Green Tea Protects Against Psoralen Plus Ultraviolet A-Induced Photochemical Damage to Skin[1]

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The use of psoralens combined with exposure to ultraviolet A radiation is a major form of treatment for psoriasis and a number of other common skin diseases. Although psoralen plus ultraviolet A treatment is highly effective, careful follow-up cohort studies have shown that it greatly increases risk for the development of cutaneous squamous cell carcinoma and melanoma. Strategies to reduce the risk of cancer development in psoralen plus ultraviolet A-treated populations are highly desirable. In prior studies, we demonstrated that green tea and constituent polyphenols protect against ultraviolet B-induced carcinogenesis and reduce the growth rate of established tumors in skin. In this study, we show that pre- and post-treatment with standardized green tea extract in psoralen plus ultraviolet A treatment populations abrogates the psoralen plus ultraviolet A-induced photochemical damage to skin. Intact mouse and human skin and reconstituted human skin were employed to assess the effect of both topical and oral administration of standardized green tea extract against psoralen plus ultraviolet A-induced photodamage. Oral administration of standardized green tea extract prior to and during multiple psoralen plus ultraviolet A treatments reduced hyperplasia and hyperkeratosis in murine skin. Standardized green tea extract treatment also inhibited accumulation of c-*fos* and p53 protein induction following a single exposure to psoralen plus ultraviolet A. c-*fos* and p53 positive cells in psoralen plus ultraviolet A-treated skin were found to be increased by $55.4 \pm 13.6\%$ and $62.3 \pm 10.5\%$, respectively, compared with saline-treated unexposed control skin. Oral administration of 0.4 or 0.8% standardized green tea extract inhibited c-*fos* protein accumulation by 18.5% and 46.2% ($p < 0.05$), respectively, and p53 protein accumulation by 26.1% and 54.3% ($p < 0.05$), respectively. Similarly proliferating cell nuclear antigen staining, a marker of cell proliferation was induced (73.7%) in psoralen plus ultraviolet A-treated skin. Oral administration of 0.4% or 0.8% standardized green tea extract 1 d after psoralen plus ultraviolet A treatment was effective in reducing psoralen plus ultraviolet A-induced inflammatory responses including erythema and edema formation. When standardized green tea extract was applied to EpiDerm, a reconstituted human skin equivalent, psoralen plus ultraviolet A-induced 8-methoxypsoralen-DNA adduct formation and p53 protein accumulation were inhibited. Topical application of 0.2 mg 8-methoxypsoralen per cm^2 followed by exposure to ultraviolet A (2.5 J per cm^2) resulted in delayed erythema formation in human subjects. Pretreatment of human skin with topical application of 0.2 mg standardized green tea extract per cm^2 30 min prior to psoralen plus ultraviolet A treatment resulted in an almost complete abrogation of psoralen plus ultraviolet A-induced erythema. In summary, these data demonstrate that standardized green tea extract protects against psoralen plus ultraviolet A-induced phototoxicity by inhibiting DNA damage and diminishing the inflammatory effects of this modality. ***Key words: green tea/inflammation/phototoxicity/PUVA/skin. J Invest Dermatol 113:1070–1075, 1999***

The use of psoralens and ultraviolet A (PUVA) is a major form of treatment for psoriasis, mycosis fungoides, and other skin diseases (Parrish *et al*, 1974; Wolff *et al*, 1977; Honigsmann *et al*, 1993). Long-term follow-up studies, however, have shown that patients receiving chronic PUVA therapy are at high risk for the development of nonmelanoma skin cancer (NMSC) (Stern and Lange, 1988; Stern and Laird, 1994). In a 10 y follow-up study of 1380 patients receiving long-term PUVA therapy, an 11-fold increase in the rate of squamous cell carcinomas was observed ($p < 0.01$). About 15 y after initial treatment with PUVA, the risk of malignant melanoma also increases, especially among patients who have received 250 or more treatments (Stern *et al*, 1997). There is a clear dose–response relationship for the risk of developing these skin cancers. Patients who received less than 100 PUVA treatments have a 5-fold increased risk of squamous cell carcinoma compared with the general population and a 100-fold risk

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Abbreviations: EC, (–)-epicatechin; ECG, (–)-epicatechin-3-gallate; EGC, (–)-epigallocatechin; EGCG, (–)-epigallocatechin-3-gallate; NMSC, nonmelanoma skin cancer; PCNA, proliferating cell nuclear antigen; SGTE, standardized green tea extract; 8-MOP, 8-methoxypsoralen.

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