

# Challenges of Conducting Clinical Trials of Natural Products to Combat Cancer

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**Abstract:** Numerous drugs that the US Food and Drug Administration (FDA) has approved for use in cancer therapy are derived from plants, including taxanes such as paclitaxel and vinca alkaloids such as vinblastine. Dietary supplements are another category of natural products that are widely used by patients with cancer, but without the FDA-reviewed evidence of safety and efficacy—be it related to survival, palliation, symptom mitigation, and/or immune system enhancement—that is required for therapy approval. Nearly half of patients in the United States with cancer report that they started taking new dietary supplements after being given a diagnosis of cancer. Oncologists are challenged in providing advice to patients about which supplements are safe and effective to use to treat cancer or the side effects of cancer therapy, and which supplements are antagonistic to standard treatment with chemotherapy, radiation, and/or immunotherapy. Despite the large number of trials that have been launched, the FDA has not approved any dietary supplement or food to prevent cancer, halt its growth, or prevent its recurrence. In this article, we review the primary challenges faced by researchers attempting to conduct rigorous trials of natural products, including shortages of funding due to lack of patentability, manufacturing difficulties, contamination, and lack of product consistency. We also highlight the methods used by dietary supplement marketers to persuade patients that a supplement is effective (or at least safe) even without FDA approval, as well as the efforts of the US government to protect the health and safety of its citizens by ensuring that the information used to market natural products is accurate. We close with a summary of the most widely used databases of information about the safety, efficacy, and interactions of dietary supplements.

## Introduction

Throughout recorded human history, plants and other natural products have been used as purported treatments for cancer. Hartwell listed more than 3000 plant products reported to have been used in the treatment of cancer,<sup>1</sup> although what constituted cancer often was

### Keywords

Cancer, clinical trials, dietary supplements, natural products, patents

**Table 1.** New Small-Molecule Anticancer Drugs Approved by the FDA,<sup>2</sup> 1981-2010

Product Classification	Number Approved	Examples
Natural	11	paclitaxel (1993), romidepsin (Istodax, Celgene; 2010)
Totally synthetic	20	sorafenib (Nexavar, Bayer/Onyx; 2005), miriplatin (2010)
Derived from a natural product	32	temsirolimus (Torisel, Pfizer; 2007), vinflunine (2010), cabazitaxel (Jevtana, Sanofi-Aventis; 2010)
Synthesized, but pharmacophore is from a natural product	11	clofarabine (Clolar, Genzyme; 2005), decitabine (2006)
Synthesized, but mimics a natural product	16	dasatinib (Sprycel, Bristol-Myers Squibb; 2006), pazopanib (Votrient, Novartis; 2009)
Synthesized, but pharmacophore is from a natural product and mimics a natural product	8	vorinostat (Zolinza, Merck; 2006), degarelix (Firmagon, Ferring; 2009)

ill-defined. More recently, Newman and Cragg reported that of 98 new small-molecule anticancer drugs that had been approved by the US Food and Drug Administration (FDA) between 1981 and 2010, only 20 were synthetic. The remaining 78 drugs either were natural products (11) or were derived from natural products (67) based on a series of classifications<sup>2</sup> shown in Table 1.

The earliest anticancer drugs approved by the FDA and derived from natural (plant extract) products were the vinca alkaloids (vincristine in 1963 and vinblastine in 1965), which were isolated from Madagascar periwinkle plants found growing in Jamaica and the Philippines. They were discovered when extracts of the plant were being evaluated as potential oral hypoglycemic agents. When researchers found that the extracts reduced white blood cell counts in rats and extended the lives of mice with lymphocytic leukemia, they isolated vincristine and vinblastine as the active anticancer agents.<sup>3</sup> Subsequently, the semisynthetic analogues vinorelbine and vindesine were approved for the treatment of a variety of cancers. These agents are used today, often in combination with other drugs.<sup>4,5</sup> In 2015, clinicaltrials.gov listed more than 1200 active clinical trials evaluating one or more of these vinca alkaloids, in combination with other drugs, as interventions in clinical trials to treat cancer.<sup>6</sup> Clinicaltrials.gov is a website sponsored by the National Institutes of Health (NIH) that lists clinical trials across the United States

Another important addition to the anticancer armamentarium was the taxane family of drugs. Paclitaxel was first isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) in the state of Washington as part of a collection program undertaken by the US Department of Agriculture on behalf of the National Cancer Institute.<sup>7</sup> Various *Taxus* leaves had been used by Native Americans to treat disease and in the traditional Asiatic Indian (ayurvedic) medicine system to treat cancer and other diseases. The precursor of paclitaxel, baccatin III, occurs in abundance in the needles of various *Taxus* species. These plants pro-

vide a ready supply of baccatins, which are converted to paclitaxel and synthetic docetaxel, both of which have been approved by the FDA and currently are used in the treatment of multiple cancers.<sup>7</sup>

### Clinical Trials of Dietary Supplements and Foods

The successful use of extracts of plants collected for their potential medical application contrasts sharply with the failure of clinical trials to lead to the regulatory approval of common foods and dietary supplements (eg, green tea; pomegranate; lycopene; soy; mistletoe; vitamins C, D, and E; selenium; resveratrol) as treatments for cancer. Americans spent more than \$36 billion in 2014 on dietary supplements.<sup>8</sup> Nearly half of patients with cancer reported that they started taking new dietary supplements after being given a diagnosis of cancer,<sup>9</sup> and 58% of people who consume dietary supplements report they do so for the prevention or treatment of cancer.<sup>10</sup>

Dietary supplements derived from plants (eg, ginger, garlic, cannabis) and animals (eg, shark cartilage, scorpion venom), as well as some fruits and vegetables, have been promoted on television and the Internet for their purported ability to prevent or even treat cancer. Patients frequently ask their oncologists and other physicians whether these products are effective and safe. In many cases, the dietary supplements in question have shown antitumor activity in preclinical studies or small exploratory, nonrandomized, early-phase clinical trials, and patients come to their physicians with copies of promotional literature highlighting selected results of that research. Hospitals are not immune to supporting such promotions. For example, a Google search on January 16, 2016, for “pomegranate and cancer” identified more than 1 million websites. Of the top 4 sites listed, 3 were well-known medical centers. One of them promoted pomegranate as a “superfood” and highlighted its own

research showing that pomegranate suppresses substances that breast cancer tumors need to grow and other research reporting that pomegranate contains 2 substances “with potential to fight colon cancer.” It closed with the statement, “Further studies at [that medical center] will seek to better understand how the pomegranate can promote prevention of cancer.”<sup>11</sup>

Laboratory researchers who discover antitumor activity of compounds in preclinical studies seek out clinical researchers willing to conduct trials of the compounds in humans. However, favorable preclinical results usually do not translate to success in clinical trials. Preclinical studies in vitro often involve continuous exposure to high concentrations of a natural product of interest. This type of exposure is typically not possible in humans, particularly in the case of oral medications that might have limited bioavailability. Additionally, clinical trials are expensive relative to preclinical studies. Because natural products cannot be patented in themselves, the manufacturers of natural products do not have the patent protection afforded the manufacturers of pharmaceuticals and, with few exceptions, do not have the pricing power that would allow them to pay trial costs. Funding for the trials that have been launched comes from the National Center for Complementary and Integrative Health (NCCIH), formerly the National Center for Complementary and Alternative Medicine (NCCAM), or from an aggregation of small grants from the American Society of Clinical Oncology (ASCO), disease-specific cancer foundations, and investigators’ institutions that later are expanded with larger grants from philanthropists who believe that a supplement may help patients and are eager to sponsor trials that can demonstrate safety and efficacy.

More than 1000 clinical trials of dietary supplements are reported at clinicaltrials.gov. The goal of these trials is to provide physicians with reliable answers to patients’ questions about the safety and efficacy of the dietary supplements and foods promoted for their potential impact on cancer. Table 2 shows the number of cancer-related clinical trials of selected dietary supplements and foods reported at clinicaltrials.gov in November 2015. Preclinical efficacy does not necessarily predict success in humans, and as mentioned earlier, none of the trials of dietary supplements have yet led to regulatory approval. Furthermore, clinical trials of dietary supplements have produced conflicting results, as is seen in the case study of pomegranate in prostate cancer that appears later in this article.

### ***Rigor in Clinical Trial Design***

Although clinical trials of natural products often evaluate commonly consumed compounds, they nonetheless are testing “drug” endpoints and must meet high standards

**Table 2.** Cancer-Related Clinical Trials of Selected Dietary Supplements and Foods<sup>12</sup>

Agent	Number of Clinical Trials of Use of Agent to Target Cancer
Vitamins	750
Tea	59
Soy	56
Selenium	47
Mistletoe	14
Grapes	13
Pomegranates	13
Lycopene	11
Resveratrol	11

of trial design and patient safety. In the United States, the trial design must be reviewed by the FDA through the Investigational New Drug (IND) application process. The IND application describes the drug’s source and manufacturing process, in addition to results of laboratory testing that demonstrate consistency of the active ingredients as well as potential contaminants. The IND application also summarizes (and includes) the detailed protocol for the trial, including patient selection, dosing, administration (eg, intravenous vs oral), safety information, and endpoints.

### ***Common Clinical Trial Endpoints***

Clinical trials of dietary supplements and foods may evaluate either a single agent or a natural product in combination with approved or experimental cancer therapies. Some trials focus on efficacy in disease modification, and the endpoints consist of cancer prevention, progression-free survival, recurrence-free survival, overall survival, or biomarkers predictive of survival, such as prostate-specific antigen doubling time (PSA-DT) in prostate cancer. Other trials focus on improvements in quality of life, such as a decreased number of adverse events<sup>13</sup> or increased tolerance to chemotherapy.<sup>14</sup> Dose-finding studies have also been used to determine whether low doses can have the same effect as high doses, and how many pills can be consumed safely and consistently.<sup>15,16</sup>

Pharmacokinetic (PK) endpoints can be important, especially in phase 1 studies, in which understanding the way the body processes a drug is critical to further stages of drug development. For example, PK analysis in clinical trials was needed to determine that oral doses of ascorbic acid (vitamin C) are consistently subtherapeutic and that only intravenous administration can result in therapeutic levels.<sup>17</sup> However, PK studies often are not possible for some natural products, such as fruits and vegetables,

because the active ingredient is sometimes unknown. Trials also determine safety, particularly when a food or dietary supplement is used in doses higher than those commonly suggested on labels or consumed at meals. Combination trials also may evaluate interactions of a drug with food, as in the measurement of the effects of grapefruit juice on the PK action of sunitinib (Sutent; Pfizer; NCT01743300).

### Why Natural Products Fail to Gain Regulatory Approval

To date, the FDA has not approved any food or dietary supplement as a drug for cancer prevention or treatment. The simple explanation for this is that no phase 3 clinical trial of a dietary supplement or food has shown sufficient efficacy and safety in preventing or treating cancer. What is striking is that there have been so many phase 2 trials with promising results and so few follow-up phase 3 trials. A likely explanation is that manufacturers of dietary supplements perceive a positive phase 2 trial result as sufficient to promote their product without having to go through the rigor and expense of a randomized, placebo-controlled phase 3 trial.

#### *Lack of Patent Protection Limits Financial Incentives to Fund Phase 3 Trials*

The general lack of patent protection for dietary supplements and food products means that manufacturers generally do not benefit from FDA approval in the way that manufacturers of proprietary compounds do. Without patent protection, the manufacturer faces price pressure from competitors and cannot obtain enough profits from high product prices to pay for the costs of large phase 3 trials. However, in most cases, the manufacturers do not need FDA approval to earn money selling food and dietary supplements claimed to help prevent and/or treat cancer. Consumers learn about the health benefits of dietary supplements not from physicians, for whom FDA approval would be important, but through promotions on the Internet and television and by naturopaths. The health claims of these sources are usually based on pre-clinical findings or the results of small, early-phase clinical trials that may sound as impressive to the general public as claims based on a phase 3 trial.

A recent change in policy enacted by the US Patent and Trademark Office (USPTO) compounds the challenges for manufacturers. The USPTO asserts that natural products no longer can be patented because of the Supreme Court's 2013 decision in *Association for Molecular Pathology v Myriad Genetics*,<sup>18</sup> in which the court ruled that the isolation of genes that are found in nature does not make them patentable. On March 4, 2015, the USPTO

updated its guidelines for patent examiners, instructing them to reject patent claims that seek to protect all purified natural products, not just DNA.<sup>19</sup> This new guideline makes patenting extracts of natural products much more problematic, and some patent attorneys question whether paclitaxel would be approved today. However, for drugs like nanoparticle albumin-bound paclitaxel (also called nab-paclitaxel; Abraxane, Celgene), a fast-dissolving form of paclitaxel, the manufacturing and/or formulation process may be novel enough to allow a new composition of matter patent to be obtained or prior patent protection to be maintained.

#### *Manufacturing Difficulties Also Challenge Clinical Researchers*

Researchers attempting to conduct clinical trials of foods and dietary supplements frequently encounter manufacturing problems that are not experienced in the manufacture of pharmaceuticals synthesized in large quantities. For a clinical trial of pulverized muscadine grape skin, for example, a single manufacturer's extract was selected. However, the researchers learned that the contents of various bottles of the manufacturer's extract might have been harvested from different farms, with different soil types and different weather conditions, so that they differed in the amounts of the active ingredients. In addition, different parts of the fruit, juice, skin, or seeds have different levels of active ingredients and also require different manufacturing processes. To ensure that the level of active ingredients was consistent across batches, the researchers undertook extensive testing and isolated one batch (for a single season) of grape skin extract for use in the trial.<sup>20</sup> However, reports of the trial results should always be partially qualified to warn that the results apply only to the batch of the manufactured product tested and not necessarily to similar products of other manufacturers or even to other batches of the same product from the same manufacturer. That said, the results of research can be extended to additional batches by controlling the concentration of what are assumed to be the active ingredients.

A far more troubling manufacturing problem is that dietary supplements and food processing plants do not necessarily maintain the same level of product consistency and quality control used in proprietary drug manufacturing. For example, PC-SPES was marketed as a mixture of 8 herbs that individually had estrogenic activity, stimulated natural killer cell activity, and/or inhibited 5 $\alpha$ -reductase.<sup>21</sup> It was promoted to patients with prostate cancer as a means of supporting healthy prostate function and boosting the immune system. Its name is a combination of PC (for "prostate cancer") and the Latin word *spes* ("hope"). Clinical trials showed that treatment with PC-SPES quickly lowered PSA levels in

patients with prostate cancer and also improved quality of life and reduced pain.<sup>22</sup> Researchers were surprised that an over-the-counter herbal remedy could have such an immediate and substantial impact on the PSA level, so they conducted analyses of the compounds in PC-SPES. They discovered that samples of PC-SPES contained one or more of the following: the synthetic nonsteroidal estrogen diethylstilbestrol (DES)<sup>23</sup>; warfarin, a blood thinner; and indomethacin, a drug used to decrease inflammation.<sup>24</sup> All of these were FDA-regulated drugs. Other researchers found that PC-SPES contained additional estrogenic organic compounds that are distinct from DES and estradiol.<sup>25</sup> Because FDA-regulated compounds were included in PC-SPES, it was taken off the market in 2002, resulting in its manufacturer going out of business. These events caused the reliability of clinical trial results to be called into question. Moreover, patients who believed those trial results could have been harmed by the consumption of PC-SPES, underscoring the importance of quality control in the design and conduct of clinical trials of natural products.

Similarly troubling to clinical researchers are data from the University of Guelph, Ontario, Canada, showing that nearly all of 44 herbal products sold in North America and tested by researchers include substitutions, contaminants, or fillers.<sup>26</sup> Following up on that study, the New York State Attorney General's Office conducted additional testing of products from major retailers, including Walmart, Walgreens, GNC, and Target. A *New York Times* article about that investigation reported that 4 of 5 of the top-selling store brands of herbal supplements did not contain any of the herbs listed on their labels. At Walgreens, ginseng pills contained only powdered garlic and rice, and what was being sold as *Ginkgo biloba*—a Chinese plant promoted as a memory enhancer—contained little more than powdered radish, houseplants, and wheat (despite a claim on the label that the product was wheat- and gluten-free). The attorney general sent cease-and-desist letters to the 4 retailers, demanding that they remove the identified products (the lots that were tested) from their shelves and explain the procedures used to verify the ingredients in their supplements.<sup>27</sup> If patients cannot trust big-name retailers like Walgreens and Walmart, whom can they trust? The long-term answer is that patients should buy products that have been individually tested. As long as such testing is voluntary and rare,<sup>27</sup> however, the only advice that can be given is “buyer beware.”

## Regulation of Dietary Supplements

If researchers are not confident of the compounds in supplements, they will have no justification to move forward

with rigorous testing of the supplements. In the United States, dietary supplements are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994, which defines a dietary supplement as (1) a vitamin or mineral; (2) an herb or other phytochemical; (3) an amino acid; (4) a dietary substance used to supplement dietary intake and increase total dietary intake (eg, enzymes or tissues from organs or glands); or (5) a concentrate, metabolite, constituent, or extract of any of the foregoing. It is worth noting that foods such as fruits and vegetables are specifically excluded from this definition, even when sold as extracts.

The Food Additives Amendment of 1958, which updated the Food, Drugs, and Cosmetic Act of 1938, created to regulate food additives, is also sometimes employed by dietary supplement manufacturers to support claims of safety and implied government approval. The amendment defined food additives and said that an additive was “generally recognized as safe” (GRAS) if it had a long history of use before 1958 or, as specified in the FDA implementing regulations, if there is “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”<sup>28</sup> Some dietary supplements (eg, pomegranate juice and celery seed) were considered GRAS based on long-standing use.<sup>29</sup> The manufacturers of other dietary supplements retain independent panels of experts to affirm the safety of their products in a process, known as self-affirmation, that does not involve FDA review. The dietary supplement manufacturer derives 2 benefits from GRAS status of its product: (1) supplement marketing materials can include the GRAS designation; and (2) the product can be included as an additive in food products, opening new markets. However, the FDA explicitly restrained one company from using GRAS status in conjunction with health claims for a supplement, saying in a warning letter that the company's products “are not generally recognized as safe and effective for the above referenced uses and, therefore, the products are new drugs” that require an IND application and full FDA review before marketing.<sup>30</sup>

The DSHEA allows manufacturers of dietary supplements to use labels that include 3 types of claims: (1) nutrient content (eg, “high in calcium”); (2) “structure-function” or nutrition support (eg, “vitamin C prevents scurvy” or “calcium builds strong bones”); and (3) disease-related claims. Disease-related claims are the only claims that require FDA authorization based on a review of scientific evidence and substantiation. If the FDA does not review the evidence, the product label is required to state the following: “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, mitigate, or prevent any disease.”<sup>31</sup>



The FDA has approved only 3 cancer-related model claims for diet under the DSHEA<sup>31</sup>:

- “Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers.”
- “Low fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some types of cancer, a disease associated with many factors.”
- “Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, Vitamin A, or Vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Broccoli is high in vitamin A and C and is a good source of dietary fiber.”

The FDA is very specific about what must be included and excluded in these claims. In the third and most specific claim, for example, the FDA requires that the claim characterize fruits and vegetables as “foods that are low in fat and may contain dietary fiber, Vitamin A, or Vitamin C”; that it characterize specific foods as a “good source” of one or more of the following: dietary fiber, Vitamin A, or Vitamin C; and that it not specify types of fats or fatty acids or types of dietary fiber that may be related to the risk of cancer.<sup>31</sup> When a disease-specific health claim is made for a supplement, the FDA requires rigorous, large-scale clinical testing equivalent to what is required for the approval of pharmaceuticals.

The US Federal Trade Commission (FTC) also has a role in regulating dietary supplements under legislation pertaining to its mandate to ensure “truth in advertising.” According to the FTC, advertising for dietary supplements and foods must meet 3 requirements<sup>32</sup>:

- Advertising must be truthful and nondeceptive.
- Advertisers must have evidence to back up each of their claims.
- Advertisements cannot be unfair.

### How Supplement Manufacturers Elude Regulatory Limits

The US regulatory framework has been generally ineffective in removing unsafe supplements or supplements with no active agents from the market, and even less effective in stopping unsupported health claims from boosting sales. Food products are not classified as dietary supplements, so they are not covered by the DSHEA, nor are any dietary supplements that were widely sold before passage of the DSHEA in 1994 covered. Even for DSHEA-covered supplements, the enforcement task is monumental, as the number of food supplements grew

from 4000 in 1994 to approximately 75,000 in 2008.<sup>33</sup> In addition, the FDA must meet the very high legal standard of demonstrating “significant or unreasonable risk” in order to stop the sale of a supplement, which helps explain why ephedra-containing weight loss supplements were not removed from the market for more than 10 years, even after they had been shown to cause hundreds of deaths and thousands of adverse effects.<sup>34</sup>

Another promotional force, Internet-based marketing, appears to be unfettered by federal laws. Nine years after passage of the DSHEA, a team of pharmacologists analyzed the health content of all websites listed on the first page of search results for each of the 8 most widely used herbal supplements (Ginkgo biloba, St John’s wort, echinacea, ginseng, garlic, saw palmetto, kava kava, and valerian root). They found that 76% were retail sites either selling products or directly linked to a vendor, and that 81% of the retail sites made one or more health claims. Of the health claims, 55% were to treat, prevent, diagnose, or cure specific diseases—most without the required FDA disclaimer saying that the health claims had not been verified.<sup>35</sup>

Press releases from dietary supplement industry groups also appear to be unconstrained by evidence. A study of dietary supplement industry press releases advocating supplement use based on 46 clinical studies of dietary supplements published between January 1, 2005, and May 31, 2013, found that more than 90% of the studies had reported neither benefit nor harm from using the supplement. Those press releases were referenced by 148 news stories on the websites of 6 organizations that inform manufacturers, retailers, and consumers about supplements.<sup>36</sup> An implication of these findings is that academic literature used to support claims is assumed to be “the truth” without regard to the likely existence of other studies with conflicting findings.

### Case Study: Pomegranate Juice and Extract for Prostate Cancer Prevention and Treatment

The case of pomegranate juice and extract illustrates the roles of Internet promotion, the FTC, and negative trial results in the marketing of a natural product for the treatment and/or prevention of cancer. Patients with prostate cancer searching Google to learn about the value of consuming pomegranate juice to slow the growth of their cancer are likely to be led to believe they will benefit substantially, despite the lack of strong evidence supporting that conclusion. As mentioned earlier, Google returns more than 1 million links in a search for “pomegranate and cancer,” and most are for sites that promote the sale of natural products. Even when the sites include references

to published studies, they may be overly promotional. For example, the second site returned by a Google search for “pomegranate and cancer” presented a published review reporting that pomegranate juice resulted in an increase in mean PSA-DT from 15 months at baseline to 54 months after treatment in men with rising PSA levels following surgery and/or radiation treatment.<sup>37</sup> PSA is a biomarker associated with prostate cancer growth. Differences in mean PSA-DT values generally are much larger than differences in median PSA-DT values because individual PSA-DT values can increase to hundreds or even thousands of months when measured in patients whose PSA levels are growing very slowly. Even when median PSA-DT values are used, sites referencing studies<sup>38,39</sup> that found statistically significant increases in median PSA-DT values of approximately 6 months<sup>16</sup> fail to report that those studies had no placebo control groups and found no dose effect. Furthermore, those sites do not mention that median PSA-DT values generally rise by several months in the patient population involved in the trial, even in the absence of treatment.<sup>40</sup> Finally, the authors of the published review did not report that although PSA-DT values are associated with progression-free and overall survival in prostate cancer,<sup>41</sup> the Prostate Cancer Working Group discourages the use of change in PSA-DT as a primary endpoint because its clinical significance is uncertain.<sup>42</sup> Despite these shortcomings and no clear demonstration of anticancer activity, the promotion of these trial results led to skyrocketing sales of POM Wonderful pomegranate products to more than \$150 million annually by 2012, from less than \$12 million annually 9 years earlier.<sup>43,44</sup>

In 2010, the FTC filed a complaint against POM Wonderful. It alleged that the prostate cancer claims made by the manufacturer were false and unsubstantiated because, among other reasons, the study that POM Wonderful relied on to support its claims was neither “blinded” nor controlled.<sup>45</sup> After an FTC administrative law judge supported the findings and a US Court of Appeals supported the FTC’s decision,<sup>46</sup> POM Wonderful stopped referring to prostate health in its advertisements. However, POM Wonderful continues to promote the antioxidant activity of pomegranate juice. The public continues to associate antioxidant activity with prostate cancer prevention—indeed, a Google search for “prostate cancer and antioxidants” on December 13, 2015, found more than 1.1 million websites.

The US Court of Appeals demanded that POM Wonderful complete a “randomized and well-controlled human clinical trial” in order to support its claims. The results of just such a trial were published in July 2015. The phase 3 clinical trial of pomegranate extract in men with rising PSA levels following local therapy enrolled 166 participants.

The median increase in PSA-DT was 1.6 months (from 12.9 months at baseline to 14.5 months after treatment) for patients consuming extract and 4.5 months (from 11.1 to 15.6 months) for those in the placebo group.<sup>47</sup> A smaller group of 17 patients consumed pomegranate juice and experienced a 7.6-month increase in PSA-DT, but the trial was not powered to draw any conclusions about juice vs placebo. Despite these new results, most websites identified by a Google search of “pomegranate and prostate cancer” continue, many months after publication of the phase 3 study, to report the results of the earlier studies and do not mention the new study. There appears to be no incentive, or convenient mechanism, to update patient perceptions of the value of natural products when clinical trials report negative results. Physicians asked about pomegranate and prostate cancer can say that the juice is safe but that they are unsure whether there is any benefit of increasing PSA-DT.

### Providing Answers to Patients

Physicians face a challenging landscape when advising patients about dietary supplements. A review of multiple national opinion surveys showed that a large proportion of Americans who use dietary supplements believe that physicians do not know enough about these products and that physicians may be biased against supplements. As a result, patients avoid discussing the use of dietary supplements with their doctors. Many users also felt the potential health benefits of some supplements were so great that they would continue to take them even if they were shown evidence from scientifically conducted clinical studies that the supplements were ineffective.<sup>48</sup> So what is a physician/provider to do?

Several resources provide information on the safety and efficacy of natural products:

1. The National Cancer Institute provides detailed information on dietary supplements on 2 sites that are freely available to physicians and patients:

- Complementary and Alternative Medicine for Health Professionals <http://www.cancer.gov/about-cancer/treatment/cam/hp>
- Complementary and Alternative Medicine for Patients <http://www.cancer.gov/about-cancer/treatment/cam/patient>

The site for health professionals provides detailed information on more than 20 dietary supplements that are widely marketed and about which questions may arise during discussions between oncologists and patients. The health professional site includes an overview, general information and history, preclinical/animal studies (in vitro and

animal studies), human studies (epidemiologic studies, intervention studies, and clinical trials), and information on adverse effects. The site is maintained by a Physician Desk Query (PDQ) board composed of physicians, researchers, pharmacists, naturopaths, and patient advocates and is coordinated and managed by the NCCIH at the NIH. The site is updated multiple times each year.

2. The Natural Medicines Comprehensive Database includes detailed information on a vast array of dietary supplements and data on each commercial formulation that is available for sale (<http://naturaldatabase.therapeuticresearch.com/>). The information in the database, which is resold through Epocrates and Micromedex, is available separately for patients and health professionals. Both versions provide the following information:

- Updates on the safety and effectiveness of each product and ingredient
- Interactions between natural products and other medications
- A “seal of approval” made available by the team that compiles the database that purports to reflect safety, efficacy, and product quality
- Specific conditions for which the product is accepted by the authors

This data source is unique in its inclusion of tens of thousands of commercial product names and in its extensive drug-drug interaction data. The health professional version provides more detailed information from preclinical and clinical trials with references. The database covers more than 1100 herbs and dietary supplements and is a continuously updated version of a 1999 book compiled by the Therapeutic Research Faculty that covered 964 herbs and dietary supplements. In that book, safety had been proved for only 15% of the listed products and effectiveness for the indicated condition had been demonstrated for only 11%.<sup>49</sup> In 2005, a review found that only 5% of herbs and dietary supplements had been rated effective.<sup>50</sup>

3. Memorial Sloan Kettering Cancer Center maintains a website—About Herbs, Botanicals & Other Products—that provides objective and evidence-based information that can be helpful for judging a product’s traditional and proven uses, possible benefits, interactions with medicines or other herbs, and possible adverse effects. The database, which can be accessed at no cost at <https://www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs>, contains information on more than 300 herbs, dietary supplements, and “alternative” cancer treatments, and it is well researched and well written.

Although these sites provide valuable data for physicians, pharmacists, and patients, few practitioners have the time or interest to stay up to date on the safety, efficacy, and drug interactions of the dietary supplements that their patients may be consuming or considering. In the future, health care providers, in particular physicians who treat cancer, need to encourage database providers such as Micromedex (<http://support.micromedex.com/support/request/>) and Epocrates (<https://www.epocrates.com/sfsc.do?mode=email>) to incorporate more data on natural products into the large databases of information on drug safety, efficacy, and interactions that physicians rely on for informing their patients. It is also necessary to continue to subject dietary supplements to rigorous testing in order to obtain additional evidence to be included in these databases. The gold standard for assessing the safety and efficacy of drugs is randomized, placebo-controlled clinical trials. The same rigorous quality control and testing used to evaluate any compound for which disease-specific health benefits are claimed must also be applied to dietary supplements and other natural products before physicians can be confident in recommending them for their patients.

#### Acknowledgements

Supported by the Johns Hopkins University School of Medicine 2015 Passano Clinician Scientist Career Development Award and P30 CA006973/CA/NCI NIH HHS awarded to the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

#### Disclosures

Dr Paller’s clinical research on natural products is supported by funding from Believe Big, the Billi and Bernie Marcus Foundation, and the Community Foundation for the National Capital Region. Muscadine grape skin extract was provided by Muscadine Naturals. Dr Carducci’s and Dr Paller’s clinical research on pomegranate extract was supported by POM Wonderful.

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