Integrating Botanicals into Oncology Care: Consideration of FDA Regulation of Botanical Products and Botanical Clinical Trials

Running Title: Integrating Botanicals into Oncology Care

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- Dr. Berman declares a history of consulting with Immunogen and has served as an advisory board member for Immunogen, Eisai, and AstraZeneca.
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Abstract

Modern cancer pharmacotherapy consists of contributions from natural products, their structural analogues, and chemotherapies. Interest in natural products is being revitalized in oncology. Natural products may be classified as food, dietary supplements, drugs, or cosmetics depending on their intended use. A natural product intended to prevent, diagnose, cure, mitigate, or treat disease would be regulated as a drug. Most natural products are regulated as dietary supplements, intended to affect the structure or function of the body. In 2023, Americans spent around $58 billion on dietary supplements, with a majority intended to prevent or treat cancer. Almost 50% of newly diagnosed patients with cancer report taking dietary supplements after diagnosis. Botanicals, natural products made from plants, plant parts, or plant extracts, are one of the most highly-used supplements. The natural product market is zealous to promote their supplements and often claim their products will help in combatting disease. Unlike with FDA-approved drugs, botanical dietary supplements may be marketed without proving they work as claimed and do not require clinical trials. To date, only four botanical drug products have been approved for marketing as prescription drugs in the U.S. Here, we evaluate the current paradigm for dietary supplement marketing and FDA approval and its impact on the treatment of patients with cancer. We underscore the need for rigorous clinical trials for clinicians to access sufficient evidence-based data to advise on the safety and efficacy of these products, alone or in conjunction with active treatment for cancer.

Introduction

Historical use of plant-based medicine dates back 60,000 years, with written evidence documenting use 5000 years ago.(1) As late as the 1890s, herbs or herbal combinations contributed to 59% of the products in the U.S. Pharmacopoeia.(2) Currently, interest in natural products is being revitalized, with thousands of botanical dietary supplements available over the counter and 1 in 5 adults in the U.S. reporting herbal product use.(3)

Cancer is one of the leading medical conditions associated with the use of herbal and dietary supplements, with more than 60% of patients diagnosed with cancer using these products to not only treat cancer, but also to improve quality of life and mitigate toxic drug side effects.(4) After being diagnosed with cancer, up to 50% report starting to take dietary supplements.(5) The number of herbal and dietary supplements being used concurrently can range from a median of 7 products during chemotherapy to as much as 11 before and after chemotherapy.(6) While herbal and dietary supplement use is especially prevalent among patients with a higher level of income and education, 90% of those not using herbal supplements in underprivileged populations (e.g., uninsured minority cancer patients) state they are interested in gaining more information; with 70% expressing an expectation that their oncologist will address the safety and potential benefits of these practices.(7) Patients with cancer may use botanical dietary supplements in combination with conventional therapies for many reasons, such as reducing side effects of chemotherapy, slowing progression of cancer, and improving quality of life. Despite the prevalent use of botanical products amongst patients with cancer, rigorous clinical trials in this space are lacking, leaving oncologists with little information on how to advise patients on botanical use during cancer treatment.

Here, we evaluate the current landscape for dietary supplement marketing, focusing on U.S. Food and Drug Administration (FDA) regulation of botanical supplements vs. botanical drugs, challenges in botanical drug clinical trials, and the impact on the treatment of patients with cancer. We underscore the need for rigorous clinical trials so that clinicians may access sufficient evidence-based data to either advise on the safety and efficacy of these products, either alone or in conjunction with active treatment for cancer.

FDA Classification of Botanical Products

A natural product, including a botanical or product made from plants, plant parts or plant extracts, may be classified as a dietary supplement, drug, conventional food, or cosmetic under the Federal Food, Drug, and Cosmetic Act (FD&C), depending on its intended use (see Fig. 1).[6] Intended use is established by product labeling, advertising, and distribution circumstances, according to the Dietary Supplement Health and Education Act (DSHEA) of 1994. This manuscript will focus on the regulation of botanical supplements and botanical drugs. If a botanical product is intended to "affect the structure or function" of the human body (a structure-function claim) or describes general well-being from consumption of a nutrient or dietary ingredient, then it is viewed as a dietary supplement.(8) DSHEA broadly defines a dietary supplement as "a product (other than tobacco) intended to supplement the diet" that contains one of more dietary ingredients.(8) Dietary ingredients include vitamins, minerals, herbs or other botanicals, amino acids, or concentrates, metabolites, constituents, extracts or combinations of any of the preceding items.(8) A *botanical* (or herbal) dietary supplement is a dietary supplement that contains 1 or more herbs or bother botanicals, including a plant or plant parts valued for their medicinal or therapeutic properties, flavor, and/or scent.(9)

A major difference between a dietary supplement and (botanical) drug is that dietary supplements may not claim to "diagnose, cure, mitigate, treat, or prevent disease." Any product making one of those claims will be regulated as a drug, botanical or otherwise. However, the structure-claims made by dietary supplement manufacturers are often vaguely worded claims of health benefits. For example, an *Echinacea* product might claim to "support the body's natural defenses" when most people use it to treat or prevent the common cold. For supplements, these claims do not have to be substantiated by the manufacturer, and they are regulated similarly to foods.

Natural Products and Cancer Treatment

In oncology drug development, natural products have contributed vastly to pharmacotherapy. Chemotherapy initially consisted of nitrogen mustards used in gas warfare during World War II, later used to fight leukemia.(10) In 1955, the National Cancer Institute (NCI) created the Cancer Chemotherapy National Service Center (CCNSC) to evaluate more compounds to potentially treat cancer. While CCNSC evaluated mostly compounds with well-known chemical structures, including synthetics and fermentation products, the program expanded its purview in 1960 to screen extracts of natural products, both plant and animal, as well as complex mixtures of compounds of unknown structures. The U.S. Department of Agriculture collaborated with CCNSC's plant program to supply NCI with plants for anticancer

screening. Over the ten-year duration of this project, one thousand sampled plant extracts were sent to NCI to test their anticancer potential.(11) One of them, *Camptotheca acuminata*, a Chinese tree sample, demonstrated potent anticancer activity in an *in vivo* mouse model. Decades later, after extensive research, two camptothecin analogs, topotecan and irinotecan, received FDA approval for use against ovarian, lung, breast, and colon cancers. A few years later, a sample from the bark of the *Pacific yew* tree would eventually yield paclitaxel, one of the most potent chemotherapy agents ever developed. Today, more than half of chemotherapies are derived from natural sources, such as plants, microbes, animals, and marine sources. (See Table 1 for a list of selected chemotherapeutic agents with their natural origins.)

Botanicals have also been evaluated for their potential to mitigate toxicity of chemotherapy and prevent cancer. Using phytochemical antioxidant supplements, such as vitamins and carotenoids, during chemotherapy and radiation therapy has been controversial. A study by Bairati *et al,* gave 540 patients with head and neck cancer undergoing radiation therapy daily supplements of α-tocopherol (vitamin E) and β-carotene.(12) While the researchers found that the two supplements, when given together, were associated with lower rates of adverse effects, a non-significant trend for higher rates of local recurrence in the supplement group was evident, implying that antioxidant supplements may protect tumor tissues from radiation, as well as normal tissues.(13) Moreover, in the Alpha-Tocopherol, Beta-Carotene Prevention (ATBC) Study, involving more than 29,000 male smokers, daily α-tocopherol (50 mg) for a median of 6.1 years *decreased* the risk of prostate cancer, while β-carotene (20 mg) *increased* the risk of lung cancer and overall mortality.(14) In contrast, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), designed to assess the effect of selenium and vitamin E alone and in combination as supplements to prevent prostate cancer in over 35,000 men at average risk, found an increased risk of prostate cancer with vitamin E given alone that approached statistical significance, and after longer follow-up, confirmed vitamin E supplementation significantly increased the risk of prostate cancer among healthy men.(15)

No Longer "Natural:" Chemotherapy vs. True Botanicals

Though derived from natural sources, camptothecins and paclitaxel chemotherapies are not botanical products – they are derivatives, or highly purified single molecular entities, and are excluded from the definition of botanicals. The FDA defines *botanicals* as products that include

plant materials, algae, macroscopic fungi, and combinations thereof. This definition also excludes products containing animals or animal parts and/or minerals, except when these ingredients compose a minor part of a traditional botanical preparation (e.g, traditional Chinese medicine, Ayurvedic medicine) and byproducts from fermentation of yeast, bacterial, plant cells, or other microscopic organisms if the used to produce a single molecular entity (e.g., antibiotics, amino acids, and vitamins). Botanicals are one of the most highly-used supplements, after vitamins, minerals, and omega-3 fatty acids.

Several advantages exist for choosing to study botanical supplements or drugs. The standard approach for oncological drug development has been to isolate, synthesize, and administer the singular chemical compound presumed efficacious against disease from a source. This drug development process from source to finished product is extremely costly, complex, and time-consuming, taking up to 12-15 years before a product can be marketed in the US, with costs over $1 billion.(16) In contrast, herbal therapies have been used for thousands of years, embedded in cultural tradition. According to the WHO, approximately 80% of African and Asian countries rely on herbal medicines for fundamental health care.(17) "[Herbal] medicines of proven quality, safety, and efficacy, contribute to the goal of ensuring that all people have access to care. For many millions of people, herbal medicines… are the main source of health care, and sometimes the only source of care. It is also culturally acceptable and trusted by [many]," according to 2013 WHO Direct-General, Dr. Margaret Chan.(17) Herbal use is part of cultural tradition, with use spanning generations; they are also relatively inexpensive. Moreover, botanical products represent complex mixtures composed of numerous chemical entities. Even in extensively studied plants, only a small proportion of their components have been isolated and characterized. These botanical constituents, known and unknown, may have synergistic activities. Synergism is the cooperative interaction of substances to reach a combined effect greater than the sum of their separate effects.(18) In certain instances, after separation and purification from herbal extracts, the pharmacological effects of bioactive constituents may diminish or even disappear. For example, despite clinically verified pharmacological effects of the anti-malarial compound artemisinin, dried whole-plant Artemisia annua *L.,* its botanical source, is more effective than a comparable dose of pure artemisinin, due in part, to pharmacokinetic synergism of *A. annua* constituents.(19) The level of artemisinin in the bloodstream with whole-plant *A. annua L.* was found to more than 40-fold higher than that in a group treated with pure artemisinin.(18) *A. annua* flavonoids, specifically, can inhibit the cytochrome P450 enzymes (CYPs) that metabolize artemisinin, thus increasing its bioavailability in the whole plant source.(19) In a counter scenario, evidence also exists that

the presence multiple components in a botanical extract may buffer the toxicity of single constituent.(20)

FDA Regulation of Botanical Products

Today, dietary supplements are regulated in the same way as conventional foods, under FDA's Center for Food Safety and Applied Nutrition (CFSAN). Through regulating dietary supplements similarly to foods, the FDA ensures consumer access to a wide array of health-related products. Consequently, minimal oversight exists for these products, leaving safety and product consistency to be potentially problematic. In particular, dramatically different levels of suspected active ingredients have been documented in several studies. For example, an analysis of 25 available ginseng products found a 15- to 200- fold variation in ginsenosides and eleuthrosides, two ingredients believed to have biological activity.(21) Inconsistency in product quality may be related to lack of or limited standardization along the many steps of manufacture, including agriculture-related aspects (e.g., accurate identification of the specific herb in accordance with its scientific name, quality of seeds and seedlings, growth conditions, harvesting, avoidance of pollutants), shipping, processing, packing, and distribution. This makes it challenging for patients and providers to ascertain the precise contents of their supplements.

Under DSHEA, botanical drugs are regulated no differently than from non-botanical drugs; both are overseen by the FDA's Center for Drug Evaluation and Research. A botanical is considered a drug if it bears a disease claim, meaning the product intends to mitigate, treat, cure, diagnose, or prevent a disease or its related symptoms, as defined by the Food, Drug & Cosmetics (FD&C) Act. The regulatory intent was not to create botanical drugs as a separate category of therapeutic agents, but to ensure the same degree of confidence in their quality and utility as nonbotanical drugs. In 2016, the FDA published the revised *Botanical Drug Development Guidance for Industry*(9), providing additional flexibility for early-phase clinical trials but reinstated that botanicals are treated like any other new drugs with the same level of confidence that clinical data from adequate and controlled trials and quality standards will support New Drug Application (NDA) approvals.

In the U.S., clinical trial design for any investigational new drug must be reviewed by the FDA through the Investigational New Drug (IND) application process. Filing an IND application notifies the FDA that a pharmaceutical agent will be used in an experimental way. All studies that use a drug, botanical or otherwise, not approved for marketing by the FDA, or an approved

drug being used for an indication that is not listed on the approved label (or used in a new combination of approved drugs), will always require an IND. This applies to botanical products even with a long history of use.

As of December 2022, however, the FDA proposed to amend its regulations on IND applications to exempt certain clinical trials of lawfully marketed foods and dietary supplements from IND requirements for products evaluated as drugs.(22) Under the proposal, clinical studies to evaluate botanical drug products would *not* have to be conducted under an IND if the study is not intended to support a drug development plan or a labeling change, and no potential for significant risk to the health, safety, or welfare of subjects would be involved. While exempt from IND requirements, such clinical trials would still be subject to other regulations designed for safety, such as requirements for informed consent and review institutional review boards (IRBs). This proposed provision would help reduce the regulatory burden of conducting clinical trials for these products while still ensuring public safety.

At this time, however, clinical investigators may still try to apply for an IND exemption. Exempted studies may not be designed to support approval of a new indication or change in label, should not be intended to support a change in the advertising for the product, or involve a route of administration dosage level, or patient population that significantly increases the risks associated with the drug. They should be conducted in compliance with IRB and informed consent regulations.

The final step before a new drug can be marketed and sold in the U.S. is the submission of an NDA. The NDA contains data gathered during animal studies and human clinical trials, usually conducted under an IND. Of note, of all the commercial botanical INDs submitted to the FDA, less than 5% of the drug products progress to phase 3 trials, a strong predictor of eventual NDA submission.(23)

Finally, botanical drugs can be regulated as prescription or as over-the-counter (OTC) drugs. To be included in an OTC monograph, botanical drugs must have pre-existing published data showing they are generally safe and effective, including clinical study results.(24) OTC monograph drugs can be marketed without approved drug applications under the FD&C Act if they meet certain applicable requirements. Senna and psyllium husk are examples of botanical drugs FDA-approved for OTC use to treat constipation.(24) Leaves, pods, or dried extracts of the senna plant contains chemicals called sennosides, the active ingredients that irritate the bowel lining to cause a laxative effect and used in preparing proper dosing of the OTC products.

Challenges in Botanical Clinical Trials and Approvals as Drugs

While thousands of botanical supplements are openly marketed in the U.S., only four prescription botanical drugs have been FDA has approved to date, Veregen® (sinecatechins), Mytesi™ (crofelemer), Filsuvez® (birch triterpenes), and NexoBrid® (anacaulase-bcdb), among hundreds of NDA submissions. Veregen (sinecatechins), extracted from green tea leaves, was approved in 2006 as an ointment for genital warts by Germany's MediGene. Fulyzaq (crofelemer), from the red sap of the *Croton lechleri* plant, a South American tree, is a drug from Salix Pharmaceuticals approved in 2012 for the treatment of diarrhea in patients with HIV/AIDS on retroviral therapy. Filsuvez® is a 10% birch triterpenes gel for the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in adult and pediatric patients 6 months and older. EB is a debilitating inherited skin disease that causes a person's skin to be so fragile it can be injured just from touch. NexoBrid® is a mixture of proteolytic enzymes extracted from the stems of pineapple plants indicated for eschar removal in adults and pediatric patients with deep partial thickness and/or full thickness thermal burns.(25) The enzymes dissolve burn wound eschar while preserving viable tissue.(26) Of note, no food or dietary supplement has ever been approved by the FDA as a drug for cancer prevention or treatment.

Several factors may explain the lack of natural products with FDA approved indications as botanical drugs. The main one being that no phase 3 clinical trial of a natural product has demonstrated significant efficacy and safety for cancer treatment or prevention. Despite a multitude of phase 2 trials with promising results, follow-up phase 3 trials are scarce. Dietary supplement manufacturers may promote their product based on results from a phase 2 trial, thus choosing to forgo the more rigorous and expensive randomized, placebo-controlled phase 3 trial.(27)

When manufacturers choose to pursue conducting a phase 3 clinical trial for their natural product, quality control of botanical products poses unique challenges. Botanical product clinical trials must meet drug endpoints, including high standards of trial design and patient safety. This is inherently challenging when botanicals are naturally heterogeneous, containing mixtures with many presumed active components or mixtures where the active compounds may not be known or fully characterized.(23) Due to differences in plant origins, geographic areas of cultivation and practices, climate, time of harvesting and manufacturing protocols, the chemical composition of botanical formulations may vary greatly.(23) Therefore, conventional chemistry, manufacturing, and controls (CMC) approaches used for quality control of small molecules are sometimes not

sufficient in the botanical space. Due to the natural heterogeneity of botanical drugs and inherent uncertainty about the active constituents, it is critical to ensure consistency of the therapeutic effect amongst marketed drug batches.(9) Generally, a “totality of evidence” approach can support therapeutic consistency, as previously described in the updated Botanical Drug Development Guidance for Industry, considering the following:

- Botanical raw material control (e.g., agricultural practice and collection);
- Quality control by chemical test(s) (e.g., analytical tests, including spectroscopy and/or chromatography to capture active or chemical constituents of a botanical drug substance) and manufacturing controls (e.g., process validation);
- Biological assay (reflecting the drug’s known or intended mechanism of actions) and clinical data (for details regarding clinical data use in ensuring therapeutic consistency).(9)

Additionally, botanical providers have openly noted in public meetings that the existing marketing of botanical dietary supplements, including its lack of patent protection and meaningful exclusivity, significantly disincentivizes rigorous drug development.(28) Funding shortages due to lack of patentability remains a primary challenge faced by researchers planning to conduct rigorous natural product trials.(27) In a series of decisions beginning in 2010, the Supreme Court established stringent rules for patent eligibility, excluding “products of nature” from being patentable.(29) On March 4, 2015, the U.S. Patent and Trademark Office (USPTO) updated its guidelines for patent examiners to reject patent claims seeking to protect purified natural products, which may include natural product extracts.(27) Without patent protection of dietary supplements, manufacturers inevitably face price pressure from competitors and may not earn profits substantial enough to cover the cost of large phase 3 trials. This may not be the case for long, however. On September 6, 2024, representatives introduced the *Patent Eligibility Restoration Act (PERA)*, bipartisan legislation to restore patent eligibility to inventions across many fields, including natural products. If *PERA* gets passed by Congress, natural materials, like dietary supplements, that are “isolated, purified, enriched, or otherwise altered by human activity” or “employed in a useful invention or discovery” may be eligible for patents.(30) Currently, funding for botanical trials has come from the National Center for Complementary and Integrative Health (NCCIH) or from collective smaller grants from the American Society of Clinical Oncology (ASCO), disease-specific cancer foundations, and investigators’ institutions, to be followed by larger grants from philanthropists wanting to sponsor a clinical trial to prove safety and efficacy of a supplement they believe will benefit

patients.(27) Irrespective of patentability, under DSHEA, FDA approval is not required for manufacturers to sell supplements, as long as they do not claim to treat, mitigate, cure, diagnose or prevent cancer or its related symptoms. Companies may circumvent the disease claim stipulation by advertising their product “may help relieve” certain symptoms or “may help prevent” recurrence or development of disease, along with including the ubiquitous disclaimer on the label that “these statements have not been evaluated by the FDA.”(31)

Due to these strict regulations, and the stipulation that manufacturers cannot market their botanical products as drugs while undergoing testing in clinical trials, companies may be disincentivized to go through the regulatory process to approve their botanical products as drugs and often opt instead to market their products as dietary supplements. This means less evidence of safety and efficacy for these products will be available for consumers and providers.

Regulation of Botanical Product Marking

While the FDA can pull products from the market and levy fines for adverse reactions, the Federal Trade Commission (FTC) can remove products and/or fine companies at fault for making false claims, supplements may be marketed without proving they work as claimed. This contrasts with products intended to be used as drugs, which must be proven safe and effective through rigorous clinical trials before being marketed in the U.S. The FTC regulates food and dietary supplement advertising as it does for all consumer products by enforcing truth-in-advertising laws, applying the same standards across all forms of advertising, whether in newspapers, magazines, online, in the mail or on billboards and buses.(32) Federal law says that ads must be truthful, not misleading, and backed by scientific evidence, especially when health claims are used.(32) In 2010, for example, the FTC filed a complaint against POM Wonderful 100% Pomegranate Juice and POMx supplements, as the company was “deceptively advertising the products could treat, prevent, or reduce the risk of heart disease, prostate cancer, and erectile dysfunction, and were clinically proven to have such benefits.”(33) POM Wonderful has since stopped referring to health-related claims in its advertisements. The Commission’s cease and desist order, affirmed by the appellate court, required POM’s “future disease treatment and prevention claims to be supported by at least one randomized, well-controlled human clinical trial, and other health benefit claims to be supported by competent and reliable scientific evidence.”(33). Dietary supplement manufacturers cannot legally make disease claims without approval of an NDA, but, nonetheless, unsubstantiated medical claims for many botanical dietary supplements are pervasive in literature, media, or on the internet. The FDA Final Rules of January 5, 2000 (and subsequent amendments) differentiate disease

claims from structure-function claims (sometimes called health claims), but these distinctions are nuanced with cause for confusion.(28) For example, a dietary supplement can claim to benefit heart health, but not to prevent heart disease or it can claim to improve bone health, but not to prevent osteoporosis.(28) Moreover, disease claims can be propagated throughout the community by parties other than the manufacturers.(28) As a result, some consumers self-medicate using botanical dietary supplements while regulatory oversight of their safety and efficacy is insufficient.(28)

Final Considerations, Resources, and Future Directions

The demand for natural oncology products in patients diagnosed with cancer is pervasive. Without FDA-reviewed evidence of safety and efficacy of natural products to treat cancer or symptoms related to disease or treatment, oncologists lack the necessary data to advise on their use in the clinical setting. According to a review of multiple national opinion surveys, a large proportion of patients who use dietary supplements do not believe their physicians know enough about these products, while physicians may also be biased against supplements. Consequently, patients may avoid discussing their dietary supplement use with their doctors. Non-disclosure on herbal supplement use may impose safety risks, including herb-drug interactions, and may significantly impair oncologist-patient communication and trust.(34) Health care providers should address supplement use with their patients. Several resources exist to educate patients and physicians about natural product safety and efficacy (see Table 2). In addition, several academic institutions with dedicated integrative oncology centers, including the Zakim Center for Integrative Therapies and Healthy Living at the Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center's Integrative Medicine Program, and the Integrative Medicine Program at Fred Hutchinson Cancer Center, now offer integrative oncology services that include pharmacologic review of dietary supplements with a clinical pharmacist. Through this review, clinicians will be better served to advise patients of the safety of their desired supplement regimen in conjunction with antineoplastic therapies.

Ultimately, randomized, placebo-controlled trials remain the gold standard for assessing the safety and efficacy of drugs, botanical or otherwise. Only with adequate quality control and testing of dietary supplements can health care providers feel confident in their recommendations about whether their patients can safely take them. However, additional changes are needed to improve and promote high-quality research. A critical element will be designating specific

standards for herbal products to ensure product consistency amongst studies. Patent protection (through *PERA*, for example) would help expedite research in this field so that manufacturers investing in these expensive studies and documenting product efficacy would yield a financial return to support these efforts.

In summary, for most of the ~20,000 herbal products available in the US, little to weak evidence exists regarding safety or efficacy. However, as one third to one half of all pharmaceutical drugs were originally derived from plants, it is likely effective therapies can be derived directly from the natural environment. Moreover, at least 60% of patients with cancer are using these products(4) and with the diminished cost, cultural significance of use, and potential synergism with components of whole-plant products vs. using isolated compounds, consumption of herbal products will continue to grow. Changes to herbal product regulation could dramatically improve the appropriate use of herbs. By creating national standards for specific herb constituents, greater incentives for research, and revising study designs to reduce cost and duration, more high-quality research can be conducted in this important field. With evidence from results of these trials, clinicians will be able to advise on the safety and efficacy of these products in the context of treating cancer or preventing it from occurring or recurring.

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Figure 1 Legend:

Legend for Figure 1: Botanical Product Classifications. A botanical product intended for use in preventing, diagnosing, curing, mitigating, or treating disease meets the definition of a drug (FD&C Act, Section 201(g)(1)(B)) and would thus be subject to drug regulation. Authorized Health Claim: Under certain circumstances, however, a product that meets the definition of a drug may be subject to a different regulatory scheme. For example, when a conventional food or dietary supplement bears a health claim about reducing risk of a particular disease and the claim is made in accordance with an authorizing regulation issued under section 403(r)(1)(B) of the FD&C Act (21 USC 343(r)(1)(B)), such a product would not necessarily be regulated as a drug solely because its labeling contains such a claim. (9) OTC: over-the-counter. (Adapted from FDA: CDER Guidance for Industry – Botanical Drug Development [2016; ref 9]).

Table 1: Selected botanical, marine, and bacterial sources of chemotherapy used in oncology

Chemotherapeutic Drug	Natural Source	Indications
Topotecan, Irinotecan	*Camptotheca acuminata* (Happy tree)	Solid tumors, including ovarian, lung, breast, and colon cancers
Paclitaxel	*Pacific yew* tree bark	Solid tumors, including breast, ovarian, endometrial, cervical, prostate, gastroesophageal, and head and neck cancer, as well as sarcoma
Vincristine	*Madagascar periwinkle*	Solid tumors and hematologic malignancies, including leukemia, lymphoma, neuroblastoma, and Wilms tumor.
Trastruzumab emtansine	*Maytenus ovatus*	HER2-positive breast cancer
Etoposide	*Mayapple* plant	Solid tumors, including testicular, prostate, bladder, stomach, and lung cancer
Trabectedin	*Sea squirt*	Liposarcoma, leiomyosarcoma
Daunorubicin	*Streptomyces peucetius*	Leukemia, Kaposi's sarcoma

Table 2: Herbal product resources

Organization	Resource	Description	Website
The National Center for Complementary and Integrative Health (NCCIH)	HerbList™	An app for research-based information about herbal products	https://www.nccih.nih.gov/health/herblist-app
The National Cancer Institute (NCI)	Websites	Two websites: one for healthcare professionals and one for patients	https://www.cancer.gov/about-cancer/treatment/cam/hp https://www.cancer.gov/about-cancer/treatment/cam/patient
NatMed	NatMed Pro	Online database for food, herbs, and supplements	https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements.aspx
Memorial Sloan-Kettering Cancer Center	About Herbs, Botanicals & Other Products	Online database and an app	https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs
EfficaSafe; in partnership with the Society for Integrative Oncology (SIO)	EfficaSafe	Herb-drug-supplement interaction platform	https://www.efficasafe.com https://integrativeonc.org/member-benefits/about-efficasafe/

Figure 1