare that they have no competing interests.

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Supplementary information

The online version does not contain supplementary material.

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