

Botanicals in Dermatology: Essential Oils, Botanical Allergens, and Current Regulatory Practices

Sarah Mortimer, BS* and Margo Reeder, MD*†

Largely because of their perceived safety, the use of essential oils and other botanically derived products has become increasingly popular. Recent evidence raises concern about the safety of these products, frequently found in cosmetics and sought as an alternative to standard medical treatments. Essential oils are challenging to standardize because of the variable growing conditions, genetics, and harvesting of botanicals. There exists a potential for adverse reactions, in particular allergic contact dermatitis. Furthermore, these products are often sold without prior Food and Drug Administration approval of efficacy and safety. This review focuses on the composition of essential oils, their common associated botanical allergens, and current regulation practices of botanical drug products in the United States and Europe.

In recent years, the use of botanically derived products and natural ingredient remedies has been increasingly popular.¹ In the United States, recent inquiries show that as many as 20% to 60% of adults, and up to 70% of 31- to 40-year-old patients, report having used an herbal product.^{2,3} In a 2009 Italian study, participants were questioned on their reasons for use of herbal remedies and the top reasons cited include the perceived safety of botanical products in comparison with synthetic preparations, curiosity about alternative remedies, and desire for an alternative treatment.³ Interestingly, reasons for choosing botanical products vary by sex: men often seek alternative medicines, whereas women are more likely to value cosmetic benefits.³ Botanicals are often used topically in cosmetics as a means of hydrating, moisturizing, softening, cleansing, and coloring, and as fragrance.¹ Furthermore, there are data suggesting botanicals provide antioxidant, anti-inflammatory, antibacterial, antifungal, sun blocking, and wound healing abilities.⁴⁻¹¹ Although these products may have some benefit, they are often sold without prior Food and Drug Administration (FDA) approval of efficacy and safety because of the complexities in regulatory practices in both the United States and Europe. Therefore, with use of these products topically or otherwise, there exists the potential for adverse reactions, in particular allergic contact dermatitis.

*From the *University of Wisconsin School of Medicine and Public Health; and †Department of Dermatology, University of Wisconsin School of Medicine and Public Health, Madison.*

Address reprint requests to Sarah Mortimer, BS, University of Wisconsin School of Medicine and Public Health, One South Park St, 7th Floor, Madison, WI. E-mail: mortimer2@wisc.edu.

The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000244

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Botanical Drugs

The FDA defines a botanical drug as a “product consisting of vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof.”¹² Under the Federal Food, Drug, and Cosmetic Act 21 (g)(1), drugs, including botanical drugs, are used for diagnosis, cure, mitigation, treatment, or prevention of disease.¹² Botanical drug products may be purchased as a solution, powder, capsule, elixir, topical, or injection and may contain complex mixtures, lack distinctive active ingredients, and have significant prior human use.¹³ A botanical drug product is manufactured from a botanical drug substance with addition of excipients, mixing, blending, granulating, tabulating, encapsulating, or performing other dosage procedures, followed by packaging. If there is no further processing of the botanical drug substance, it can be packaged as a drug product.¹² Permethrin, ingenol mebutate, and sinecatechins are a few examples of plant-based drug products. Permethrin is approved under the over-the-counter (OTC) drug monograph as a topically applied drug for treatment of lice. Permethrin is of the pyrethroid family, which are synthetic chemicals that act like the natural extracts from the chrysanthemum flower.¹⁴ Ingenol mebutate is found in the sap of the plant *Euphorbia peplus* and is FDA-approved under the OTC drug monograph as a cytotoxic agent for the treatment of actinic keratoses.¹⁵ Sinecatechins are derived from green tea leaves and are used in an ointment base for treatment of genital and perianal warts.¹² In contrast to the previously described botanical drug products, sinecatechins [registered trademark of Medigene AG (Martinsried, Germany) under the name of Veregen] are the only botanical product that meets the botanical drug product definition within the Botanical Guidance and has had an approved new drug application (NDA) for marketing as a prescription drug.¹²

Botanical Products

A botanical product is defined as “a finished, labeled product that contains vegetable matter, which may include plant materials, algae, macroscopic fungi, or combinations of these.”¹² Therefore, depending in part on its intended use, a botanical product may be a food, dietary supplement, drug, medical device, or cosmetic.¹² Intended use is determined by a product’s claims made on the labeling, websites, advertising, and what the consumers expect from the product.¹² Various botanical products are available for consumers, and among the most popular are essential oils.

Essential Oils

Essential oils are defined by the International Organization for Standardization as a product made by distillation with either water or steam, by mechanical processing of citrus rinds, or by dry distillation of natural materials.¹⁶ The essential oil must be isolated by physical means and then is further separated from the water phase.¹⁶ These oils are primarily used as a means of aromatherapy and can be applied topically via massage, facial oil, lotions, creams, and baths or by inhalation via steam inhalations, aromatic spritzers, and diffusion.¹⁶ Each oil produced can have more than 100 different constituents.¹⁷ Even the same plant species, for example 2 plants of the *Melaleuca alternifolia* species, can produce a highly variable composition of constituents.¹⁷ Among the 100 different principal components, there are monoterpene and sesquiterpene hydrocarbons, alcohols, esters, ethers, aldehydes, ketones, and oxides.¹⁷

Uses of Botanicals and Essential Oils

Botanical medicine and herbalism, originating in ancient China and Egypt, has a long tradition of use outside of conventional medicine.¹⁸ Indigenous cultures used herbs in their healing rituals, whereas other cultures used herbal therapies as treatments in more traditional medical system settings. In the early 19th century, chemical analysis became available and scientists began to determine, extract, and modify the ingredients from plants with recorded use.¹⁹ Nowadays, herbal components are often judged as both efficacious and well tolerated by the majority of users.³ Moreover, their medical potential seems vast with an estimated 250,000 flowering plants around the world, and more than 85,000 plant species are documented for medical use.²⁰ The varieties of botanical extracts available are innumerable. *Aloe vera* is the most commonly used medicinal plant.³ It is often used for its moisturizing and emollient effects on burns, sunburns, abrasions, and inflammation.³ Roman chamomile, clary sage, eucalyptus, fennel, frankincense, geranium, ginger, helichrysum, lavender, lemon, lemongrass, mandarin, neroli, patchouli, and peppermint are also emerging as widely used natural ingredients for essential oils.¹⁶

Across the nation, botanical products are sold in venues such as beauty salons, spas, massage studios, markets, private sellers, and essential oil parties. Hospitals have incorporated products like

aromatherapy with essential oils into their care options, such that patients can purchase products for at-home use through an integrative medicine department.

Limited Evidence of Efficacy and Possible Adverse Reactions

Despite some success in the dermatology industry, few botanical products have been studied for therapeutic efficacy, and the scientific support of preparations is often lacking.¹ Of the most common botanicals used, there are few with notable efficacy. There are an estimated 20,000 herbal products in the United States, and, of that estimation, there is some scientific evidence for the efficacy of ginkgo, garlic, St. John’s wort, soy, and kava.²¹ This scientific evidence is often undermined by poor methodology, inconsistent outcome measures, conflicting results, and therefore, a lack of conclusive studies on efficacy of herbal products.²¹ Medicinal herbs that are ingredients in various cosmetic and topical remedies are present in different concentrations and preparations, and their therapeutic attributes have not been documented.³

Furthermore, virtually all herbal medicines have a list of undesired effects, with the most common adverse reaction being allergic contact dermatitis.^{3,22,23} There is also the possibility of irritant contact dermatitis, contact urticaria, and of additional concern is the potential for photosensitization, phototoxic reactions, airborne dermatitis, interaction with other drugs, and poisoning.^{1,3,22} *Aloe vera*, arnica, chamomile, propolis, tea tree oil, and marigold are common in the industry; yet, all are well documented as both allergens and irritants.^{3,24–28} In a study done by the University of Ferrara, Italy, 6.22% of topical herbal product users reported 1 or more adverse cutaneous reactions, with a prevalence higher in women than men.³ The risk of adverse reactions to botanical products depends on age, integrity of skin, method of application, and composition of oil.¹⁶

As an example of botanicals in the industry, topically applied essential oils as well as essential oils in perfumes and cosmetics have been repeatedly identified as the cause for allergic contact dermatitis and photosensitization.^{22,29,30} A retrospective study performed by the Department of Dermatology at the University of Gottingen, Germany, analyzed the patch test results from the years 2000 to 2008 and found that of the 15,682 patients tested with at least 1 essential oil, 637 (4.06%) reacted positively to at least 1 essential oil.³¹ Of essential oils tested, ylang-ylang oil was the most commonly positive on patch testing, followed by lemongrass oil, jasmine absolute, sandalwood oil, and clove oil.³¹ Table 1 shows a list of well-known essential oils that are common botanical allergens. The photosensitizing effect seen with essential oils is often thought to be due to the constituents within the essential oils that are psoralens, known for their photosensitization properties, which may include 5-methoxypsoralen, bergapten, imperatorin, methoxsalen, 4,5,8-trimethylpsoralen (TMP), and bergamottin.^{22,54} Allergic contact dermatitis to essential oils has been reported in a number of different occupational groups, but the determination of the sensitizing agent responsible is difficult because of the various

TABLE 1. Common Botanical Allergens with Typical Composition, Medicinal Usage, and Suggested Patch Testing Methodology

Botanical Allergen (Official Trade Name)	Description	Medicinal Use	Patch Testing (Concentration, % w/w)
<i>A. vera</i>	Mixture of beta-sitosterol, salicylic acid, magnesium lactate. ³²	Wound healing, antiinflammatory, and analgesic. ³²	10% pet ^{a33}
Clove oil	Extract of <i>Eugenia caryophyllus</i> . Eugenol, caryophyllene, eugenyl acetate, isoeugenol, carvacrol, thymol, cinnamaldehyde. ^{31,34}	Antimicrobial, antioxidant, antifungal. ³⁴	2.0% pet ³⁵
Jasmine absolute	Extract of <i>Jasminum officinale</i> . Main constituents include benzyl acetate, benzyl benzoate, phytol acetate, isophytol, phytol, linalool, eugenol, squalene, indole, benzyl alcohol, cis-jasmone, and methyl linolenate. ³¹	Muscle relaxation, cough suppressant, antianalgesic and aromatherapy during labor. ³⁶	2.0% 3.0% pet 10.0% pet 5.0%–10.0% pet ^{33,35}
Lavender oil	Extract of <i>Lavendula angustifolia</i> or <i>Lavendula officinalis</i> . Extracted consequently with hexane and ethanol to give an absolute. ³⁵ Main constituents are linalyl acetate, linalool and β -caryophyllene. ³⁷	Antimicrobial, antifungal, topical muscle relaxant, sedative, and antidepressant effects. Cosmetic usage as fragrance in shampoos and soaps, as well as aromatherapy. ³⁷	2.0% pet 1.0% pet or alc 16% pet ^{33,35}
Lemongrass oil	Extract of <i>Cymbopogon citratus</i> . Contains more than 23 compounds; main constituents are geraniol, neral, and β -myrcene. ³⁸	Antiinflammatory, antimicrobial, antitussive, antirheumatic, and analgesic. ³⁸	2.0% pet ³³
Marigold oil	Extract of <i>Calendula officinalis</i> . The main constituents include steroids, terpenoids, triterpenoids, flavonoids, phenolic acids, carotenes, faradiol, rutin, caffeic acid, and chlorogenic acid. ³⁹	Wound healing, antiinflammatory, antioxidant, and antimicrobial. ⁴⁰	10% pet ³³
Peppermint oil	Extract of <i>Mentha piperita</i> . The oil contains more than 30 known components; most significant components are menthol, menthone, menthyl acetate, menthofuran, eucalyptol, limonene, and pulegone. ^{41,42}	Topical preparations are used to calm pruritus, irritation, and inflammation. Also used as an analgesic, anesthetic, antibacterial, antifungal, and antibiofilm. ⁴¹	1.0% pet 1.0%–2.0% pet 2.0% pet ³³
Propolis	A resinous mixture collected from bees and also known as bees' glue. Composition varies considerably depending on source plant, location, and time of collection. The main sensitizers have been identified to be 3-methyl-2-butenyl caffeate and phenylethyl caffeate. ⁴³	Antiinflammatory, antimicrobial, antioxidant, wound healing, and treating burns. ⁴⁴ Propolis is found in cosmetics, creams, ointments, lotions, toothpaste, mouthwashes. ³³	10.0% pet pure ³³
Rose oil, Bulgarian	Extract of <i>Rosa alba</i> L. Main constituents include geraniol, heneicosane, nonadecane, and citronellol. ⁴⁵	Antimicrobial, antioxidant, antispasmodic, and aromatherapy. ⁴⁶	2.0% pet ^{33,35}
Rosemary oil	Extract of <i>Rosmarinus officinalis</i> . Main constituents include carnosol, carnosic acid, and caffeic acid. ⁴⁷	Rubefacient, antimicrobial, carminative, antidepressive, antispasmodic, and anticarcinogen effects. ⁴⁷	10% pet 5.0% alc ³³
Sandalwood oil	Extract of <i>Santalum album</i> L. More than 100 constituents have been identified and the main constituents include alpha-santalol and beta-santalol. ⁴⁸	Anticarcinogenic, antiviral, bactericidal, antiinflammatory, and extensively used in fragrance and aromatherapy. ⁴⁸	1.0% pet 2.0% pet 10% pet 2.0%–10% pet East Indian, 10% pet ^{33,35}
Sweet bay (Laurel) oil	Extract of <i>Laurus nobilis</i> . Main constituents include 1,8-cineole, β -caryophyllene, linalool, limonene, eugenol, and geraniol. ³¹	Antiinflammatory, analgesic effects, and antibacterial. ^{49,50}	2.0% pet ³³

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TABLE 1. (Continued)

Botanical Allergen (Official Trade Name)	Description	Medicinal Use	Patch Testing (Concentration, % w/w)
Tea tree oil	Extract of <i>M. alternifolia</i> . Consists of almost 100 compounds; most significant ingredients are terpinen-4-ol and 1,8-cineole. ⁵¹	Antiseptic, antifungal, antiviral properties applied to skin lesions, infections, insect bites, rashes, and mouth ulcers. ^{51,52}	1.0% pet pure ^{33,35}
Ylang-ylang oil	Extract by steam distillation of <i>Cananga odorata</i> . This extract consists of a total of 52 compounds; main constituents include linalool, germacrene D, and β -caryophyllene. ⁵³ It is fractioned into 4 different grades. The first fraction contains 20%-40% of the whole distillate. This is the finest part and is used for the commercial patch testing allergens and for perfume. The following fractions are used for such things as soaps and cosmetics. ³⁵	Aromatherapy, antipruritic, antiinflammatory, antimicrobial, antibiofilm, insecticidal, laxative, and dandruff treatment. ⁵³	2.0% pet 5.0% pet 10% pet 1.0%–5% pet synthetic, 10% pet ^{33,35}

pet indicates petrolatum.

concentrations and components contained in the oil.²⁹ Moreover, the components of an essential oil often undergo what is called a quenching effect, where the various oil components have complex interactions that reduce the sensitization potential of 1 component when combined with the mixture.³⁰

In addition to the various risks of herbal remedies, there are some herbal treatments, particularly Chinese herbal creams, that have been shown often to contain corticosteroids without documentation.²² In a large scale study on the constituents of Chinese herbal remedies, 24% of samples were adulterated with significant amounts of corticosteroids.⁵⁵ Most frequent adulterants include clobetasol propionate and dexamethasone.²² There have also been incidences of mercury exposure and poisoning from the use of cosmetic skin lightening products. Although mercury and mercury salts are prohibited for use in cosmetic products in the United States, they are unfortunately still accessible to US patients in the global marketplace.⁵⁶

Regulation of Botanical Products in the United States

The options for development of a botanical product are expansive and dependent on the intended use. Intended use includes cosmetic, drug, food, conventional food or dietary supplement with unqualified or qualified health claim, or dietary supplement with structure/function claims that comply with all food and drug requirements.¹³ The intended use may be established in a number of ways such as claims stated on the product label, consumer perception establishing the product's reputation, or ingredients that cause a product to be considered a drug because of well-known therapeutic use.¹³ The FDA regulation is then dependent on the intended use of the product.¹³

A product marketed under use as a cosmetic is regulated differently than that marketed under use as a drug, and a valid example of this is essential oils.¹³ Essential oils can be marketed as a

cosmetic by promoting attractiveness, cleansing, and beautifying.¹³ However, they can also be marketed as a botanical drug declaring that their scent has certain aromatherapy benefits and will help, for example, with nausea, headaches, anxiety, or sleep.¹³ Another example of dual use is massage oils, which can be used for cosmetic reasons such as fragrance and drug reasons such as soothing muscle ache and pain.¹³ Under the Federal Food, Drug, and Cosmetic Act, the only aspect of cosmetics that requires approval by the FDA before going to market is the color additive.¹³ If the product is a drug, it must receive premarket approval by the FDA through the new drug application process or align with the OTC drug review whereby it contains ingredients that are recognized as safe, effective, and not misbranded.¹³ However, a botanical can also be listed as a dietary supplement, which does not require FDA approval of efficacy and safety before being sold on the market.¹²

In 1994, The FDA passed the Dietary Supplement Health and Education Act, defining a more distinct category for dietary supplements that contain 1 or more mineral, vitamin, amino acid, herb botanical, concentrate, metabolite, constituent, or extract.¹² Herbal products fall under the category of supplement and therefore may not claim to "diagnose, cure, mitigate, treat, or prevent illness".¹² They can, however, make claims about the structure and function of their product in relation to health benefits.²¹ The law does not require these products to have FDA approval of efficacy and safety before being sold on the market and also does not require the reporting of postmarketing adverse events of the product.²⁰ However, the FDA can take action against unsafe herbal products by first proving their harm.¹² This is in direct contrast to drugs, which first must provide evidence of safety and efficacy before the FDA will approve them for market.²¹

In contrast to drugs, botanically derived products and supplements are not under formal regulation or standardization process.

TABLE 2. FDA Regulation of Botanical Products in the US Marketplace^{12,13}

	Botanical Products in Vitamins and Dietary Supplement		
	Synthetic, Highly Purified Drugs	Botanical Drug	Ingredients in Cosmetics
FDA Premarket Approval	Marketed in the United States under (1) an OTC drug monograph whereby it contains ingredients that are recognized as safe, effective, and not misbranded or (2) an approved NDA (new drug application) or abbreviated NDA for prescription. Must identify active ingredient.	Marketed in the United States under (1) an OTC drug monograph whereby it contains ingredients that are recognized as safe, effective, and not misbranded or (2) an approved NDA (new drug application) or abbreviated NDA for prescription. A botanical drug is not required to do so (although the FDA recommends that this is done if feasible).	The only aspect of cosmetics that requires approval by the FDA before going to market is the color additive.
FDA Postmarket Monitoring	Drug products approved are subject to postmarketing recordkeeping and reporting requirements.	Drug products approved are subject to postmarketing recordkeeping and reporting requirements.	Neither the law nor FDA regulations require specific tests to demonstrate the safety of individual products or ingredients. The law also does not require cosmetic companies to share their safety information with FDA.
Labeling of Functions Requirement	Intended use in diagnosing, preventing, mitigating, treating, or curing disease.	Intended use in diagnosing, preventing, mitigating, treating, or curing disease.	Intended use: cleanse, beautify, or promote attractiveness.
Examples	Paclitaxel	OTC: cascara, psyllium, senna NDA: sinecatechins	(1) Claims a benefit related to a classical nutrient deficiency disease (and discloses the prevalence of the disease in the United States), (2) describes how the product is intended to affect the structure or function of the human body, (3) characterizes the documented mechanism by which the product acts to maintain such structure or function, or (4) describes general well-being from consumption of the product. Essential oils, vitamins, minerals, herbs, amino acids, enzymes

Standardization is a process used to ensure a consistent product and often involves identifying and measuring specific chemicals.⁵⁷ According to the National Institutes of Health, the components responsible for the effects of botanical drugs have most often not been identified or clearly defined and therefore do not meet criteria for standardization.⁵⁷ This means, if botanical products were to be subject to standardization, a single chemical chosen for standardization may not be an indicator of the actual efficacy or potency of the composite mixture of ingredients. Even when there is attempted standardization of herbal products, as in a 2003 study on echinacea products, it was found that the amount of standardized content did not match the labeling in nearly half of the samples of echinacea product on the market.⁵⁸ Botanical preparations face challenges with standardization as a result of the plants' own variability in growing conditions, genetics, and harvesting procedures or as a part of the production process or, further, chemical reactions (oxidation) that can occur in the product.^{1,59}

The Center for Drug Evaluation and Research, a division of the US FDA, has released a "Guidance for Industry-Botanical Drug Products" to provide feedback on the FDA's current standing on botanical drug products to protect the public consumer and provide incentive to research and development manufacturers.¹² The issued Guidance for Industry does not confer any rights or bind the FDA or the public but serves as an explanation as to how a botanical drug may be marketed under an OTC drug monograph and when FDA regulations for marketing of a new drug application require approval.¹² In addition, the guidance discusses several areas in which the FDA does apply regulatory policies to botanicals, which differ from those applied to synthetic, semisynthetic, highly purified, or modified drugs.¹² For example, the Guidance states that both purification and identification of the active ingredients in the botanical product are optional.²⁰ Presently, of the numerous botanical products available on the market, sinecatechins are the only botanical product that meets the botanical drug product definition within the Botanical Guidance.¹² Cascara, psyllium, and senna are a few botanical drugs that are included in the OTC drug review because of their published data on safety, effectiveness, and well-controlled clinical study results.¹² Table 2 reviews the regulations of botanical products within the US marketplace.

Another major avenue of use and distribution of botanically derived products is aromatherapy. Aromatherapy is currently unregulated and unlicensed for both the practice of aromatherapy as well as the manufacture of aromatherapy products.¹⁶ American Herbal Products Association, a nonprofit organization, released a trade requirement and guidance policy for labeling of undiluted essential oils used topically and offered for retail sale.¹⁶ The trade requirement and guidance policy details known essential oil adulterants such as raw materials, heavy metals, genetically modified organisms, microbes, and mycotoxins, and labeling requirements.⁵⁹ However, these guidance policies are put forth by the American Herbal Products Association itself as a way to promote responsible commerce in herbal supplements as well as encourage its members and nonmember companies to adopt these policies.⁶⁰

This exemplifies the lack of involvement and enforcement of the FDA in this industry.

Regulation of Botanicals in Europe

Differences exist between regulation of botanical products in the United States and Europe. Within the European Union, the quality of the herbal medicinal product must be demonstrated. Furthermore, to have market access for medicinal products containing herbal substances/preparations, they must be classified under 1 of 3 categories according to a recent directive change of the European Parliament and Council, in regard to traditional herbal medicinal products.⁶¹ In the first category, a product can be classified under the traditional medicinal use if there are sufficient safety and efficacy data. The second category describes a product that can be classified under well-established medicinal use requirements if the active ingredients are supported by scientific literature or there are at least 10 years of use within the Union with recognized efficacy and safety. The third category is for products that have undergone evaluation through a marketing authorization application consisting of only safety and efficacy data from the associated company or a combination of the company's studies and historical data.⁶¹ Even with the regulatory pathway in place, to be available on the market, the quality of the herbal medicinal product must always be demonstrated.⁶¹

CONCLUSIONS

The perceived benignity of botanically derived products may in fact be a misconception. With the reported occurrence of adverse skin reactions to topically applied herbal preparations on the rise combined with the lack of scientific proof showing that these natural compounds are safer than synthetic ones, the reasons for seeking out these products may be misguided. Of additional concern is the challenge of identification of the active constituent and therefore standardization. This issue may be inherent to the plant because of genetics, growing conditions, and harvesting or varied because of manufacturing procedures or chemical reactions within the products. However, the lack of standardization and regulation placed on botanically derived products along with their increase in popularity could be responsible for the rise of adverse reactions.

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