J Plant Growth Regul (1990) 9: 19–25

Journal of
Plant
Growth
Regulation

Herbicidal Activity of the Antibiotics Geldanamycin and Nigericin

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Received January 31, 1989; accepted June 13, 1989

Abstract. Geldanamycin and nigericin, phytotoxic metabolites from a strain of *Streptomyces hygroscopicus*, were tested for herbicidal activity and selectivity on a range of crop and weed species. In petri dish bioassays, geldanamycin reduced radicle growth of all species tested, whereas nigericin inhibited 7 of 10. The two compounds in mixture appeared to be additive rather than synergistic in effect. In assays with seeds and seedlings in field soil, geldanamycin showed significant preemergence activity on proso millet, barnyardgrass, garden cress, and giant foxtail. It had no postemergence herbicidal effect on any of the species tested. Nigericin had preemergence activity on garden cress and large crabgrass and postemergence activity on garden cress and velvetleaf. The postemergence effect of nigericin on velvetleaf was especially striking, with leaves showing symptoms of injury within 24–48 h of treatment. Doses as low as 0.3 kg/ha caused damage. The primary herbicidal effect of both compounds was slowing of seed germination or seedling growth, although some plants were killed, especially at higher rates of application. Herbicidal effects were most pronounced for 1 to 2 weeks after treatment and diminished thereafter.

Much current interest exists in discovering natural products that will increase or decrease plant growth. Such compounds have potential for development as herbicides and plant growth regulators. They may also serve as "starting points" for laboratory syntheses to optimize biological activity. Because these compounds are produced by organisms, or are similar thereto, most will be readily degraded in the environment. Thus, the problems of excessive persistence, accumulation, and biomagnification sometimes associated with synthetic pesticides would be minimized.

Microorganisms, especially strains of *Streptomyces*, are the major source of medicinal antibiotics. These microorganisms would, therefore, appear to be a promising group to investigate for plant growth-regulating compounds. Herbicidal activity has been reported for a number of metabolites produced by *Streptomyces* strains: anisomycin and toyocamycin (Yamada et al. 1972); bialaphos, and glufosinate derived therefrom (Fischer and Bellus 1983; Sekizawa and Takematsu 1982; Seto et al. 1983); cycloheximide (Ellis and McDonald 1970; Riov and Goren 1979; Sekizawa and Takematsu 1982); herbicidins A and B (Arai et al. 1976; Haneishi et al. 1976); and herbimycins A and B (Iwai et al. 1980; Omura et al. 1979).

We have been screening soil microorganisms for the production of herbicidal, insecticidal, and plant growth-regulating metabolites (Heisey et al. 1985; Heisey et al. 1988a,b; Mishra et al. 1987a,b). One of our isolates, a strain of *Streptomyces hygroscopicus*, produced culture broth that strongly inhibited germination and growth of garden cress. The herbicidal compounds were identified as geldanamycin and nigericin (Heisey and Putnam 1986). Both compounds are known antibiotics, however, their herbicidal activity and selectivity on a range of plant species have not previously been evaluated. We report here the results of such an investigation.

Materials and Methods

Isolation of Antibiotics

Geldanamycin and nigericin were obtained from a strain of *Streptomyces hygroscopicus* (Heisey and Putnam 1986) cultured in A-9 liquid medium (Warren et al. 1955). Geldanamycin was

Michigan Agricultural Experiment Station journal article no. 13012.

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purified with chromatography on silica gel (Heisey and Putnam 1986). Nigericin was also purified with chromatography on silica gel as well as with the methods of Liu et al. (1980).

Bioassays in Petri Dishes

Geldanamycin, nigericin, and a 1:1 mixture of both were tested in the laboratory on seeds of five monocots and five dicots. The compounds were dissolved in methanol and applied to 5.5-cm diameter disks of Whatman no. 1 filter paper. Control disks received an equivalent volume of methanol. The treated disks were air-dried, placed in 1.5 × 6-cm polystyrene petri dishes, and moistened with 1.5 ml distilled water. The following seeds were added: barnyardgrass (*Echinochloa crusgalli* Beauv.), corn (*Zea mays* L. cv. Pioneer 3780), cucumber (*Cucumis sativus* L. cv. Pikmaster), garden cress (*Lepidium sativum* L. cv. Burpee's Curlycress), large crabgrass (*Digitaria sanguinalis* (L.) Scop.), green foxtail (*Setaria viridis* (L.) Beauv.), redroot pigweed (*Amaranthus retroflexus* L.), soybean (*Glycine max* (L.) Merr. cv. Corsoy 79), tomato (*Lycopersicon esculentum* Mill. cv. Chico III), and wheat (*Triticum aestivum* L. cv. Frankenmuth). Dishes containing corn and soybean were given an additional 1.5 ml distilled water 2 days later because of the greater water uptake of these seeds. Bioassays were incubated in the dark at 28°C. Radicle growth was measured after 3 (crabgrass, foxtail, and tomato) or 4 days. The dose inhibiting radicle growth to 50% that of the control (ID_{50}) was determined from the resulting dose–response curves. Since all bioassays were initially moistened with 1.5 ml water, the concentration (in μg/ml or ppm) of nigericin, geldanamycin, and the 1:1 mixture in the dishes is equivalent to the dose per dish multiplied by 0.67.

Corn was not inhibited in the initial bioassay by doses of nigericin up to 25 μg/dish. A second bioassay with nigericin, similar to the first but with doses up to 200 μg, was performed on corn.

The surface/volume (S/V) ratio of seeds was determined for use in comparing the sensitivity of the various plant species to the herbicidal compounds. Surface area was calculated by multiplying the cross-sectional area of the seeds by a conversion factor (crabgrass 2.2; cucumber 2.3; tomato 2.4; wheat, foxtail, and cress 2.5; pigweed 2.9; barnyardgrass 3.5; soybean 4.0; corn 5.0) based on the typical geometric shape of the seeds. The cross-sectional area was measured with a leaf area meter for three lots of 50 (corn and soybean) or 100 seeds for each species. Corn and soybean seeds, which were too large for the area meter, were first photocopied on clear plastic sheets. The resulting silhouettes were measured on the meter. Seed volume was determined by water displacement for three lots of 100 seeds each.

Bioassays in Soil

Geldanamycin and nigericin were tested preemergence on seeds and postemergence on seedlings in field soil in a greenhouse at the Pesticide Research Center of Michigan State University. Barnyardgrass, garden cress, large crabgrass, giant foxtail (*Setaria glauca* (L.) Beauv.), proso millet (*Panicum miliaceum* L.), and velvetleaf (*Abutilon theophrasti* Medic.) seeds were planted 3–6-mm deep in rows in Spinks loamy sand soil in 20 × 14-cm styrofoam flats.

For preemergence application, geldanamycin and nigericin were dissolved in dichloromethane and applied to the soil surface of the seeded flats with a glass reagent sprayer at the rate of 2 ml solution per flat. The dichloromethane evaporated rapidly, leaving a thin deposit of the antibiotic on the soil surface. Control flats were sprayed with dichloromethane lacking geldanamycin and nigericin. Treatments and controls were replicated five times for geldanamycin and four times for nigericin. The flats were placed in a greenhouse and uniformly watered from above with a motor-driven boom sprayer. Shoots were harvested 12 (cress and barnyardgrass), 13 (velvetleaf), 15 (proso millet and giant foxtail), or 18–19 (large crabgrass) days after spraying, oven-dried, and weighed for biomass determination.

For postemergence treatments, geldanamycin was formulated as an aqueous suspension in distilled water (containing 0.25% X-77 surfactant). Nigericin was dissolved in a small volume of dichloromethane, and the resulting solution was added to distilled water (containing 0.25% X-77 surfactant) at the rate of 0.06 ml/ml water. The suspensions of both compounds were shaken vigorously and immediately sprayed on 8-day-old seedlings with a glass reagent sprayer at the rate of 2 ml/flat. Control flats were sprayed with a similar volume of distilled water for geldanamycin treatments and the dichloromethane/water mixture for nigericin. Treatments and controls were replicated five times for geldanamycin and four times for nigericin, placed in a greenhouse, and watered from below. Shoots were harvested 10 days after spraying, oven-dried, and weighed.

Results

Bioassays in Petri Dishes

Geldanamycin inhibited radicle elongation of all species (Fig. 1). Pigweed and tomato were most sensitive (ID_{50} 2 μg/dish), followed by cucumber and cress (ID_{50} 5–6 μg/dish). Crabgrass, corn, wheat, and soybean were least sensitive ($ID_{50} \geq 24$ μg/dish). Geldanamycin was more inhibitory than nigericin to 7 of 10 species tested, on the basis of ID_{50} values. Crabgrass, which was more sensitive to nigericin than geldanamycin, was an interesting exception.

Nigericin inhibited radicle growth of many, but not all, species (Fig. 1). Cress, crabgrass, pigweed, and tomato were most sensitive (ID_{50} 4–8 μg/dish), whereas soybean, cucumber, and corn were most resistant ($ID_{50} > 25$ μg/dish). Corn was not inhibited by nigericin amounts up to 200 μg/dish. Radicle growth of corn and foxtail appeared to be stimulated by certain nigericin doses, however, this effect was not statistically significant.

Geldanamycin and nigericin in a 1:1 mixture appeared to be additive rather than synergistic in effect (Fig. 1). Radicle elongation of the species treated with the mixture typically was intermediate that of treatments receiving comparable amounts of the two pure compounds.

The effects of geldanamycin and nigericin on radicle growth of seeds was significantly ($p \leq 0.05$) correlated to the logarithm of the surface/volume ratio of the seeds (Fig. 2). Species having small seeds and thin, two-sided seeds with highest S/V

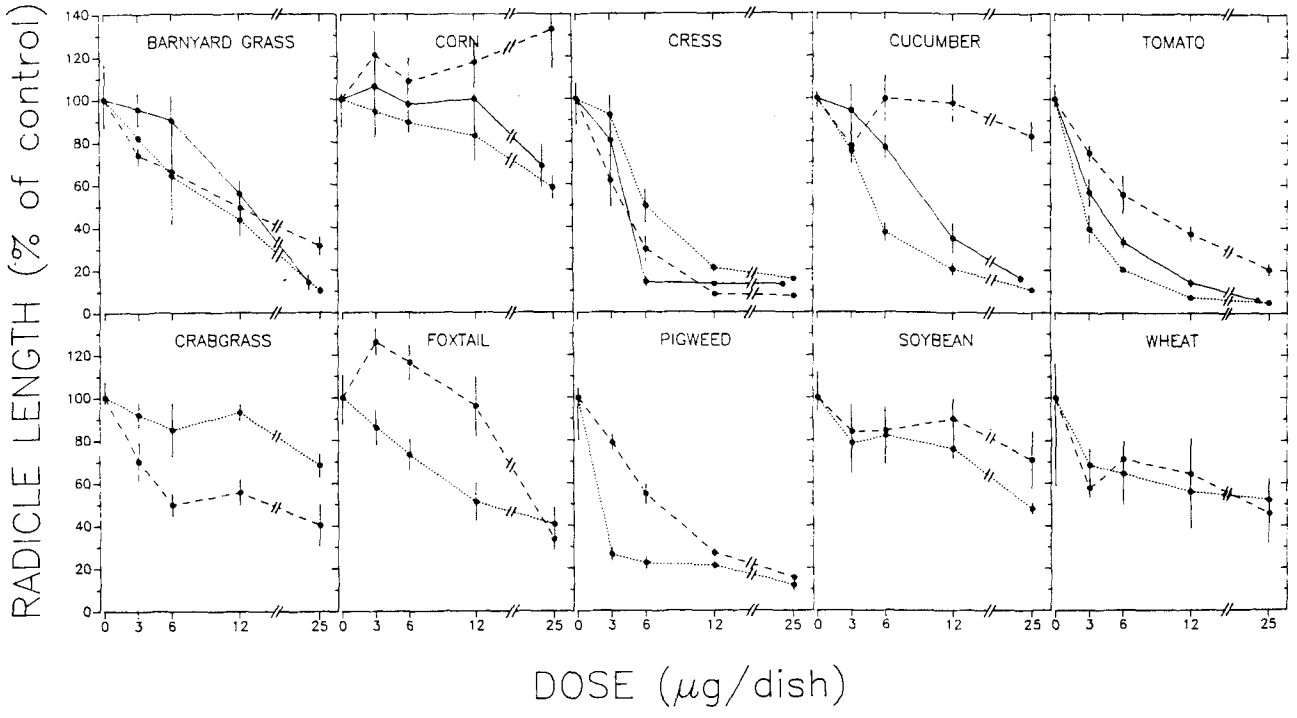


Fig. 1. Dose–response graphs of seeds exposed in petri dishes to geldanamycin (dotted lines), nigericin (dashed lines), and a 1:1 mixture of both compounds (solid lines). Each datum is the mean of four replicate dishes ± SE of 20 (crabgrass, foxtail), 15 (pigweed), or 10 (all other) seeds. For controls (0 μg/dish treatments), the upper SE bar applies to nigericin, and the lower bar to geldanamycin and the 1:1 mixture.

ratios generally were most sensitive to both compounds. Several exceptions occurred: crabgrass was less sensitive to geldanamycin; cucumber was more sensitive to geldanamycin and less sensitive to nigericin; and corn was less sensitive to nigericin, than S/V ratio alone would predict.These results indicate other factors are also important in determining the sensitivity of certain species to geldanamycin and nigericin. Neither compound was selective for only monocots or only dicots.

Bioassays in Soil

The effect of geldanamycin differed greatly between preemergence and postemergence treatments. Shoot biomass was significantly inhibited by preemergence applications of 0.3 kg/ha or more for proso millet, 0.6 kg/ha or more for barnyardgrass and garden cress, and 4.5 kg/ha for giant foxtail (Table 1, Fig. 3). Proso millet was especially sensitive, with shoot biomass reduced to less than 40%

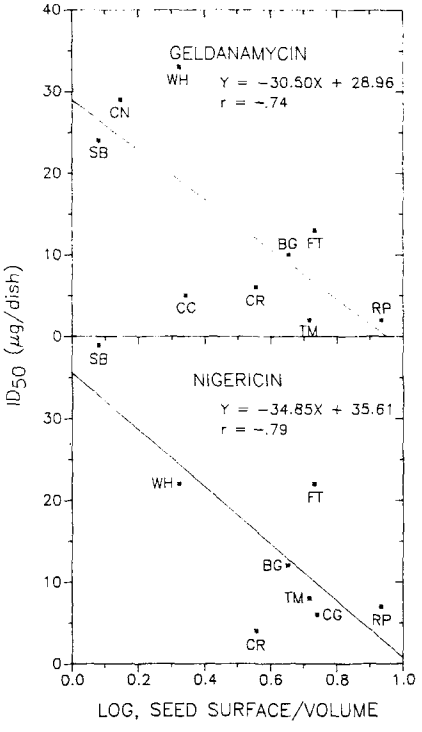


Fig. 2. Relationship of ID_{50} (of radicle elongation) for geldanamycin and nigericin with the logarithm of surface/volume ratio of seeds. Species for which an ID_{50} could not reliably be determined (large crabgrass for geldanamycin, corn and cucumber for nigericin) were excluded in correlation analyses. SB, soybean; CN, corn; WH, wheat; CC, cucumber; CR, garden cress; BG, barnyardgrass; TM, tomato; FT, green foxtail; CG, large crabgrass; RP, redroot pigweed.

Table 1. Effect of preemergence geldanamycin application on shoot growth of several plant species.

	Geldanamycin preemergence application (kg/ha)						
	0	0.3	0.6	1.1	2.2	4.5	LSD (0.05)
Species tested	Shoot biomass as percent of control						
Barnyardgrass	100 (55)[a]	92	79	61	51	49	18
Giant foxtail	100 (20)	88	99	97	97	75	23
Garden cress	100 (189)	95	82	61	47	32	16
Large crabgrass	100 (34)	124	118	127	138	140	38
Proso millet	100 (39)	32	28	27	34	37	29
Velvetleaf	100 (83)	97	116	86	92	89	30

[a] Values in parentheses are actual shoot weight (mg/flat) of control plants.

Table 2. Effect of postemergence geldanamycin application on shoot growth of several plant species.

	Geldanamycin postemergence application (kg/ha)						
	0	0.3	0.6	1.1	2.2	4.5	LSD (0.05)
Species tested	Shoot biomass as percent of control						
Barnyardgrass	100 (591)[a]	97	96	101	99	95	NS[b]
Giant foxtail	100 (195)	131	126	133	122	107	NS
Garden cress	100 (95)	106	138	126	125	122	NS
Large crabgrass	100 (222)	119	111	95	115	96	NS
Proso millet	100 (216)	79	89	85	98	97	NS
Velvetleaf	100 (263)	100	100	97	105	104	NS

[a] Values in parentheses are actual shoot weight (mg/flat) of control plants.
[b] Analysis of variance was not significant at $p = 0.05$.

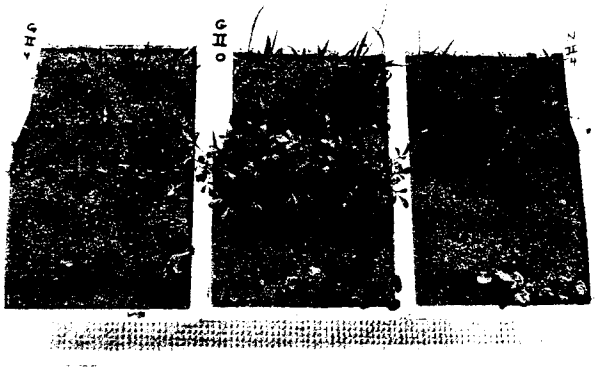


Fig. 3. Effect of geldanamycin (left) and nigericin (right) applied preemergence at 4.0 lb/acre (4.5 kg/ha). Control (center) received no geldanamycin or nigericin. Plant species readily visible are velvetleaf (front); garden cress (center); large crabgrass, proso millet, and barnyardgrass (rear). Note strong inhibition of barnyardgrass, proso millet, and garden cress by geldanamycin and garden cress by nigericin.

Table 3. Effect of preemergence nigericin application on shoot growth of several plant species.

	Nigericin preemergence application (kg/ha)						
	0	0.3	0.6	1.1	2.2	4.5	LSD (0.05)
Species tested	Shoot biomass as percent of control						
Barnyardgrass	100 (44)[a]	106	136	121	94	84	19
Giant foxtail	100 (32)	108	96	74	77	65	52
Garden cress	100 (146)	94	84	37	2	2	24
Large crabgrass	100 (36)	103	103	109	95	70	25
Proso millet	100 (30)	—	125	100	63	79	44
Velvetleaf	100 (64)	124	99	90	126	91	48

[a] Values in parentheses are actual shoot weight (mg/flat) of control plants.

of the control value by all application rates. Shoot biomass of barnyardgrass and garden cress was reduced to approximately half that of controls by applications of 2.2 kg/ha. Large crabgrass appeared to be stimulated by preemergence applications, especially at the highest doses. Postemergence applications of geldanamycin, in contrast, did not statistically effect any of the species (Table 2).

Nigericin had both preemergence and postemergence activity. Growth of garden cress was strongly reduced by preemergence applications of 1.1 kg/ha or more, and germination was almost totally inhibited by 2.2 kg/ha or more (Table 3, Fig. 3). Large crabgrass was moderately inhibited by preemergence applications of 4.5 kg/ha. Postemergence applications of nigericin reduced biomass of garden cress and velvetleaf at all doses, but inhibition at the highest doses was not statistically different from inhibition at the lowest doses (Table 4, Fig. 4). The postemergence effects of nigericin on velvetleaf were especially striking (Fig. 5). Leaves contacted by the nigericin spray began to show small brown lesions within 24–48 h of application. Young, emerging leaves or leaves in the primordial stage during spraying were stunted and malformed as they later emerged.

The preemergence effects of geldanamycin and nigericin were most dramatic during seedling emergence. Inhibition diminished over time thereafter. Leaf damage and inhibitory effects caused by postemergence applications of nigericin exhibited a similar pattern. Although some plants were killed outright, especially at the higher applications, the predominant herbicidal effect of both compounds was

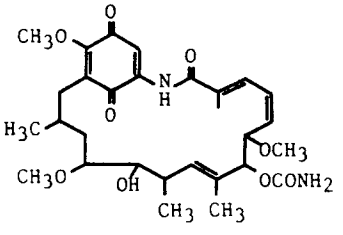
Table 4. Effect of postemergence nigericin application on shoot growth of several plant species.

	Nigericin postemergence application (kg/ha)						
	0	0.3	0.6	1.1	2.2	4.5	LSD (0.05)
Species tested	Shoot biomass as percent of control						
Barnyardgrass	100 (383)[a]	138	124	158	133	108	38
Giant foxtail	100 (190)	104	103	106	85	77	31
Garden cress	100 (95)	51	33	38	50	52	31
Large crabgrass	100 (268)	86	84	108	103	81	24
Proso millet	100 (167)	116	85	107	95	119	35
Velvetleaf	100 (248)	66	51	50	48	53	23

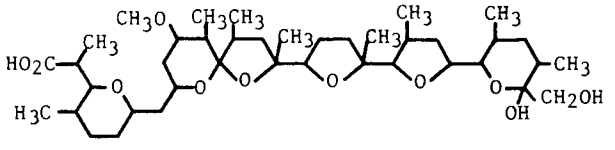
[a] Values in parentheses are actual shoot weight (mg/flat) of control plants.

Fig. 4. Effect of nigericin applied postemergence at 0 (control, left), 0.25, 0.5, and 1.0 (right) lb/acre (0, 0.3, 0.6, 1.1 kg/ha). Plant species readily visible are velvetleaf (front), garden cress (center), proso millet and barnyardgrass (rear). Note strong effect of nigericin on velvetleaf and garden cress.

Fig. 5. Injury to velvetleaf caused by postemergence application of 0.5 lb/acre (0.6 kg/ha) nigericin. Note malformation and necrosis of leaves. Photo taken 8 days after treatment.



A



B

Fig. 6. Structure of (A) gendanamycin (MW 560) and (B) nigericin (MW 725).

sublethal inhibition of seed germination and/or seedling growth. Seedlings that survived the initial treatment tended to outgrow the inhibition as time progressed. The effect of geldanamycin applied preemergence to garden cress at 4.5 kg/ha was an interesting exception. Many of the garden cress seeds germinated, but the resulting seedlings rapidly died after emergence.

Discussion

Geldanamycin (Fig. 6) is a benzoquinoid ansamycin antibiotic that inhibits protozoa, fungi, bacteria, tumor cells, and DNA synthesis (DeBoer et al. 1970; Yamaki et al. 1982). Its mode of action on higher plants is unknown. The strong inhibition of germinating seeds, but lack of postemergence effect on larger seedlings, suggests geldanamycin is more readily taken up by roots of germinating seeds and young seedlings than by foliage. Geldanamycin may also be more inhibitory to processes occurring during germination or growth of emerging seedlings than to growth of older seedlings. Structurally, geldanamycin is identical to herbimycin B, except

for a methoxyl on carbon 17 (Iwai et al. 1980; Rinehart and Shield 1976). The herbimycins, a related group of ansamycin antibiotics produced by a *Streptomyces hygroscopicus* strain, also have strong preemergence herbicidal activity (Iwai et al. 1980; Omura et al. 1979).

Nigericin (Fig. 6) is a polyether antibiotic that inhibits Gram-positive bacteria, mycobacteria, and certain plant pathogenic fungi (Harned et al. 1951; Shoji et al. 1968). It influences transport of alkali cations across cell membranes (Henderson et al. 1969; Pressman et al. 1967; Sze 1980) and inhibits photophosphorylation of isolated spinach chloroplasts (Shavit and San Pietro 1967). In our petri dish assays, nigericin strongly inhibited radicle growth of germinating seeds. These bioassays had been kept in the dark, and since the young seedlings would have relied on seed reserves rather than on photosynthesis for growth, a herbicidal effect other than inhibition of photophosphorylation is indicated.

The herbicidal effects of geldanamycin and nigericin appear to be limited by poor uptake of the compounds by plants. The high molecular weights of both (geldanamycin 560, nigericin 725) suggests this is likely. In petri dish bioassays, where seeds are surrounded by a solution or suspension of the compounds, inhibition was more dramatic than when seeds or seedlings were in soil. Geldanamycin and nigericin have very low water solubility and would, therefore, have limited downward movement when applied to the soil surface in preemergence treatments. Absorption by foliage also appears to be limited. Garden cress and velvetleaf, the species most responsive to postemergence applications of nigericin, both showed a nearly constant dose–response, regardless of the amount of nigericin applied. This result suggests nigericin absorption by shoots is low and quickly saturated. A similar explanation may account for the lack of postemergence activity of geldanamycin.

Geldanamycin and nigericin, at certain doses, both stimulated growth of some plants in petri dish bioassays and in soil in the greenhouse. Many other herbicidal compounds have been reported to have a similar stimulatory effect on plant growth at subtoxic concentrations (Ries 1976). The mechanisms for this effect are unclear.

Although geldanamycin and nigericin both have herbicidal activity, neither is sufficiently potent or persistent in its naturally occurring state to warrant use as a commercial herbicide. The finding that nigericin injures velvetleaf, a major agricultural weed that is difficult to control with many presently available herbicides, suggests further investigation of its effect on this species may prove worthwhile.

Acknowledgments. We thank K. Cassidy, R. Rollins, K. Sauter, J. Thomasson, and C. Whitenack for their help.

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