PC-SPES Inhibits Colon Cancer Growth in Vitro and in Vivo

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ABSTRACT

PC-SPES is a mixture of eight herbs with antiproliferative activity in prostate cancer cell lines and antitumor effects in animal models of prostate cancer. In addition, evidence of clinical efficacy in advanced prostate cancer has been reported. PC-SPES has also been shown to have antitumor activity against several other cancer cell lines including breast and neuroepithelial cancer, melanoma, and leukemia cell lines. Because of these findings, we investigated the effects of PC-SPES in vitro in colon cancer cell lines SW-480, SW-620, and DLD-1 and in vivo in the Apo min mouse, a murine model for intestinal carcinogenesis. For the in vitro studies, colon cancer cell lines were exposed to an ethanolic extract of PC-SPES compared with a diluent control [ethanol ≤ 0.3% (v/v)]. PC-SPES resulted in a marked suppression of cell proliferation in all colon cancer cells studied. PC-SPES (3 μM) caused a 95% inhibition of cell proliferation of the DLD-1 colon cancer cell line, and similar results were observed in the SW-480 and SW-620 colon cancer cell lines. Cell cycle analysis demonstrated a drastic (≥60%) accumulation of cells in the G2/M phase with a concomitant decrease of cells in the G0/G1 phase in all colon cancer cell lines studied after treatment with PC-SPES (1.5 μM/ml for 48 h). Western blot analysis demonstrated a decrease in protein levels of β-tubulin in the SW-620 cell line exposed to PC-SPES. Terminal deoxynucleotidyl transferase-mediated nick end labeling analysis revealed an increase in apoptotic colon cancer cells incubated with PC-SPES. For the in vivo studies, female 4-5-week-old Apo min mice were randomized to two groups: a PC-SPES-treated group (n = 11) received 250 mg/kg/day (0.2 ml) PC-SPES via gastrointestinal gavage; and a control group (n = 10) received 0.2 ml of the vehicle solution (1.5% carboxymethylcellulose with 0.2% Tween 20) via gastrointestinal gavage. Both groups were treated five times a week for 10 weeks. After treatment, the gastrointestinal tract was dissected for polyp scoring by two observers blinded to treatment. The Apo min mice given PC-SPES had a 58% reduction in tumor number and a 56% decrease in tumor load. No effect on either food intake or body weight was observed in the treated versus sham groups. The present study is the first to report the potent activity of PC-SPES against colon cancer. Both cell cycle arrest and apoptosis occurred after treatment with PC-SPES. This suggests that the components of this herbal mixture, either independently or in combination, act in colon cancer, resulting in a drastic effect on tumor initiation and tumor progression.

INTRODUCTION

Colon cancer continues to be a leading cause of mortality, with an estimated 48,100 new deaths in the United States in 2002 (1). Unfortunately, the current therapeutic modalities for advanced disease are limited. Alternative options for patients with malignancies include herbal treatments that have been used for many years throughout the world (2, 3). Previous studies have documented the potent activity of an herbal mixture termed PC-SPES (BotanicLab, Brea, CA) in a variety of cancer cells including prostate, breast, and neuroepithelial cancer cells and melanoma and leukemia cells (4-7).

PC-SPES is a proprietary herbal blend that has been used since 1996 by thousands of men for "prostate health." The name derives from PC, for prostate cancer, and SPES, the Latin word for hope. The preparation includes eight different herbs: Scutellaria baicalensis Georgi, Rhabdosia rubescens, Isatis Indigotica Fort, Panax notoginseng Burk, Ganoderma lucidum Karst, saw palmetto as Serenoa repens, Dendranthema morifolium Tzvel, and Glycyrrhiza glabra L. Several of these preparations are imported from China, and one (saw palmetto) is from the United States.

Androgen antagonists and estrogenic drugs such as diethylstilbestrol are used in advanced prostate cancer. In common with these drugs, PC-SPES also induces a sharp decline in serum levels of prostate-specific antigen. However, a prostate-specific antigen response to PC-SPES is observed in many prostate cancer patients who have failed conventional androgen-deprivation therapy, suggesting that this herbal blend may have anticancer activity beyond androgen ablation (4, 8).

Ethanolic extracts of PC-SPES show significant cytostatic and cytotoxic activity against both prostatic and leukemic cancer cell lines, in which decreased rates of cell proliferation, reduced clonogenicity, and cell cycle alterations have been observed (9). The cytostatic and cytotoxic effects of PC-SPES are common to all tumor cell lines studied, regardless of their origin or hormone receptor status. A flavonoid (baicalin) found in PC-SPES inhibits proliferation of the MCF-7 breast cancer cell line, the HL-60 leukemia cancer cell line, and the NB4 myeloblastic/promyelocytic leukemia cell line (6), indicating that PC-SPES has potent activity against many cancer cell types.

Additionally, PC-SPES has been shown to have antitumor activity in vivo in murine models of carcinogenesis. PC-SPES inhibited the growth of androgen-independent prostate cancer cells (DU-145) implanted in male BNX nu/nu triple immunodeficient mice (7).

The development of genetic murine models has allowed the investigation of dietary interventions in established models of carcinogenesis. Apc min is a murine model of intestinal carcinogenesis originally derived from a germ-line mutation induced in founder animals by ethyl-nitrosourea treatment (10). The Min mutation creates a stop codon resulting in a truncated protein. Heterozygous Min mice develop multiple tumors throughout the gastrointestinal tract within a few weeks after birth. The mutation in this murine model is similar to that found in the human disease familial adenomatous polyposis coli, an inherited form of colon cancer. However, because a mutation of the APC gene is one of the earliest gene mutations that occurs in the adenoma-carcinoma sequence even in sporadic tumors (11-13), observed effects of chemopreventive agents in this model may be applicable to both sporadic and inherited forms of colon cancer. Apc min mice have been used to test the chemopreventive effect of NSAIDs (14-19) and other pharmacological interventions (20), as well as certain dietary factors (21-26).

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3 These abbreviations are: NSAID, nonsteroidal anti-inflammatory drug; TUNEL, terminal deoxynucleotidyl transferase-mediated nick end labeling; CMC, carboxymethylcellulose; XTT, 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide inner salt; PI, propidium iodide.

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Because of the potent anticancer activity demonstrated in vitro against several cancer cell lines and in in vivo models of prostate cancer by PC-SPES, we chose to investigate the effects of PC-SPES against colon cancer in vitro using colon cancer cell lines and in vivo using the Apc<sup>min</sup> mouse.

MATERIALS AND METHODS

**PC-SPES.** PC-SPES was obtained from BotanicLab, Inc. Each 320-mg capsule of herbal powder was extracted with 70% ethanol as reported previously (10). The ethanol extracts were kept at −20°C, and dilutions were made in the same culture media used for all in vitro studies. For in vivo studies, the capsule extract was suspended in 1.5% CMC with 0.2% Tween 20 (Sigma Chemical Co., St. Louis, MO) as described previously (7).

**Cell Lines.** Human colon cancer cell lines (SW480, SW620, and DLD-1) were obtained from American Type Culture Collection (Manassas, VA). All cell lines were maintained and cultured in RPMI 1640 (Life Technologies, Inc., Grand Island, NY) with 10% fetal bovine serum, and 1% penicillin/streptomycin as reported previously (27).

**Analysis of Cell Proliferation.** Cell viability was assayed in triplicate using an XTT assay (28). Briefly, 5000 SW480, SW620, and DLD-1 cells were seeded in 100 μl of media in each well of 96-well flat-bottomed microplates (Corning Glass Works, Corning, NY). Cell populations were harvested and plated at 75–80% confluence and detached by mild trypsinization. PC-SPES was added at various concentrations (0.2, 0.4, 0.8, 1.5, and 3.0 μl/ml) to each triplicate well. Appropriate solvent controls produced no cytotoxic effects. At 72 h, XTT labeling mixture (Roche Molecular Biochemicals, Indianapolis, IN) was added, and cells were further incubated for 4 h. The absorbance of the samples was measured using a microplate (ELISA) reader (THERMOMax Microplate Reader; Molecular Devices, Sunnyvale, CA).

**Measurement of Cell Cycle Phase Distribution.** Colon cancer cell lines DLD-1, SW480, and SW620 were cultured in either diluent [control; ethanol content ≤ 0.2% (v/v)] or 1.5 μl/ml PC-SPES for 48 h. Cell cycle analysis was performed by DNA staining with PI. Briefly, 2 × 10<sup>5</sup> adherent cells were detached by trypsinization. Detached cells and the floating dead cells were centrifuged and washed twice with 1 ml of cold 1× PBS (Life Technologies, Inc.). Supernatant was aspirated, cells were resuspended in 1 ml of PBS, and then 3 ml of cold 100% ethanol was added, and cells were incubated at −20°C overnight. The cells were washed twice with 1 ml of 1× PBS. After the last wash, 100 μl of PI solution (50 μg/ml PI + 0.05 mg/ml RNase A; Sigma Chemical Co.) were added, and the cells were incubated while protected from light at room temperature for at least 2 h before analysis. DNA analysis was performed using fluorescence channel 3 in an Epic XL flow cytometer (Coulter Electronics, Inc., Miami, FL). Analysis was performed with Software System II Triad.

**Measurement of Apoptosis.** Measurement of apoptosis was performed by the TUNEL method using an in situ cell death detection kit (Roche Molecular Biochemicals, Indianapolis, IN) as described previously (29). Briefly, SW480, SW620, and DLD-1 cells incubated with either 3.0 μl/ml PC-SPES or diluent [final concentration of ethanol ≤ 0.2% (v/v)] for 48 h. For quantification, three different fields (≥300 cells/field) were counted by light microscopy by an observer blinded to treatment.

**Western Blot Analysis.** Western blot analysis was performed as described previously (27). Briefly, SW480 and SW620 cells were incubated for 72 h in the presence or absence of 1 μl/ml PC-SPES. The cells were then detached by trypsin treatment and lysed at 4°C in radiomunoprecipitation assay buffer [50 mm Tris-HCl (pH 7.4), 1% NP40, 0.25% sodium deoxycholate, and 150 mm NaCl] supplemented with one tablet of protease inhibitor mixture (Boehringer Mannheim, Indianapolis, IN). The cell lysates (20 μg/lane) were electrophoresed on 10% SDS-PAGE (Bio-Rad, Hercules, CA). The proteins were transferred onto Hybond nitrocellulose membranes (Amersham Lifesciences, Piscataway, NJ). The membranes were blocked for 1 h at room temperature with 5% blocking solution and incubated with the respective antibody overnight at 4°C. Mouse anti-β-tubulin and anti-α-tubulin monoclonal antibodies and goat anti-β-actin polyclonal antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). After washing three times with PBS/0.1% Tween 20, the membranes were incubated for 30 min with either horseradish peroxidase-conjugated goat or antinouse IgG antibody (Santa Cruz Bio-technology). After washing three times with PBS/0.1% Tween 20, the membranes were developed with an enhanced chemiluminescence Western blotting detection kit (Amersham, Piscataway, NJ). The intensity of the bands was analyzed by densitometry with a GS-17 Calibrated Imaging Densitometer (Quantity One 4.0.3 software; Bio-Rad).

**Animals.** Female C57BL/Jd-Min<sup>−/−</sup> Apc<sup>min</sup> mice from our breeding colony were selected for this study. We established our colony from founder mice obtained from The Jackson Laboratory (Bar Harbor, ME). Mice were weaned at 4–5 weeks of age, at which time they were genotyped by PCR analysis, and Min<sup>−/+</sup> mice were randomized to treatment and sham treatment groups. All animals were fed a standard AIN-93G purified diet (Dyets, Inc., Bethlehem, PA) and offered distilled water ad libitum.

The PC-SPES-treated group (n = 11) received 250 mg/kg/day (0.2 ml) PC-SPES by gastrointestinal gavage five times a week. The sham-treated group (n = 10) was given 0.2 ml of the vehicle solution (CMC and 0.2% Tween 20 without PC-SPES) by gastrointestinal gavage five times a week. All protocols for the animal studies were approved by the University of California, Los Angeles Animal Care and Use Committee and were in accordance with the NIH Guide for the Care and Use of Laboratory Animals (30).

After 10 weeks of treatment, animals were sacrificed by exsanguination under isoflurane anesthesia (Abbot Laboratories, North Chicago, IL). The entire gastrointestinal tract was dissected as described previously (20) and immediately placed in PBS (Life Technologies, Inc., Rockville, MD) that had been precooled to 4°C. Polyp scoring and tumor load were performed by two observers [S. H. and R. W. I.] blinded to the treatment that the animals received as described previously (20).

**Statistics.** PRISM statistical analysis software (GraphPad Software, Inc., San Diego, CA) was used for statistical analysis. Data were expressed as means ± SE. Student’s t test was used to assess the difference in polyp number and tumor load between the treatment and control groups and for the TUNEL studies (P ≤ 0.05). Effects on cell proliferation and cell cycle distribution were evaluated by one-way ANOVA. Dunnett’s multiple comparison test was used to identify significant treatment effects (P ≤ 0.05) for the food intake, body weight, XTT assays, and cell cycle studies.

RESULTS

**In vitro Studies**

**Inhibition of Colon Cancer Cell Growth**

PC-SPES significantly suppressed cell proliferation in colon cancer cell lines SW480, SW620, and DLD-1 after 72 h of PC-SPES exposure (Fig. 1). The control experiments with ethanol alone [≤0.3% (v/v)] had no effect on cell proliferation. All cell lines studied demonstrated a dose-dependent inhibition of proliferation. The greatest inhibition (95%) was observed in the DLD-1 colon cancer cell line at 3 μl/ml PC-SPES (Fig. 1).

**In vivo Studies**

**PC-SPES INHIBITS COLON CANCER IN VITRO AND IN VIVO**

Fig. 1. Dose-response effects of PC-SPES in colon cancer cell lines (DLD-1, SW480, and SW620). All cells were treated with PC-SPES (0.2–3.0 μl/ml) or diluent (control) for 72 h. Each point represents the mean of three independent experiments ± SE; **, P ≤ 0.01.
Measurement of Cell Cycle Phase Distribution

Cell cycle analysis demonstrated that PC-SPES treatment resulted in a marked (≥60%) accumulation of cells in the G₂-M phase of the cell cycle in DLD-1, SW480, and SW620 colon cancer cells after exposure to PC-SPES (1.5 μl/ml) for 48 h. Cells in the G₀-G₁ phase concomitantly decreased (Fig. 2; *, P ≤ 0.05; **, P ≤ 0.01).

Measurement of Apoptosis

TUNEL Assay. Apoptosis in colon cancer cell lines was assessed by the TUNEL method. PC-SPES treatment (3 μl/ml, 48 h) resulted in a significant (P ≤ 0.01) increase in the percentage of apoptotic cells relative to control in DLD-1 (47% of cells), SW480 (13% of cells), and SW620 (8% of cells; Fig. 3).

Effects of Estrogen on Colon Cancer Growth. Because the activity of PC-SPES in prostate cancer has been thought to be, at least in part, due to its estrogenic effects, we examined the antiproliferative action of estradiol [10⁻⁷ to 10⁻⁹ M] on colon cancer cell lines (SW480, SW620, and DLD-1). Prostate cancer cell line PC-3 was used as a positive control. Estradiol had no effect on the cell growth of any of the colon cancer cell lines tested at any of the concentrations (Fig. 5). Estradiol (10⁻⁷ M) resulted in a 17% inhibition of growth of the prostate cancer cell line PC-3, which was consistent with other studies (Ref. 31; Fig. 4).

Western Blot Analysis: Microtubule Proteins. Western blot analysis revealed decreased expression of β-tubulin in colon cancer cell line SW620 exposed to PC-SPES (1 μl/ml) for 72 h. Densitometry analysis revealed a 27% reduction in β-tubulin compared with the control band (β-actin). No changes in α-tubulin were observed (Fig. 5).

In Vivo Studies

Polyp Number

Oral PC-SPES treatment (250 mg/kg/day) of Apcmin mice resulted in a significant decrease in polyp number in the medial and distal segments of the small intestines (73% and 67%, respectively; both Ps ≤ 0.01; Table 1). Similarly, a significant decrease (58%; P ≤ 0.01) was observed in the sum of all four intestinal segments that were evaluated (Table 1). No difference occurred in the total number of polyps in the proximal intestine or the colon. The effects of PC-SPES
observed in tumor initiation in the Apc<sup>min</sup> mice were similar to those reported after treatment with the NSAID sulindac (120 ppm in drinking water), in which we found a 49% reduction in polyp number (20).

**Tumor Load**

Treatment with PC-SPES resulted in a significant decrease in tumor load in each segment of the small intestine (34% proximal, 77% medial, and 76% distal; all P < 0.05). No change in tumor load was observed in the large intestine between the control and treatment groups. A significant change in the sum of all four intestinal segments was found (56%; P < 0.05; Table 1).

**Food Intake and Body Weight**

Suppression of polyp number and tumor load was unrelated to difference in caloric intake between the sham-treated and PC-SPES-treated groups. No difference in body weight (Fig. 6) or food intake (Fig. 7) occurred between these two groups.

**DISCUSSION**

DiPaola et al. (4) initially demonstrated *in vitro*, in mice as well as in patients, that PC-SPES induced potent estrogenic activity and androgen ablation against prostate cancer. However, PC-SPES is also effective in androgen-independent prostate cancer (8). Additionally, PC-SPES has anticancer properties against other forms of cancer *in vitro*, including leukemia cells (6). Because of the potent anticancer activity of PC-SPES, we elected to study its effects against colon cancer *in vitro* and *in vivo*.

Our *in vitro* studies demonstrated that PC-SPES significantly suppressed proliferation of colon cancer cells. The magnitude of inhibition of proliferation observed in colon cancer cells was similar to that achieved against several prostate cancer cell lines at the same concentrations of PC-SPES (10).

To examine the mechanism that might account for the effects of PC-SPES in colon cancer cells, we investigated its effects on cell cycle distribution. A marked accumulation of colon cancer cells in the G<sub>2</sub>-M phase of the cell cycle occurred with a concomitant decrease of cells in the G<sub>0</sub>-G<sub>1</sub> phase. These results were similar to the activity of PC-SPES when cultured with PC-3 and DU-145 prostate cancer cells, of LNCaP prostate cancer cell line exposed to diethylstilbestrol (5, 10), but different from the effect observed in LNCaP cells after treatment with PC-SPES, in which G<sub>1</sub> cell accumulation is more prominent (6, 10). These findings suggest that PC-SPES has a marked effect on colon cancer proliferation due to cell cycle arrest. In support of this observation, cyclin-dependent kinase inhibitor p27<sup>Kip1</sup> has been shown to be induced after treatment with PC-SPES in LNCaP cells (6). Additionally, the present study demonstrated that the colon cancer cell line SW620 cultured with PC-SPES (1 µl/ml) for 48 h had a decreased level of expression of β-tubulin. The decrease in β-tubulin could result in altered microtubule assembly in colon cancer, which might account for the accumulation of cells at the G<sub>2</sub>-M phase of the cell cycle, as reported previously in prostate cancer (32). Our findings were consistent with those of other studies, which have demonstrated that a component of PC-SPES, *G. glabra*, altered microtubule structure and caused G<sub>2</sub>-M cell cycle arrest in prostate and breast cancer cells (33).

Down-regulation of β-tubulin was only observed in the SW620 cell line, whereas inhibition of growth occurred in all colon cancer cell lines studied. Thus, we investigated other mechanisms that might account for the observed results. Because other studies have demonstrated that PC-SPES has antiapoptotic activity against prostate cancer (7), we investigated the effect of PC-SPES on apoptosis by using the TUNEL method. We found a marked increase in the percentage of

### Table 1 Effects of treatment with PC-SPES on polyp number and tumor load in each of the intestinal segments of the small intestine and all of the large intestine in Apc<sup>min</sup> mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Polyp number</th>
<th>Tumor load</th>
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<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>10</td>
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<tr>
<td>PC-SPES</td>
<td>11</td>
<td>11</td>
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<table>
<thead>
<tr>
<th>Segment</th>
<th>Control</th>
<th>PC-SPES</th>
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<tbody>
<tr>
<td>Small intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>6.7 ± 1.5</td>
<td>5.4 ± 1.3</td>
</tr>
<tr>
<td>Medial</td>
<td>7.0 ± 1.4</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Distal</td>
<td>3.3 ± 0.6</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Large intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>1.9 ± 0.4</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>Medial</td>
<td>1.9 ± 0.4</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Distal</td>
<td>2.1 ± 1.4</td>
<td>2.1 ± 1.4</td>
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<tr>
<td>Total intestine</td>
<td></td>
<td></td>
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<tr>
<td>Proximal</td>
<td>17.2 ± 3.1</td>
<td>17.2 ± 3.1</td>
</tr>
<tr>
<td>Medial</td>
<td>17.2 ± 3.1</td>
<td>17.2 ± 3.1</td>
</tr>
<tr>
<td>Distal</td>
<td>17.2 ± 3.1</td>
<td>17.2 ± 3.1</td>
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*a* Four-cm segments of the small intestine were evaluated for polyp number and tumor load (mm<sup>2</sup>); the entire large intestine was evaluated.

*<sup>b</sup>* Total intestine corresponds to the sum of each segment of the small intestine plus the value for the large intestine.

*<sup>c</sup>* P < 0.01 relative to control group.

*<sup>d</sup>* P < 0.05 relative to control group.
activity of this herbal mixture. The observations in the Apc
both cell cycle arrest and apoptosis independent of the estrogenic
suggests that PC-SPES has potent anticancer effects and results in
may be acting on several genes associated with early tumor progres-
will need to be confirmed in other animal models of colon cancer and
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