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Safety of Purified Isoflavones in Men With Clinically Localized Prostate Cancer

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Abstract: *Our purpose was to evaluate the safety of 80 mg of purified isoflavones administered to men with early stage prostate cancer. A total of 53 men with clinically localized prostate cancer, Gleason score of 6 or below, were supplemented with 80 mg purified isoflavones or placebo for 12 wk administered in 2 divided doses of 40 mg to provide a continuous dose of isoflavones. Compliance, changes in plasma isoflavones, and clinical toxicity were analyzed at baseline, 4, and 12 wk. A total of 50 subjects completed the 12-wk intervention. A continuous, divided-dose administration of 80 mg/day of purified isoflavones at amounts that exceeded normal American dietary intakes significantly increased (*$P < 0.001$*) plasma isoflavones in the isoflavone-treated group compared to placebo and produced no clinical toxicity. With the current evidence on the cancer preventive properties of isoflavones, these results are significant and offer promise for these phytochemicals to be developed as potent agents to prevent cancer progression.*

Introduction

The American Cancer Society estimates that there will be about 218,890 new cases of prostate cancer (CaP) in the United States in 2007, and about 27,050 men will die of this disease. (1) Recently, the proteasome has been proven to be an excellent target for developing anticancer drugs (2–5), including for CaP, as demonstrated by in vitro, cell culture, animal, and clinical results using various inhibitors including Velcade and Bortezomib (PS-341) (4–7). In animal studies, proteasome inhibitors suppress tumor growth and angiogenesis as either a single drug or in combination with other cytotoxic agents (8,9). More recent studies of proteasome inhibitors such as PS-341 (bortezomib, Velcade) in animal models and in patients with hormone refractory CaP resulted in both prostate-specific antigen (PSA) and tumor volume decreases, demonstrating potential clinical application in CaP therapy. However, there are several toxicities that have been reported with these agents that include nausea, fatigue, diarrhea, peripheral neuropathy, and reversible thrombocytopenia (4–7). Therefore, it is necessary to identify proteasome inhibitors with similar potency to PS-341, with a relative favorable toxicity profile.

Epidemiological and laboratory studies have demonstrated that several nutrients, including isoflavones, could induce apoptosis, suppress the formation and growth of human cancers including CaP (10–17). Population studies have consistently reported lower incidence of clinically evident disease in populations consuming isoflavones. An inverse relationship between dietary intake, plasma (11–16), and prostatic fluid (17) concentrations of isoflavones and the incidence of CaP and benign prostatic hyperplasia (BPH) has been observed in these populations, demonstrating the potential role of isoflavones in mediating epigenetic effects. Specifically, our previous data (18) indicated that similar to bortezomib and Velcade (PS-341), purified isoflavone, genistein is a potent proteasome inhibitor, and the genistein-induced proteasome inhibition was accompanied by induction of apoptosis in these lymph node carcinoma of the prostate cell lines. In vitro data have consistently shown that genistein modulates cell proliferation (16–20), angiogenesis (21,22), tumor cell invasion and tumor metastasis (22,23,24), cell cycle regulation (25), and induction of apoptotic cell death (18) and functions as an antioxidant (23,26), indicating that these purified isoflavones are promising chemopreventive agents with several cellular effects that are both genomic and nongenomic.

In addition to population and laboratory studies, earlier Phase I trials have demonstrated the safety of whole soy and purified isoflavones with single- and multiple-dose administration in healthy, early stage, or treated prostate cancer patient cohorts (27,29) relative to those observed adverse events

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(AEs) seen in the PS-341 trials (4–7), demonstrating promise and thus the potential to be tested as chemopreventive agents in Phase II clinical trials. However, these previous Phase I trials have varied significantly in the dose and type of isoflavone used (purified isoflavones, soy products, or food made from soy products) and have targeted disease-free men as well as men with varying stages of CaP. To date, there have been no randomized clinical trials demonstrating the safety of using purified isoflavones in early stage CaP patient populations. Our broad and long-term goal objective is to systematically develop safe, nontoxic nutrients as agents for chemoprevention of CaP that can be consumed safely over long periods to prevent progression in early stage, high-risk, and disease-free populations or those agents that can delay or prevent epithelial transformation using validated biomarkers to monitor changes in disease progression and incidence. The specific aim of this randomized, double-blinded, placebo-controlled trial was to recruit and randomize men with early stage CaP to receive 80 mg of purified isoflavones in 2 divided doses of 40 mg (Prevastein HC® 80 mg/day, IND #61,949 Kumar) vs. a placebo for a 12-wk period and observe changes in markers of clinical toxicity of the study agent.

Materials and Methods

This was a placebo-controlled, randomized, double-blinded clinical trial conducted in a cohort of men recruited from member institutions of the Moffitt Community Clinical Oncology Program (CCOP) Research Base approved by the institutional review boards (IRBs) at these institutions. Men between the ages of 50 and 80, diagnosed with localized CaP [Gleason Score 2–6; patients with a Gleason primary pattern 4; (4+1 or 4+2) were not eligible] based on pathological assessment from biopsy specimens, with no prior or current therapy for CaP or history of cancer except nonmelanoma skin cancer, were eligible. Patients who received neoadjuvant hormonal therapy, vegans, and/or soy users, as ascertained by baseline food records, were excluded from the study. Subjects with a known history of hepatic and/or renal disease, prostatitis, BPH, urinary tract infection, on antibiotics within 30 days of registration, or with a body mass index (BMI) greater than 32 kg/m^2 were excluded from the study. The agent that was used in this clinical trial is a botanical test compound developed from Novasoy400 (Archer Daniels Midland Company, Decatur, IL) called Prevastein HC, a soy-based isoflavone concentrate extracted to assure that the ratio of isoflavones as well as the aglycone and glycoside isoforms are maintained as they would be found in soybeans and unfermented soy foods. This product and placebo were provided to us for the duration of this trial. Dr. Kumar obtained and holds an investigator-held Investigational New Drug approval from the Food and Drug Administration (FDA) for this dose and use (#61,949). The purified isoflavone capsules were standardized based on isoflavone content and maintained on a stability monitoring program to ensure that there is no reduction in active component during the period of use. They are produced under current food Good Manufacturing Practices and a Hazard Analysis and Critical Control Point program. Thus, although recruitment occurred over a 3-yr period, we did not anticipate batch-to-batch variation or inconsistency in isoflavone content between batches of this agent**.** When stored unopened in original packing and under recommended storage conditions, the shelf life is 4 yr from the date of manufacture. To preserve the double blind, supplies of study agents were labeled with numeric codes by the CCOP Research Pharmacy, which housed and dispensed the coded supplements to the investigators. Prevastein HC capsules and matching placebo capsules were hard gelatin capsules packaged in 150 cc white high-density polyethylene bottles, with 100 capsules per bottle.

On determination of eligibility and the granting of informed consent, patients were registered using a telephone based registration and randomization system (30) determined by a preset algorithm. These assignments were stratified by Gleason Score (2, 3 vs. 4, 5, and 6). Subjects were assigned to 1 of 2 arms: The intervention arm will be provided supplementation with isoflavones in the form of Prevastein HC, in the form of 2 pills (40 mg each) to total 80 mg per day to provide a continuous dose biologically active isoflavones, and those in the control group will receive an identical placebo providing inert ingredients. To avoid possible confounding due to vitamin/mineral deficiencies and prevent the use of other nonstandardized supplements, which may contain isoflavones or other large doses of antioxidants, a standard formulation containing 100% U.S. recommended daily allowance for vitamins (Pan American Lab Company [Miami, FL] brand name PBA Multi Vitaformula) was provided by the investigators to subjects in both groups during the entire study period. The duration of the intervention was 12 wk, with scheduled follow-up at 4 wk and with the study ending at 12 wk.

Subjects provided baseline demographic anthropometric, medical, and family history of cancer, alcohol, tobacco use, and nutritional history including nutritional supplement use. Subjects completed weekly 2-day food records, verified by interview to ensure compliance to diet and instruction to avoid isoflavone-rich foods, and records were analyzed using the University of Minnesota Nutrition Data System Research version for analysis of nutrient composition at the Arizona Diet and Behavioral Assessment Center (www.azdiet-behavior.azcc.arizona.edu). Compliance to study agent was monitored by requiring subjects to complete a daily Study Agent Intake log and pill count and analysis of plasma isoflavones (daidzein, glycitein, and genistein) at baseline, 4 wk, and 12 wk using high-performance liquid chromatography and extraction procedure developed by Craft Technologies, Inc. (Wilson, NC). Safety was monitored by using a daily symptom log and measurement of safety markers at the baseline enrollment visit, 4 wk, and at 12 wk by analysis of a comprehensive metabolic panel, (spectrophotometry, ion selective electrode hexokinase), and

a complete blood count (electronic cell sizing sorting cytometry/microscopy) at LabCorp Diagnostic Laboratories in Tampa, Florida. To evaluate and ensure subject safety, any change in medical condition and use of concomitant medications were monitored throughout the study period. All safety and compliance data were collected at baseline, 4, and 12 wk.

All AEs were captured on the Adverse Event CRF regardless of whether they were related to study drug. AEs were reported from the time the subject signs the informed consent to the end of study participation (e.g., completion of the protocol, lost to follow up, drop). At each contact with the subject, AEs were assessed and recorded in the source documents on the Adverse Event Case Report Form. The severity of the event was determined using the National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events, version 2.0 (http://ctep.info.nih.gov). If not listed in the CTC, a general grading system was applied as follows: mild = causing no limitations of usual activities; moderate = causing some limitations of usual activities; and severe = inability to carry out usual activities. All AEs, including laboratory abnormalities that in the opinion of the study physicians are clinically significant, were followed according to good medical practices and documented. Serious AEs still ongoing at the end of the study period were followed up to determine the final outcome. There were no proscribed medications. Concomitant medication information was collected every 4 wk to assist in determining AE attribution. A patient's treatment was suspended in any of the following circumstances: 1) allergic reaction to product, 2) change in stool frequency, 3) development of clinical evidence of progression of disease, 4) abnormal blood chemistry, and 5) request of patient or MD. Subjects with changes in blood chemistry were referred to their primary physician. Subjects who demonstrated an unexpected AE, likely to be related to study agent, were unblinded. At the conclusion of the study, all investigators were unblinded with respect to their subject's treatments and were responsible for informing their subjects of their actual treatment. AEs were reported to the Moffitt CCOP Research Base Operations Center, the FDA, and the local IRB. The Moffitt CCOP Research Base Operations Center also notified the study agent sponsor of all reported AEs and ensured that the FDA was notified per guidelines.

Statistical Methods

At the conclusion of the intervention, a pooled *t*-test was used to compare the 2 group mean change of plasma isoflavone levels, markers of clinical toxicity, including symptoms at the 2-sided 0.05 significance level. If the equal variances between 2 groups did not meet, a Satterthwaite *t*-test was used. Paired *t*-tests were, in addition, used to compare posttreatment vs. pretreatment changes for each group in symptoms and plasma isoflavone concentrations. Paired *t*-tests were justified in this case. Even if the data are only approximately normally distributed, the test is robust with respect to the normality assumption. These tests were 2-sided at 0.05 significance levels. Although compliance was monitored, we employed "intent to treat principle" in all group comparisons. Subjects were analyzed according to the group into which they were randomized without regard to compliance or actual diet. All the analysis was implemented in SAS version 9.

Results

Of 53 men, 50 recruited completed the intervention and were able to provide complete data pretreatment and posttreatment including serum and plasma for analysis. A total of 3 subjects dropped out of the study including 1 from the placebo group and 2 from the isoflavone-treated group. Reasons for dropping out of the study included noncompliance to study agent (1 subject) and Grade I to II AEs that resulted in 2 subjects not willing to continue and dropping out of the study. Thus, a 94.3% subject retention rate was achieved in the subjects recruited.

Initial comparison of baseline demographic variables such as age, race, anthropometrics measurements such as height, weight BMI, smoking history, family history of cancer, and personal history of BPH are presented in Table 1. Although no significant differences were observed in the 2 groups on these variables, notably, over 50% of prostate cancer patients in both groups were former or current smokers and had a mean BMI >25. Subjects in both groups reported similar

Table 1. Demographic Characteristics of Subjects at Baseline

Characteristic	Treatment Group	Placebo Group	*P* Value
N	25	28	
Age (yr)	71.75 ± 6.39	71.92 ± 5.59	0.92
Weight (lb)	180.34 ± 24.51	186.57 ± 19.81	0.31
Height (cm)	176.15 ± 8.55	176.43 ± 5.90	0.89
Body mass index (kg/m^2)	26.31 ± 2.49	27.18 ± 3.35	0.21
Race, No. (%)			
White	23 (92.00)	27 (96.43)	0.56
Black	1 (4.00)	1 (3.57)	
Unknown	1 (4.00)	0 (0.00%)	
Former or current smoker, No. (%)			
Yes	16 (64.00)	15 (53.57)	0.44
No	9 (36.00)	13 (46.43)	
Former or current alcohol, No. (%)			0.08
Yes	14 (56.00%)	22 (78.57%)	
No	11 (44.00%)	6 (21.43)	
Family history of cancer, No. (%)			0.53
Yes	5 (20.83)	4 (14.29)	
No	19 (79.17)	24 (85.71)	
History of benign prostatic hyperplasia, No. (%)			0.96
Yes	7 (28.00)	8 (28.57)	
No	18 (72.00)	20 (71.43)	

Table 2. Plasma Isoflavones at Baseline and Months 1 and 3 by Group

Value	Treatment Group ($N = 23$)			Placebo Group ($N = 27$)			P Value[a]	P Value[b]
	Baseline (mcg/ml)	Month 1 (mcg/ml)	Month 3 (mcg/ml)	Baseline (mcg/ml)	Month 1 (mcg/ml)	Month 3 (mcg/ml)		
Diadzein mean (SD)	0.0245 (0.0211)	0.3401 (0.2292)	0.2135 (0.1311)	0.0270 (0.0257)	0.0229 (0.0157)	0.0220 (0.0160)	0.71	<0.01
Glycitein mean (SD)	0.0024 (0.0014)	0.0103 (0.0097)	0.0091 (0.0089)	0.0026 (0.0015)	0.0023 (0.0013)	0.0025 (0.0015)	0.64	<0.01
Genistein mean (SD)	0.0179 (0.0112)	0.5421 (0.3688)	0.3954 (0.2299)	0.0211 (0.0209)	0.0163 (0.0097)	0.0169 (0.0164)	0.52	<0.01

a: Two sample *t*-tests comparing treatment group with placebo group at baseline.
b: Two sample *t*-tests comparing treatment group with placebo group at Month 1 or Month 3.

average intake of macronutrients and micronutrients at baseline. Although intake of protein, fats, cholesterol, and percent fat intake to total caloric intake increased slightly in the treatment group during the intervention, this was not reflected as significant changes in weight, as caloric intake remained stable. No significant changes in anthropometric variables such as weight and BMI were observed during the study period.

Plasma isoflavone levels (daidzein, glycitein, and genistein; Table 2) at baseline, 4, and 12 wk were analyzed. Significant increases in plasma daidzein ($P < 0.0001$), glycitein ($P < 0.0001$), and genistein ($P < 0.0001$) were observed from baseline to 4 wk in the treatment group compared to the placebo group. Similarly, significant increases in plasma daidzein ($P < 0.0001$), glycitein ($P = 0.01$), and genistein ($P < 0.0001$) were observed from baseline to 12 wk in the treatment group compared to the placebo group (Figs. 1–3). Compared to plasma isoflavones daidzein and genistein, changes in plasma glycitein were observed to be relatively lower, although they were significantly higher in the isoflavone-treated group compared to the placebo.

All anticipated and unanticipated, Grades I to III, constitutional, dermatological, gastrointestinal (GI), metabolic, and pain symptoms of AEs were documented on all subjects throughout the study period as displayed in Table 3. Most AEs were Grade I and II events in both groups, with 2 events that were identified as Grade III in the treatment arm and determined to be unrelated to agent provided in the study. These reported Grade III events were constitutional symptoms of fever related to a viral infection and were determined to be unrelated to the agent. Anticipated Grade I AEs reported included GI symptoms such as bloating, loss of appetite, dyspepsia, and diarrhea, which were reported by both groups (5 subjects in the treatment group and 7 in the placebo group). Grade II events reported included abdominal pain. One subject in the treatment arm reported a dermatalogical symptom that was determined to be unrelated to agent. Grade I metabolic/laboratory changes in serum alanine transaminase (ALT), increases in lipase, amylase, hyperphosphatomia, and hypercalcemia were observed in both groups and considered possibly related to study agent. All AEs were Grade I and II and occurred in both groups and did not produce clinical toxicity.

Discussion

To our knowledge, our study was the first randomized, placebo-controlled clinical trial of purified isoflavones in men with localized prostate cancer patients, at amounts that exceeded normal American dietary intakes, to demonstrate significant and progressive increase in plasma without producing clinical toxicity. We were able to demonstrate that in a cohort of men with localized prostate cancer, compliance to a multidose daily regimen of supplements and diet could be achieved while maintaining weekly diet and symptom records and attendance to follow-up visits, interviews,

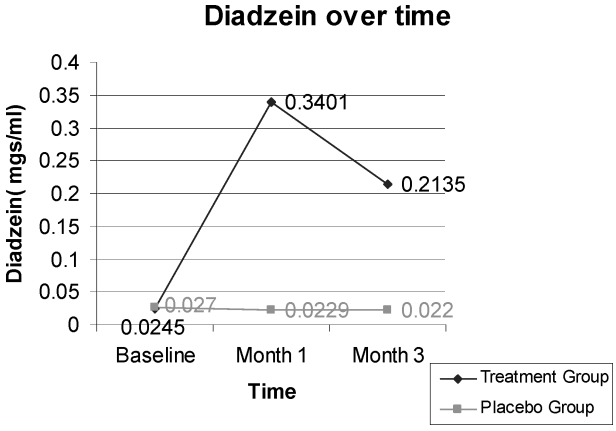

Figure 1. Change in plasma isoflavone diadzein by group and time.

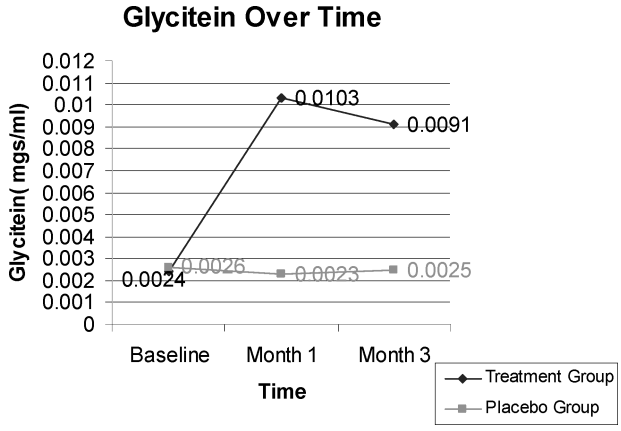

Figure 2. Change in plasma isoflavone glycitein by group and time.

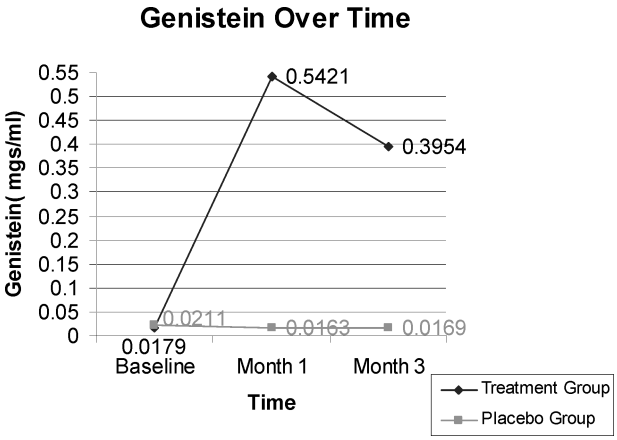

Figure 3. Change in plasma isoflavone genistein by group and time.

and blood draws to monitor compliance, safety, and toxicity, although these visits were not aligned with their normal surveillance visits. The retention rate of 94.3% indicates that this cohort was highly motivated and willing to participate in chemoprevention trials during the period of active surveillance.

Based on the results of earlier observations, to maximize compliance, increase bioavailability, and ensure safety in this clinical trial, the agent formulation, dose, and administration of isoflavones and the markers of safety were carefully selected. Japanese men, who have the lowest rate of prostate cancers, consume an estimated 60 to 80 mg of isoflavones per day as part of their habitual diets as compared to 1 mg per day consumed by Western populations (29). In our previous study of isoflavone supplementation in the early stage patient cohort (34), we used whole soy isoflavones at a dose of 60 mg in 60 g soy protein based on the studies of Japanese intake of soy isoflavones. At this dose, with a 3-mo intervention, we observed moderate modulation in steroid hormones and serum total PSA. In that clinical trial using whole soy isoflavones, 17 subjects were unable to complete the study compared to 3 in this trial using purified conjugated isoflavones. Subjects reported constipation and GI symptoms such as bloating, discomfort, diarrhea, and pain in both the groups, which were attributable to the soy protein content of these supplements and which required early stopping of these subjects from the study. Other Phase I and II trials (27–33) using soy isoflavone supplements in disease-free and men with prostate cancer have reported minor side effects such as breast changes, increased frequency of hot flashes, and lowered libido. Unlike those reported in the earlier trials, patients did not report these symptoms related to estrogenic effects at this dose during this period of intervention. Because we provided the subjects with purified isoflavones, we did not anticipate the GI symptoms as observed in previous studies attributed to soy protein. However, Grade I AEs of GI symptoms such as bloating, loss of appetite, dyspepsia, abdominal pain, and diarrhea were reported equally by both groups during the 3-mo intervention. These symptoms may be attributed to normal GI symptoms that are experienced by men in this age group as a consequence of varying dietary intake and intolerances. Similarly metabolic/laboratory changes in serum ALT and increases in lipase, amylase, hyperphosphatomia, and hypercalcemia were observed in equal numbers in both groups; we were unable to determine if these were possibly related to study agent or placebo. However, all such metabolic events were Grade I and II and occurred in both groups and did not

Table 3. Adverse Events by Category and Grade

	Prevastein HC ($N = 25$)		Placebo ($N = 28$)		
Category	No. of Subjects	No. of Subjects	No. of Subjects	No. of Subjects	P Value[a]
All adverse events	30	35	27	31	NS
By grade					NS
Grade 1	24	28	24	28	
Grade 2	4	5	3	3	
Grade 3	2	2	0	0	
By causality					NS
Unrelated	9	9	6	6	
Unlikely	7	8	3	3	
Possible	12	15	12	15	
Probable	2	3	6	7	
By expected					NS
Expected	12	16	15	18	
Unexpected	18	19	12	13	
By symptom					NS
Constitutional symptoms	1	1	1	1	
Dermatology	1	1	0	0	
Gastrointestinal	5	8	7	7	
Metabolic	14	14	15	16	
Pain	9	11	4	7	

a: P value indicates number of the episodes of adverse events comparing treatment arm to placebo arm.
Abbreviation is as follows: NA, not applicable.

produce clinical toxicity. One subject in the treatment arm reported a dermatalogical symptom, which was determined to be unrelated to agent by the study physician.

In one of the first Phase I clinical trials to examine the clinical characteristics and pharmacokinetics of purified soy isoflavones (28), 30 healthy men ingested a single dose of 1 of 2 isoflavone preparations purified from soy. The delivered doses of genistein (1, 2, 4, 8, or 16 mg/kg body wt) were higher than those previously administered to humans; however, no clinically significant behavioral or physical changes after treatment were observed. Although elevations in lipoprotein lipase and hypophosphatemia that were possibly related to the treatment were reported, no clinical toxicities were observed. They concluded that dietary supplements of purified isoflavones administered to humans in single doses exceeding normal dietary intake manyfold resulted in minimal clinical toxicity. Most important, the potent agent that has the significant effect on prostate carcinogenesis is isoflavones and not the soy protein. Thus, purified isoflavones preparations may be the ideal choice of agent in clinical trials. Studies have also illustrated (34) large variability in isoflavone databases and food labeling, thus reinforcing the need to use purified isoflavones in intervention trials. The choice of using purified isoflavones at a dose of 80 mg per day without the soy protein was based on these studies.

Similarly, in a multidose study of purified isoflavones, genistein and daidzein were rapidly cleared from plasma and excreted in urine. Pharmacokinetic data for continuous dose administration were similar to single-dose administration for the isoflavones investigated except that slightly longer circulation times for daidzein (27) were observed. Other Phase I clinical trials using purified isoflavones were able to demonstrate that considerable quantities of isoflavones were excreted in urine as conjugates. The mean elimination half-lives with both formulations were 3.2 h for free genistein and 4.2 h for free daidzein. The mean pseudo half-lives were 9.2 h for total genistein and 8.2 h for total daidzein (28). The studies demonstrate that genistein and daidzein (free and total) were rapidly cleared from plasma and excreted in urine. There may thus be a need for providing a continuous dose of isoflavones, mimicking the intake of Asian populations known for their daily intake. Variability in absorption of soy foods has been observed in human clinical trials and attributed to intake of other nutrients that alter the gut flora, the composition of ethnic diets, and individual differences (35). Urinary excretion increases with dose, frequency, and length of time the supplement is used. A threefold to fivefold increase in plasma levels of isoflavones was observed in the study reported by Seow et al. (36) with varying doses of isoflavone intake between the 25th and 75th percentiles. In observing the pharmacokinetics of isoflavones in healthy women, Setchell et al. (37) determined that after a single-bolus ingestion of 10, 20, or 40 g of isoflavones from soy nuts, peak serum daidzein and genistein concentrations were attained after 4 to 8 h, and elimination half-lives were 8.0 and 10.1 h, respectively, thus requiring multiple doses per day to maintain elevated plasma isoflavones. To produce a significant and continuous dose of isoflavones, we provided isoflavones in 2 divided doses of 40 mg purified conjugated isoflavones to total 80 mg per day. Compliance to the study agent and dose was monitored by standard pill counts, diet records, and plasma isoflavone levels and by providing subjects with a list of foods rich in isoflavones to avoid. To eliminate other micronutrient deficiencies and to ensure that subjects did not consume other nutritional supplements with isoflavones, we provided the cohort with a standard multivitamin/mineral pill during the entire course of the study. As a result, we were able to significantly increase plasma diadzein, glycitein, and genistein levels in the treatment group, with a steep increase noted in the 4-wk period, compared to increases at 12 wk, although the plasma levels continued to remain higher in the isoflavone-treated group throughout the treatment period compared to men in the placebo arm. Compliance to dietary restriction of isoflavone-rich food is demonstrated by the unchanged, low plasma levels of isoflavones observed in the control group in the double-blinded, randomized clinical trial.

The concept of delaying or preventing transformation using nutrients as chemopreventive agents remains a viable goal for the future of cancer control. As demonstrated by our previous work, purified isoflavones are potent proteasome inhibitors (18). We have now demonstrated that purified isoflavones at this dose of 80 mg administered in 2 divided doses to provide a continuous dose is generally well tolerated, with no clinical toxicity, in contrast to the observed AEs observed with whole soy protein supplementation by our group and others and the toxicities observed in the PS-341 trials and thus offers promise to be developed as a potent chemopreventive agent to prevent cancer progression and for CaP prevention. Based on the promising results of our studies regarding the relative safety, a definitive Phase II clinical trial, powered to examine the effects of a standardized purified isoflavone preparation in inhibiting the progression to CaP in larger cohort diagnosed of early stage CaP or at high risk, is a logical next step.

Acknowledgments and Notes

The research study was funded by the National Institute of Health—National Cancer Institute U10 CA81920. Address correspondence to Nagi B. Kumar, Ph.D., R.D., FADA, Associate Professor, Division of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida College of Medicine, 12902 Magnolia Drive, Tampa, FL 33612. Phone: 813-903-6885. FAX: 813-903-7183. E-mail: Nagi.Kumar@moffitt.org.

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