Efficacy of β-Ionone in the Chemoprevention of Rat Mammary Carcinogenesis

Suzanne G. Yu, Peter J. Anderson, and Charles E. Elson*

Department of Nutritional Sciences, University of Wisconsin—Madison, 1415 Linden Drive, Madison, Wisconsin 53706

Secondary products of plant mevalonate metabolism suppress the synthesis of mevalonate, the rate-limiting substrate for the synthesis of isoprenoid intermediates essential for cell proliferation. *d*-Limonene is an effective anticarcinogen when tested with chemical carcinogens. This monoterpene also causes the regression of chemically established tumors. Geraniol suppresses the growth of transplanted tumors. The potency of β-ionone in suppressing 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) activity exceeds that of either monoterpene. In parallel trials, the efficacies of equimolar intakes (36 mmol/kg of diet) of *d*-limonene and geraniol were compared with that of β-ionone in the chemoprevention of 7,12-dimethylbenz[*a*]anthracene-initiated mammary cancer. The monoterpenes decreased tumor multiplicity by 45% ($P < 0.001$). The impact of β-ionone on tumor multiplicity was ~2x that of the monoterpenes ($P < 0.001$). Tumor incidence and latency were affected to varying degrees. The locus of the action of the isoprenoids is postulated to be in the suppression of the sterol-resistant HMGR activity, which is characteristic of neoplastic cells. Dietary guidelines advocate the consumption of fruits, vegetables, and cereal grains, the major sources of diverse isoprenoids.

Keywords: *Chemoprevention; β-ionone; mevalonate; d-limonene; geraniol*

INTRODUCTION

β-Ionone is a potent inhibitor of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) activity (Yu et al., 1994), the product of which is the rate-limiting substrate for the synthesis of sterols and the isoprenoid intermediates essential to the progression of the cell cycle (Goldstein and Brown, 1990). β-Ionone and its oxygenated analogs are widely distributed in plant products (Eslava et al., 1974; Feofilova and Arbuzov, 1975; Gueldner et al., 1985; Norman et al., 1985; Salt et al., 1986; Wei et al., 1986; Wilson et al., 1981). Physiological functions attributed to β-ionone include the inhibition of the growth of fungi (Gueldner et al., 1985; Salt et al., 1986; Wei et al., 1986; Wilson et al., 1981) and the regulation of the synthesis of mevalonate-derived constituents (Eslava et al., 1974; Feofilova and Arbuzov, 1975; Norman et al., 1985).

The dual actions, the suppression of hepatic HMGR activity and tumorigenesis, have been reported for diverse mevalonate-derived secondary plant products including monoterpenes, e.g. *d*-limonene, geraniol (Elson, 1995; Elson and Qureshi, 1994; Elson and Yu, 1994), and β-carotene (Moreno et al., 1994). Other than modestly reducing blood cholesterol levels, these isoprenoids have little impact on tumor-free animals. The cholesterol-suppressive impact of β-ionone (Yu et al., 1994) is greater than that of either *d*-limonene (Qureshi et al., 1988) or geraniol (Fitch et al., 1989).

We now evaluate the chemopreventive potency of dietary β-ionone in the 7,12-dimethylbenz[*a*]anthracene (DMBA) rat mammary carcinogenesis model. The antitumorigenic activity of dietary geraniol has been recorded in tumor transplant models (Shoff et al., 1991; Yu et al., 1992). We further compare the chemopreventive potency of this monoterpene with that of *d*-limonene, the first monoterpene shown to be effective in studies employing chemical carcinogens (Elegbede et al., 1984; Haag et al., 1992; Maltzman et al., 1989; Mehta and Moon, 1991; Russin et al., 1989; Wattenberg, 1985; Wattenberg and Coccia, 1991; Wattenberg et al., 1989).

* Author to whom correspondence should be addressed [telephone (608) 262-1332; fax (608) 262-5860; elson@nutrisci.wisc.edu].

MATERIALS AND METHODS

Chemicals. β-Ionone [95% purity, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one, FW 192], *d*-limonene [98% purity, (*R*)-4-isopropenyl-1-methyl-1-cyclohexene, FW 136], geraniol (98% purity, *trans*-3,7-dimethyl-2,6-octadien-1-ol, FW 154), and DMBA were purchased from Sigma Chemical Co. (St. Louis, MO).

Animals, Diets, and Tumor Induction. Female Sprague-Dawley rats, 30–35 days of age (Harlan Sprague-Dawley, Madison, WI), were fed powdered Purina Rodent Laboratory Chow 5001, a constant-formula, cereal-based diet for 5 days. After acclimitization, the individually caged rats were randomly assigned to four diet groups ($n = 32$). Corn oil (5% by weight) was added to the same lot of Laboratory Rodent Chow. Each experimental diet contained additionally 36 mmol/kg of β-ionone, *d*-limonene, or geraniol. The isoprenoids were dissolved in corn oil prior to being mixed with the chow. The diets, mixed biweekly, were held under refrigeration. The rats were fed the experimental diets for 2 weeks. Tumors were then induced as described by Huggins (1979) with the exception that the level of DMBA was reduced by 50% to increase tumor latency. Specifically, the rats at 54 days of age were given a single gastric intubation of a suspension of DMBA in sesame oil (65 mg of DMBA/kg of body weight). The DMBA was administered by a Research Animal Resource Center (RARC) technician who was blind to the experimental design. The dietary regimens were continued for 22 weeks with the diet being replaced at 2-day intervals. The rats were weighed at 6–10-day intervals, and starting on day 44 post-DMBA, the rats were palpated for the presence of soft tissue masses (tumors) at 3–5-day intervals. Rats showing a sign of distress, for example a substantial weight loss, a hemorrhage, or an ulcerated tumor, were euthanized under CO_2. Censored

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Table 1. Influence of Dietary Isoprenoids on Tumor Incidence, Latency, and Multiplicity

group	final wt (g)	latency[a] (days)	tumor incidence	tumor multiplicity (tumors/rat)
control	257 ± 16[a,b]	74	91	2.9 ± 1.6[a]
d-limonene	253 ± 16[a]	78	75	1.5 ± 1.5[b]
geraniol	261 ± 16[a]	84	81	1.6 ± 1.3[b]
β-ionone	256 ± 19[a]	>151	41	0.7 ± 1.2[c]

[a] Days post-DMBA required for 50% of rats to develop a stable tumor. [b] Values not sharing a common superscript are different ($P < 0.01$).

control rats (38%) were on the study for 96 ± 24 days, whereas censored experimental rats (39%) were on the study for 110 ± 23 days ($P < 0.01$). The experiment was terminated at 22 weeks post-DMBA. To confirm the efficacy of dietary β-ionone in the prevention of DMBA-initiated mammary carcinogenesis, tumors in surviving β-ionone and control rats were excised and sent to the RARC Diagnostic Laboratory for histological evaluation.

Data Analysis. The software (StatView, Abacus Concepts, Berkeley, CA) used for the analysis of treatment-mediated effects included nonparametric Friedman and Wilcoxon tests for the analyses of tumor latency and ANOVA and Fisher's protected least significant difference (PLSD) for tumor multiplicity and body weight. Means and standard deviations are presented in the table.

RESULTS

Weight Gain. Group differences in body weight gain were not significant at any time point. At the termination of the 165-day feeding period, the body weights of the control group of rats matched those of the experimental groups (Table 1).

Tumor Incidence, Latency, and Multiplicity. During the 151 days following the administration of DMBA, the presence of a tumor was confirmed in 91% and 41%, respectively, of the rats in the control and β-ionone groups. The monoterpenes had little impact on the incidence of tumors in the *d*-limonene (75%) and geraniol (81%) groups. According to one measure of tumor latency, the time required for 50% of the rats in a group to develop a stable tumor, a tumor detected at all subsequent examinations, latency in the monoterpene groups differed little from that in the control group. β-Ionone, on the other hand, substantially increased tumor latency (Table 1). A second approach to evaluating the impact of the treatments on tumor latency is shown on Figure 1. The time course for stable tumor appearance for each treatment group was significantly greater than for the control ($P < 0.001$, Wilcoxon). Whereas the time course for tumor appearance in the *d*-limonene group was similar to that of the geraniol group ($P = 0.14$, Wilcoxon), that of the β-ionone group was significantly increased in comparisons with both ($P < 0.001$, Wilcoxon).

The dietary isoprenoids decreased ($P < 0.001$) tumor multiplicity (Table 1). An analysis (PLSD) of the effects of the dietary isoprenoids showed that tumor multiplicity in the β-ionone group (0.8 tumor/rat) was less ($P < 0.01$) than that in the monoterpene groups (1.4−1.6 tumors/rat). Tumor multiplicity in the control group (2.8 tumors/rat) was nearly double that of the monoterpene groups. As previously stated, censored experimental rats had 14 additional days to develop tumors. Nevertheless, tumor multiplicity for the euthanized control rats (3.5 ± 1.9 tumors/rat) was 60% greater than that for the experimental (2.2 ± 1.5 tumors/rat). These data confirm that censoring rats from treatment groups did not skew the data toward a lower tumor multiplicity.

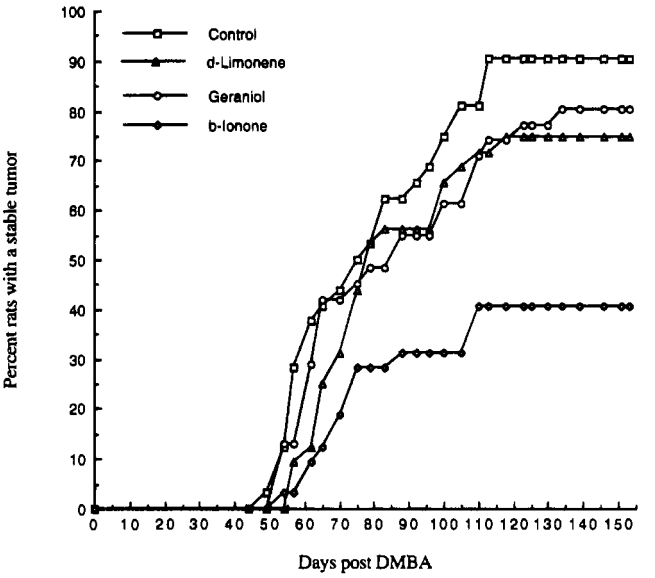

Figure 1. Time to appearance of first stable tumor, a tumor present at all subsequent palpations, in DMBA-treated rats. Experimental diets were fed for 14 days prior to and for 151 days following DMBA administration.

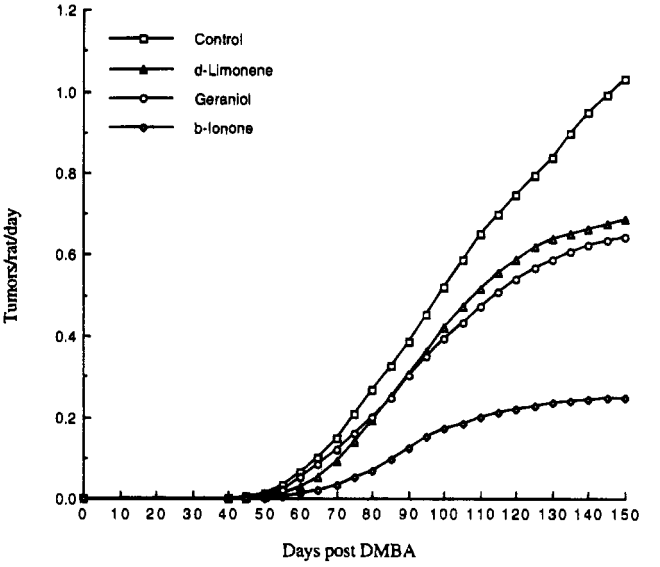

Figure 2. Relative impacts of *d*-limonene, geraniol, and β-ionone on time to appearance of each tumor and tumor multiplicity. Values on the abscissa are the quotients of the cumulative number of palpable mammary tumors divided by the cumulative number of rat days on study.

Tumor multiplicity in surviving, tumor-bearing controls (2.9 ± 1.1 tumors/rat) also was greater ($P < 0.001$) than of the experimental groups (1.5 ± 0.9 tumors/rat).

The combined impacts of the isoprenoids on tumor appearance and multiplicity are plotted in Figure 2. The abscissa values are the quotients of the cumulative number of palpable mammary tumors divided by the cumulative number of rat days on study. This plot carries forward data from euthanized rats and incorporates regressing tumors. Treatment effects were significant ($P < 0.001$, Friedman); Wilcoxon analysis reveals significant differences (all $P < 0.001$) between the β-ionone and control groups, between the β-ionone group and each of the monoterpene groups, and between each of the monoterpene groups and the control group.

Histopathology. At the termination of the study 85% (17/20) and 24% (6/25), respectively, of the surviving rats in the control and β-ionone groups had palpable

tumors. At least one histologically confirmed tumor was present in each of the 17 control rats. The tumors consisted of 63% adenocarcinomas, 16% adenomas, 10% fibroadenomas, and 10% benign masses. The nine tumors excised from the six β-ionone-treated rats consisted of four (44%) adenocarcinomas, two (22%) adenomas, and three (33%) benign masses. The benign masses included a keratin inclusion cyst, an atypical hyperplasia, and a lobular hyperplasia. Three of the rats in the β-ionone group proved to be tumor-free.

DISCUSSION

Dietary β-ionone proved to be a highly effective, side-effect-free anticarcinogenic agent. Its chemopreventive impact, evaluated in terms of time to tumor appearance, tumor multiplicity, and tumor incidence, was greater than that of a diet containing equimolar quantities of geraniol or *d*-limonene (36 mmol/kg of diet). Geraniol, previously shown to be tumor-suppressive in transplant models (Shoff et al., 1991; Yu et al., 1992), was as effective as *d*-limonene in this DMBA model. An extended evaluation revealed that the incidence of histologically confirmed tumors in rats receiving β-ionone (36 mmol/kg of diet) was one-third that of the control rats at 22 weeks. Under identical DMBA protocols, the incidence of mammary tumors in rats receiving *d*-limonene (72 mmol/kg of diet) was two-thirds (Elegbede et al., 1984) to three-fourths (Russin et al., 1989) that of the controls at 18 weeks. Tumor incidence in rats receiving menthol, an oxygenated cyclic monoterpene (64 mmol/kg of diet), was 85% that of controls (Russin et al., 1989). The relative potencies of the three isoprenoids tested here and menthol parallel their HMGR-suppressive actions (Elson, 1995). We feel that one of the chemopreventive actions of the isoprenoids lies in the suppression of the sterol-resistant HMGR activity (Case et al., 1995; Elson and Qureshi, 1995), which is characteristic of neoplastic and other rapidly dividing cells (Azrolan and Coleman, 1989; Brown et al., 1987; Bruscalupi et al., 1985; Engstrom and Schofield, 1987; Giron et al., 1993; Gregg et al., 1986; Janssen et al., 1987; Saleh et al., 1985; Siperstein and Fagan, 1964; Yachnin et al., 1984).

These studies do not rule out the possibility that the antitumorigenic action of β-ionone is in part coupled to its binding to a cellular retinol binding protein or receptor. Retinol, retinyl acetate, retinoic acid, β-carotene, and β-ionone share a common cyclohexenyl ring. Each binds to β-lactoglobulin, one of a superfamily of hydrophobic molecule transporters (Godovac-Zimmermann, 1988). A comparison of the binding affinities of retinol, retinyl acetate, and retinoic acid, 2×10^{-8} M (Fugate and Song, 1980; Dufour and Haertle, 1991), with that of β-ionone, 6×10^{-7} M (Dufour and Haertle, 1990), to β-lactoglobulin suggests that β-ionone is not likely to influence retinoid binding to a protein. A preliminary study (Repa and Clagett-Dame, personal communication) showed that β-ionone does not bind to the human α-, β-, and γ-retinoic acid receptors (Repa et al., 1993).

Although many ligands that bind to the retinoid X receptors have high affinities for the retinoic acid receptors (Allenby et al., 1993), it is not known whether β-ionone will bind to the highly selective retinoid X receptors.

Lengthy feeding trials demonstrate that the isoprenoids are not toxic to normal tissues (Hagan et al., 1967). These FEMA and GRAS agents have an advantage compared to other chemopreventive and chemotherapeutic agents in being cytostatic only to tumor cells. The widespread presence of these and related isoprenoids in plant-derived foods may explain the diet/cancer and diet/cardiovascular disease interrelationships (Elson, 1995; Elson and Yu, 1994).

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