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Evaluation of the Aromatase Inhibition Potential of Freeze-Dried Grape Powder

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Abstract

Objective—To determine the role of freeze-dried grapes as a potential aromatase inhibitor by testing of plasma hormone levels.

Methods—A six-week study was conducted involving postmenopausal women during which 94 g of freeze-dried grape powder was consumed in addition to their usual diet. Plasma hormones were measured before and after the treatment.

Results—Of the 18 women involved in the study, average age and body mass index were 61.4 years and 24.4 respectively. For the hormone levels studied, the following median (interquartile range) percentage changes from baseline to six-week values were found: estradiol +11.8% (−34.4%, +44.2%), $p = .42$; estrone +3.4% (−15.7%, +12.9%), $p = .64$; estrone sulfate +5.3% (−19.9%, +56.3%), $p = .35$; testosterone −1.5% (−14.7%, +10.7%), $p = .97$; and androstenedione +12.6% (−17.1%, +49.1%), $p = .15$. The hormone levels did not significantly change between baseline and six weeks. Further, the changes that were observed did not tend to go in the

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hypothesized direction (estrogens and conjugates increased slightly, and testosterone decreased slightly). Only androstenedione showed a trend toward change in the hypothesized direction.

Conclusions—In this study, there was no evidence that plasma hormone levels are altered by six weeks of daily consumption of 94 g of freeze-dried grape powder.

Keywords

biobanking; breast cancer; epidemiology; grape seed extract

INTRODUCTION

The etiologic role of estrogens in the pathogenesis of breast cancer is widely accepted and well documented (Clemons & Goss, 2001; Henderson & Bernstein, 1996). It has been demonstrated repeatedly that estrogens can induce and promote mammary tumors in rodents (Bernstein & Ross, 1993). Epidemiologic studies in humans have consistently demonstrated that early menarche, late menopause, nulliparity, late age at first full-term pregnancy, and obesity in postmenopausal women are associated with significantly increased risk of breast cancer (Henderson & Bernstein, 1996). All of these risk factors are thought to arise because of length of exposure to estrogen. Evidence in support of an association between estrogens and breast cancer includes studies of endogenous estrogen levels that were performed by Henderson and Bernstein (1996). These studies have suggested that, in addition to length of exposure, increased levels of estrogen might also be related to breast cancer risk. Similar observations were reported from a large prospective study in which women with high serum levels of estrogen, particularly free estradiol (E2), the most potent and biologically active estrogen, were at substantially elevated risk for developing breast cancer (Key, Appleby, Barnes, & Reeves, 2002; Toniolo, Levitz, & Zeleniuch-Jacquotte, 1995).

The main pathway for estrogen biosynthesis is through the conversion of androstenedione to estrone (E1) and testosterone to estradiol (E2), catalyzed by cytochrome P450, CYP19 (aromatase), an enzyme that is present in the ovary as well as in many non-endocrine tissues (fat, muscles, normal and malignant breast tissues). In addition, there are also other enzymatic pathways that act to *decrease* levels of estrogen. Conjugation (addition) of a sulfate group, or sulfation, is the major metabolic pathway for estrogen in humans that is involved in the removal of active estrogens. The two most important members of the human sulfotransferase (SULT) family are SULT1E1 and SULT1A1, with 1E1 having the highest affinity for estrogen, but SULT1A1 being more widely expressed (Weinshilboum et al., 1997; Weinshilboum & Wang, 2004).

Aromatase inhibitors have been introduced recently into the clinic for the therapy of breast cancer for both advanced disease (Ingle & Suman, 2005) and in the adjuvant setting (Ingle, 2011). When administered to postmenopausal women, aromatase inhibitors effectively inhibit the peripheral synthesis of estrogens, leading to a more than 90% reduction in circulating estrogen levels (Demers, 1994; Geisler et al., 1996; Paridaens, Roy, & Nooij, 1998). A recent meta-analysis of data from randomized breast cancer clinical trials have demonstrated the superiority of aromatase inhibitors over tamoxifen for women with early breast cancer (Dowsett, Cuzick, & Ingle, 2010).

Grapes are known to contain important active compounds, including flavones and isoflavones, which have actions similar to aromatase inhibitors. These flavones and isoflavones have been shown by computer modeling and confirmed by site-directed mutagenesis to inhibit the aromatase enzyme (Chen, Zhang, & Sherman, 2003); further, red wine extracts have been also shown to reduce aromatase activity (Chen et al., 2003; Eng, Ye, & Williams, 2003). Therefore, the possibility that natural food constituents, such as isoflavones, might inhibit estrogen synthesis represents an exciting, potentially chemopreventive strategy. However, it is also known that the same flavones might also inhibit estrogen sulfate conjugation, which is catalyzed by SULT (Eaton, et al., 1996; Gibb, Glover, & Sandler, 1987). A study using grape seed extract was found to inhibit aromatase activity and reduce androgen-dependent tumor growth in a breast cancer xenograft model (Kijima, Phung, Hur, Kwok, & Chen, 2006). The goal of this study was to determine whether consumption of freeze-dried grape powder would alter estrogen levels in 19 postmenopausal women. We hypothesized if serum levels of estrogen decrease after consuming freeze-dried grape powder, then the next logical step would be to propose further clinical studies to test whether this change is associated with reduced risk of breast cancer.

METHODS

Participants

Eligible participants were postmenopausal women of at least 18 years of age or older. Postmenopausal was defined as women who had both ovaries removed or no menstrual period for at least 12 consecutive months. Eligibility criteria included: (a) current non-smoker, (b) willing to maintain current weight, (c) ability to give informed consent and complete food records alone or with assistance, (d) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and (e) willing to provide research blood. Women were excluded if they had: (a) a history of allergic or other adverse reaction to grapes, (b) current use of hormone therapy, including estradiol, estrone, and progestins, (c) a personal history of cancer, including ductal carcinoma in situ of the breast, and (d) a personal history of diabetes or glucose intolerance. Subjects were not excluded for having a history of basal or squamous cell skin cancer or lobular carcinoma in situ of the breast.

Subjects were also asked to keep food records for nine days of the study, including three days at study start (days 1–3), three days at study midpoint (days 21–23), and three days at study end (days 40–42). Subjects were reminded with a phone call prior to days 21 and 40 to complete these. The food records were used to estimate usual intake of grapes, grape juice, and red wine.

Intervention: Freeze-Dried Grape Powder

The grape powder used in this study was a composite of fresh red, green, and blue-black California grapes (seeded and seedless varieties) that have been frozen, grounded with food-quality dry ice, freeze-dried, and re-grounded using Good Manufacturing Practices for food products throughout. The powder was processed and stored to preserve the integrity of the biologically active compounds found in fresh grapes. As with fresh grapes, the powder is known to contain resveratrol, flavans (including catechin), flavonols (including quercetin),

anthocyanins, and simple phenolics. The mixture of various grapes in the powder was designed to reflect the mix and proportion of varieties that comprise the majority of the California grape harvest in a given year, which in turn represents the variety of grapes available to consumers to eat. The powder in this study was a blend of 2001 and 2003 grape powders. An analysis of the freeze-dried table grape powder used in this study is included in the supplemental materials. The freeze-dried powder was kept in moisture-proof containers at −70°C until distributed to the participants. Subjects were asked to keep the powder in an air-tight container in their freezer.

For the study, women were asked to consume 94 g of grape powder each day for six weeks, in addition to their usual diet. This amount of grape powder was selected to maximize the likelihood of meaningful results while considering the need to avoid a weight gain during the study period. Ninety-four grams of grape powder contains approximately 400 kilocalories. A nutrient analysis of the freeze-dried table grape powder is included in the supplemental materials. Subjects were asked to return any unused powder at the end of the study.

Objective

The objective of this study was to determine whether consumption of freeze-dried grape powder would alter estrogen levels in 19 postmenopausal women. We hypothesized that serum levels of estrogen would be lower after, compared with before, six weeks of daily consumption of 94 g of freeze-dried grape powder.

Outcomes—Hormone Measurements

Plasma measurements of plasma E1, E2, E1-conjugates, E1-sulfates (E1-S), testosterone, and androstenedione were conducted on samples collected before and after six weeks of daily grape powder intake. Samples were measured to assess the potential net effects of grape powder on blood hormone levels. The assays were conducted utilizing combined gas chromatography (GC) negative chemical ionization tandem mass spectrometry (MS) (GM/NCI/MS/MS) and liquid chromatography (LC) electrospray tandem MS (LC/ES/MS/MS) (Pharmanet, Princeton, NJ). Since steroids are present in all human tissues and plasma, calibration samples were prepared in water. Quality control samples (QCs) were prepared in either serum or plasma and fortified to achieve higher QC levels. For each analyte, a deuterated internal standard (IS) was added. Sample cleanup was achieved with Bond Elute solid phase extraction cartridges. Two aliquots were collected from the cartridges. The first aliquot contains E1-S, and the second contains other analytes. The first aliquot was subjected to LC/MS/MS to detect E1-conjugates. It was also hydrolyzed to E1 and subjected to GC/MS/MS to make it possible to calculate the total E1-conjugate concentration. The other analytes were subjected to derivatization with pentafluorobenzoyl chloride, fluorox, and MSTFA. These reagents react with 3-hydroxy, 3-keto, and 17-hydroxy groups respectively. The derivatized analytes, together with their respective internal standards, were injected onto a DB-17GC column.

Sample Size

This study was powered with a sample size of 19 to detect a mean change of 30% or greater in hormone levels from baseline to six weeks. Differences smaller than this were judged a priori to be unlikely to have clinical relevance.

Statistical Methods

The percentage change between pre-intervention (baseline) and six weeks post-intervention hormone levels was calculated as 100 × [(six weeks – baseline)/baseline]. Wilcoxon signed-rank tests were used to test the null hypothesis that the average percentage change was equal to zero. Pre- and post-intervention serum levels of plasma E1, E2, E1-conjugates, and E1-S, as well as the change between the two timepoints, were also reported descriptively with median and interquartile range (IQR). The correlation of patient's age and body mass index (BMI) with hormone levels was estimated using Spearman's rank correlation coefficient (r). Significance tests were two-sided with $\alpha = 0.05$. Analysis was performed using SAS (version 9.2).

The study protocol was approved by the Institutional Review Board of the Mayo Clinic. The study was registered at Clinical-Trials.gov (registration no. NCT00611104).

RESULTS

Nineteen postmenopausal women were enrolled in this study. One patient was subsequently excluded because she did not meet the inclusion criteria of being postmenopausal or having had both ovaries removed; she was 44 years old and had undergone a hysterectomy but retained both ovaries and had baseline estradiol values consistent with premenopausal levels. Thus, the final sample for analysis included 18 patients. In the remaining 18 women, the mean age at enrollment was 61.4 years; mean BMI was 24.4 (Table 1). Among these 18 women, patient adherence and the level of compliance was judged to be high due to the low adverse side effects and minimal additional work on the part of the subjects. Only three subjects returned any unused grape powder at the end of six weeks. Out of 84 (47 g) packets distributed per subject, one subject returned only 2%, one returned 8%, and another returned 46%. The remaining 15 subjects did not return any unused powder. Dietary records were reviewed for usual intake of grapes, grape juice, and red wine, and no unusual dietary changes were noted. Results remained unchanged when these three subjects were excluded from analyses (data not shown).

As shown in Table 2, hormone levels did not change significantly between baseline and after six weeks of dietary supplement with freeze-dried grapes. Further, the changes that were observed did not tend to go in the hypothesized direction (estrogens and conjugates increased slightly, testosterone decreased slightly). Only androstenedione showed a trend toward change in the hypothesized direction.

We examined the effect of BMI and age on baseline hormone levels and changes in hormone levels across the six-week intervention period. Age showed weak to moderate (negative) correlations with every hormone level at baseline (Table 3). Baseline BMI showed moderate to strong (positive) correlations with every hormone level at baseline (Table 3). Age was

weakly correlated ($r = -0.28$) with percentage change in testosterone but showed correlations <0.20 in magnitude with percentage change in estradiol, estrone, estrone sulfate, and androstenedione (data not shown). Baseline BMI was weakly correlated with percentage change in estrone ($r = 0.30$) and androstenedione ($r = 0.23$) but less so with changes in other hormone levels.

There was a small but statistically significant ($p = .008$) change in BMI between baseline and six weeks (median +0.20, range −0.11 to +0.71), with over half (59%) experiencing a small increase. However, percentage change in hormone levels was generally not correlated with the change in BMI; the percentage change in androstenedione showed a weak correlation ($r = -0.21$) with BMI change, and even smaller correlations were observed for percentage change values of other hormones. The findings were similar for body weight, which showed a median increase of 0.6 kg (range: −0.3 to +1.6), $p = .01$.

DISCUSSION

Our study examined the potential use of freeze-dried grape powder as an aromatase inhibitor with the hope to infer its use as a natural means to reduce breast cancer risk. Our data showed that hormone levels do not change significantly after six weeks of dietary supplementation, and also mostly do not show trends in the hypothesized direction in postmenopausal women taking 94 g of grape powder daily. Only androstenedione showed a trend toward change in the hypothesized direction (increase) with a median percentage change from baseline of +12.6% ($p = .15$).

We examined the effect that BMI and age would have on hormone levels. We know that both age and BMI have been shown in various studies to be associated with an increased risk of breast cancer (Yang, Chang-Claude, & Goode, 2011). As one would expect, age and baseline BMI were correlated with baseline hormone levels to varying degrees, but neither was correlated with changes in hormone levels. The change in BMI and body weight between baseline and six weeks was statistically significant but small, and changes in hormone levels were not correlated with the change in BMI or body weight for the most part. The small trend toward weight gain seen in our study may be related to the 400 kilocalories found in the daily grape powder. Such a weight gain over a longer period has the potential to decrease both subject compliance and long-term acceptability of the dietary supplement.

Although the sample size in this study was relatively small and this could be seen as a limitation, the study was powered to detect a mean change of 30% or greater in hormone levels from baseline to six weeks. Differences smaller than this judged a priori were unlikely to have clinical relevance. The observed median percentage change values were well below 30% for all hormone levels; thus, we do not believe that the study's negative findings are a result of insufficient statistical power. One study subject was excluded from our analyses because although she met our enrollment criteria of being without menses for over 12 months, she had had a hysterectomy without oophorectomy. Therefore, she was hormonally premenopausal, thus was excluded from analyses.

The grape powder used in this research study is not considered a supplement, and is not available for sale commercially. It is made simply from whole fresh grapes that are ground, freeze-dried, and blended to make a powder, so it is essentially a whole food. Thus, product safety is not applicable. It is designed for use solely in research studies as a replacement for fresh grapes, to provide a useable whole grape product, which is available year-round for research.

Many are studying and trying to understand ways in which women can reduce their risk of breast cancer development based on known associated risk factors and further understanding of risk associated with estrogen exposure. Grape seed extract (GSE) has been a “hot topic” with not only breast cancer research but also for colon cancer, hypertension, hyperlipidemia, to name a few. In another, similar study (Wahner-Roedler et al., 2014), we examined whether there was any evidence of estrogen suppression by GSE. After 12 weeks of supplementation with GSE, we found no evidence that GSE, in the four daily doses administered, did not significantly decrease estrogen or increase androgen precursors. Similarly, the results from this study indicate that the grape powder as utilized does not function as an aromatase inhibitor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of 18 Postmenopausal Women at Baseline

Characteristic	Frequency (%)
Age (years)	
Mean (SD)	61.4 (8.3)
Median (range)	60 (49–81)
Age category, *n* (%)	
<50 years	1 (5.6%)
50–54 years	2 (11.1%)
55–59 years	6 (33.3%)
60–64 years	2 (11.1%)
65–69 years	6 (33.3%)
≥70 years	1 (5.6%)
BMI	
Mean (SD)	24.4 (3.7)
Median (Range)	24.3 (15.9–32.3)
BMI category, *n* (%)	
<18.5 (underweight)	1 (5.6%)
18.5–24.9 (normal weight)	10 (55.6%)
25–29.9 (overweight)	6 (33.3%)
≥30 (obese)	1 (5.6%)
ECOG performance score, *n* (%)	
0	16 (88.9%)
1	2 (11.1%)
Estradiol, pg/ml	
Median (IQR)	4.5 (2.2, 7.6)
Estrone, pg/ml	
Median (IQR)	21.5 (14.9, 26.4)
Estrone sulfate, pg/ml	
Median (IQR)	199.5 (89.1, 258.5)
Testosterone, pg/ml	
Median (IQR)	179.5 (127, 268.8)
Androstenedione, pg/ml	
Median (IQR)	454.5 (371, 649.8)

IQR: Interquartile range, 25th and 75th percentile.

TABLE 2

Change in Hormone Levels Between Baseline and Six Weeks Among 18 Postmenopausal Women in the Mayo Clinic Freeze-Dried Grape Study

Median (IQR)	Six Weeks	Change (Six Weeks – Baseline)	Percentage Change (Six Weeks – Baseline)/Baseline	*p*-value[a]
Estradiol, pg/ml	5.3 (2.1, 7.5)	+0.3 (−1.2, +1.8)	+11.8% (−34.4%, +44.2%)	.42
Estrone, pg/ml	22.9 (15.2, 29.3)	+1 (−4.4, +3.1)	+3.4% (−15.7%, +12.9%)	.64
Estrone sulfate, pg/ml	185.5 (102.9, 255.5)	+9.5 (−55.3, +69.5)	+5.3% (−19.9%, +56.3%)	.35
Testosterone, pg/ml	190 (126, 260.3)	−3 (−23, +15.8)	−1.5% (−14.7%, +10.7%)	.97
Androstenedione, pg/ml	480 (354.5, 686.5)	+54 (−52, +238.5)	+12.6% (−17.1%, +49.1%)	.15

IQR: Interquartile range, 25th and 75th percentile.

[a] *p*-value from Wilcoxon signed-rank test of null hypothesis that the average percentage change between baseline and six weeks is equal to zero.

TABLE 3

Correlations of Age and BMI with Baseline Hormone Levels

Spearman's rho (*r*)	Age	Baseline BMI
Baseline hormone levels		
Estradiol	$r = -0.29$	$r = 0.80$
Estrone	$r = -0.31$	$r = 0.71$
Estrone sulfate	$r = -0.20$	$r = 0.66$
Testosterone	$r = -0.14$	$r = 0.55$
Androstenedione	$r = -0.44$	$r = 0.54$