

## Podophyllin in Dermatology: Revisiting a Historical Drug

### Abstract

Podophyllin is a cytotoxic material extracted from *Podophyllum peltatum* and *Podophyllum hexandrum* and is widely used for the treatment of genital warts. This article reviews the chemistry of podophyllin and its active components along with the mechanism of action in various dermatoses. Furthermore, the documented uses of podophyllin in various dermatological disorders have been described along with the side effects of the drug. Based on the available literature, a clinical guideline is being proposed so as to minimize the side effects. Further studies should be carried out on its use in a lower concentration in other dermatoses, especially premalignant and malignant skin diseases.

**Keywords:** Cutaneous malignancies, genital warts, Podophyllin resin, podophyllotoxin

### History

Podophyllin is a cytotoxic material extracted from the mayapple plant – *Podophyllum peltatum* (from North America), *Podophyllum hexandrum* (from Himalayan regions of the Asian continent).<sup>[1]</sup> One of the first uses of this agent as medicine had been mentioned in The Leech Book of Bald, an English medicinal book (900–950 AD), where podophyllotoxin-related lignans were used for treating cancer.<sup>[2]</sup> Native Americans used podophyllin as an antihelminthic, as a purgative and laxative, as a suicidal potion, and for treating deafness and snake bites.<sup>[3]</sup> Indians introduced it to the Britishers for use as a cathartic, an anthelmintic, and misuse as a lethal poison. Podophyllin was included as a cathartic and cholagogue in the first U.S. Pharmacopoeia, dating from 1820.<sup>[4]</sup>

John King discovered the resin podophyllin in 1835.<sup>[5]</sup> Kaplan had reported the successful use of topical 25% podophyllin in venereal warts treatment in 1942.<sup>[6]</sup>

### Chemistry

Podophyllin resin consists of the following active components: Podophyllotoxin, 4'-demethyl podophyllotoxin,  $\alpha$  – peltatin and  $\beta$  – peltatin. Podophyllotoxin is the most abundant lignan in podophyllin and has potent anticancer properties. Podophyllotoxin is present in higher

concentrations in *P. hexandrum* (40%) as compared to *P. peltatum* (20%).<sup>[7,8]</sup> It has also been isolated from species belonging to the sections *Linum*, *Dasylinum*, and *Linopsis* which represent other alternative sources of podophyllotoxin.<sup>[9]</sup> In addition, endophytic fungi (*Phialocephala fortinii*, *Fusarium oxysporum*) have also been reported as sources of podophyllotoxin.<sup>[10]</sup>

Podophyllotoxin is an aryltetralin lignin and contains a five-ring system (A, B, C, D, and E rings) [Figure 1]. The planar tetracyclic group ABCD has four ends with oxygen atoms at the functional group with an aromatic ring E located at position 1 in alpha configuration and a bond with a degree of free rotation.<sup>[9]</sup> The stereochemical properties at C4 determine the affinity for tubulin.<sup>[11]</sup> A and E rings are essential for its activity, aromatization of ring C leads to loss of activity, and the free rotation of the E ring is necessary for the antitumor effect.<sup>[12]</sup>

### Mechanism of Action

Podophyllotoxin inhibits the formation of microtubules. *In vitro*, it reversibly binds to tubulin dimers giving rise to podophyllotoxin-tubulin complexes which stop the further formation of the microtubules at one end but do not halt the disassembly at the other end, thereby interrupting the dynamic equilibrium between the assembly and disassembly

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of microtubules and leading to the degradation of the microtubules. It also suppresses cellular nucleoside transport.<sup>[9,13]</sup> Cells treated with podophyllotoxin get arrested in the metaphase of the mitosis and subsequently undergo necrosis. Furthermore, an antiviral effect of podophyllotoxin has also been demonstrated.<sup>[14]</sup> Various structure-activity relationship studies on several podophyllotoxin analogs have shown that the core structure of deoxy podophyllotoxin is responsible for cytotoxicity.<sup>[15]</sup>

The mode of action of podophyllotoxin is comparable to colchicine, paclitaxel, and vincristine-like alkaloids and for their mode of action, these compounds are called spindle poisons. They allow the cells to enter the mitosis, but the doubled chromosomes do not separate, and the cells cannot duplicate and growth stops.<sup>[16]</sup> The podophyllotoxin-derivatives such as etoposide, teniposide, and etopophos have a completely different mode of action and are DNA topoisomerase II inhibitors.<sup>[17]</sup>

### Clinical Uses

Various uses of podophyllin in dermatology have been documented by Miller<sup>[18]</sup> in 1985. However, its use has been discouraged in benign skin conditions because of the local irritation and also the increasing use of topical steroids. The irritative properties of podophyllin were the basis for its use in the treatment of molluscum contagiosum and pruritic conditions. It has shown comparable efficacy to 10% KOH in the treatment of molluscum contagiosum in a recent study from Iraq.<sup>[19]</sup> Recently, a case report by Sharquie (2014) has shown the successful use of podophyllin 25% gel for the treatment of keratoacanthoma.<sup>[20]</sup>

Podophyllin has also been tried with varying success in the topical treatment of premalignant and malignant skin lesions such as actinic keratoses, keratoacanthoma, basal cell carcinoma, squamous cell carcinoma, and also as a systemic agent in the management of uterine carcinoma.<sup>[20-28]</sup> However, the mixed response and the high relapse rate forced researchers to abandon its use as an antineoplastic agent.

Presently, podophyllin resin is used successfully for the topical treatment of anogenital warts. However, only Podofilox 0.5% gel has received FDA approval to be used in the treatment of anogenital warts.<sup>[29]</sup> It has also been tried for the treatment of cutaneous warts, but the results have not been so encouraging, which could be because of less drug penetration due to the thick horny layer.

Von Krogh has described the factors which can determine the therapeutic response of topical podophyllin therapy in anogenital warts.<sup>[30]</sup> The best response was seen with warts located in moist areas rather than on keratinized skin. All the dermatoses where the use of podophyllin has been reported are compiled in [Table 1].



Figure 1: Structure of Podophyllotoxin

Table 1: List of various dermatoses where Podophyllin has been used

Viral Infections	Condyloma acuminata
	Verruca vulgaris <sup>[31]</sup>
	Plantar and periungual warts <sup>[32]</sup>
	Molluscum contagiosum <sup>[19,33]</sup>
Fungal Infections	Tinea capitis <sup>[34]</sup>
Benign Dermatoses	Acanthosis nigricans <sup>[35]</sup>
	Black hairy tongue <sup>[28]</sup>
	Contact dermatitis <sup>[21]</sup>
	Lichen simplex chronicus <sup>[36]</sup>
	Pyogenic granuloma <sup>[37]</sup>
	Seborrheic keratosis <sup>[38]</sup>
Premalignant Dermatoses	Actinic keratosis <sup>[27]</sup>
	Arsenical keratosis <sup>[22]</sup>
	Bowen's disease <sup>[22]</sup>
	Keratoacanthoma <sup>[20]</sup>
Malignant Dermatoses	Basal cell carcinoma <sup>[25]</sup>
	Squamous cell carcinoma <sup>[24]</sup>
	Mycosis fungoides <sup>[38]</sup>

### Side Effects

#### Cutaneous side effects

1. Acute inflammatory reaction with necrosis.
2. Peripheral erythematous halo, erythema, edema, and ulceration.
3. Balanitis and phimosis in men with long redundant foreskin.<sup>[31]</sup>
4. Severe chemical burn with scarring and fistula formation in the anogenital area.<sup>[39]</sup>

5. Allergic sensitivity and dermatitis due to allergy to benzoin, a frequently used base for podophyllin, and contamination of podophyllin resins with guaiacum wood.<sup>[39]</sup>
6. Epithelioma-like hyperplastic infiltrated reaction to the application of podophyllin.<sup>[40]</sup>
7. Podophyllin cells – Bizarre, enlarged epithelial cells with a clumped pyknotic nucleus, seen after the application of podophyllin to normal skin, verruca vulgaris, and condyloma acuminata. There is no cellular atypia.<sup>[31]</sup>
8. Squamous cell carcinoma-like changes in unsuccessfully treated penile warts.<sup>[41]</sup>
9. Corneal damage and anterior uveitis – when applied over warts around the eyes.<sup>[41,42]</sup>

### Systemic side effects

The antimitotic effects of podophyllotoxin are partly responsible for the systemic toxicity which occur when the drug is applied to large areas of the skin or prolonged contact with the skin.<sup>[18]</sup> The tissues with a high rate of proliferation (bone marrow, lymph follicles, and intestinal mucosa) are most susceptible to toxicity. Neurotoxicity could be related to its *in vitro* ability to bind microtubular protein and to inhibit the axoplasmic flow.<sup>[43]</sup>

Systemic side effects have been reported in isolated case reports mostly; however, clinicians must be aware of its appropriate clinical use and method of application to avoid these adverse effects. Following are the side effects reported till now:

1. Headache (most common 7%), nausea, vomiting, and diarrhea are also common side effects.<sup>[29,43]</sup>
2. Adynamic ileus.
3. Fever.
4. Tachypnea.
5. Tachycardia.
6. Leukopenia, anemia, thrombocytopenia, and elevated liver enzymes.<sup>[44]</sup>
7. Peripheral neuropathy, acute confusion, lethargy, coma, and death. The CNS toxicity is reversible with recovery starting within 10 days after the exposure, whereas the peripheral neuropathy often takes months to resolve, and occasionally leaves behind residual deficits which can persist for years.<sup>[45]</sup>
8. Urticaria and hyperpyrexia
9. Oliguria, Anuria.
10. Marked leukocytosis.<sup>[46]</sup>
11. Podophyllin is embryotoxic and fetal anomalies such as preauricular skin tags, limb malformations, septal heart defects, simian crease, and polyneuritis have been reported with its use in pregnancy.<sup>[47]</sup>

Podophyllin poisoning resulting due to both topical application and oral consumption has been reported in adults and children as well. Ward *et al.*<sup>[48]</sup> had reported the first fatality from the topical application of the drug

in 1954. Podophyllin had been used as a suicidal agent in the past. The fatal dose of podophyllin resin for humans is 0.3 gm to 0.6 gm or as little as half teaspoonful of 25% podophyllin resin in benzoin tincture.<sup>[49]</sup>

### Clinical Guidelines to be Followed for Topical Podophyllin Application

1. Podophyllin application should be performed as an office procedure.
2. It should be stored in narrow-mouthed bottles to prevent evaporation which may lead to an increased concentration of podophyllin. Old, discolored, dried, or gritty preparations should not be used.
3. The drug applications should be limited to small areas of intact skin along with the use of Vaseline in the periphery of the lesion so as normal skin is not affected.
4. The volume of the solution applied should be kept minimal ( $\leq 0.4\text{--}0.5$  mL for *P. emodi*-based podophyllin).<sup>[7]</sup>
5. The solution should be allowed to dry properly, and the initial test application should remain in place for 1 h, and then can be washed off.
6. In case of an uneventful first application without any inflammation, the resin can be left on for 4–6 h before washing off on subsequent applications.
7. An allergic reaction to the benzoin should be suspected if pruritis develops.
8. Alcoholic beverages, general anesthesia, and CNS depressants should not be used for several hours after treatment.
9. Podophyllin is contraindicated for use during pregnancy.

### Preparations Available

1. Podophyllin 20% solution in tincture benzoin.
2. Podophyllin (25%), salicylic acid (5%) paint.
3. Podophyllotoxin 0.15% cream.
4. Podofilox 0.5% gel.
5. Cantharidin 1%, podophyllin 2%, salicylic acid 30% (CPS1) solution.

Centers for disease control and prevention (CDC) has recommended podofilox 0.5% gel for the treatment of anogenital warts. Podofilox gel (using a finger or applicator) should be applied to anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle has to be repeated for up to four cycles as per response. The clinician should initially demonstrate the proper application technique to the patient. In case of incomplete response or no response, it has to be discontinued. The total wart area treated should not exceed 10 cm<sup>2</sup>, and the total volume of podofilox used should not exceed 0.5 mL per day.<sup>[29,50]</sup>

The main advantage of pure podophyllotoxin over podophyllin is the better efficacy and the absence of quercetin and kaempferol-induced side-effects. In addition,

podophyllotoxin can be self-applied by the patient, thereby reducing hospital visits and better compliance.

## Conclusion

Podophyllin resin is an old drug with proven cytotoxic properties, and there is a need for further studies for the use and efficacy of podophyllin in other dermatological disorders, especially cutaneous malignancies. Furthermore, widespread availability of Podoflox (pure podophyllotoxin) is warranted in India.

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## Conflicts of interest

There are no conflicts of interest.

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