From Plant to Patient: A Historical Perspective and Review of Selected Medicinal Plants in Dermatology

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Skin conditions are a common health concern faced by patients of all ages. For thousands of years, plants have been used to treat various skin conditions, including acne, vitiligo, and psoriasis, to name a few. Today, with increasing patient preference for natural therapies, modern medicine is now more than ever incorporating age-old knowledge of herbal remedies useful in treating skin conditions into modern-day treatments. This review covers various plant-derived therapeutics (polyphenon E [sincatechins], psoralen, salicylic acid, anthralin, podophyllotoxin, and Filsuvez [birch triterpenes, oleogel-S10]) that have demonstrated scientific evidence of clinical efficacy for dermatologic disorders. The discovery, composition, history of use, and current uses in dermatology are summarized for each botanical ingredient.

Keywords: Anthralin, Medicinal plants, Podophyllotoxin, Polyphenon E, Salicylic acid

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INTRODUCTION

Skin conditions have been a significant health concern since the beginning of civilization, continuing to account for a substantial portion of the global illness burden and affecting millions of people worldwide. For thousands of years, cultures around the world have used plant-derived remedies to treat various ailments, including skin conditions. Each culture utilized resources available in their environment through a combination of resourcefulness and trial and error. Many of these herbal remedies were specifically developed for treating skin conditions. The ancient Egyptians documented the treatment of skin conditions in the Edwin Smith and Ebers papyri, dating back to BC 1600 and BC 1550, respectively (Ferreira et al, 2021). These papyri provide the first references to cutaneous wounds, ulcers, and tumors and the use of medicinal plants to treat them. For example, Egyptians are credited with the first use of phototherapy for repigmentation. After ingesting the *Ammi majus* L (Apiaceae) plant that contains a natural photosensitizing psoralen, they exposed themselves to sunlight with the intention of repigmenting their skin. Today, psoralen plus UVA (PUVA) phototherapy is used to treat vitiligo, a depigmentation condition (Ferreira et al, 2021). Egyptians, specifically Cleopatra, also bathed in sour milk, which contains lactic acid and acts as an exfoliant to rejuvenate the epidermis similar to the alpha-hydroxy acids found in today's chemical peels (Rajanala and Vashi, 2017). Ochre-rich mixtures found in the Blombos Cave in South Africa are thought to have been used for skin protection about 100,000 years ago (Pastore et al, 2015). These and many other records from the clay tablets of the Sumerians, the texts and theories of Hippocrates in the Corpus Hippocraticum, and the medical encyclopedia De Medicina from Celsus during the Roman Empire contain examples of plant-derived medicines used to treat skin conditions and maintain aesthetics (Pastore et al, 2015). Natural products play a significant role in the process of drug discovery globally and are a source of many approved pharmaceutical substances (de la Torre and Albericio, 2020; Newman and Cragg, 2016; Zhang et al, 2020).

According to the World Health Organization, about 25% of the drugs in our contemporary medical pharmacopeia are derived from plants (Qazi and Molvi, 2016). Herbal medicines are popular owing to their benefits in terms of safety, efficacy, and low risk for adverse effects. Although plant-based remedies are a part of conventional medicine in Eastern continents, including Europe and Asia, the United States Food and Drug Administration (FDA) does not currently regulate all products released to consumers, and dermatologists thus consider such products as alternative therapies rather than as first-line treatments (Bedi and Shenefelt, 2002; Shoaib et al, 2022). Emerging in vitro, in vivo, and clinical research shows that some plant-derived medications have promising efficacy in the treatment and prevention of certain skin conditions (Shoaib et al, 2022). Antibacterial, antidermatophytic, antioxidant,

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Abbreviations: 8-MOP, 8-methoxypsoralen; CTCL, cutaneous T-cell lymphoma; DPCP, diphenylcyclopropenone; EB, epidermolysis bullosa; EGCG, epigallocatechin gallate; EMA, European Medical Agency; FDA, Food and Drug Administration; HPV, human papillomavirus; PUVA, psoralen plus UVA; SA, salicylic acid; SSA, supramolecular salicylic acid; STAT3, signal transducer and activator of transcription 3; STSG, split-thickness skin graft transplantation; TCM, traditional Chinese medicine

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anti-inflammatory, antiproliferative, and chemoprotective properties of herbal medicines and their bioactive compounds have been extensively studied for their potential in treating melanoma and nonmelanoma skin cancers, dermatophytosis, atopic dermatitis, psoriasis, and acne (Raut and Wairkar, 2018; Shoaib et al, 2022).

Considering the current relevant literature, further investigation is required to gain clearance for many products derived from plants that are used to treat skin problems. Therefore, the traditional practices and ethnobotanical knowledge found in this review and others like it may be used as a foundational element in finding and developing new bioactive natural products for the treatment of different skin conditions. In this review, we explore the discovery and composition, history as a drug, and current uses of various plant compounds in dermatology, including polyphenon E, psoralen, salicylic acid (SA), anthralin, podophyllotoxin, and oleogel-S10.

POLYPHENON E

Discovery and composition

Polyphenon E is an FDA-approved botanical drug consisting of a standardized mixture of catechin derivatives from *Camellia sinensis* (L) Kuntze (Theaceae), commonly known as green tea (Nair et al, 2021). The phenolic content of the composition is approximately 65% epigallocatechin gallate (EGCG), 25% various catechins—including catechin, epicatechin, epigallocatechin, catechin-3-gallate, epicatechin-3-gallate, and gallocatechin-3-gallate (Figure 1)—and <1% caffeine (Sinicrope et al, 2021; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al, 2018). EGCG comprises the primary active component. *C sinensis* has a long history in Chinese culture and traditional Chinese medicine (TCM). Although tea from the plant's leaves is commonly consumed worldwide today, it was first popularized in China during the Tang dynasty (Yang et al, 2014). However, its use as a medicinal herb dates back even further,

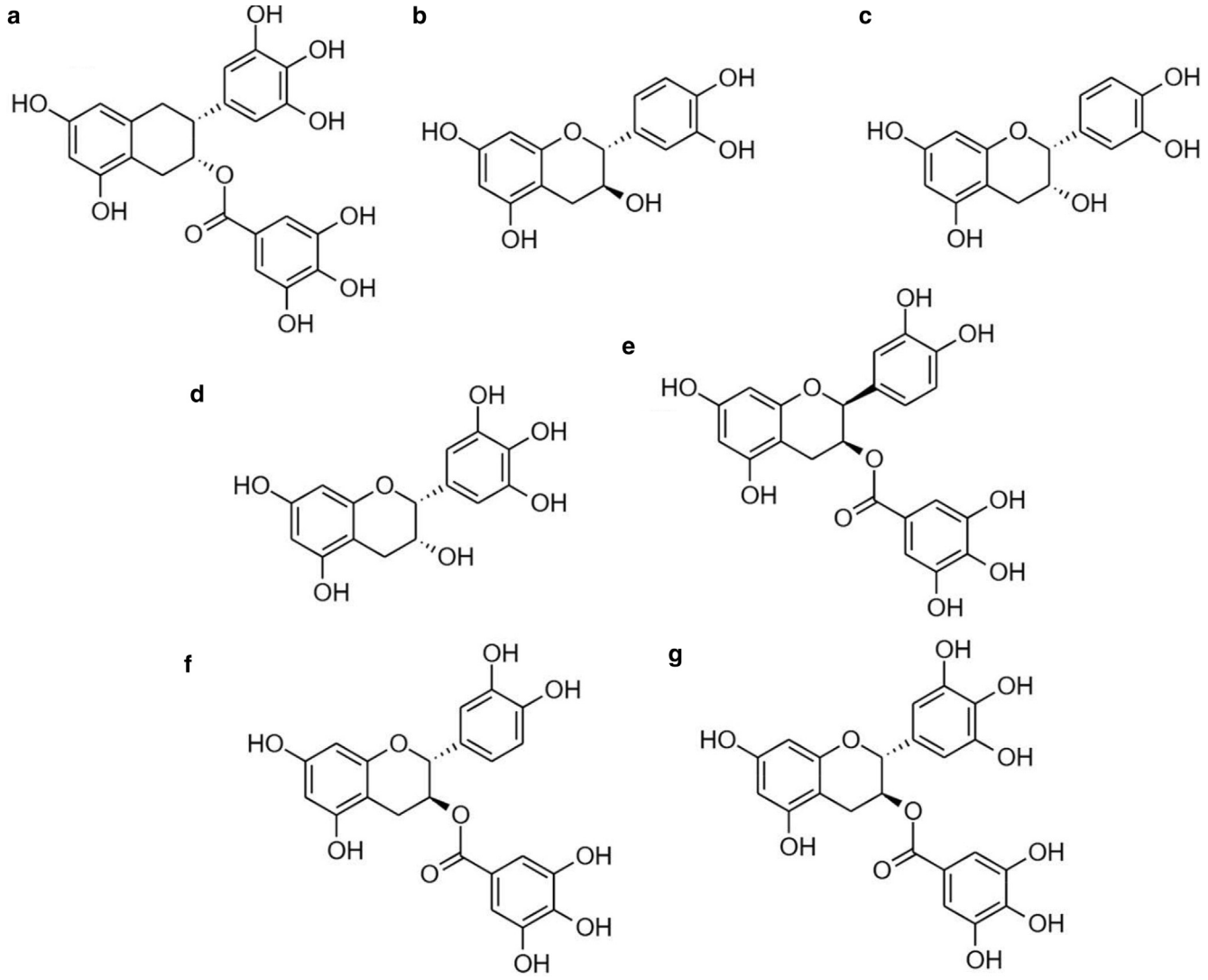

Figure 1. Major constituents of polyphenon E. (**a**) Epigallocatechin gallate (65%) is the most prevalent compound in the extract and is thought to be responsible for most the mixture's biological activities. (**b**) Catechin (1.1%). (**c**) Epicatechin (9%). (**d**) Epigallocatechin (4%). (**e**) Epicatechin-3-gallate (6%). (**f**) Catechin-3-gallate (0.2%). (**g**) Gallocatechin-3-gallate (4%).

likely for thousands of years. Its medicinal uses have been described in famous TCM texts such as the Cha Jing (Tea Bible), the Ben Cáo Gang Mu, and the Xin Xiu Ben Cao and include references to use as a diuretic, anti-inflammatory, and mucolytic, among others.

Mode of action

Polyphenon E and EGCG have a complicated biological activity that is not fully understood but appears multifaceted. Despite the lack of a well-defined mechanism of action, polyphenon E has been of high interest in the field of dermatology for 3 primary reasons: its anti-inflammatory activity, antioxidant activity, and regulation of cellular growth and proliferation, all of which may be interconnected. Murine models have shown that EGCG inhibits the expression of the important inflammatory cytokines TNF-α and IL-1β through the inhibition of the enzyme inducible nitric oxide synthase, which in turn affects multiple different skin conditions (Khalatbary and Ahmadvand, 2011). In addition, EGCG, along with various minor compounds present in polyphenon E, has consistently demonstrated strong antioxidant activity in vitro (Nguyen et al, 2015; Ning et al, 2016). This activity has been used to explain, in part, the various chemopreventative effects, such as through the inhibition of transcription factors such as suppression of the reduction–oxidation–sensitive transcription factors NF-κB and activator protein-1 (Kim et al, 2014; Klaunig, 1992). These transcription factors are also important parts of the inflammatory response, which has been hypothesized to explain EGCG's use in the treatment of condyloma acuminatum (Diţescu et al, 2021).

Early work with green tea catechins and extracts demonstrated the ability to inhibit various DNA and RNA polymerases as well as 12-O-tetradecanoylphorbol-13-acetate–induced tumor promotion in vitro (Nakane and Ono, 1989; Ruch et al, 1989). Further in vitro study of polyphenon E has demonstrated that the regulation of cellular growth and carcinogenesis by EGCG is very complicated and involves multiple distinct pathways, including the G1-phase arrest through the stimulated expression of p21 and DEC1, inhibition of GFs EGFR and IGFR-1, and the enhancement of gap junctional communication (Chu et al, 2017; Shimizu et al, 2008, 2005; Sigler and Ruch, 1993). EGCG has also been shown in vitro to induce apoptotic gene expression in multiple different cancerous cell lines, which may be another explanation for its use in the treatment of condyloma acuminata (Chu et al, 2017; Jiang et al, 2022; Khan et al, 2020). In vitro and in vivo models have demonstrated EGCG's ability to deactivate p53 and cell cycle signal transduction pathways typically activated by UVR (Yusuf et al, 2007). Both the antioxidant activity and effects on cell cycle regulation of polyphenon E are thus hypothesized to contribute to its broad list of potential dermatologic applications, such as condyloma acuminatum, acne, and skin cancer.

History as a drug

In contemporary times, the Japanese tea company Mitsui Norin first began research on the extract in 1980 before patenting the formulated mixture in 1983. The first clinical trial of green tea catechins took place at the Chinese Academy of Medical Sciences (Beijing, China) for condyloma acuminatum, also known as anogenital warts (Cheng et al, 1998). These trials demonstrated rates of improvement for human papillomavirus (HPV)–infected condyloma acuminata ranging from 52.9 to 87.9% after treatment with a 5–20% polyphenon E gel and cure rates ranging from 29.4 to 61%. As a result of these promising early clinical trials, beginning in the early 2000s, clinical research on the green tea mixture accelerated, and 2 phase III clinical trials were conducted in Germany and the United States that supported the use of polyphenon E to treat condyloma acuminatum (Stockfleth et al, 2008; Tatti et al, 2008). Both trials examined polyphenon E 15% ointment versus 10% ointment. The first clinical trial examined 503 patients and recorded a significant difference in the rates of complete clearance of all baseline and new anogenital warts for both the 15% ointment (52.6%) and the 10% ointment (50.8%) versus the vehicle control (37.3%) (Stockfleth et al, 2008). The other study reported similar findings after examining 503 patients using the same methodology, with 57.2% and 56.3% complete clearance reported in the 15% ointment and 10% ointment groups, respectively, versus 33.7% in the vehicle control (Tatti et al, 2008). In 2006, after these clinical trials and associated toxicity studies, the United States FDA approved the use of Veregen Ointment 15% (the brand name for polyphenon E) for the treatment of anogenital warts (Wu et al, 2008). Veregen became the first botanical drug approved by the FDA and remains 1 of only 4 botanical drugs, along with Mytesi (Crofelemer), Filsuvez (birch terpenes, Oleogel S-10), and NexoBrid (anacaulase-bcdb), to ever be approved by the agency (Ahn, 2017; Heo, 2023; Shoham et al, 2024). Since its approval, Veregen reached annual sales of $4.5 million as of 2017 and has been investigated for several other potential medicinal uses, including against cancer and COVID-19 (Song et al, 2009; Zhang et al, 2021).

Uses in dermatology today

Polyphenon E remains approved only for use in treating condyloma acuminatum, but various other potential dermatologic uses have been investigated. Therefore, its primary function in dermatology remains as a treatment for condyloma acuminatum and other types of warts. Further studies have supported its use for the treatment of genital warts in various patient cohorts, including HIV-positive patients, immunocompromised patients, and children (Bilenchi et al, 2018; Grandolfo and Milani, 2017; Nikfarjam et al, 2021). In addition, a recent clinical trial demonstrated that polyphenon E 10% was effective in reducing the recurrence rate of external genital warts after laser carbon dioxide ablative therapy from 29 to 5% after 3 months (Puviani et al, 2019). Furthermore, little to no adverse effects have been reported with topical application or consumption of polyphenon E, with only rare cases of liver injury reported, which were likely unrelated to the drug's consumption (Kumar et al, 2016; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) et al, 2018).

Acne. Polyphenon E and other *C sinensis* extracts have been proposed as a topical or oral treatment for acne vulgaris. A 2020 review of green tea extracts identified 9 clinical trials for acne vulgaris and noted that although ineffective when taken orally, topical application of *C sinensis* extracts

was effective at reducing noninflammatory acne lesions compared with a placebo, with no significant adverse effects reported (Kim et al, 2021). However, further clinical trials are necessary to assess the utility and safety of green tea extracts for acne.

UV-induced skin damage and skin cancer. Green tea extracts have shown some anticancer properties in various studies; many researchers have hypothesized that this may make them effective in addressing UV-related skin damage and skin cancers (Filippini et al, 2020). However, research on the efficacy of polyphenon E and other green tea extracts regarding these conditions remains inconclusive and requires further research. Studies in human cell models have shown that topical application of green tea catechins (EGCG) may provide significant protection against UVR versus a placebo, specifically through the deactivation of p53, inhibition of leukocyte infiltration, and inhibition of prostaglandin metabolite production, although there remains conflicting research regarding the exact relationship between polyphenon E and p53 (Katiyar et al, 1999; Khan et al, 2020; Mnich et al, 2009). Although a significant amount of in vitro data supports the existence of chemopreventative and anticarcinogenic properties of EGCG, clinical data remain limited. An early randomized, double-blind, placebo-controlled comparison study that compared UVB-irradiated skin treated with topical EGCG with that treated with placebo found greater increases in caspase-3–active keratinocytes on skin treated with EGCG (Yao et al, 2005). However, this study was limited to only 3 volunteers, and a great deal of further clinical research is needed to promote the use of polyphenon E and green tea catechins for protection against UV-induced skin damage and skin cancers.

Topical wound healing and anti-inflammatory properties. Polyphenon E and green tea extracts have been examined as topical wound-healing agents. This is in large part due to their in vitro efficacy at inhibiting the growth of bacteria that cause wound infections, such as methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Ibrahim Alghamdi, 2023; Umashankar et al, 2018). In addition to its antibacterial properties, EGCG has also been demonstrated to possess in vitro antiviral activity against HIV, influenza A, hepatitis B, hepatitis C, and others and antifungal activity against *Candida albicans* (Steinmann et al, 2013). Along with its anti-infective properties, polyphenon E may play a role in wound healing by stimulating TGF-β1, which promotes wound contraction and protects against scaring (Klass et al, 2010). Polyphenon E has many anti-inflammatory properties, which are again largely attributed to its high level of antioxidant compounds (Jakubczyk et al, 2020). EGCG may also play a role in downregulating the inflammatory response through negative regulation of toll-like receptor 4 signal transduction (Byun et al, 2012). These in vitro results have led to further in vivo research, and one study found that consumption of 2 commercial green tea beverages significantly increased radical scavenging levels of the skin by almost 30% in comparison with a control group (Megow et al, 2017). In addition, administration of ECGC through a poly-γ-glutamate–based microneedle has shown promise as a means of treating atopic dermatitis in mice by preventing the accumulation of ROS (Chiu et al, 2021). A recent double-blind, clinical trial for cutaneous scar healing also revealed a significant increase in M2 macrophages, decreased scar thickness, and increased scar elasticity compared with a placebo in human volunteers (Ud-Din et al, 2019).

PSORALEN

Discovery and composition

Psoralen is a furanocoumarin commonly found in various plants of the Apiaceae, Rutaceae, and Moraceae plant families, including fig, rue, celery, parsley, fennel seeds, and parsnip. It is a planar, tricyclic compound with a furan ring fused to a coumarin moiety (Figure 2). Oxsoralen (8-methoxypsoralen [8-MOP], methoxsalen) is the common medically used psoralen (Buhimschi et al, 2020). Evidence suggests that psoralen and exposure to sunlight was a remedy used to treat vitiligo in Egypt and India since BC 1200 (Pathak and Fitzpatrick, 1992). Herbalists boiled the leaves, seeds, or roots of specific plants such as *Ammi majus* or *Cullen corylifolium* (L) Medik. (synonym *Psoralea corylifolia*) of the Apiaceae and Fabaceae plant families, respectively, and then the infusion was ingested or applied to the skin, followed by skin exposure to sunlight (Pathak and Fitzpatrick, 1992). Centuries later, Egyptian researcher Abdel Monem El Mofty identified 8-MOP as the active compound responsible for these effects (Bethea et al, 1999).

History as a drug

PUVA therapy with psoralen can be traced back to ancient Egypt since 1200 BC. However, modern development of PUVA therapy began in the 1940s when El Mofty identified the active compound responsible and used methoxsalen and sunlight to treat vitiligo (Bethea et al, 1999). In the 1970s, dermatologists and pharmacologists at Harvard Medical School and Massachusetts General Hospital introduced photochemotherapy to the treatment of psoriasis by combining orally administered photoactive 8-MOP and exposure of skin to UVA radiation (Pathak and Fitzpatrick, 1992). This initiated the treatment of a variety of skin conditions with PUVA photochemotherapy.

Today, a specific formulation of methoxsalen called Oxsoralen Ultra is used for PUVA therapy. It can be taken orally for systemic therapy or applied topically through hand and foot soaks or through baths for total body coverage in the outpatient setting. Oral treatment must be taken about 75 minutes prior to treatment, and dose is individualized (Farahnik et al, 2016). Patients choosing soak or bath treatment undergo treatment for approximately 30 minutes, are

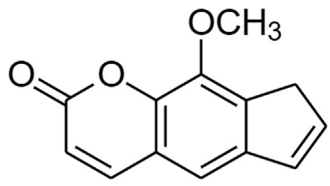

Figure 2. Chemical structure of 8-methoxypsoralen. The 8-methoxypsoralen is known to intercalate in DNA helices, forming cross-links with thymine and cytosine bases when exposed to UVR.

patted dry, are required to wait for another 30 minutes, and are then exposed to UVA in a light box for total body or systemic treatment or a specialized light box accommodating only the hands or feet (Farahnik et al, 2016). Depending on the patient's dose, light will be administered for several seconds to minutes. PUVA treatment is administered in 2 phases known as the initial clearing phase and the maintenance phase once 95% of the skin affected is successfully treated (Farahnik et al, 2016). These treatments are given at variable frequencies each week and for variable lengths depending on the skin condition treated. The use of psoralens with UVA light has ultimately contributed to the development of photodynamic therapy, which is now used to treat many medical conditions, including nonmelanoma skin cancers (Zhao and He, 2010).

Mode of action

Psoralens are aromatic compounds with an absorption band in the 200–350-nm range (Bethea et al, 1999). When exposed to UVA radiation, psoralen intercalates into DNA forming monoadducts and covalent interstrand cross-links with thymine and cytosine bases (Buhimschi et al, 2020). This action suppresses DNA synthesis and is responsible for psoralen's clinical efficacy. PUVA therapy was originally believed to reduce cell replication rate of keratinocytes through the formation of adducts with photoactivation. However, in 1996, Johnson et al (1996) showed that it was not keratinocytes that were affected by PUVA therapy but rather lymphocytes in the epidermis of patients with psoriasis. Thus, 8-MPO/UVA can also affect the cell's microenvironment by altering the secretion of signaling molecules and promoting anti-inflammatory effects (Bethea et al, 1999).

Uses in dermatology today

PUVA photochemotherapy has been approved by the FDA to treat hyperproliferative skin disorders, including psoriasis, cutaneous T-cell lymphoma (CTCL), and vitiligo (Bhatia et al, 2021). The therapy's mechanism of action varies slightly depending on the condition. However, the common underlying factor is its ability to target or destroy the cells mediating the skin disease. In addition, psoralen can be taken either orally or applied topically about 30 minutes after a light meal and 1–2 hours before exposure to UVA radiation, the amount of which is dependent on the patient's skin phototype (Bhatia et al, 2021). However, long-term PUVA therapy does have adverse effects, including freckling, wrinkling, and increased risk of skin cancer (Stern and PUVA Follow-Up Study, 2012). As such, it is important to include regular skin examinations in the patient's treatment plan.

Psoriasis. Psoriasis is a chronic skin condition caused by an overactive immune system producing excessive skin growth, which eventually leads to scaly, itchy patches of skin. PUVA phototherapy is a common treatment for chronic psoriasis, with the potential for long-term remission due to its antilymphocytic potential (Madigan and Lim, 2016). One study found that both keratinocyte expression of proapoptotic factors, including P53 and Fas, and lymphocyte suppression of BCL-2 antiapoptotic factors increased (El-Domyati et al, 2013). A second study found that BAX proapoptotic proteins were also increased in patients with psoriasis after PUVA treatment (Tomková et al, 1998). Although its risks include acute toxicity and risk of cancer, PUVA is overall advantageous for patients with refractory psoriasis not well-controlled on topical therapies alone and darker skin types (Madigan and Lim, 2016).

Vitiligo. Vitiligo is an autoimmune disorder that causes depigmentation in the skin. PUVA therapy treats vitiligo by inducing repigmentation of lesions over prolonged treatment by stimulating melanocytes (Bae et al, 2017). More specifically, the treatment stimulates degenerative changes in melanocytes and keratinocytes such as pyknosis of nuclei, vacuolization of melanocytic cytoplasm, and absent nucleoli (Anbar et al, 2012). This occurrence is then followed by improvement and a significant increase in active melanocytes after treatment (Anbar et al, 2012). PUVA therapy in combination with other modalities has also shown more promising results in the treatment of vitiligo. Combination calcipotriol and PUVA therapy showed statistically significant improvement of vitiligo, with more intense repigmentation with the combination-treated patients than in the patients treated with PUVA only (Cherif et al, 2003). Similarly, combination low-dose azathioprine and oral PUVA therapy showed greater improvement in repigmentation of patients with vitiligo than in those receiving PUVA therapy alone (Radmanesh and Saedi, 2006).

CTCL. CTCL is a lymphoma in the skin caused by neoplasms of T cells. The most common subset of CTCL is mycosis fungoides, which presents with scaly, erythematous patches that can progress to tumors (Marka and Carter, 2020). Patients with thin plaques and patches require less time for clearance than those with infiltrated plaques, and PUVA should not be used for tumor-stage mycosis fungoides (Tarabadkar and Shinohara, 2019). PUVA has been shown to be effective against CTCL in an extracorporeal system called photopheresis. In this system, blood is treated with radiation outside of the body and then transfused to the patient, causing an immune response against the CTCL cells remaining in the blood, thereby preventing the progression of the disease (Edelson, 1987; Pathak and Fitzpatrick, 1992). A more recent study found that PUVA therapy caused an increase in IL-10 and IFN-γ concentrations in patients, which indicates cytokine expression, and inflammatory reaction plays a role in mitigating CTCL (Karamova et al, 2022). Ultimately, PUVA therapy helps to treat CTCL through extensive damage to diseased cells.

SA

Discovery and composition

SA (Figure 3), also known as 2-hydroxybenzoic acid or orthohydrobenzoic acid, is a phenolic acid that is commonly found in the bark of willow trees, sweet birch, meadowsweet, or the leaves of the wintergreen plant (Lin and Nakatsui, 1998). It is composed of an aromatic benzene ring with a carboxyl and hydroxyl functional group. Salicin, the bioactive component of willow bark, was first extracted by Italian researchers Brugnatelli and Fontana in the early 1800s (Arif, 2015). Subsequently, German pharmacologist Johann Buchner purified salicin and named it after the willow tree's genus

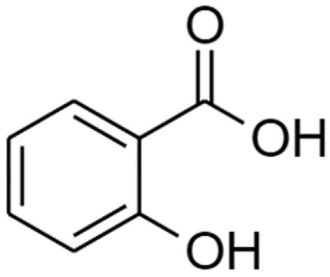

Figure 3. Chemical structure of salicylic acid. Salicylic acid promotes epithelial cell separation and desquamation, making it of clinical relevance in various dermatologic conditions.

Salix (Arif, 2015). Its derivative acetyl SA (aspirin) is widely used as an oral anti-inflammatory and analgesic today.

History as a drug

SA has been used for more than 2000 years as a topical agent to treat various skin conditions, in addition to its analgesic and antipyretic properties (Lin and Nakatsui, 1998). Hippocrates prescribed willow bark and leaves for the external treatment of pain and fever. Later, Pliny the Elder, a Roman author and naturalist, used willow bark to treat calluses and corns in the first century AD (Arif, 2015). In 1757, Reverend Edward Stone rediscovered the antipyretic properties of willow. Less than a century later, in 1824, Italian researchers Brugnatelli and Fontana extracted salicin from willow bark, and German pharmacologist Buchner named it after the Latin root for willow, *Salix* (Arif, 2015). In 1838, Raffaele Piria, an Italian chemist, determined the molecular formula of SA. In the 1860s, SA was discovered to soften and exfoliate the stratum corneum. Later, German dermatologist Paul Gerson Unna described the dermatologic uses of SA, specifically its chemical peeling property, in 1882 (Arif, 2015; Borelli et al, 2020). German chemist Felix Hoffmann modified SA to create acetylsalicylic acid, which we now know as aspirin, in 1897 (Miner and Hoffhines, 2007). Today, SA is used in creams, gels, and cleansers for the treatment of various skin conditions, most notably acne vulgaris, by speeding up skin cell shedding.

Mode of action

The mechanism of action of SA was originally poorly understood, and the compound was thought to be a keratolytic agent causing the lysis of keratin filaments (Davies and Marks, 1976). However, it is now understood that SA dissolves intercellular material, thus promoting epithelial cell separation and desquamation (Davies and Marks, 1976). Specifically, SA acts to extract desmosomes, which are proteins vital for cell-to-cell adhesion, and reduces the integrity of the upper layer of stratum corneum, which is subsequently more easily shed and replaced (Arif, 2015). Early studies suggested that SA does not impact epidermal thickness (Lodén et al, 1995). However, in a more recent study, a 30% supramolecular SA (SSA) peel was shown to increase epidermal thickness after activation of basal keratinocytes in patients with moderate-to-severe acne vulgaris (Shao et al, 2023). The SSA treatment was shown to improve the acne vulgaris in these patients by first improving the skin microenvironment (Shao et al, 2023). SA is approved for over-the-counter acne creams, and many products contain concentrations of 0.2−5% SA, which indicates strong preference for this compound and its wide clinical application (Arif, 2015).

Uses in dermatology today

Today, SA is found in more than 80 topical treatments commonly used to treat a variety of skin conditions, including acne vulgaris, melasma, warts, photodamage, freckles, lentigines, and ichthyosis (Arif, 2015; Lin and Nakatsui, 1998). Although stronger concentrations remain prescription only, many popular brands have incorporated SA into over-the-counter treatments that allow greater accessibility to patients. In addition, SA is available in a variety of forms and vehicles, including gels, creams, lotions, and solutions used daily as cleansers, serums, moisturizers, and other skincare. Topically applied SA absorbs through the skin, and absorption can be enhanced using a hydrophilic ointment or layering with occluding topicals (Lin and Nakatsui, 1998). Owing to its desquamation capabilities, it enhances the penetration of other topicals into the skin and is used as an adjunct therapy in many topical skincare regimens. For instance, there is a marked increase in penetration of topical corticosteroids used for the treatment of psoriasis when combined with 2−10% SA (Lebwohl and van de Kerkhof, 2018). However, owing to its percutaneous absorption, it does have the risk of causing systemic toxicity and can also cause allergic reactions with redness, itching, and burning if not used carefully and as instructed by a provider.

Acne. Acne is a prevalent skin condition affecting about 10% of the population, with manifestations ranging from comedones to cysts. SA is a common topical agent used to treat acne owing to its antibacterial, anti-inflammatory, and skin microbiome−regulating properties. Being a lipophilic agent, it also has comedolytic properties. Shao et al (2023) showed that a 30% SSA peel decreased the presence of *S aureus* and *Cutibacterium acnes* after treatment of patients with moderate-to-severe acne vulgaris. This suggests a therapeutic role in regulating the skin microbiome. The study also showed significantly reduced proinflammatory cytokines such as IL-1a and IL-6 after treatment, suggesting that it reduces redness and inflammation typically associated with acne breakouts (Shao et al, 2023).

Warts. Warts are benign skin growths that are typically not associated with pain and can go away on their own over time. In the case that they do not disappear, a variety of therapies are used to treat them, including SA. SA is first-line over-the-counter therapy for warts and is typically prepared at a concentration ranging from 10 to 60% (Lipke, 2006). SA's keratolytic therapy destroys the virus-infected epidermis. Although SA is an advantageous treatment owing to its relatively low cost, negligible pain, and usual effectiveness, it does require weeks to months of treatment time, needs strict patient compliance, and possesses a risk for toxicity in children (Lipke, 2006).

Ichthyosis. Ichthyosis is a hyperkeratotic genetic skin condition in which the skin dries, thickens, and forms scales. SA has been shown to remove thick scales of ichthyosis vulgaris in a gel preparation containing 60% propylene glycol, 20% ethanol, and 6% SA (Baden and Alper, 1973). More

recent studies indicate that topical keratolytic agents and emollients, including lactic acid, SA, and 5% urea, can be successful in treating neonatal patients with ichthyosis (Deffenbacher, 2013). However, it is important to recognize that the increased permeability in skin of patients with ichthyosis can cause increased absorption and transcutaneous toxicity, especially in infants (Deffenbacher, 2013). Thus, an appropriate dosage is required.

ANTHRALIN

Discovery and composition

Anthralin (1,8-dihydroxy-9-anthrone) or dithranol is an anthracene compound (Figure 4) that was first synthesized in 1916 as a derivative of the plant-derived natural product, chrysarobin. The exact anthracene structure consists of hydroxyl groups of at C-1 and C-8 and an oxo group at C-9 of an anthracene molecule (Ashton et al, 1983). Chrysarobin was initially obtained from the sap of the araroba tree *Vataireopsis araroba* (Aguiar) Ducke in the Fabaceae family (synonym *Andira araroba* Aguiar) in Brazil and is known as Goa powder or Bahia powder (Ashton et al, 1983). The use of Goa powder then spread to other areas of the world such as China and India, the latter of which saw the powder become popular among local populations for treatment of ringworm (Ashton et al, 1983; Steger and Hollander, 1982). The powder was known to have irritative properties in relation to the skin because workers who harvested the sap wore face protection to avoid such effects (Ashton et al, 1983). In 1876, Alexander John Balmanno Squire of Hong Kong became the first doctor to widely promote Goa powder as a treatment for psoriasis (Steger and Hollander, 1982).

Mode of action

Although the exact mechanism of action of anthralin remains uncharacterized, it is hypothesized that the compound possesses antiproliferative and anti-inflammatory effects (Reichert et al, 1985). In vitro studies have demonstrated that anthralin inhibits monocyte secretion of TNF-α, IL-6, and IL-8, all of which are important inflammatory cytokines (Mrowietz et al, 1997). A study in a mouse keratinocyte models demonstrated decreased EGFR expression through the activation of NF-κB (Jalian et al, 2007). Anthralin has also been shown to accumulate in the mitochondria in vitro, inducing apoptosis through the disruption of membrane potential and the release of cytochrome c (McGill et al, 2005).

History as a drug

The first antipsoriatic preparation of anthralin was procured over 100 years ago in Germany by Galewsky (Ashton et al, 1983). He optimized an anthralin formulation of 0.5% SA and liquor carbonis detergens in an ointment base or 0.05–0.1% anthralin in acetone. Despite extensive research since the early 1900s, no anthrone derivatives other than anthralin were found to be as effective in treating psoriasis (Ashton et al, 1983).

Anthralin was first used clinically in Germany by Galwesky and Unna (Ashton et al, 1983). Initial clinical studies at the time were limited but included 10 years of good results, with anthralin in psoriasis by Galewsky and Kromayer showing effective use in 600 patients (Ashton et al, 1983). In a separate study, the Ingram regimen (coal tar, light therapy, and anthralin) demonstrated complete resolution of psoriatic lesions in 95% of 2120 patients. Average clearance times were 19.5 days for outpatients and 15.2 days for inpatients (Maclennan and Hellier, 1961). Other studies compared anthralin with PUVA, demonstrating that 82% of anthralin-treated patients cleared in 20.4 days and 91% of PUVA patients cleared in 34.4 days (Rogers et al, 1979). One of the earliest studies in the United States by Beerman et al (1935) reporting the use of anthralin ointment in 23 outpatients with psoriasis demonstrated clinical resolution of all patients with 4 months of treatment. In the majority of these studies, skin irritation and discoloration were among the most frequent side effects. Anthralin is currently pregnancy prescribing category C and is not recommended for pregnant or nursing mothers (Roy and Forman, 2013).

Uses in dermatology today

Psoriasis. Anthralin was one of the earliest topical agents promoted for psoriasis treatment and was first widely used in Germany and later in Great Britain for treatment of the condition. Anthralin was never popular with American physicians as a psoriasis treatment owing to its side effects of skin irritation and discoloration. Despite its early popularity in Europe, anthralin has fallen out of favor with many contemporary dermatologists (Ashton et al, 1983). However, there has been research in using either reduced doses of anthralin or anthralin derivatives with the goal of reducing cutaneous side effects. In current dermatologic practice, anthralin is commonly prescribed as short-contact therapy to mitigate side effects (Roy and Forman, 2013).

Since its introduction to the United States, several different brands of anthralin have been developed, including Drithocreme, Anthra-Derm, and Micanol. These formulations are available in a cream or petroleum base with concentrations of 0.1, 0.25, 0.5, and 0.1%. Micanol is unique because it uses a semicrystalline monoglyceride matrix, which stabilizes anthralin and protects it against oxidation, leading to fewer adverse effects (Roy and Forman, 2013).

Psoriatec is a formulation of anthralin that is FDA approved for use in plaque psoriasis and psoriasis of the scalp. There is

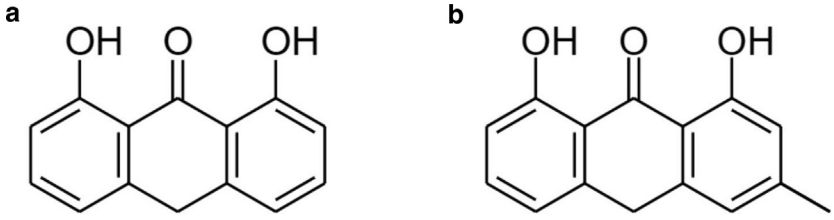

Figure 4. Chemical structures of anthralin and chrysarobin. (**a**) Anthralin. (**b**) Chrysarobin. Chrysarobin is the natural product from which anthralin is the semisynthetic derivative.

also evidence that anthralin is effective in patients with psoriasis who have failed other topical medical therapies. A recent 2015 multicenter study showed that the majority of patients with moderate-to-severe scalp psoriasis had marked improvement in symptoms (88 and 96%, respectively) after using a 1% anthralin shampoo (Menter et al, 2015). There are few head-to-head studies comparing anthralin or anthralin formulations with different topical agents used in psoriasis, so more research is needed in this area.

Alopecia areata. Anthralin is also used off label for patients with alopecia areata, particularly those who are refractory to immunotherapy. Owing to the safety of anthralin, it can be used in children and adults with extensive alopecia areata, including alopecia totalis (Roy and Forman, 2013). One retrospective study evaluated 47 patients with severe hair loss (50% of hair) that were resistant to any other topical or systemic treatment for at least 6 months. Of these, 22 were treated only with diphenylcyclopropenone (DPCP), and 25 were treated with DPCP and anthralin for at least 30 weeks. Complete hair regrowth was observed in 36.4 and 72% of the patients, respectively (Durdu et al, 2015). In addition, a systematic review that examined 4 studies totaling 69 pediatric patients with alopecia areata who were treated with anthralin found complete response rates of 32−33%, accompanied by relapse rates between 9.5 and 64% (Barton et al, 2022).

Mycosis fungoides. Anthralin may have a role in the treatment of plaque/patch mycosis fungoides. Anthralin produces erythema that is similar to that of treatment modalities used to treat mycosis fungoides, namely UVB light, electron beam radiation, and topical carmustine. In one study, 12 patients between the ages of 40 and 77 years with patch mycosis fungoides were treated with 0.25−1.0% ointments that were applied at bedtime and washed off in the morning, and it was found that 6 of the 12 patients experienced complete clearing, and 1 patient had partial clearing (Zackheim, 1992). Therapeutic effects of anthralin were appreciated after only 1−2 weeks of treatment.

FILSUVEZ (BIRCH TRITERPENES)

Discovery and composition

Filsuvez, also known as Oleogel-S10 in clinical studies, is a relatively new herbal wound-healing gel containing betulin-rich triterpene extract (Figure 5) from birch bark, specifically of *Betula pendula* Roth, *Betula pubescens* Ehrh, and hybrids of both species in the Betulaceae family (Schwieger-Briel et al, 2019, 2017). Filsuvez was FDA approved in December 2023 as a botanical drug and was previously approved in the European Union and Great Britain for the treatment of epidermolysis bullosa (EB) according to the EASE phase 3 randomized, control study (Torres Pradilla et al, 2024). Its formulation is as follows: 10 mg dry extract from birch bark and 90 mg refined sunflower oil per 100 mg of product. A total of 72−88% of the birch bark extract are comprised of betulin as well as betulinic acid (0.5−6%), lupeol (2−8%), oleanolic acid (0.1−2%), and erythrodiol (0.5−2%) (Kern et al, 2019; Schwieger-Briel et al, 2019). The bark and leaves of the Betulaceae family have historically been used in traditional medicine throughout Europe for various conditions, including but not limited to increased hair growth, prevention of dandruff, renal gravel, urinary tract infections, and rheumatism; blood purification; and treatment of asthma, hindered diuresis, and splenomegaly (Rastogi et al, 2015).

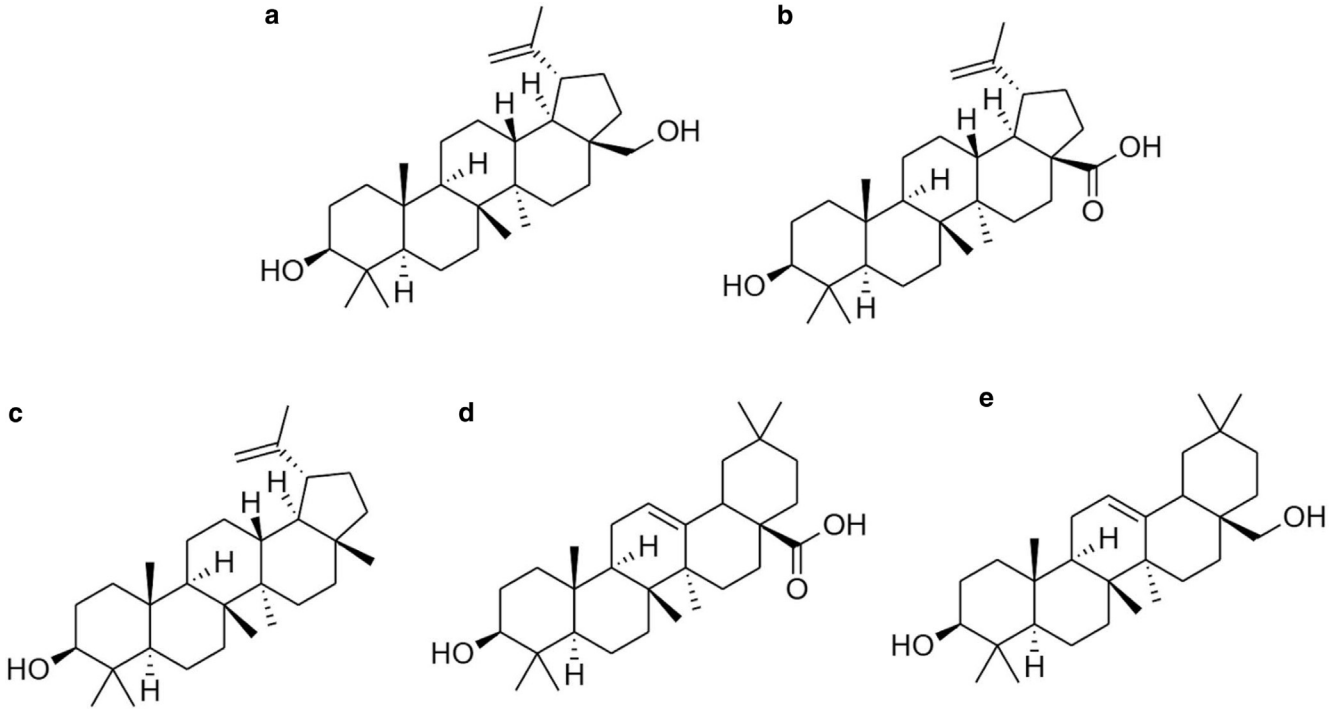

Figure 5. Birch natural products found in the Oleogel-S10 formulation, of which betulin is the primary active component (72−88%). (**a**) Betulin. (**b**) Betulinic acid. (**c**) Lupeol. (**d**) Oleanolic acid. (**e**) Erythrodiol.

Mode of action

Wound healing occurs in 3 stages. It begins with the inflammatory phase, where mediators are released to recruit macrophages, phagocytes, and granulocytes to the wound site for cleaning. In the second phase, inflammation subsides as skin cells proliferate and migrate to close the wound. The third and final phase, which is the longest, involves the differentiation, maturation, and remodeling of skin cells to restore the tissue (Scheffler, 2019). Inflammation mediators such as COX-2, IL-6, and IL-8 are temporarily upregulated by the dry extract from birch bark, thanks to its stabilization of their mRNA (half-life increases by a factor of 3.5). This process involves p38 MAPK and human antigen R (Schwieger-Briel et al, 2019). The dry extract from birch bark influences the cell migration of primary human keratinocytes through the induction of IL-6 and signal transducer and activator of transcription 3 (STAT3). Stabilization of *IL6* mRNA by the dry extract from birch bark leads to upregulation of the transcription factor STAT3. Another effect on keratinocytes is the enhanced formation of lamellipodia, filopodia, and stress fibers. These structures appear as keratinocytes are stimulated to migrate, continuing until they re-establish contact with neighboring cells. Clinically, this manifests in accelerated re-epithelialization (Scheffler, 2019). In the final stage of wound healing, dry extract from birch bark stimulates keratinocyte differentiation markers, promoting the maturation of the skin barrier. During the early differentiation phase, the expression of involucrin and keratin 10 increases, followed by the upregulation of transglutaminase in the late phase. Ultimately, the birch bark extract specifically triggers terminal differentiation, driving the apoptosis-like transition of keratinocytes into corneocytes (Scheffler, 2019).

History as a drug

Betulin derived from birch bark was observed first in 1788 by Lowitz, but Mason coined the term in 1831 (Adepoju et al, 2023). In 1995, an article published in *Nature Medicine* on betulinic acid's effect on malignant melanoma dramatically increased the scientific interest in triterpenes (Scheffler, 2019). Betulin was processed into an herbal pharmaceutical ingredient for the first time when it was discovered that it gelatinizes oils and stabilizes water-in-oil emulsions as a solid stabilizer. Since then, several studies have been conducted on Oleogel-S10's efficacy in wound healing, including 2 phase II studies: one on split-thickness skin graft transplantation (STSG) and another on patients with dystrophic EB. In Metelmann's study, 24 randomized patients received STSG on their upper legs and had Oleogel-S10 applied to the distal or proximal half the wound, with the other half serving as an intraindividual control (Metelmann et al, 2015). The Schwieger-Briel (2017)'s study evaluated the efficacy of the compound on 10 patients with dystrophic EB by treating one half of each patient's wound with Oleogel-S10 and covering it with a nonadhesive wound dressing, whereas the other half of the lesion was only covered with a nonadhesive wound dressing to serve as a control. Both studies found faster re-epithelialization of wounds in patients. Furthermore, 3 phase 3 studies have been conducted on Oleogel-S10's efficacy in wound healing. The first of these studies, the Barrtt study, was a combined study program consisting of 219 patients that evaluated whether Oleogel-S10, combined with the standard of care (a nonadhesive moist wound dressing), accelerated re-epithelialization of (STSG) donor site wounds better than the standard of care alone. The results showed that wounds closed faster with Oleogel-S10 than without it (15.3 vs 16.5 days) (Barret et al, 2017). The Frew study compared intraindividually the efficacy and tolerability of Oleogel-S10 with fatty gauze dressing with Octenilin wound gel with fatty gauze dressing in accelerating the healing of superficial partial-thickness burn wounds of 48 patients. The percentage of patients with earlier wound healing was significantly higher for Oleogel-S10 (85.7%) than for Octenilin wound gel (14.3%) (Frew et al, 2019). The Kern study (EASE) determined the efficacy and safety of Oleogel-S10 in 223 patients with EB compared with those of treatment with a vehicle control gel. Oleogel-S10 resulted in 41.3% of patients with complete target wound closure within 45 days, compared with 28.9% in the control gel arm (Kern et al, 2019). All studies revealed that Oleogel-S10 was well-tolerated. Two other clinical studies also discovered that birch bark extract is effective in the treatment of actinic keratoses (Adepoju et al, 2023; Huyke et al, 2009, 2006).

Uses in dermatology today

EB. Oleogel S-10 has been shown to improve wound healing of patients with EB, a rare condition that causes fragile, blistering skin (Schwieger-Briel et al, 2017). EB affects approximately 1 in 17,000 live births, and it is estimated that there are around 500,000 people living with the condition worldwide (figures from DEBRA International). EB is caused by >1500 known variants in at least 20 genes encoding anchoring and other proteins of the dermoepidermal junction (Has et al, 2018; Schwieger-Briel et al, 2019). Over 30 distinct subtypes have been identified, each inherited through either an autosomal dominant or recessive pattern and exhibiting diverse clinical manifestations (Has et al, 2020). Oleogel-S10 was approved by the European Medical Agency (EMA) in 2016 under the trade name Episalvan for the treatment of partial-thickness wounds in adults; however, it is no longer licensed. The EMA approved the gel again in 2022 under the trade name Filsuvez for the treatment of EB in adults and children aged ≥6 months (Häsler Gunnarsdottir et al, 2023). In 2023, the FDA approved Amryt Pharma's new drug application for Oleogel-S10 in treating dystrophic and junctional EB.

PODOPHYLLOTOXIN

Discovery and composition

Podophyllotoxin was discovered (Figure 6) in the stem resin of *Podophyllum* species from the Berberidaceae family, specifically from *P emodi* Wall. ex Hook.f. & Thomson, *P peltatum* L (North America), and *P hexandrum* Royle (Himalayan regions of the Asian continent) plants (Canel et al, 2000; Shah et al, 2021). Of the varieties of *Podophyllum*, *P emodi* contains the greatest amount of podophyllotoxin. Therefore, this species is preferable to *P peltatum* as a source of the natural product (Hartwell and Schrecker, 1951). Different civilizations have used plant extracts with high

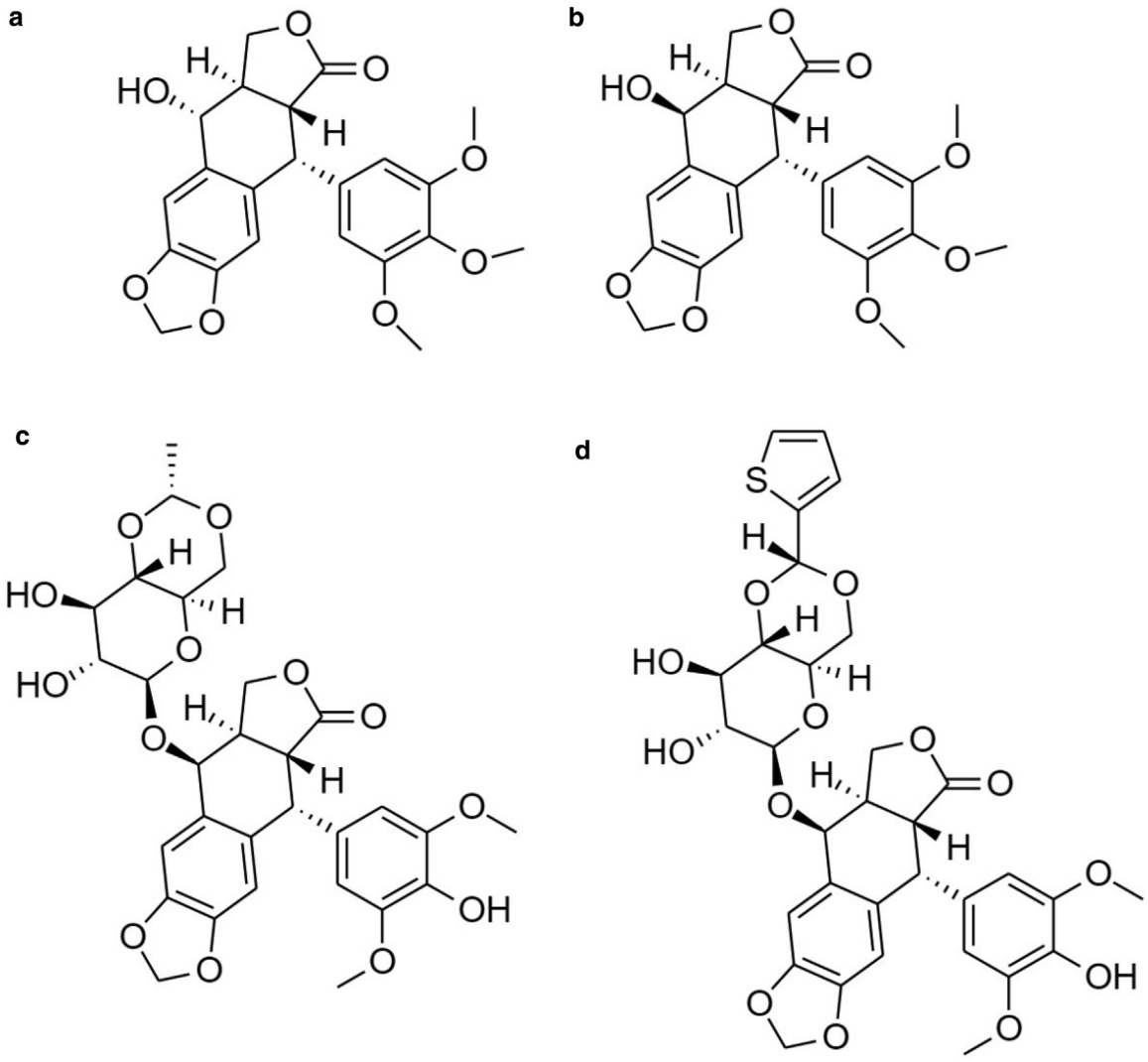

Figure 6. Chemical structures of podophyllotoxin and the semisynthetic derivatives epipodophyllotoxins, etoposide, and teniposide. (**a**) Podophyllotoxin. (**b**) Epipodophyllotoxins. (**c**) Etoposide. (**d**) Teniposide. The side effects of podophyllotoxin have limited its use in medicine. FDA approved that etoposide, teniposide, and etopophos (etoposide phosphate) are semisynthetic drugs of podophyllotoxin and have been widely used in cancer treatment. In the cell, the cleavage complexes between the enzyme and its DNA substrate are stabilized by these derivatives. FDA, Food and Drug Administration.

concentrations of podophyllotoxin or podophyllotoxin analogs extensively in traditional medicine as treatments for helminth infections and poisonings and as cleaning agents (Newman et al, 2003). In the 1940s, Kaplan (1942) reported the effective use of podophyllin (25%) for the treatment of venereal warts. The compound is primarily obtained from the podophyllin, the alcohol-soluble fraction of *Podophyllum* species.

Mode of action

Podophyllotoxin inhibits eukaryotic topoisomerase II, leading to double-stranded DNA breaks. It arrests mitosis at the metaphase stage by binding to protein subunits of spindle microtubules, such as tubulin. It also inhibits the transfer of nucleosides within cells (Guerram et al, 2012; Loike and Horwitz, 1976). The toxin exerts its cytotoxic effects by disrupting epithelial cell metabolism, leading to the necrosis of visible wart tissue (Long and Stringfellow, 1988, Oslen and Dart, 2004). Souza et al (2012) demonstrated that podophyllotoxin disrupts the cellular cytoskeleton and blocks oxidation enzymes in citric acid cycle, which interferes with nutrition of cells; it also reduces mitochondrial activity and reduction of cytochrome oxidase activity.

The active ingredients in podophyllin resin are podophyllotoxin, 4′-dimethyl podophyllotoxin, α-peltatin, and β-peltatin. Initial studies reported that podophyllotoxin has potent anticancer properties, which greatly increased interest in its antimitotic effect. Since then, the structural base of the compound has been used in the designing and development of new medicinal agents (Giri and Lakshmi Narasu, 2000; Guerram et al, 2012; von Krogh, 1981). Podophyllotoxin is an aryl-tetralin lignin that consists of a 5-ring system (ABCD) with 4 chiral centers (C1−C4). Four oxygen atoms are located at the ends of the functional groups, and the aromatic ring E is located at position 1 with an alpha configuration. C4 has unique stereochemical properties that determine the molecule's mechanism of action (Arora, 2010; You, 2005). It was revealed that the modification at the C4 center can change

the molecule's inhibitory activity, drug resistance profile, water solubility, and antimitotic activities (affinity for tubulin).

In addition, podophyllotoxin has been shown to have antiviral properties. Several structure-activity relationship research on different podophyllotoxin derivatives have demonstrated that the cytotoxicity of deoxy podophyllotoxin is attributed to its core structure (Hadimani et al, 1996; Singh et al, 2022). By inhibiting microtubule protein polymerization and demonstrating G2/M blockage, podophyllotoxin has shown excellent anticancer activity. According to reports, podophyllotoxin blocks the colchicine-binding site during microtubule assembly (Cortese et al, 1977). The tubulin units were dramatically reduced by podophyllotoxin derivatives, according to fluorescent tubulin polymerization studies. On the basis of the molecular mechanism, these podophyllotoxin conjugates induce caspase-3−dependent death in A549 cancer cells (Kamal et al, 2014). The application of 6-methoxy podophyllotoxin to human bladder cancer (5637) and myeloid leukemia (K562) cell lines resulted in a significant reduction in tumor cell viability and the induction of programmed cell death. Furthermore, after 6-methoxy podophyllotoxin treatment, the expression of topoisomerase II and tubulin beta 3 chain was suppressed in tumor cells (Zhao et al, 2019, 2015). In addition, the carbon−sulfur bond at the 4-position (C-4) of the carbon ring of podophyllotoxin decreased the inhibitory effect of dosage on tubulin polymerization, improving its therapeutic effect (Bai et al, 2012; Zhao et al, 2019, 2015).

History as a drug

Miller (1985) outlined several dermatologic applications for podophyllin in 1985. Owing to the local irritability and rising popularity of topical steroids, it has been recommended for use in benign skin disorders. The use of podophyllin in the management of molluscum contagiosum and pruritic diseases is based on its irritative qualities (Al-Sudany and Abdulkareem, 2016). In 1820, podophyllin was included in the United States Pharmacopoeia, and its resin was used to treat venereal warts (Horwitz and Loike, 1977). Licensed healthcare providers may administer a 10−25% podophyllin tincture made with a benzoin solution. It has been established that podophyllotoxin has various effects. An extract of *P peltatum* inhibits the reproduction of the measles virus and the herpes simplex type 1 virus (Truedsson et al, 1985). The successful use of podophyllin 25% gel for the treatment of keratoacanthoma was demonstrated in a 2014 case report (Sharquie and Noaimi, 2014). Podophyllotoxin cream (0.15−0.5%) is currently being used as a topical therapy for condylomata acuminata (anogenital warts). The cream (0.5%) in a benzoin tincture is marketed as Podofilox, which has been approved by the FDA for use in the treatment of anogenital warts. It has also been used to treat cutaneous warts, but these results have not been as promising (Kreuter and Wieland, 2013; von Krogh, 1981). This could be due to the thick coating that may prevent drug penetration. Because podofilox has few side effects, patients can self-apply medication at home, which decreases the number of hospital visits and improves compliance. In New Zealand, podophyllotoxin is a prescription medicine that is available as a 0.15% w/w cream (Wartec) and 5 mg/ml solution (Condyline) for the treatment of external condylomata acuminata (Lacey et al, 2003).

Podophyllotoxin and its derivatives can be used to treat a variety of ailments that can be categorized into the following groups: (i) reactions to transplantation rejection; (ii) skin conditions such as psoriasis, fungal infections, and alopecia areata; (iii) tropical diseases such as malaria and schistosomiasis; (iv) collagenosis (connective tissue diseases) such as polyarteritis nodosa and sarcoidosis; (v) mental illness (caused by viruses) such as dementia and psychoses; and (vi) neurological diseases such as multiple sclerosis and myasthenia gravis (Leander et al, 1988).

Uses in dermatology today

Podophyllotoxin has been used to treat condylomata acuminata and other sexually transmitted infections that cause wart formation in the genital or anal area. HPV causes the formation of warts and is transmitted through sexual activity, including both vaginal and anal intercourse. Over 70 HPV subtypes have been identified, with 35 targeting the anogenital epithelium, each varying in its potential to cause malignancy. For this reason, podophyllin resin has been used in the treatment of condylomata acuminata. When podophyllotoxin is extracted from the raw plant as podophyllin resin, genotoxic enzymes are eliminated (Lin et al, 2009). In addition, it was demonstrated to cause dysplastic development in animal models that was comparable with carcinoma in situ (Kaminetzky et al, 1959; Sindhuja et al, 2022).

As a promising and generally safe medication for the treatment of genital warts, podophyllotoxin is also an FDA-approved active ingredient in Wartec ointments and Condylox liquids. For treating external warts, podophyllotoxin is recommended for topical application in combination with compound benzoin tincture (Workowski et al, 2015). Podofilox eliminated 74% of condylomata acuminata in a randomized controlled trial comparing it with a placebo, whereas just 18% of the condylomata were cleared in the group receiving the placebo. Systemic effects were not detected in this trial therapy (Greenberg et al, 1991). In a randomized controlled trial comparing self-administered podophyllotoxin with 25% podophyllin applied in a clinical setting for the treatment of condylomata acuminata, podophyllotoxin (podofilox) proved to be more effective and cost-efficient than other clinical treatments (Lacey et al, 2003).

According to Longstaff and von Krogh (2001), podophyllotoxin's most frequent adverse effects include stinging, burning, redness, swelling, and discomfort at the application site. Even at very high concentrations, podophyllotoxin exhibits much lower toxicity than podophyllin resin (Longstaff and von Krogh, 2001). Given scientific evidence that podofilox is embryotoxic in rats at systemic doses 250 times the recommended maximum human dose (Thiersch, 1963), it is classified as a category-C medication for use during pregnancy.

In addition to their importance for dermatology, podophyllotoxins can treat psoriasis vulgaris. Despite having less potent effects than deoxypodophyllotoxin in all circumstances, podophyllotoxin nevertheless displayed significant

ichthyotoxic activity and phytogrowth inhibitory actions (Gordaliza et al, 2000; Lerndal and Svensson, 2000). Psoriasis, rheumatoid arthritis, and Sindbis virus are all affected by podophyllotoxin and its analog chemicals, which also have effects against cytomegalovirus. Rheumatoid factor concentrations significantly decreased in patients receiving podophyllotoxin derivative therapies for 6 months. The ability of podophyllotoxin derivatives to suppress adrenal steroidogenesis, reduce cytokine levels, and directly block TNFs are considered anti-inflammatory properties of these compounds (Carlström et al, 2000; Truedsson et al, 1985).

Future applications of podophyllotoxin

The most well-known applications of podophyllotoxin analogs, including etoposide and teniposide (Figure 6), are their use in the treatment of cancer (Ayres and Loike, 1990; Fan et al, 2021). These anticancer medications are used to treat lung cancer, Wilms' tumor, different genital tumors, non-Hodgkin's lymphomas, and other types of lymphomas. Cocktail therapies, which mix other approved chemotherapeutic drugs with proven methods of battling cancer and viral diseases, are currently being used with the aim of improving therapeutic effectiveness. The combination of cisplatin and podophyllotoxins is effective in treating neuroblastomas and has shown stronger efficacy against human genital infections. Etoposide, a semisynthetic analog of podophyllotoxin, has just undergone phase II clinical trials (ClinicalTrials NTC04356690) as a reformulated medication to treat patients with COVID-19 with cytokine storm complications, although further trials were deemed unsuccessful (Halpin et al, 2023[1]; Zhao et al, 2021).

In addition to the existing podophyllotoxin analogs, the modification of various carbon groups on the molecule's structure has resulted in new derivatives that have been recently investigated for their anticancer activity. For instance, podophyllotoxin's C-4 position has been chosen as a modification target to design more effective compounds against drug resistance (Liu et al, 2015). Podophyllotoxin can be modified synthetically, which has increased interest in the synthetic production of the toxin. *Podophyllum* species are currently only found in a limited number of locations owing to increased demand for podophyllotoxin as well as forest destruction, habitat loss, and climate change. Future efforts to provide an adequate supply of podophyllotoxin to satisfy the demand for this treatment option will depend critically on techniques such as biosynthesis and the utilization of plant cell cultures (Khaled et al, 2013).

CONCLUSION

Medicinal plants have a significant potential for treating a variety of skin disorders, serving as an excellent source of active compounds. Advances in understanding the mechanistic basis of action for plant-derived natural products as well as new developments in the fields of bioinformatics and network pharmacology will further enable the discovery of novel bioactive small molecules of pharmaceutical interest in the future.

This review provides a brief synopsis of the history of plant derivatives used for a variety of dermatologic skin conditions. Six plant-derived dermatologic therapies were explored in detail, including polyphenon E, psoralen, SA, anthralin, podophyllotoxin, and Filsuvez. Specifically, the discovery and chemical composition and historical and current clinical applications in dermatology were described. These cases offer insight into the promise that traditional plant-derived medicines may hold in fueling the future of drug discovery for the treatment of dermatologic conditions.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: CLQ; Funding Acquisition: CLQ, AI; Writing - Original Draft Preparation: AI, BK, TOM, PCS, TZP; Writing - Review and Editing: CLQ, AI

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMs)

The author(s) did not use AI/LLM in any part of the research process and/or manuscript preparation.

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