Feeding Tomatoes to Hamsters Reduces their Plasma Low-density Lipoprotein Cholesterol and Triglycerides

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ABSTRACT: Hamsters were fed semipurified diets containing green or red freeze-dried tomato powders. Compared to the control diet devoid of tomatoes, a 59% and 44% reduction low-density lipoprotein (LDL) cholesterol was induced by both the green and red tomatoes, respectively. The corresponding reductions in very low-density lipoproteins (VLDL) were 45% and 35% and in plasma triglyceride concentrations 47% and 31%, respectively. Plasma levels of high-density lipoproteins (HDL) were unaffected. Fecal deoxycholic and lithocholic acid concentrations of hamsters on tomato diets were higher than those on control diets. Possible contributions of major components of green and red tomatoes to these beneficial effects are discussed.

Key Words: green tomatoes, red tomatoes, cholesterol, triglycerides, tomatine, hamster

Introduction

DIETS THAT ARE HIGH IN SATURATED FAT AND CHOLESTEROL elevate plasma cholesterol in male hamsters and humans by suppressing the rate of low density lipoprotein (LDL) receptor-mediated clearance of LDL particles from blood (Spady and Dietschy 1988). As is well known, elevated concentrations of LDL cholesterol present a risk factor for cardiovascular disease (Expert Panel 1988). While high LDL and triglyceride concentrations are considered such risks, high density lipoprotein (HDL) particles are considered beneficial. A low ratio of LDL to HDL and low plasma triglyceride levels decreases risk.

The composition of green and red tomatoes differs in components that may be associated with human health. These include the red carotenoid pigment lycopene present in red but not in green tomatoes and the glycoalkaloids α-tomatine and dehydrotomatine. Lycopene may contribute to the cholesterol lowering effect of the red tomatoes (Gerster 1997). On the other hand, since tomatine is reported to form strong in vitro (Micich 1993) and in vivo (Friedman and others 2000) insoluble complexes with cholesterol, relatively high concentrations of the glycoalkaloids α-tomatine and dehydrotomatine in the green tomatoes compared to red ones (Friedman and Levin 1995, 1998) may enhance the cholesterol-lowering effect of green compared to red tomato diets.

Male hamsters and humans respond similarly to high-fat and high-cholesterol diets by increasing concentrations of plasma cholesterol concentrations (German and others 1996; Scheiber and others 1994). The objective of this exploratory study was to find out whether feeding green and red tomato diets to hamsters would induce lowering of plasma lipoprotein and triglyceride levels. The results show that this expectation was realized.

Results

THE LIPOPROTEIN CHOLESTEROL AND TRIGLYCERIDE CONCENTRATIONS in plasma from hamsters fed the 3 diets (see the "Materials and Methods" section) are shown in Table 1. The results show a 59% and 44% reduction in LDL cholesterol in hamsters fed green and red tomatoes, respectively. The corresponding reductions in plasma triglyceride levels were 47% and 31%, respectively. Very low density lipoprotein (VLDL) cholesterol also decreased significantly in the hamsters fed the tomato diets, but high density lipoprotein (HDL) cholesterol was unaffected. The LDL/HDL ratio of the animals fed the green tomato diets decreased 59% compared to the control.

Table 2 shows total feed consumption, feed efficiency, weight gains, and liver weights of the hamsters after 21 d on the control and tomato diets. Red and green tomato feeding resulted in 12% and 20% lower weight gain and 9% and 18% lower feed intake. The total feed intake of animals on the tomato diets were lower, and the amount of tomato diets required to gain weight was higher.

The protein in all diets consisted of approximately 50% vegetable protein and 50% casein (Table 3). Tomato solids are high in free amino acids and contain about 15% protein (protein ∇ N $\times$ 6.25; Tables 4 and 5). The only fiber in these tomato diets originated from tomatoes. Although tomato solids also have a high content of dietary fiber (22% to 24%), about 80% of tomato dietary fiber is insoluble (Table 4). Table 6 lists the fecal concentrations of excreted cholesterol, coprostanol, and 2 bile acids, deoxycholic and lithocholic acids. Table 6 also shows significant increases in fecal deoxycholic acid content of hamsters fed green tomatoes and of fecal lithocholic acid content of hamsters on both green and red tomato diets. The cellulose based diets had no effect on either bile acid levels.

Table 1—Effect of control and tomato-containing diets on lipoprotein cholesterol and triglyceride distribution in hamsters fed for 21 d

Diet	VLDL (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	total (mg/dL)	triglyceride (mg/dL)	LDL/HDL
Control	139 ± 4.5	52 ± 10.3	130 ± 9.4	313 ± 17.9	627 ± 74	0.41 ± 0.07
Green tomato	77.0 ± 9.1*	21 ± 3.2*	130 ± 7.3	228 ± 14.6*	333 ± 25*	0.17 ± 0.02*
Red tomato	98.2 ± 9.2*	29 ± 3.4*	112 ± 3.2	240 ± 12.6*	432 ± 28*	0.26 ± 0.02

[a] Values are means ± SEM, n=8. [b] mg/dL X 0.0259 = mmol/L.
* Indicates significant differences from control, p<0.01.

Table 2—Effect of control and tomato diets on feed intake, weight gain, final body weight, feed efficiency, and liver weights of hamsters fed for 21 d

Diet	Feed intake, g	Final body weight, g	Weight gain, g	Liver weights, g	Feed efficiency	Liver/body, weight
Control	219.0 ± 3.5	118.6 ± 2.4	71.8 ± 1.8	7.0 ± 0.11	3.1 ± 0.05	5.87
Green tomato	180.4 ± 8.7*	95.5 ± 4.4*	48.6 ± 3.9*	5.1 ± 0.33*	3.8 ± 0.17*	5.33
Red tomato	195.4 ± 7.0*	104.1 ± 3.7*	57.0 ± 3.8*	5.8 ± 0.35*	3.5 ± 1.2*	5.54

[a]Values are means ± SEM, n=8.
* For feed intake, the green and red tomato diets are significantly different from the control at p<0.0002 and 0.013, respectively. The corresponding values for body weights are p<0.002 and 0.14 and for liver weights, p<0.001 and 0.004, respectively. For feed efficiency, p=0.05.

Table 3—Composition of tomato-free and tomato-containing diets[a]

Ingredients (g/Kg)	Control diet	Green tomato diet	Red tomato diet
Corn oil, stripped	35.0	15.3	16.0
Polyunsaturated fat	25.9	14.6[b]	14.2[b]
Cellulose	109.0	0	0
Corn starch	488.0	101.5	99.0
Available (digestible) carbohydrate	488.0	364.1	387.9
Dehydrated tomato	0	610.1	593.8
Soybean isolate	94.9	0.0	18.1

[a] American Institute of Nutrition (1977). Ingredients are reported on a dry weight basis. The following ingredients were also included in all diets: butter, 90 g; olive oil, 25 g; vitamin free casein, 105.1 g; DL-methionine, 3.0 g; choline bitartrate, 3.0 g; hamster mineral mix, 35.0 g; hamster vitamin mix, 10.0 g; and cholesterol, 2.0 g.
[b] Amount derived from corn oil and tomatoes. The values for green (0.2 g/kg) and red (0.4g/kg) tomatoes are based on data listed in USDA (1984).

Table 4—Tomatine concentration and proximate composition of green and red tomatoes

Tomato component	Green tomatoes	Red tomatoes
Tomatine, mg/kg fresh weight	48	0.4
Tomatine, mg/kg dry weight	743 ± 0.8[b]	0.7± 0.3[b]
Solid content, %	6.4[c]	5.8[c]
Moisture content, %	93.6	94.2
N, %[a]	2.49	2.11
Fat, %[a]	3.24	3.20
Ash, %[a]	10.31	10.02
Insoluble fiber,%[a]	19.76 ± 0.77[d]	17.03 ± 0.72[d]
Soluble fiber,%[a]	4.26 ± 0.68[d]	4.91 ± 0.68[d]

[a] Dry weight basis. [b] n = 3. [c] After freeze-drying. [d] n = 6.

Table 5—Free and total (free plus protein-bound) amino acid content of dehydrated tomatoes

Amino acid, g/16 g N	Green tomatoes		Red tomatoes	
	Free	Total	Free	Total
Alanine	0.52	2.5	0.32	2.1
Arginine	0.87	3.3	0.54	3.0
Aspartic acid	2.47	9.6	6.26	12.0
Cystine	nd[a]	0.85	nd	1.2
Glutamic acid	2.04	26.0	16.9	38.0
Glycine	0.24	2.3	0.11	2.3
Histidine	1.02	2.6	0.92	2.1
Isoleucine	0.63	2.1	0.22	1.7
Leucine	0.50	3.2	0.21	2.8
Lysine	0.90	3.7	0.48	3.0
Methionine	0.16	1.3	0.24	1.3
Phenylalanine	1.23	2.9	0.86	2.5
Proline	nd	2.0	nd	1.7
Serine	2.08	3.5	1.14	2.6
Threonine	1.32	2.7	0.80	2.4
Tryptophan	nd	0.85	nd	0.86
Tyrosine	0.78	2.1	0.20	1.6
Valine	0.64	2.5	0.16	1.9
Total amino acids	15.4	74.0	29.4	83.1

[a] nd = not detected.

Table 6—Excreted fecal cholesterol, coprostanol, deoxycholic, and lithocholic acids (mg/100 g)[a]

Diet	Cholesterol	Coprostanol	Deoxycholic acid	Lithocholic acid
Control	211 ± 65	164 ± 57	219 ± 76	264 ± 46
Green tomato	114 ± 39	135 ± 23	414 ± 72*	415 ± 5*
Red tomato	102 ± 26	170 ± 40	217 ± 48	505 ± 67*

[a] Values are means ± SEM for cholesterol and coprostanol: n = 8 for control, 6 for green tomato, 7 for red tomato diets; for deoxycholic and lithocholic acids: n = 7, for control; 6, for green tomato; 7, for red tomatoes.
* Indicates significant difference from control, p<0.05.

Discussion

BOTH TOMATO DIETS RESULTED IN LOWER LDL CHOLESTEROL, and the green tomato diet lowered total plasma cholesterol as well. Both green and red tomato feeding resulted in differences in feed intake, weight gain, and fecal excretion of bile acids that could affect plasma cholesterol. Some of the lower intake and weight gain may have been due to the lower bulk density of the freeze-dried tomato ingredients.

Generally, efforts designed to decrease cholesterol absorption must take into account both dietary and endogenous cholesterol since diet and bile constitute 2 major sources of cholesterol available for absorption (Scheibner and others 1994; Wilson and Rudel 1994). Many vegetable components, including protein, fat, fiber, and phytosterols, have been shown to affect plasma cholesterol. The cholesterol-lowering effects of fiber (Moundras and others 1997) may be due to its ability to enhance fecal excretion of cholesterol and bile acids. Fiber induces both enhanced liver excretion and diversion of intestinal steroids to the feces (Daggy and others 1997). However, soluble dietary fiber is the form that reduces plasma cholesterol(Kritchevsky 1988). The tomato powders appear to stimulate bile acid excretion.

Cholesterol levels were significantly lowered in rats fed plant proteins compared to those fed animal proteins (Morita and others 1997; Sautier and others 1986). Tomatoes contain both free and protein-bound amino acids (Table 5). Thus (a) free amino acids contribute significantly to the total amino acid profiles of both green and red tomatoes, for example free lysine constitutes about 20% to 25 % of the total, and free methionine, about 12% to 18% (Table 5); and (b) with reference to the FAO/WHO recommendations described elsewhere (Friedman 1996), the essential amino acid content of tomatoes is indicative of a good quality protein. Since good quality plant proteins are reported to lower cholesterol, these considerations suggest that the protein and amino acid components of tomatoes probably contribute to the observed reduction of cholesterol.

Conclusions

WE HAVE DEMONSTRATED THE SELECTIVE REDUCTION BY TOmato diets of plasma LDL (bad) cholesterol as well as triglyceride concentrations, while HDL (good) cholesterol remained unaffected. Several tomato components may act additively or synergistically to induce the observed reduction in LDL-cholesterol and triglyceride levels by the tomato diets. These include fiber (Kritchesvsky 1988), protein (Morita and others 1997), free amino acids (Sanchez and Hubbard 1989), lycopene and other antioxidants (Gerster 1997; Anese 1999), tomatine (Friedman and others, 2000), and polyunsaturated fat (USDA 1984). Obviously, this work points to the need for additional studies to better

define the roles of various tomato components that may be responsible for the beneficial effects. No less challenging, but potentially beneficial for human health, would be an assessment whether the cited effects in hamsters parallel those in humans.

Materials and Methods

Test compounds

Freshly harvested green and red commercial fresh market tomatoes, variety 761, donated by DNA Plant Technology Corporation (Oakland, Calif., U.S.A.) were freeze-dried immediately to arrest maturation. They were then ground into green and red powders to pass a 0.5-mm mesh sieve. Deuterated sterol standards were obtained from Medical Isotopes (Concord, N.H., U.S.A.). Hamsters were supplied by Simonsen Laboratories (Gilroy, Calif., U.S.A.).

Tomato composition

The α-tomatine content of green and red tomatoes was determined by high-performance liquid chromatography (HPLC) as previously described (Friedman and Levin 1995, 1998; Friedman and others 1997; Fig. 1). Tomato powders were analyzed for insoluble and soluble fiber, N, and ash content by standard methods (AOAC 1990; Prosky 1988; Table 4). The amino acid content of green and red tomato powders (Table 5) was determined by Nestle Quality Assurance Laboratory (Dublin, Ohio, U.S.A.; Sarwar and others 1983). Four separate analyses were carried out: (a) free amino acids were determined on a Beckman 6300 Amino Acid Analyzer using ninhydrin; (b) total amino acids: the sample was hydrolyzed in 6 M HCl under N_2 for 24 h at 110 °C, evaporated to dryness, reconstituted in lithium buffer, and analyzed as described above; (c) sulfur amino acids: the sample containing cystine and methionine was oxidized with performic acid for 24 h at 4 to 7 °C; the resulting cysteic acid and methionine sulfone were determined as described above; and (d) tryptophan was analyzed by HPLC with fluorescence detection.

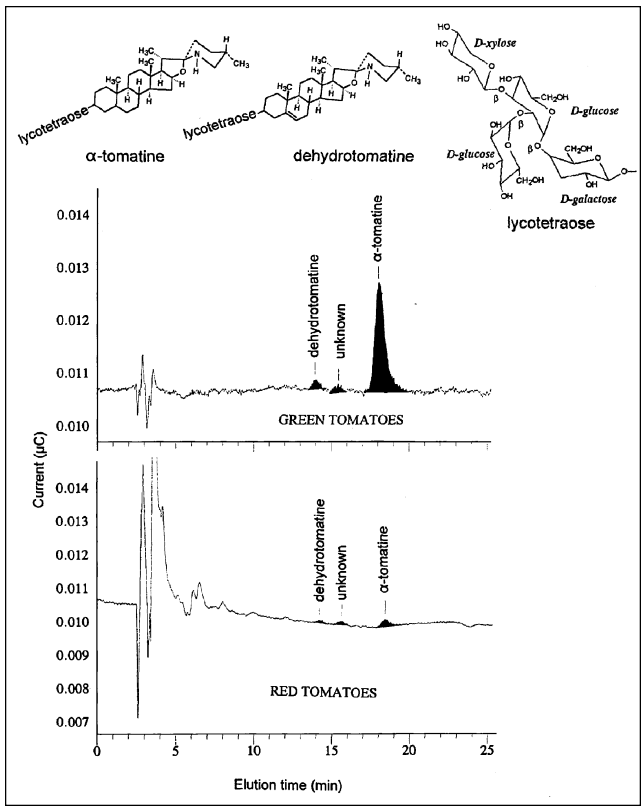

Fig. 1—Structures and HPLC chromatograms with amperometric detection of the major glycoalkaloid α-tomatine and minor glycoalkaloid dehydrotomatine (in a ratio of about 10:1) isolated from green and red tomatoes used in this study. The unknown peak may be another minor glycoalkaloid.

Feeding studies

Hamsters (8/diet) were randomly assigned to the cellulose, green tomato, or red tomato diets. The feed composition of the diets are given in Table 3. The animal experiments were conducted as previously described (Yokoyama and others 1998). All animal procedures were approved by the Animal Care and Use Committee, Western Regional Research Center, Albany, Calif., which follows National Institutes of Health guidelines for the care and use of laboratory animals (NRC 1985).

Lipoprotein analyses

Total cholesterol was measured by the cholesterol oxidase method and lipoprotein cholesterol by size exclusion chromatography as described previously (German and others 1996; Yokoyama and others 1998).

Fecal analysis for dietary sterols

The procedure described by Lutjohann and others (1993) was modified as follows. Dietary cholesterol absorption was determined by feeding animals 21 mg/g each of d_6-cholesterol and d_4-sitostanol in their diet for the last 5 d of the study. Feces collected the last day of the study were freeze-dried for analysis. The dried feces (100 mg) were ground and added to a 10 mL glass test tube. To this was added 10 mL of distilled water and 1 mL of 1 M NaOH in 90% ethanol. The mixture was heated for to 67 °C for 1 h. The samples were then cooled to room temperature and 1 mL of distilled water was added. The neutral sterols were extracted 3 times with 3 mL hexane. The hexane was evaporated with dry nitrogen at 50 °C. The dried sample was then brought up to 100 μL with dichloromethane. A Waters Silica Sep-Pak cartridge was prepared for each sample by wetting with 5 mL hexane. The sample (25 μL) in dichloromethane was added to the cartridge and then eluted with 2.5% 2-propanol-97.5% hexane. The solvent was removed with the aid of a stream of dry nitrogen. The residue was derivatized with 100 μL of N,O-*bis*(trimethylsilyl)trifluoroacetamide (BSTFA) containing 1% trimethylchlorosilane (TMCS) (Pierce, Rockford, Ill., U.S.A.) by heating to 70 °C for 15 min.

The deuterated sterol analysis was performed on an HP-5890 Series II gas chromatograph equipped with an HP5972 Mass Selective Detector (Hewlett-Packard, Fullerton, Calif., U.S.A.) similar to that described by Lutjohann and others (1993). The column used was a 30 m, DB-5MS with a 0.25 mm internal diameter (id) and 0.5 mm film thickness (J&W, Folsom, Calif., U.S.A.). Helium was used as the carrier gas, with a head pressure of 10 p.s.i. The injector and transfer line temperature was set to 280 °C. The oven temperature program was set at an initial 60 °C for 1 min, then ramped at 30 °C/min to 275 °C, held for 25 min, then ramped at 10 °C/min to 300 °C, and then held for 10 min. The sample (1 μL) was then injected into the column. Selected Ion Monitoring (SIM) was done at a rate of 3.7 cycles/sec in the SIM mode. The compounds and their molecular ion peaks (M^+) that were scanned

for include: (a) 5α-cholestane, 372.4; (b) d_6-coprostanol, 376.4 (M^+ - 90); (c) d_6-coprostanone, 392.4; (d) d_6-cholesterol, 464.4; and (e) d_4-sitostanol, 492.5.

Fecal bile acid analysis

To approximately 50 mg freeze-dried and ground fecal sample was added 1 mL of 1 M NaOH in 90% ethanol. The suspension was incubated at 67 °C for 1 h, cooled to room temperature, diluted with 1 mL deionized H_2O, and extracted with hexane to remove neutral sterols. The aqueous portion was transferred to a 50 mL tube to which was added 0.6 mL NaOH. The solution was then autoclaved at 130 °C for 1 h, cooled, acidified with HCl to pH 1, extracted with 5 mL chloroform-methanol (2:1, v/v) and centrifuged for 5 min at 500 × g. The lower phase was then transferred to a 2-mL screw-cap vial. The extraction procedure was repeated twice. The internal standard 5-α-cholestane (1 mg in hexane) was then added to the combined extracts and the solution was evaporated under a stream of nitrogen.

Methyl esters of the bile acids were prepared as follows: MeOH/HCl (1 mL, 0.5 M) was added to the residue and the solution was incubated at room temperature for 2 h. The solvent was then evaporated under nitrogen at 55 °C and the sample transferred with methanol to a 2 mL autosampler vial with a 100 mL insert. The methyl esters were then silylated with BSTFA with 1% TMSCS at 55 °C for 20 min (see above). One μL of this solution was used for gas chromatography (GC) analysis (Hewlett-Packard Model 5890 series gas chromatograph equipped with an FID and split/splitless injection port and DB-5MS 30m × 0.25 mm × 0.5 mm column (J&W Scientific, Folsom, Calif., U.S.A.). The temperature program set at 100 °C was held for 2 min and then programmed to increase by 35 °C/min to 278 °C, where it was held for 37 min.

Statistics

Analysis of variance (ANOVA; SAS 1987) and Dunnett's test (Dunnett 1955) were used to compare treatment means with their corresponding control means. The analyses include Dunnett's one-tailed test for a decrease from the control diet, which was meant for the comparison of the green and red tomato diets.

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