Perspective, Opinion, Commentary

A New Pathway: Botanical Drugs and the FDA

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The botanical drug industry appears to be on a trajectory of growth. There is an enormous body of research literature on many plant-derived products. However, botanicals carry additional complexities beyond those of conventional synthesized drugs. Perhaps because of this, the FDA created the Botanical Drug Pathway to tailor approval methods to drugs of vegetable origin. This pathway first began in 2004 and currently there are four drugs that have been approved, with more on the way.

Natural and botanical products have continued to gain momentum with both patients and clinicians. According to the American Botanical Council's report, herbal dietary supplement spending surpassed 15 billion dollars in the US just in 2023.[1] These are all over-the-counter (OTC) products available without a prescription and with minimal regulatory burden. However, the concept of "botanical drugs" remains a point of contention in the medical field, with many of its opponents arguing that there is a lack of evidence regarding the safety and effectiveness of these agents. Despite these claims, there is in fact an enormous body of research literature on many plant-derived products. Numerous studies have looked at herbal medicine across different fields such as endocrinology, psychiatry, dermatology, urology, and many others.[2-5]

However, it is true that botanicals carry additional complexities beyond those of conventional synthesized drugs. To at least some degree, botanical agents are philosophically distinct from molecular drugs: rather than relying on a single studied ingredient, they consist of a group of potentially active molecules derived from the plant. Thus, it can be difficult to standardize the amount of "active" ingredient that the plant of origin will have, since plants are affected by different conditions such as climate and soil, and the ratio of individual components may vary substantially between harvests.[6] Secondly, naturally-derived products can also be contaminated and result in the presence of heavy metals, pesticides, and microbes in the final product, which if ingested can have deleterious effects.[7] Additionally, the stability during storage and the extraction method used can affect both the quantity and the quality of the desired molecule. Thus, these products necessitate a different approach than conventional Food and Drug Administration (FDA) approval methods.

This long-standing need led to the development of the Botanical Drug Pathway. Starting in 1972, botanical products went under review when the FDA first introduced the over-the-counter (OTC) drug review. This process was created to ensure the safety of active components of OTC drugs. Subsequently in 1994, the FDA approved the Dietary Supplement Health and Education Act (DSHEA).[8] This was the first effort to regulate safety and labeling requirements, but it did not require prior approval. In 2004, the FDA first published a draft of the Botanical Drug Development Guidance for Industry, which provided a framework for botanical drugs to be approved. This draft was finalized in 2006, and the first drug that gained approval under this pathway was sinecatechins (Veregen®), a green tea extract for the treatment of genital warts, approved the same year. Since its original publication, the guideline has been revised and updated, with the latest version released in 2016. The Botanical Drug Development Guidance for Industry contains the distinctions that make the botanical pathway unique as compared to traditional pathways, such as accommodating the complex mixtures inherent in botanical products, addressing the lack of a single identifiable active ingredient, and considering substantial prior human use as part of the safety assessment.

This process begins in preclinical development, which involves phytochemical characterization, tests for preclinical toxicity and herb-drug interactions. If successful, the drug progresses to manufacturing and quality control. In this stage, the manufacturer must comply with good manufacturing practices (GMP). This is to assure that the quality control process is closely monitored, to achieve rigorous batch-to-batch consistency and ensure that the product remains chemically stable over its shelf life. After this, an Investigational New Drug (IND) application can be filed, and the drug can progress to clinical trials, where it is held up to the same standards of safety and efficacy as drugs undergoing conventional application. If the trials show reassuring results, the manufacturer can submit a New Drug Application (NDA) and begin the process of FDA-approval. Adverse effects for the drug will continue to be monitored during post-marketing surveillance.[9] While this pathway has unique elements tailored to the safety of botanical compounds, like the conventional pathway, it also includes aspects like post-marketing surveillance, Investigational New Drug (IND) applications, and Good Manufacturing Practice (GMP) compliance.

To date, approved botanical drug products include sinecatechins (VEREGEN®), crofelemer (Mytesi®), birch triterpenes (FILSUVEZ®), and anacaulase-bcdb (NexoBrid®) (See Table 1). Sinecatechins come from the leaves of the

Table 1. Currently approved botanical drugs in the United States.

Trade Name	Botanical Component	Year of Approval	Manufacturer	Indication	Mechanism of Action (MOA)
VEREGEN®	Sinecatechins *(Camellia sinensis)*	2006	ANI pharmaceuticals	Condyloma acuminata	Unspecified, but has been shown to inhibit angiogenesis and decrease inflammation in vitro[15,16]
Mytesi®	Crofelemer (*Croton lechleri*)	2012	Napo Pharmaceuticals	Non-infectious diarrhea in adult patients with HIV/AIDS	Inhibition of luminal chloride ion channels of enterocytes[17]
FILSUVEZ®	Birch triterpenes (different silver birch species)	2023	Chiesi Group	Epidermolysis Bullosa	Unspecified, but has been shown to decrease inflammation, increase tissue formation, and create a new epidermal barrier in vitro[18]
NexoBrid®	Anacaulase (extracted from pineapples)	2022/ 2024	MediWound	Thermal burns in adults (2022) and subsequently in children (2024)	Proteolytic enzymes dissolve non-viable tissue[19]

green tea plant *Camellia sinensis* and it is indicated for the treatment of condyloma acuminata.[10] Crofelemer is derived from the plant latex of *Croton lechleri* and is indicated for non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy.[11] The preparation of birch triterpenes comes from a mix of different species of silver birch and is indicated for the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa in adult and pediatric patients 6 months of age and older.[12] Finally, anacaulase is a biologic—a mixture of proteolytic enzymes—from the stems of pineapple plants used to treat thermal burns.[13] This product is a botanical biologic that leverages cultured plant cells to produce the enzymes in a controlled setting, eliminating the inconsistencies of extracting the compound from field-sourced pineapple plants. As a topical medication, the pharmacokinetics of this medication can be more variable in clinical trials. All four of these drugs had to follow the steps of the Biologic License Pathway in order to gain approval. It should be noted that other drugs such as cascara, psyllium, and senna are included in the over-the-counter (OTC) drug review, which only focuses on the safety and efficacy of active ingredients.[14]

Moving forward, the number of botanical drugs undergoing this path is likely to keep growing. For instance, Menerba, a mixture of multiple herbs that have been used in traditional Chinese medicine preparations, is undergoing phase III trials after having received FDA manufacturing approval. If approved as a new drug, Menerba will be an oral drug to treat vasomotor symptoms in menopause by modifying estrogen receptor transcription.[20,21] Another example includes Zabalafin hydrogel, which has recently advanced into phase 2b trials.[22] This drug is also of botanical origin and it is being examined as a treatment for the inflammation, microbial imbalance, and itch of atopic dermatitis. Finally, drugs from other botanical origins such as cannabis are being studied for a variety of applications. Nabiximols is a intranasal botanical drug, approved in the UK, being studied for different conditions such as multiple sclerosis and chronic cancer related pain.[23,24]

Although this pathway was established relatively recently, with only four drugs approved to date, these initial approvals provide crucial lessons. They underscore the importance of standardization, consistency, and rigorous testing to ensure the production of safe and effective products. Botanical drugs hold much promise, and as technology and industrial capabilities continue to develop, the quality and quantity of botanical products extracted will increase. Artificial Intelligence (AI) may also play a significant role in the advancement of botanical drugs. In particular, AI is being studied to identify potential new drugs and optimize drug target selection.[25] As the production of drugs from herbal origins continues and likely escalates, the Botanical Pathway will be an invaluable tool to guarantee they are up to par with required standards. Regularly updating these guidelines will be crucial to ensure consumer safety and product efficacy. This is especially important as reports of adverse effects and potential toxicity from unregulated supplements continue to emerge. For instance, studies have found that certain supplements are contaminated with harmful substances such as pesticides and heavy metals, which can increase the risk of liver disease. Additionally, some products have been found to contain undeclared pharmaceutical ingredients, leading to serious health risks. In this context, clinicians are likely to place greater emphasis on botanical standardization in their clinical practice and recommendations.[26]

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