The Daily Oral Administration of High Doses of *trans*-Resveratrol to Rats for 28 Days Is Not Harmful[1]

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ABSTRACT *trans*-3,5,4′-Trihydroxystilbene (*trans*-resveratrol) is a phytochemical present in peanuts, grapes and wine with beneficial effects such as protection against cardiovascular disease and cancer prevention. The purpose of this study was to evaluate whether high doses of *trans*-resveratrol have harmful effects on Sprague-Dawley rats. *trans*-Resveratrol was administered orally to male rats for 28 d at a dose of 20 mg/(kg · d), 1000 times the amount consumed by a 70-kg person taking 1.4 g of *trans*-resveratrol/d. Body weight, and food and water consumption did not differ between rats treated with *trans*-resveratrol and the control group. Hematologic and biochemical variables were not affected by the treatment. Histopathologic examination of the organs obtained at autopsy did not reveal any alterations. These results support the view that repeated consumption of *trans*-resveratrol at 20 mg/(kg · d) does not adversely affect the variables tested in rats. J. Nutr. 132: 257–260, 2002.

KEY WORDS: • trans-resveratrol • phytochemicals • polyphenols • rats

trans-3,4′,5-Trihydroxystilbene (*trans*-resveratrol)[3] is a phytochemical synthesized in various plant species such as grapes, peanuts and wine (1,2). It is one of the active ingredients of traditional Japanese and Chinese Ko-jo-kon medicine, which uses the dried powdered roots of *Polygonum cuspidatum* Sieb. et Zucc. for the treatment of human fungal, inflammatory, hypertensive, allergic and lipid diseases (3–5). In 1992, Siemann and Creasy detected its presence in red wine and suggested that it was one of the components that conferred the protection against arteriosclerosis and coronary heart diseases associated with the moderate consumption of red wine (2,6).

Furthermore, *trans*-resveratrol has been suggested in many studies to be an antioxidant (7–9), a modulator of lipid and lipoprotein metabolism (2,10), an inhibitor of platelet aggregation (11,12) and a vasorelaxing agent (13,14). It has also been reported to be a potential chemopreventive agent because it is involved in the inhibition of tumor initiation, promotion and progression (15). Despite its health-enhancing properties, *trans*-resveratrol intake as a dietary supplement requires a safety assessment (16,17) because its potential use as a chemopreventive agent is of great interest.

The aim of the present study was to assess the effects of the repeated oral administration of *trans*-resveratrol to Sprague-Dawley rats. Therefore, we evaluated the effect on growth and development in an animal model of the daily consumption for 28 d of 20 mg/kg of *trans*-resveratrol, 1000 times the amount that may be consumed by a person drinking one glass of red wine a day.

MATERIALS AND METHODS

Chemicals and dose preparation. *trans*-Resveratrol, supplied by PharmaScience (Montreal, Canada), was chemically pure. Before use, its purity was assessed by HPLC coupled to a diode-array UV detector, and a chromatogram that showed a single peak at 306 nm, its maximum absorbance, was obtained. The use of a diode-array UV detector allowed the confirmation of the identity of the peak by its spectrum (data not shown). Due to its low solubility in water, *trans*-resveratrol was suspended in 10 g/L carboxymethylcellulose at a constant volume of 10 mL/kg body before each administration. The dose was adjusted according to the animal weight to ensure a constant dose. Dose preparation and administration were performed in dim light to avoid the photochemical isomerization of *trans*-resveratrol to the *cis* form. All other reagents were commercially available, analytical grade chemicals.

Animals. Male Sprague-Dawley rats, weighing 165–175 g, came from breeding colonies (Harlan Ibèrica, Barcelona, Spain) and were quarantined for 1 wk. They were housed in cages (n = 3/cage) kept at 22 ± 3°C, with 40–70% relative humidity and controlled lighting that provided a 12-h light:dark cycle. Water and a solid diet (Rodent Toxicology Diet, B&K Universal, Molins de Rei, Spain) were consumed ad libitum.[4] No traces of *trans*-resveratrol were detected in the commercial diet, nor in the plasma from control rats, as revealed by the analyses performed using the method of Juan et al. (18). Handling and killing of the rats were in full accordance with the European Community guidelines for the care and management of laboratory animals. All animal manipulations were carried out in the morning to minimize the effects of circadian rhythm.

Rats were randomly divided in two groups, a resveratrol group (n = 8) and a control group (n = 6). Rats in the first group were orally administered 20 mg/kg of *trans*-resveratrol suspended in 10 g/L car-

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[3] Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; *trans*-resveratrol, *trans*-3,5,4′-trihydroxystilbene.

[4] The commercial diet contained (g/kg): 160.4 crude protein; 26.0 crude fiber; 467.4 carbohydrate; 29.5 lipid; 42.2 ash; 8.2 calcium; 6.9 total phosphorous; 1.8 magnesium; 2.5 sodium; 4.0 chloride; 6.5 potassium. Trace elements were (mg/kg): 0.41 selenium; 0.58 cobalt; 1.72 iodine; 100.00 zinc; 80.00 manganese; 24.00 copper; 113.00 iron. The vitamins levels were 1500 IU/kg vitamin A; 1875 IU/kg cholecalciferol; 128 IU/kg vitamin E; 19 mg/kg vitamin K; 18 mg/kg thiamine; 14 mg/kg riboflavin; 18 mg/kg vitamin B-6; 25 μg/kg vitamin B-12; 3 mg/kg folic acid; 92 mg/kg nicotinic acid; 30 mg/kg pantothenic acid; 300 μg/kg biotin; and 1670 mg/kg choline chloride.

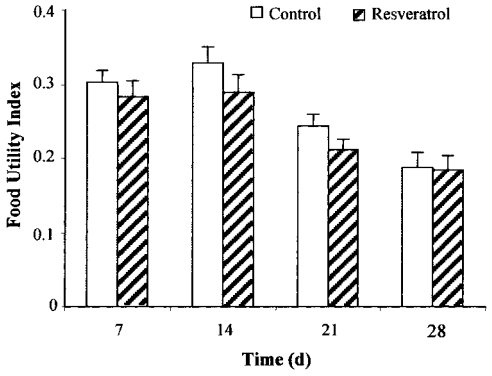

FIGURE 1 Food utility index (feed efficiency, g gain/g feed) of male Sprague-Dawley rats after oral administration of 20 mg/kg of *trans*-3,5,4′-trihydroxystilbene (*trans*-resveratrol) ($n = 8$) compared with control rats ($n = 6$). Results are expressed as means + SEM. Differences over time ($P < 0.05$): 1 wk = 2 wk > 3 wk = 4 wk. Groups did not differ, $P > 0.05$.

boxymethylcellulose every d for 28 d. Those in the second group were administered 10 mL/kg of 10 g/L carboxymethylcellulose during the same period.

Skin, eyes, mucous membranes, respiratory system, autonomic and central nervous system conditions, somatomotor pattern and behavior were examined daily. Body weight, as well as food and water consumption, was recorded daily. Growth rate was calculated as the difference between the final weight and the initial weight divided by 28 d. Feed efficiency was calculated as the weekly body weight gain divided by the food consumption.

Hematology and clinical chemistry. At the end of the study, rats were deprived of food overnight, anesthetized with ether and blood was collected by cardiac puncture (1 mL into EDTA for hematology, 1 mL into sodium citrate for coagulation studies and 2 mL into sodium heparin for blood clinical chemistry). Blood was centrifuged at 1500 × *g* (model TJ-6 centrifuge, rotor TH-4 with buckets, Beckman Coulter, Fullerton, CA) for 15 min, and the plasma was immediately removed from the cells. All samples were processed within 4–6 h.

The following hematologic variables were determined with a Cell-Dyn blood analyzer (Abbott Diagnostics Division, Santa Clara, CA): erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total and differential leukocyte count and platelet count. Prothrombin time, partial activated thromboplastin time and fibrinogen were assessed with the Coagulation analyzer (Sysmex CA-6000™; Sysmex UK, Milton Keynes, UK). The biochemical constituents, glucose, cholesterol, triglycerides, HDL, LDL, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, total proteins, creatinine, urea, sodium, potassium, chloride, calcium and inorganic phosphorous, were determined with a Roche/Hitachi 747 clinical analyzer (Mannhein, Germany) with reagents from Roche Diagnostics.

Pathology

Gross necropsy. Detailed gross necropsy, including careful examination of the body external surface, orifices and cranial, thoracic and abdominal cavities and their contents was performed in both groups. The brain, lungs, spleen, heart, liver, kidney, adrenal and testicle were excised, trimmed of any adherent tissue and their wet weights immediately recorded. Results were expressed as organ weight relative to 100 g body weight.

Histopathology. The excised organs were fixed in 1.23 mol/L buffered formalin (pH 7.4) and the samples were sent to the Laboratorio de Diagnóstico Cito-Histológico (Barcelona, Spain) for histopathologic study. The tissues were then treated with graded alcohol, embedded in paraffin, sectioned in 5-μm slices and stained with hematoxylin and eosin for examination under the light microscope.

Statistics. Results were expressed as the mean ± SEM. Statistical differences between means were compared by Student's *t* test. Differences over time were established by ANOVA (STATISTICA 6.0 for Windows software, StatSoft, Tulsa, OK). The $P < 0.05$ level was taken as significant.

RESULTS

Body weight, food and water consumption. Daily oral administration of *trans*-resveratrol at 20 mg/kg did not cause adverse effects or mortality during the experimental period. Body weight of the resveratrol group increased from 170 ± 2 g ($n = 8$) on d 1 to 307 ± 7 g ($n = 8$) on d 28. In the control group, the body weight increased from 172 ± 2 g ($n = 6$) on d 1 to 327 ± 10 g ($n = 6$) on d 28. Growth rates were 4.9 ± 0.2 g/d in the resveratrol group and 5.6 ± 0.4 g/d in the control. The groups did not differ in food or water consumption.

Feed efficiency (**Fig. 1**) was highest during the first 2 wk; it decreased significantly in wk 3 and remained constant until the end of the study, with no differences between the resveratrol and control groups.

Hematology and clinical chemistry. The results of the hematologic tests carried out at the end of the study did not differ between groups (**Table 1**). *trans*-Resveratrol treatment did not affect serum lipids, enzymes, electrolytes or other metabolites except AST, which was 30% higher in the treated than in the control group (**Table 2**).

Pathology

Gross necropsy. At the end of the study, rats were subjected to a detailed postmortem examination of internal organs, which did not show macroscopic differences in size, color or texture.

The repeated oral administration of *trans*-resveratrol did not affect the final relative weights (g/100 g body) of lungs, spleen, heart, liver, kidney or adrenal gland. However, relative brain weight was greater in the treated (0.56 ± 0.02 g/100 g) than in control rats (0.45 ± 0.02 g/100 g). The weight of a

TABLE 1

Hematological variables of control and trans-resveratrol–treated rats[1]

Hematological variables	Control	Resveratrol
Red blood cells		
Erythrocytes, 10^{12}/L	6.90 ± 0.10	6.86 ± 0.13
Hemoglobin, g/L	130.3 ± 2.0	131.3 ± 2.2
Hematocrit	0.39 ± 0.005	0.39 ± 0.009
Mean corpuscular volume, fL	57.54 ± 0.72	58.90 ± 0.75
Mean corpuscular hemoglobin, pg	19.34 ± 0.17	19.48 ± 0.26
Mean corpuscular hemoglobin concentration, g/L	336.4 ± 2.7	330.8 ± 2.1
White blood cells		
Leukocytes, 10^9/L	6.77 ± 0.21	6.82 ± 0.78
Neutrophils, %	17.93 ± 2.96	18.83 ± 0.63
Lymphocytes, %	78.08 ± 2.48	76.77 ± 1.04
Monocytes, %	0.36 ± 0.06	0.70 ± 0.18
Eosinophils, %	1.77 ± 0.25	1.81 ± 0.22
Basophils, %	1.86 ± 0.91	1.82 ± 0.30
Platelets		
Platelets, 10^9/L	657 ± 21	671 ± 15
Mean platelet volume, fL	5.08 ± 0.17	5.56 ± 0.17

[1] Values are means ± SEM, $n = 6$ (control) or 8 (treated). Groups did not differ, $P > 0.05$.

TABLE 2

Clinical biochemistry variables of control and trans-resveratrol–treated rats[1]

Clinical biochemistry	Control	Resveratrol
Glucose, *mmol/L*	4.67 ± 0.23	4.25 ± 0.34
Cholesterol, *mmol/L*	2.07 ± 0.11	2.32 ± 0.14
Triglycerides, *mmol/L*	0.38 ± 0.05	0.45 ± 0.06
HDL, *mmol/L*	1.57 ± 0.06	1.70 ± 0.08
LDL, *mmol/L*	0.33 ± 0.08	0.41 ± 0.06
AST,[2] *IU/L*	77.3 ± 2.31	103.20 ± 3.94*
ALT, *IU/L*	31.25 ± 1.60	32.66 ± 6.80
Bilirubin, *μmol/L*	1.36 ± 0.14	1.89 ± 0.16
Total protein, *g/L*	54.70 ± 2.17	57.38 ± 1.33
Creatinine, *μmol/L*	43.70 ± 3.20	50.5 ± 1.40
Urea, *mmol/L*	4.52 ± 0.43	5.59 ± 0.28
Sodium, *mmol/L*	142.80 ± 1.29	141.92 ± 0.69
Potassium, *mmol/L*	3.45 ± 0.28	3.93 ± 0.27
Chloride, *mmol/L*	110.60 ± 1.73	108.78 ± 0.40
Calcium, *mmol/L*	2.33 ± 0.06	2.48 ± 0.06
Inorganic phosphorus, *mmol/L*	2.28 ± 0.28	2.68 ± 0.11

[1] Values are means ± SEM, $n = 6$ (control) or 8 (treated). * Different from control, $P < 0.05$.
[2] AST, aspartate aminotransferase; ALT, alanine aminotransferase.

testicle normalized to body weight, also was greater in treated rats (0.62 ± 0.02 g/100 g for the resveratrol group and 0.56 ± 0.02 g/100 g for the control group).

Histopathology. No pathological signs were observed in the vital organs examined.

DISCUSSION

Many beneficial effects on health have been attributed to *trans*-resveratrol (3–5,15), although to our knowledge, its safety has never been studied. Although daily intake is usually low, its health-enhancing properties could induce consumers to take larger quantities. We examined the toxicity of *trans*-resveratrol to determine whether there were any adverse effects (16,17); this is necessary for studies whose goal is to confirm in vivo the health-promoting effects described in vitro. If any adverse effects are found, additional complete toxicological studies would be required. For this reason, we assessed the effects on health of *trans*-resveratrol after repeated oral administration of a dose of 20 mg/kg to rats for 28 d.

This dosage was considered carefully, taking into account that red wine is the main dietary source of *trans*-resveratrol (6). Assuming that the average concentration of *trans*-resveratrol in wine is 5 mg/L (19–21) and moderate daily consumption of wine is 250 mL, the mean daily intake of *trans*-resveratrol under these conditions is ~0.02 mg/kg. Thus, we selected a dose that was 1000 times higher than this estimate to provide a sufficiently large safety margin. The duration of the exposure was 28 d, according to the OECD guidelines (22). The plasma levels before the oral administration were measured to determine not only its intestinal absorption, but also its presence in plasma throughout treatment. Blood was extracted from the saphenous vein and *trans*-resveratrol was measured using the method of Juan et al. (18). During the first 2 h after oral administration, we found free *trans*-resveratrol, as well as glucuronide and sulfate conjugates. These results are in agreement with Andlauer et al. (23) who reported the appearance of the same compounds on the vascular side of the small intestine. However, in our study, 24 h after oral administration, the measurements indicated that *trans*-resveratrol was the main compound with concentrations of 96.5 ± 12.3 nmol/L ($n = 20$) determined in 4 rats.

An acute toxicity study was conducted to obtain firsthand information about the toxicity of *trans*-resveratrol. In this study, the dose of 2 g/kg recommended by the OECD guidelines (22) was used. The absence of symptoms, the lack of negative effect on growth and the normal appearance of vital organs in the gross necropsy suggested that *trans*-resveratrol is practically nontoxic even under these conditions.

The 28-d oral administration of a dose of 20 mg/kg did not affect the final body weight or the mean growth rate, in agreement with Turner et al. (24) and Carbó et al. (25). The oral administration of 1, 4, 10, 40, 100 and 1000 μg/d and the intraperitoneal injection of 1 mg/kg of *trans*-resveratrol to female growing rats for 6 (24) and 7 (25) d, respectively, did not alter the body weight or mean growth rate compared with the control group. Wilson et al. (26) reported that body weight and food consumption did not differ between rabbits fed a hypercholesterolemic diet supplemented with *trans*-resveratrol and controls. These results indicate that in terms of growth, *trans*-resveratrol is well tolerated by animals at the doses and routes of administration tested.

The lipoprotein profile in vivo was not affected by the oral administration of 20 mg/kg of *trans*-resveratrol, consistent with the findings of Turrens et al. (27) and Wilson et al. (26). The first group studied the effect of *trans*-resveratrol on the lipoprotein profile of normal rats that received a daily intraperitoneal injection of *trans*-resveratrol at two doses, 20 and 40 mg/kg, for 21 d. This treatment did not alter the proportion of cholesterol bound to HDL or LDL. When *trans*-resveratrol was administered to hypercholesterolemic rabbits, Wilson et al. (26) also did not find any difference in the lipoprotein profile between the control and resveratrol groups.

ALT levels, which indicate hepatic integrity, did not differ between control and treated rats. AST was significantly higher in rats treated with *trans*-resveratrol than in controls. However, both means were within reference values provided by Harlan Ibèrica and Alemán et al. (28). Ringler and Dabich (29) suggested that ALT is the most reliable variable for the evaluation of hepatic toxicity, whereas AST is not as useful because of its wide distribution. Renal function and the plasma levels of electrolytes were not different between treated and control groups, and were within reference values. In conclusion, the minor changes found in the concentration of this enzyme suggest that no important alteration of hepatic function took place in *trans*-resveratrol-treated rats.

The examination of the vital organs carried out during the autopsy revealed mild effects only on the testes and the brain; further studies are required to understand the mechanisms involved. However, the study was performed using a dose of *trans*-resveratrol that is ~1000-fold in excess of the average daily consumption of this compound.

The lack of harmful effects found in the hematology, clinical chemistry and histopatology indicates that *trans*-resveratrol has a large safety margin. Some of the health benefits cited for red wine have been attributed to the presence of *trans*-resveratrol, such as a decrease in LDL, an increase in HDL and reduced coagulation. However, none of these variables were significantly affected by high doses of *trans*-resveratrol in this study. Further studies are required to verify the health-promoting properties previously described to determine whether they took place in vivo. The absence of adverse effects at high oral doses constitutes the first step in elucidating whether *trans*-resveratrol might be used in the future as a phytochemical.

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