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Implications of Distribution of Linear Furanocoumarins within Celery

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Celery (*Apium graveolens*) has occasionally been reported to have hazardous concentrations of the carcinogenic linear furanocoumarins; therefore, fresh, healthy plant parts of the celery variety Tall Utah 52-70R, which forms the basis of all celery varieties in the market, and the new breeding line UC-08 were analyzed for linear furanocoumarin composition and concentrations to determine the relative safety of each plant part for human consumption. The older, outer celery leaves (44.9 μg/g of fresh weight) and the leaves on mature inner petioles (9.9 μg/g) contained significantly more linear furanocoumarins than the leaves on the innermost immature "heart" petioles (3.6 μg/g), heart petioles (1.5 μg/g), outer petioles (1.4 μg/g), inner mature petioles (1.0 μg/g), or the root (0.9 μg/g). Except for the leaves on mature outer or inner petioles, which had levels of furanocoumarins high enough to threaten human and animal health, all other plant parts tested had levels that are reportedly safe for handling and consumption. Implications of these findings for food safety, breeding for pest resistance, and evolutionary biology are discussed.

Keywords: *Apium graveolens; psoralen; bergapten; xanthotoxin; carcinogens; food safety; evolutionary biology*

INTRODUCTION

In an attempt to reduce cancer incidence in the United States by 50% by the year 2000, public health efforts are directed toward changing the ratio of fat to fiber in the human diet by increasing fiber intake (Smolin and Gosvenor, 1994). Therefore, consumption of vegetables as a component of the human diet will likely increase because these constitute an important source of fiber. However, some of the biosynthetic chemicals that vegetable crops produce for protection against insect herbivores, pathogens, or adverse environmental conditions can be hazardous to humans; these include the linear furanocoumarins. The linear furanocoumarins are bioactive compounds that have been isolated from species in a number of plant families including Rutaceae, Apiaceae (Umbelliferae), Asteraceae, Fabaceae, Moraceae, Pittosporaceae, Solanaceae, Brassicaceae, Amaranthaceae, Rosaceae, Cyperaceae, and Thymeleaceae (Scott et al., 1976; Murray et al., 1982; Berenbaum, 1991); these plant taxa include many of the most commonly consumed grocery vegetables.

The linear furanocoumarins are photoactivated (Zangerl and Berenbaum, 1987; Trumble et al., 1991) plant secondary metabolites that have been used since ancient times to treat human skin disorders such as skin depigmentation (vitiligo), psoriasis, mycosis fungoides, polymorphous photodermatitis, and eczema (Musajo and Rodighiero, 1962; Van Scott et al., 1975; Scott et al., 1976). However, the use of these furanocoumarins in medicine has been associated with higher incidence of skin cancer (Musajo and Rodighiero, 1962; Stern et al., 1979; Grekin and Epstein, 1981; Berenbaum, 1991).

A number of studies have demonstrated that the furanocoumarins are carcinogenic, mutagenic, and photodermatitic (Roelandts, 1984; Berkley et al., 1986; Koch, 1986; Berenbaum, 1991). Oral administration of 8-methoxypsoralen to patients for treatment of psoriasis resulted in basal-cell and squamous-cell carcinomas (Stern et al., 1979). Young (1990) reported photocarcinogenicity of psoralens to mice and humans. Celery (*Apium graveolens* L. var. *dulce*) has been among the most extensively studied vegetables for linear furanocoumarin content because of the potential for high concentrations of these compounds in the plant (Chaudhary et al., 1985; Trumble et al., 1990; Heath-Pagliuso et al., 1992; Diawara et al., 1992, 1993) and risks associated with handling or ingestion of celery (Ljunggren, 1990). A team of specialists from the Special Pathogens Branch of the Center for Disease Control and Prevention and the National Institute for Occupational Safety and Health conducted a study designed to determine furanocoumarin-related dermatitis among grocery workers (Fleming, 1990). The study revealed that 24% (30 of 127) of the workers handling celery developed contact dermatitis.

A cross-sectional epidemiological study of workers in two Oregon grocery stores revealed that handling healthy-looking celery caused photodermatitis, and these conditions worsened with ultraviolet A (UVA) light exposure (Berkley et al., 1986). The study also reported that, in addition to celery, handling potato, parsnip, carrot, citrus, parsley, and spinach also induced contact photodermatitis. In-vitro bioassays with bacterial and mammalian cells proved the furanocoumarins to be lethal and carcinogenic (Ashwood et al., 1980). The World Health Organization recognized these psoralens as causal agents of skin cancer in humans (International Agency for Research on Skin Cancer, 1983). These chemicals can reach the skin not only by contact but also through oral ingestion with the diet. Ljunggren (1990) diagnosed a serious generalized phototoxic burn in a human patient following celeriac ingestion. Finkel-

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Table 1. Distribution of Linear Furanocoumarins (Micrograms per Gram of Fresh Weight) within the Commercial Celery Variety Tall Utah 5270R (*A. graveolens* L. Var. *dulce*)[a]

	psoralen		bergapten		xanthotoxin		total	
plant part	mean	SE	mean	SE	mean	SE	mean	SE
outer leaf	3.936 b	1.214	28.002 c	4.549	17.899 c	3.660	49.836 c	8.496
inner leaf	0.168 a	0.128	4.791 b	0.571	2.988 b	0.552	7.947 b	1.163
heart leaf	0.020 a	0.017	2.419 ab	0.432	1.289 ab	0.240	3.729 ab	0.657
outer petiole	0.008 a	0.004	0.633 a	0.117	0.351 a	0.075	0.993 a	0.191
inner petiole	0.001 a	0.001	0.483 a	0.092	0.315 a	0.077	0.800 a	0.168
heart petiole	0.002 a	0.002	0.520 a	0.100	0.391 a	0.101	0.914 a	0.200
root	0.036 a	0.009	0.567 a	0.118	0.490 a	0.115	1.093 a	0.232
P	0.0001		0.0001		0.0001		0.0001	
$F_{6,54}$	26.622		61.878		46.020		58.174	

[a] Means within a column not followed by the same letter are statistically different at the 5% level using the Tukey–Kramer test (Super ANOVA, 1989). Means represent actual data; analyses based on square root transformations.

stein et al. (1994) recently reported an outbreak of photodermatitis among workers due to handling of celery containing levels of linear furanocoumarins as high as 84 μg/g of fresh weight. These furanocoumarin-related health hazards are even more serious when plants are infected with disease-causing pathogens (Scheel et al., 1963; Surico et al., 1987).

The causal agents of the dermatitis due to celery have been known since the mid 1970s as the linear furanocoumarins psoralen, 5-methoxypsoralen (bergapten), and 8-methoxypsoralen (xanthotoxin) (Austad and Kavli, 1983; Ashwood-Smith et al., 1985). These three compounds were also the major linear furanocoumarins isolated from other common grocery vegetables (Berenbaum, 1981a,b; Ivie et al., 1981; Beier, 1983; Seligman et al., 1987; Trumble et al., 1990; Diawara et al., 1992). There has been a great deal of research on the production of linear furanocoumarins in celery and their mammalian toxicity over the past 30 years (Scheel et al., 1963; Finkelstein et al., 1994). However, despite all of the fear surrounding celery handling and consumption, to our knowledge, there is no literature on the specific distribution of linear furanocoumarins within celery other than that leaves generally have higher concentrations than petioles (Berkley et al., 1986; Trumble et al., 1990; Diawara et al., 1993). Consequently, analysis of the different structures and locations within the celery plant to characterize their furanocoumarin composition and concentration for determination of the safest portions for human consumption was the major goal of this study.

MATERIALS AND METHODS

The commercial celery variety Tall Utah 52-70R and the breeding line UC-08 were obtained from germplasm resources held at the University of California—Davis, Department of Vegetable Crops. UC-08 originated from UC1, a *Fusarium*-resistant line derived from celeriac (*A. graveolens* var. *rapaceum*) and Tall Utah 52-70R (Orton et al., 1984). These two test entries were selected because Tall Utah 52-70R forms the basis of all celery varieties in the market and UC-08 is a new variety developed for disease resistance.

The two celery genotypes were seeded on February 7, 1992, at Fuji Seed Co. in Ventura, CA, and transplanted into the field on August 5, 1992. All plants were transplanted in single rows of 8 m × 76.2 cm on sandy loam soil at the University of California's Agricultural Operations field in Riverside, CA, in randomized complete blocks, with four replicates. Plots were furrow-irrigated to maintain adequate soil moisture, and local standard cultural practices were followed.

Plant Sample Collection. Sample collections for determination of furanocoumarin composition and concentration were made using fresh, healthy (nondiseased) celery at the marketable growth stage. Samples were pooled within celery genotype in each replicate. A total of 10 whole plants (including the leaves, petioles, and roots) per celery genotype were collected and transported to the laboratory (two to three plants per replicate were used). For each plant, the outermost senescing leaves and associated petioles were discarded because these were no longer fresh, and the following seven parts were separated: roots (including the underground plant base), outer healthy looking (potentially marketable) petioles and leaves, mature inner leaves and petioles, and the immature heart leaves and petioles. For the purpose of this study, the "heart" included the hidden non-fully-expanded innermost leaves and associated petioles. All samples were immediately stored at −65 °C until time of chemical analysis.

Linear Furanocoumarin Analyses. All plants were analyzed for the three major linear furanocoumarins found in *Apium* spp.: psoralen, 5-methoxypsoralen (bergapten), and 8-methoxypsoralen (xanthotoxin) (Trumble et al., 1990; Diawara et al., 1992, 1993). Extraction of linear furanocoumarins was conducted as previously described (Diawara et al., 1992; Trumble et al., 1992). Briefly, sample tubes were spiked with 5 μg of a synthetic internal standard, 7-benzyloxycoumarin [synthesized from commercially available 7-hydroxycoumarin (Aldrich Chemical, Milwaukee, WI] (Trumble *et al.*, unpublished methods). Plant samples were homogenized in distilled H_2O, extracted with toluene, and the crude extract was partially purified by passage through an Extract Clean solid phase extraction cartridge tube (Alltech Associates, Inc., Deerfield, IL) and eluted with acetone in chloroform (95:5). The purified extracts were concentrated to dryness and then reconstitued in 250 μL of hexane. HPLC analyses were carried out with a Hewlett-Packard 1040 HPLC pump and an HP 1050A diode array detector with a Chemstation data system (Hewlett-Packard, Avondale, PA). Peaks were monitored and quantified at 280 nm. An Alltech Econosil silica column (25 cm × 4.6 mm, 5 μm particle size) with a 10 mm × 4.6 mm guard column filled with the same packing material was used, eluted isocratically with hexane:tetrahydrofuran (81:19). The tetrahydrofuran (HPLC grade) from Aldrich Chemical Co. gave markedly better resolution than THF from Fisher Scientific.

Statistical Analyses. All data were analyzed as a randomized complete block design using ANOVA (Super ANOVA, 1989); the plants were the blocks, and the parts were the treatments. Statistically different means were separated at the 5% significance level using the Tukey–Kramer test (Super ANOVA, 1989).

RESULTS

Composition and concentrations of linear furanocoumarins in the commercial celery 52-70R are reported in Table 1. Psoralen, bergapten, and xanthotoxin were all present in this celery genotype. For each chemical, leaves on the outer petioles (Figure 1) generally had significantly higher levels of individual linear furanocoumarins than any other portion of 52-70R. The total concentration of all three compounds per plant part showed the same trend; the outer plant leaves had the highest amount, followed by mature inner leaves. The total concentration of linear furanocoumarins in the

Table 2. Distribution of Linear Furanocoumarins (Micrograms per Gram of Fresh Weight) within the Celery Breeding Line UC-08

	psoralen		bergapten		xanthotoxin		total	
plant part	mean	SE	mean	SE	mean	SE	mean	SE
outer leaf	0.907 b	0.214	26.453 c	4.995	12.597 c	2.296	39.958 c	6.861
inner leaf	0.262 a	0.120	7.171 b	1.036	4.508 b	0.728	11.940 b	1.766
heart leaf	0.000 a	0.000	2.221 a	0.286	1.184 a	0.139	3.407 a	0.421
outer petiole	0.033 a	0.028	1.221 a	0.316	0.457 a	0.094	1.711 a	0.404
inner petiole	0.004 a	0.004	0.785 a	0.125	0.458 a	0.102	1.247 a	0.224
heart petiole	0.002 a	0.002	1.254 a	0.144	0.729 a	0.075	1.985 a	0.215
root	0.019 a	0.003	0.420 a	0.054	0.311 a	0.043	0.750 a	0.096
P	0.0001		0.0001		0.0001		0.0001	
$F_{6,54}$	16.509		53.574		51.386		57.952	

[a] Means within a column not followed by the same letter are statistically different at the 5% level using the Tukey–Kramer test (Super ANOVA, 1989). Means represent actual data; analyses based on square root transformations.

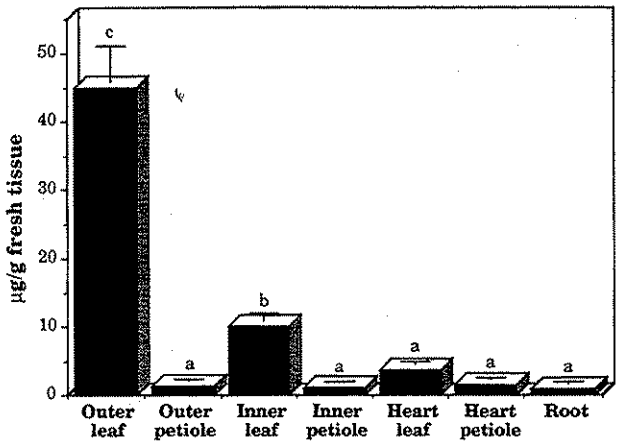

Figure 1. Distribution of linear furanocoumarins (psoralen, bergapten, xanthotoxin) within pooled values of 52-70R and UC-08 plants grown in the field in Riverside, CA. Means represent average across 20 plants (10 plants of 52-70R and 10 plants of UC-08). Extensions above bars denote standard errors. Letters above bars, if different, denote significant differences at the $P \leq 0.05$ level ($P = 0.0001$, $F_{6,123} = 60.467$), Tukey–Kramer (Super ANOVA, 1989).

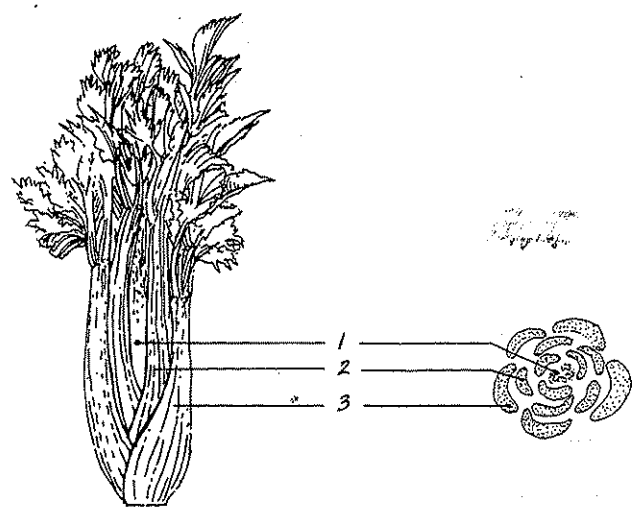

Figure 2. Diagram of the celery stalk plus a cross section showing the different plant parts: 1, heart (heart petiole, 1.5 µg/g; heart leaves, 3.6 µg/g); 2, inner petiole (inner petiole, 1.0 µg/g; leaves on inner petiole, 9.9 µg/g); 3, outer petiole (outer petiole, 1.4 µg/g; leaves on outer petiole, 44.9 µg/g).

petioles or the heart of 52-70R was less than 4 µg/g of fresh weight. Thus, when sampling for linear furanocoumarin analysis, researchers should consistently select the same plant parts (e.g. leaves on inner petioles only or leaves on outer petioles only) for observation.

As for the commercial celery 52-70R, psoralen, bergapten, and xanthotoxin were also all found in the genotype UC-08 (Table 2). No statistically significant differences were found among outer petioles, inner petioles, heart leaves and petioles (Figures 1 and 2), and the root for the concentrations of individual linear furanocoumarins. Total concentrations of all three chemicals in these plant parts also were not significantly different and were all less than 3.5 µg/g of fresh weight. However, the levels of the individual compounds bergapten and xanthotoxin in the leaves on the outer and inner petioles of UC-08 were significantly higher compared with the other plant parts; total concentrations of all three furanocoumarins in the outer or inner leaves were also significantly higher.

No significant differences were found between 52-70R and UC-08 for the total concentration of linear furanocoumarins of the different plant parts ($P = 0.695$, $F_{1,123} = 0.155$); therefore, data for the two genotypes were combined to provide a summary of linear furanocoumarin production in all plants tested. The average concentration of total linear furanocoumarins across the two genotypes (52-70R + UC-08) followed the same trend as for individual chemicals; average levels in outer leaves (44.9 µg/g) and inner leaves (9.9 µg/g) were significantly ($P = 0.0001$, $F_{1,123} = 60.5$) higher compared with the heart leaves (3.6 µg/g), heart petioles (1.5 µg/g), outer petioles (1.4 µg/g), inner petioles (1.0 µg/g), or the roots (0.9 µg/g) (Figure 1).

DISCUSSION

These results have considerable implications for food safety. Frequent reports that *A. graveolens* can have hazardous concentrations of the xenobiotic linear furanocoumarins increased concerns regarding safety among both scientists and consumers because of the carcinogenicity of the furanocoumarins. The research presented herein demonstrates that, on healthy (nondiseased) celery, the leaves on mature outer and inner petioles accounted for 90% of the total linear furanocoumarins in the commercial celery 52-70R and 85% in the breeding line UC-08. The concentrations of linear furanocoumarins in these parts of either celery genotype clearly exceeded the levels reported to cause both acute dermatitis (18 µg/g; Austad and Kavli, 1983) and chronic dermatitis (7–9 µg/g; Seligman et al., 1987). Consequently, the key to management of linear furanocoumarin toxicity from healthy celery is to avoid contact with and/or ingestion of the leaves from mature petioles; this can be achieved by trimming off most, if not all, of the visible plant leaves at harvest while wearing protective clothing. While this practice is currently the commercial standard, some *A. graveolens* is being sold untrimmed in some farmer's markets (Dercks et al.,

1990; J. T. Trumble, personal observation). Consumers should be aware that those plants may need special handling.

While there is a considerable dilution factor when only a few celery leaves are used in stews or soups, this practice should perhaps be limited to the heart and innermost leaves, which contain levels far below those known to cause human health concerns, because the linear furanocoumarins are heat stable (Ivie et al., 1981). Consumption of excessive amounts of outer celery leaves with high levels of linear furanocoumarins could result in health hazards, as was observed with celeriac (Ljunggren, 1990). Higher concentrations of linear furanocoumarins in celery leaves than in petioles have been previously reported (Berkley et al., 1986; Trumble et al., 1990; Diawara et al., 1992, 1993). Similar results were found for other species in the family Apiaceae (Zobel and Brown, 1990). All petioles tested during our study (including the outer petioles) as well as the heart leaves and heart petioles were found to be safe for both handling and consumption. In contrast to the average grocery celery, which is sometimes kept in cold storage for extended time periods and is thereby subject to increased production of linear furanocoumarins (Chaudhary et al., 1985), the plant parts tested here were from freshly harvested celery.

Results of our study have several other implications. Of the three linear furanocoumarins, bergapten was produced in the highest amounts in leaves and petioles of both celery genotypes (Tables 1 and 2). Studies by Trumble et al. (1992) and by Diawara et al. (1993) revealed a similar trend. Bergapten has been referred to as a "senescence compound" due to its increase relative to other furanocoumarins in older *Ruta graveolens* leaves (Zobel and Brown, 1991). McCloud et al. (1992) also reported higher ratios of bergapten to psoralen in older leaves of the rough lemon *Citrus jambhiri*. However, while increasing bergapten concentrations in the leaves of an aging plant may be due to changes in plant physiology, it is less clear why concentrations of linear furanocoumarins in roots remained proportionately low in the *Fusarium*-resistant UC-08. Considering that the furanocoumarins have been linked with resistance to the root-borne pathogen *Fusarium oxysporum* f. sp. *apii* (Heath-Pagliuso et al., 1992; Afek and Carmelli, 1993), the near absence of these compounds in roots suggests that an alternate mechanism of resistance is operating. In our experiment, plants were grown on *Fusarium*-free soil. Heath-Pagliuso et al. (1992) observed a significant increase in linear furanocoumarin concentration in celery and celeriac root when plants were grown on *Fusarium*-infected soils. However, they found "very little correlation" between furanocoumarin content and celery resistance to *Fusarium*.

According to Berenbaum (1991), "Coumarin biosynthesis is linked, via shikimate and phenylalanine, to biosynthesis of many other secondary metabolites, including the flavonoids, as well as to the biosynthesis of primary metabolites such as proteins." Biosynthesis of the coumarins begins with the ortho-hydroxylation of *trans*-cinnamic acid to 2-hydroxycinnamic acid (Berenbaum, 1991). The enzyme responsible for this reaction is supposedly restricted to the chloroplast. The absence of chloroplasts in the roots could explain the relatively low concentration of linear furanocoumarins in this part of the celery plant. However, some early reports on graft studies conducted in the 1960s using *Levisticum officianale* and *Pastinaca sativa* indicated that the furanocoumarins were not translocated from the site of synthesis [see Berenbaum (1991)]. Wu et al. (1972) reported that bergapten and xanthotoxin were only present in rotted areas of celery infected with *Sclerotinia sclerotiorum*. In contrast, Surico et al. (1987) detected high concentrations of these psoralens and others in healthy portions of celery plants infected with *Erwinia carotovora* and suggested that the furanocoumarins were translocated from sites of infection. During the study reported herein, at least a small amount of each of the three linear furanocoumarins was found in the roots of all plants of the two celery genotypes tested. Heath-Pagliuso et al. (1992) also detected these linear furanocoumarins in roots of healthy celery plants. It is difficult to explain the presence of furanocoumarins in the roots if these chemicals are only produced in aerial plant parts and are not translocated. Therefore, either other enzymes found in the roots are involved in linear furanocoumarin production or these chemicals are indeed translocated from the leaves to the root.

Murray et al. (1982) reported that coumarin synthesis occurred primarily in younger leaves of legumes. In contrast, these compounds apparently occurred at highest concentrations in the buds and seeds of the nonlegume *P. sativa* (Berenbaum, 1981b, 1991). Our observations showed a trend of occurrence from higher to lower concentrations as follows: outer (near senescence) leaves > inner (mature fully expanded) leaves > heart (young, not fully expanded) leaves. This rather suggests that the role of coumarins in plants varies from species to species.

In Apiaceae, the presence of coumarins has been speculated to have evolved in response to several stress factors. Zangerl and Berenbaum (1987) found that furanocoumarins are induced by UV light, suggesting that these chemicals may provide protection against mutagenic UV radiation. Others (Berenbaum and Feeny, 1981; Zangerl, 1990; Berenbaum, 1991; Trumble et al., 1991; Diawara et al., 1994) have shown that these compounds have activity against a broad spectrum of organisms and may therefore have evolved in response to herbivory. Finally, bacterial and fungal toxicities as well as viral infection have been associated with increased concentrations of linear furanocoumarins (Ashwood-Smith et al., 1985; Desjardins et al., 1989; Zobel and Brown, 1990; McCloud et al., 1992; Afek and Carmelli, 1993; Ataga et al., 1993). The allocation of high concentrations of linear furanocoumarins to the outer leaves of celery appears to support all of these hypotheses. Therefore, perhaps the best approach to understanding the evolutionary significance of linear furanocoumarins is to determine their locations and possible roles in related plant taxa.

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