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Chemical composition, traditional uses and pharmacological potential of *Podophyllum hexandrum*: An endangered medicinal plant of North-Western Himalayas

Zahid Altaf, Tahir Mushtaq, PA Sofi, Ishtiyak Ahmad Peerzada, AR Malik, Amerjeet Singh, M Iqbal Jeelani, Sabira Nissar, Jauhar Rafeeq and Peerzada Tabish Fayaz

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Abstract

Podophyllum hexandrum Royle is a useful medicinal plant and is found in the lower Himalayan zone at elevations between 2000 and 4500 meters. This herbaceous perennial plant has a number of secondary metabolites that are significant from a pharmacological standpoint. The most significant of them is podophyllotoxin, which is utilized to treat specific types of cancer and has cytotoxic and antitumor effects. Due to its vast medicinal potential, plants are also valued in many traditional medical systems. The frequency of this species has decreased in recent years due to overexploitation of the plant. The botanical, medicinal, phytochemical and pharmacological features of the plant are briefly reviewed in this article.

Keywords: Medicinal, Himalayan, botanical, phytochemical, traditional

Introduction

Medicinal plants have been widely used to treat a variety of infectious and non-infectious diseases. In fact, 25% of commonly used medicines contain compounds extracted from plants (Sabira *et al.* 2024) [40]. Among medicinal plants of North-Western Himalayas, *Podophyllum hexandrum* Royle is well known for its anti-cancerous molecule 'Podophyllotoxin'. This herbaceous species belongs to Berberidaceae family and is reported in Himalayan regions from 2000 to 4500 m amsl (Chaurasia *et al.*, 2012) [15]. The term Podophyllum is derived from ancient Greek word 'podos' means a foot and 'phyllos' means a leaf. The name refers to the resemblance of leaves to duck's foot (Kumar *et al.*, 2017) [32]. The genus Podophyllum is generally represented by three species including *Podophyllum hexandrum*, *Podophyllum peltatum*, and *Podophyllum sikkimensis*. Of these Podophyllum species, *Podophyllum hexandrum* Royle is medicinally more valuable, containing comparatively higher concentration of podophyllotoxin (Muzafar and Shajrul, 2016) [35]. *P. hexandrum* is a source of several physiologically significant metabolites with cytotoxic, antifungal, anti-inflammatory, antioxidant, and radioprotective properties (Prakash *et al.*, 2005) [36].

Distribution

It is believed to be originated from the Himalayan region. It is distributed from Indian Himalayas to Bhutan, Pakistan, Afghanistan, Nepal, Taiwan and China. In India, it is grown in the Himalayan regions between 2000-4500 m above MSL in very restricted locations in Zaskar, Suru Valleys of Ladakh, Kashmir region in Jammu and Kashmir, Lahaul, Spiti, Kangra, Chamba and Kinnaur in Himachal Pradesh, between 2000-4000 m above MSL in Kumaon and Garhwal in Uttarakhand, Sikkim and Arunachal Pradesh (Ballabh, 2002) [6]. The Himalayan region is home of numerous highly valued medicinal plants including *Podophyllum hexandrum* that grows in very restricted pockets in the Himalayan alpine and subalpine zones, now endangered in Himachal Pradesh (CAMP, 2010) [12].

Corresponding Author:
 Tahir Mushtaq
 Division of Forest Products
 and Utilization, Faculty of
 Forestry, Sher-e-Kashmir
 University of Agricultural
 Sciences and Technology of
 Kashmir, Benhama,
 Ganderbal, Jammu and
 Kashmir, India

Morphological description

The perennial herb *Podophyllum hexandrum* grows to a height of 15 to 40 cm. It has a glossy green, grand nodular rhizome that is low to the ground and numerous adventitious roots that are longer than 50 cm. Stem height ranges from 30 to 90 cm. Its few stiff branches sprout two to three umbrella-shaped, lobed leaves, which entirely unfold once the plant has flowered and are a dark green colour with brown specks. The words podos, which means foot, and phyllon, which means leaf, are combined to form the term podophyllum. The name comes from the way as leaves resemble the foot of a duck. At the tips of sturdy stems appear white or pale pink, six petaled flowers in the spring, which are followed by meaty, oval, red berries. The flower, which has six petals and six stamens, gives rise to the species name hexandrum which means six stamens and the flowers bloom from May to August. Round shaped 10-25 cm long leaves are deeply divided into three ovate, toothed lobes, which are occasionally further lobed. Fruit is big reddish-purple berry with several seeds encased in pulp. The seeds weigh roughly 20 g. it can be produced by splitting the rhizome or by seeds (Qazi *et al.*, 2011) [37].



Podophyllum hexandrum plant



Podophyllum hexandrum fruit

Active Constituent

Numerous lignans with pharmacological qualities have been found in a resin known as podophyllin, which has been identified by extensive chemical analysis of the *Podophyllum* species. These include flavonoids like quercetin and quercetin-3-glycoside, as well as podophyllotoxin, epipodophyllotoxin, and podophyllotoxone. Asadar, kaempferol, kaempferol-3-glucoside, deoxypodophyllotoxin, picropodophyllotoxin, isopicropodophyllone, 4-demethylpodophyllotoxin, podophyllotoxinglucoside, 4-dimethylpodophyllotoxinglucoside, 4-deoxypodophyllotoxin, α -peltatin, and S-peltatin (Fig. 1). Anti-tumor lignans, including podophyllotoxin and podophyllotoxin 4-O-glucoside, are found in the plant's rhizomes and roots (Broomhead, A.J. and Dewick, P.M.). The anti-cancer medications etoposide, teniposide, and etoposide—which were created as less toxic derivatives of podophyllotoxin—are currently synthesized using podophyllotoxin, which is thought to be the most significant of these non-alkaloid lignans. For example, the glycoside etoposide of podophyllotoxin was first produced in 1966 and approved by the US Food and Drug Administration.

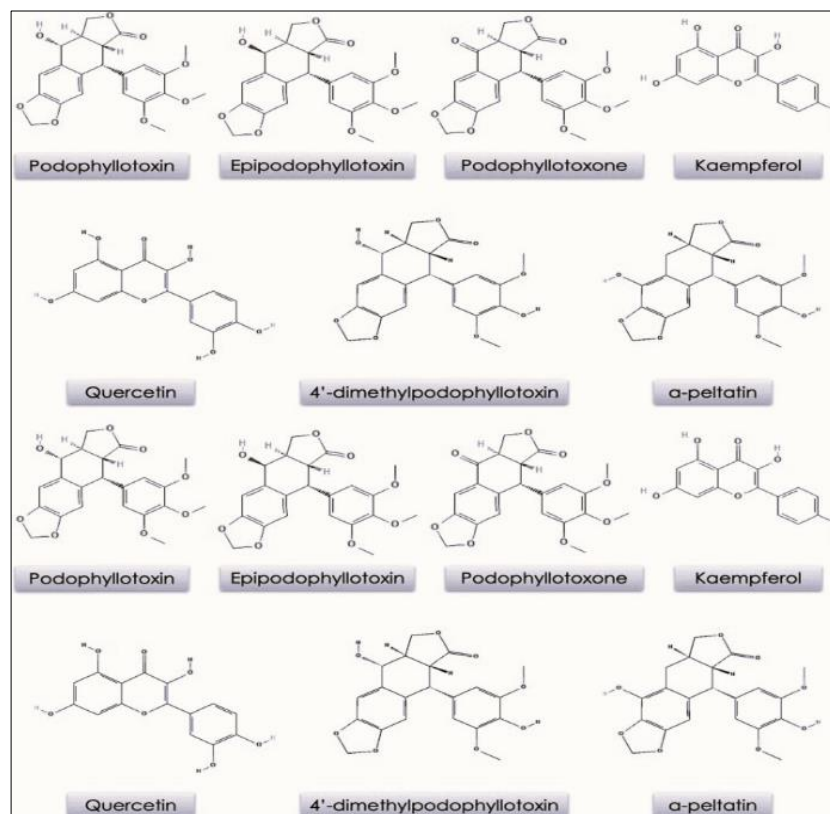


Fig 1: Active Constituents of *Podophyllum hexandrum*

Traditional Uses

In Shogran valley, Mansehra, Pakistan, the local inhabitants use the vernacular name "Ban khakhary" use the whole plant, employing it to treat diabetes, joint pain, jaundice, and heart problems (Matin *et al.*, 2001) [33].

The plant called "Ban kakri" is utilized by the local Vaidyas of the Ukhimath block, Uttarakhand, India. They use the tuber paste both orally and topically, employing it to treat a variety of ailments such as skin diseases, wounds, cancer, as a blood purifier, and for managing cough (Semwal *et al.*, 2010) [42].

In the Kedarnath Wildlife Sanctuary, Garhwal Himalaya, India, the vernacularly named "Ban kakri" root is utilized topically by the local inhabitants for its antiseptic properties and effectiveness in wound care (Bhat *et al.*, 2013) [9].

Among ethnic groups including Gujjars, Gaddis, Lahuls, Spitians, Pangwalas, and the Kinnaur tribe of Himachal Pradesh, North-western Himalaya, India, various parts of the Ban kakri plant, including the rhizome, fruit, and seed, are employed both orally and topically. This usage aims to address a range of health issues such as cancer, cough, cuts, wounds, fever, ulcers, and tumors (Samant *et al.*, 2007) [41].

The vernacularly named "Bankakri" is utilized by the people of Nathiagali, North West, Pakistan, for the treatment of stomach and liver disorders. They use the fruit and seed of the plant orally for this purpose (Begum *et al.*, 2014) [7].

Among shepherds, Chopans, Gujjars, and Bakerwals of the Kashmir Himalaya, the plant known as "Banwagun" is employed for treating warts and tumor growth in animals. They utilize the root and rhizome paste topically for this purpose (Beigh *et al.*, 2004) [8].

The "Omo-chhe," a plant known to the Bhoti tribe of Lahaul-Spiti, Himachal Pradesh, is used orally in the form of root decoction for alleviating constipation and managing asthma symptoms (Singh 2012) [43].

Among the local inhabitants and healers of the Poddar valley in Jammu and Kashmir, India, the plant called "Bankakru, rhodadari" is used orally for its hepatic stimulant, purgative, and diarrhea-relieving properties. They utilize both the rhizome and root for these treatments (Gupta *et al.*, 2013) [30].

In the Manali Wildlife Sanctuary of Himachal Pradesh, India, the plant known as "Ban kakri" is utilized both orally and topically by local Vaidyas for treating various ailments such as cancer, cough, cuts, wounds, diarrhea, fever, gastric ulcer, hepatic disease, and skin diseases. They use both the root and fruit for these treatments (Rana *et al.*, 2011) [39].

Among the people of the Bandipora District in Kashmir Himalaya, India, the plant is called "Chamandi" and the ripe fruit is eaten directly for its hepatoprotective properties.

Pharmacological Properties

Podophyllum hexandrum Royle in the past was referred to as Aindri, a medicine considered divine. Podophyllotoxin, a naturally occurring secondary metabolite found mostly in *P. hexandrum* roots, together with its congeners and derivatives, exhibits significant biological action primarily in the form of anti-HIV, anticancer, and antineoplastic medications (Airi *et al.*, 1997; Archana and Lakshmi, 2000; Chen *et al.*, 2007) [2, 3, 19]. With a higher podophyllotoxin content, the Indian podophyllum i.e., *Podophyllum hexandrum* outperforms its American equivalent, i.e., *Podophyllum peltatum* (4 percent in the dried roots in comparison to only 0.25 percent for *Podophyllum peltatum*).

A lignan that occurs naturally and has strong cytotoxicity is called podophyllotoxin. It binds to microtubules and causes mitotic arrest in metaphase, acting as a mitotic spindle toxin (Canel *et al.*, 2000) [13]. Podophyllotoxin is included in many Pharmacopoeias and used as an antiviral agent in the treatment of *Condyloma acuminatum* caused by human papilloma virus - HPV and other venereal and perianal warts. The application of podophyllotoxin cured almost all the warts completely in less time than other strategies and with fewer side effects. Podophyllotoxin and analog compounds are also active against cytomegalovirus and Sindbis virus. Podophyllotoxin is also effective in the treatment of anogenital warts in children and against *Molluscum contagiosum*, which is generally a self-limiting benign skin disease that affects mostly children, young adults, and HIV patients. Podophyllotoxin has other uses in dermatology: it is a useful agent in psoriasis vulgaris. Antitumor activity is another outstanding property of podophyllotoxin. It is effective in the treatment of Wilms tumors, different types of genital tumors (e.g., carcinoma verrucosus) and in non-Hodgkin and other lymphomas. Studies on penetration of podophyllotoxin into human bioengineered skin have demonstrated that the lignan induces acantholysis and cytolysis in the skin-equivalent model used for a wide variety of pharmacotoxicological trials. This might apply to claims of efficacy for cosmetic compounds (Datt *et al.*, 2000) [20]. Etoposide, teniposide, and etopophos—three semi synthetic derivatives of podophyllotoxin—are widely used as anticancer drugs and show promising clinical results against a range of neoplasms, including lymphoma, leukaemia, Kaposi's sarcoma, and small cell lung cancers. Refractory myeloid leukaemia, testicular lymphoid, stomach, ovarian, brain, breast, pancreatic, and small- and large-cell lung cancers are all treated with etoposide in combination therapy. Teniposide is used less commonly than etoposide and is mainly used to treat lymphomas. The effective derivatization of podophyllotoxin into etoposide and teniposide has raised interest in structural optimization as a way to produce novel derivatives with improved pharmacological profiles and increased therapeutic uses (Uden *et al.*, 1989; Qazi *et al.*, 2011) [44, 37]. Based on the active ingredients, *P. hexandrum* has the following pharmacological characteristics:

Radio protective Activity

Recent years have seen a significant investigation of *P. hexandrum's* radio protective action, which includes activities linked to cell cycle arrest in both *in vitro* and *in vivo* models, time- and dose-dependent prevention of apoptosis (programmed cell death), and free radical scavenging (Arora *et al.*, 2006a; 2006b) [4, 5]. *Podophyllum hexandrum* extracts of methanolic, hydro-alcoholic, and chloroform have been shown to provide 70-95% radioprotection in mice when given 1-2 hours before to lethal whole-body 10Gy radiation (Goel *et al.*, 2001; Goel *et al.*, 2007) [25, 26]. It has been discovered that *Podophyllum hexandrum* contains a variety of bioactive compounds, such as lignans and flavonoids (Chawla *et al.*, 2005a, b; Chawla *et al.*, 2006) [18, 4]. Numerous lignans and flavonoids have already been shown to have anti-apoptotic and antioxidant properties, which help with radioprotection (Chawla *et al.*, 2006) [4].

Anticancer Activity

Podophyllotoxin is a substance found in plant rhizomes that is used to treat a variety of cancers. Since this plant can only biosynthesize relatively small amounts of podophyllotoxin, biotechnological production of the toxin has been deemed necessary (Ahmad *et al.*, 2007) [1]. Another compound in the plant that has an antimiotic action is podophyllin. It is utilized in the treatment of cancer, particularly ovarian cancer (Board, 2003; Farkya *et al.*, 2004) [10, 21]. Numerous lignans, including podophyllotoxin, podophyllin, and berberine, found in the root and rhizome have anticancer properties such as inhibitors of microtubule assembly and are used to treat malignancies such as neuroblastoma, hepatoma, lung cancer, and testicular cancer (Giri and Lakshmi 2000; Chattopadhyay *et al.*, 2002) [3, 14].

Antifungal Activity

Using disc diffusion methods, the antifungal properties of *Podophyllum hexandrum* were examined against pure cultures of clinical isolates of *Aspergillus niger* and *Candida albicans*. For *Aspergillus niger*, the extracts' minimum inhibitory concentration (MIC) was 16.66 mg/ml in the test organisms. It was 25 mg/ml in the case of *Candida albicans*. The outcome demonstrated the plant's antifungal properties (Wani *et al.*, 2013) [45].

Cytotoxicity

It has been demonstrated that podophyllotoxin, a pharmacologically active substance, has cytotoxic properties. Podophyllotoxin derivatives are cytotoxic at the μM level (Gordaliza *et al.*, 2004) [29]. 4-demethyl-picropodophyllotoxin 7'-O-D-glucopyranoside (4DPG) has the ability to effectively stop the cell cycle during the mitotic phase and limit the multiplication of cancer cells. 4DPG is cytotoxic because, at low concentrations, it inhibits the microtubule assembly of cancer cells, resulting in apoptosis. These characteristics make 4DPG a viable anticancer medication (Qi *et al.*, 2005) [38].

Insecticidal Activity

There have been reports of this plant's dichloromethane extract having insecticidal effects on *Drosophila melanogaster* larvae. It was discovered that podophyllotoxin had an LC_{50} value of 22 $\mu\text{g}/\text{adult}$ against adults and 0.24 $\mu\text{mol}/\text{mL}$ against *D. melanogaster* larvae. However, acetyl podophyllotoxin exhibited a little amount of insecticidal activity, suggesting that the 4-hydroxyl group had a significant role in the improved insecticidal action (Miyazawa *et al.*, 1999) [34].

Anti-Inflammatory Activity

It has been reported that the aqueous extract of *Podophyllum hexandrum*, a plant with a long history of therapeutic uses in Ayurvedic literature, has anti-inflammatory properties (Prakash *et al.*, 2005) [36].

Conclusion

Podophyllum species contains numerous lignans with pharmacological properties, such as flavonoids (quercetin and quercetin-3-glycoside), podophyllotoxin, epipodophyllotoxin, and podophyllotoxone. The plant's rhizomes and roots are rich in anti-tumor lignans, including podophyllotoxin and podophyllotoxin 4-O-glucoside. This has led to the development of anti-cancer medications like

etoposide, teniposide, and etoposide, synthesized from podophyllotoxin. The research and chemical analysis of *Podophyllum* species highlight the significant role of podophyllotoxin in the synthesis of important pharmaceuticals with anti-cancer properties. Podophyllotoxin, a naturally occurring secondary metabolite found mostly in *Podophyllum hexandrum* roots, together with its congeners and derivatives, exhibits significant biological action primarily in the form of anti-HIV, anticancer, and antineoplastic medications. Antitumor activity is another outstanding property of podophyllotoxin.

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Author's Details

Zahid Altaf

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural

Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

Tahir Mushtaq

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

PA Sofi

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

Ishtiyak Ahmad Peerzada

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

AR Malik

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

Amerjeet Singh

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

M Iqbal Jeelani

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

Sabira Nissar

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

Jauhar Rafeeq

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India

Peerzada Tabish Fayaz

Division of Forest Products and Utilization, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir, Benhama, Ganderbal, Jammu and Kashmir, India