A Review on conservation status and pharmacological potential of *Podophyllum hexandrum*

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**Abstract**

*Podophyllum hexandrum* Royle syn *P. emodi* Wall. ex Hook.f. & Thoms. is a valuable medicinal plant, distributed in the lower elevations of Himalayan zone at altitudes ranging between 2000 to 45000m. It is an herbaceous perennial plant and contain various pharmacologically important secondary metabolites among which the most important is podophyllotoxin as it possess cytotoxic and antitumor properties, and also used in the treatment of certain forms of cancer. Plant has also got importance in various traditional systems of medicine because of its extensive therapeutic potential. Overexploitation of plant causes a decline in the frequency of this species in the past few years. This article briefly reviews the botanical, medicinal, phytochemical, pharmacological and conservation related aspects of the plant.

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Introduction
The term *Podophyllum* is derived from ancient Greek words 'podos' afoot and 'phyllos' a leaf. Name refers to the resemblance of leaves to duck’s foot. Plant is also known as Mayapple because of ripening of fruits in spring. The genus *Podophyllum* is generally represented by two species, the *P. hexandrum* commonly called as Himalayan Mayapple and the *P. peltatum* commonly called as American Mayapple. *Podophyllum hexandrum* Royle syn *P. emodi* Wall. ex Hook.f. & Thoms is believed to be originated from Himalayan region. It is an important medicinal plant known for valuable drug podophyllotoxin which is effective against various diseases including warts and tumors growth of skin and possess different properties such as purgative, laxative, cholagogue and emetic (Chaurasia et al., 2000).

*P. hexandrum* is a source of various biologically important metabolites and possess antioxidant, anti-inflammatory, antifungal, cytotoxic and radioprotection activity (Prakash et al., 2005; Ganie et al., 2010). *P. hexandrum* has been described as a divine drug in the Indian traditional system of medicine, the Ayurveda and has also been used in traditional Chinese system. The plant also got immense potential in Unani, and Siddha system of medicine for the treatment of various ailments (Wong et al., 2000).

Due to its high demand and unskilled overexploitation, *P. hexandrum* is becoming rare and is at the risk of danger for being extinction. This exerted huge pressure on the population may result in the extinction of species (Chaudhari et al., 2014). Present review highlights the phytochemistry, ethnomedicinal value and pharmacological activities of plant. It also provides an insight towards its conservation status which will enable the researchers to realize the existing population of *P. hexandrum* and take protective measures to conserve this highly valued species.

Geographical distribution

*Podophyllum hexandrum* is native to the lower elevations of Himalayan region. Plant is distributed from Indian Himalayas to Bhutan, Pakistan, Afghanistan, Nepal, Taiwan and China. Most of the commercial supplies come from the Central United States and from Virginia and North Carolina (Claus et al., 1974). In India, it is grown in the Himalayan regions in very restricted locations of Zanskar, Suru valleys of Ladakh, Kashmir region in Jammu and Kashmir, Lahaul, Spiti, Kangra, Chamba and Kinnaur in Himachal Pradesh, in Kumaon and Garhwal in Uttarakhand, Sikkim and Arunachal Pradesh (Chaurasia et al., 2000). In Pakistan it is distributed in the valleys of Astor, Chitral, Hazara, Dir, Murree Hills, and Swat and in Azad Kashmir (Nasir and Ali, 1972; Evans, 2002).

![Podophyllum hexandrum](image_url)

**Fig. 1.** *Podophyllum hexandrum* Qazi et al., 2011.

Morphological description

*Podophyllum hexandrum* is an erect perennial herb 15-40 cm tall. It is low to the ground with glossy green, grand nodose rhizome with many adventitious roots of length longer than 50 cm. Stem is 30-90 cm in height. 2-3 umbrella-like, lobed leaves arise on its few stiff branches, they completely unfurl after the plant has bloomed and are dark green splotted with brown. The name *Podophyllum* is taken from podos meaning a foot, and phyllon which means a leaf. Name is given due to the resemblance of the leaves to a duck's foot. In the spring, white or pale pink, 6-petaled flowers are borne at the ends of stout stems; these are followed by fleshy, oval, red berries. The flowering period is from May to August and flower has six petals and six stamens, which inspired its species, name *hexandrum* meaning six stamens.
Leaves are rounded in outline, 10–25 cm long, deeply cut into 3 ovate, toothed lobes, sometimes further lobed. Fruit is a large scarlet or reddish berry with many seeds embedded in pulp. Seed weight is about 20.0 g. It can be propagated by seed or by dividing the rhizome (Qazi et al., 2011; Li et al., 2009).

**Fig. 2.** *Podophyllum hexandrum*; fruiting stage (Chaurasia et al., 2012).

**Common names**

*Podophyllum emodi* has various local names in various languages. Plant is commonly known as Indianpodophyllum. In Lawat district Muzaffarabad, Pakistan it is known as Kakhri. In Niti Valley of Central Himalaya, India plant is known as Bankakri. Laghu patra is its Nepali name. Its name in Ayurveda is bantrapushi or Giriparpat (Rawal et al., 2009; Dar, 2003; Phondani et al., 2010).

**Active constituents of Podophyllum hexandrum**

Root of the plant has been reported to possess 56% podophyllotoxin content. Podophyllotoxin was first shown to be the active principle of podophyllin by Podwyssotzki and was obtained in a pure state in 1880. The rhizomes of *Podophyllum hexandrum* are known to contain numerous lignans which are dimerisation products of phenylpropanoid pathway intermediates linked by central carbons of their side chain (Kamil et al., 1986; Jackson and Dewick, 1984). *Podophyllum hexandrum* also contains a number of compounds with significant pharmacological properties, e.g., epipodophyllotoxin, podophyllotoxone, aryltetrahydronaphthalene lignans, flavonoids such as quercetin, quercetin-3-glycoside, podophyllotoxin glycoside, kaempferol and kaempferol-3-glucoside. In addition to podophyllotoxin, rhizomes and roots of the plant contain various others anti-tumor lignans such as, 4’-demethyl podophyllotoxin and podophyllotoxin 4-O-glucoside. Podophyllotoxin is most important for its use in the synthesis of anti-cancer drugs etoposide, teniposide and etophos. These compounds have been used for the treatment of lung and testicular cancers as well as certain leukemias. In addition, podophyllotoxin is also the precursor to a new derivative CPH 82 that has been tested for rheumatoid arthritis and other derivatives for the treatment of psoriasis and malaria (Lerndal and Svensson, 2000; Imbert, 1998).

**Fig. 3.** *Podophyllum hexandrum*; flowering stage (Chaurasia et al., 2012).

**Pharmacological properties**

*Podophyllum hexandrum* Royle was known as Aindri (a divine drug) in ancient times. Podophyllotoxin is a natural plant secondary metabolite mainly existed in the root of *P. hexandrum* and as well as its congeners and derivatives has pronounced biological activity mainly as anticancer, antineoplastic and anti-HIV drugs, etc (Airi et al., 1997; Archana and Lakshmi, 2000; Chen et al., 2007). The Indian *Podophyllum hexandrum* is superior to its American counterpart, namely, *Podophyllum peltatum* in terms of higher podophyllotoxin content (4% in the dried roots in comparison to only 0.25% for *Podophyllum peltatum*). Podophyllotoxin is a naturally occurring lignan which is gifted with potent cytotoxicity. It acts as a mitotic spindle poison, binding the microtubules and causing mitotic arrest in metaphase (Canel et al., 2000). 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).

Radioprotective Activity

P. hexandrum has been investigated extensively for its radioprotective activity in recent years, including free radical scavenging, time and dose-dependent inhibition of apoptosis (programmed cell death) and cell cycle arrest-related activities in both in vitro and in vivo models (Arora et al., 2006a; 2006b). Methanolic, hydro-alcoholic and chloroform extracts of P. hexandrum have been reported to render approximately 70-95% radioprotection in mice when administered 1-2 hours before lethal whole-body 10Gy radiation (Goel et al., 2000; Goel et al., 2001; Goel et al., 2007). P. hexandrum has been reported to contain a number of bioactive molecules including flavonoids and lignans (Chawla et al., 2005a, b; Chawla et al., 2006). Many flavonoids and lignans are already known for their antioxidant action and anti-apoptotic potential, and thus contribute towards radioprotection (Chawla et al., 2006).

Antifungal Activity

Podophyllum hexandrum was investigated for antifungal properties against pure cultures of clinical isolates of Aspergillus niger and Candida albicans using Disc diffusion methods. The minimum inhibitory concentration (MIC) of the extracts on the test organisms were 16.66 mg/ml for Aspergillus niger. In case of Candida albicans it was 25 mg/ml. result provided evidence regarding the antifungal property of plant (Wani et al., 2013).
Insecticidal Activity
Insecticidal activity of a dichloromethane extract of this plant against larvae of Drosophila melanogaster was reported. Podophyllotoxin was found to exhibit the LC50 value of 0.24 μmol/mL against larvae of D. melanogaster and a LD50 value of 22 μg/adult against adults. Acetylpodophyllotoxin however showed slight insecticidal activity indicating that the 4-hydroxyl group was an important function for enhanced activity of (Miyazawa et al., 1999).

Anticancer Activity
Podophyllotoxin, present in rhizome of plant, is used in the treatment of various types of cancer. The podophyllotoxin in this plant is biosynthesized at very low quantities, so the biotechnological production of podophyllotoxin has been considered essential (Ahmad et al., 2007). The plant also contains podophyllin, which has an antimitotic effect. It is used in the treatment of cancer, and especially in the treatment of ovarian cancer (Howes, 2001; Board, 2003; Farkya et al., 2004). The root and rhizome contains several lignans like podophyllotoxin, podophyllin and berberine which possess antitumor activities like inhibitor of microtubule assembly, used in the treatment of lung cancer, testicular cancer, neuroblastoma, hepatoma and other tumors (Giri and Lakshmi 2000; Chattopadhyay et al., 2002).

Cytotoxicity
Podophyllotoxin is a pharmacologically active compound, which has been shown to possess cytotoxic activities (Petersen and Alfermann 2001; Chattopadhyay et al., 2001). Derivatives of podophyllotoxin possess cytotoxicity at the μM level (Gordaliza et al., 2004). 4-demethyl-picrotoxophyllotoxin 7'-O-D-glucopyranoside (4DPG) effectively inhibit the proliferation of cancer cells and blocked the cell cycle in the mitotic phase. The cytotoxicity of 4DPG is due to its inhibition of the microtubule assembly of cancer cells at a low concentration, thus inducing apoptosis. These properties qualify 4DPG to be a potential antitumor drug (Qi et al., 2005).

Anti-inflammatory Activity
Aqueous extract of Podophyllum hexandrum, a plant well documented in Ayurvedic literature for various therapeutic purposes, has been reported to exhibit Anti-inflammatory property (Prakash et al., 2005).

Traditional uses
Ethnomedicinal uses
P. hexandrum rhizomes have a long medicinal history among native North American tribes who used rhizome powder as a laxative or agent that expels worms (anthelmintic). A poultice of the powder was also used to treat warts and tumorous growths on the skin. In Kashmir it has been used in traditional system of medicine from time immemorial and is locally known as Banwungun, since its red colour fruit (berry) is of the size of a small brinjal. Indian Podophyllum has a long history of usage amongst natives of the Himalayas, an aqueous extract of the roots being a common cathartic. It has also been used as a remedy in ophthalmia (Qazi et al., 2011).

The rhizome powder is used as a poultice to treat warts and tumorous growth on the skin. The traditional medicinal uses of Podophyllum hexandrum are in the treatment of colds, constipation, septic wounds, burning sensation, erysipelas, mental disorders, plague, allergic and inflammatory conditions of the skin, cancer of brain, bladder and lung, veneral warts, monocytoid leukemia, Hodgkin's disease and non-Hodgkin's lymphoma (Beutner and Vonkrough, 1990). In Lawat district Muzaffarabad, root paste is applied on ulcers, cuts and wounds and also used to treat vaginal warts (Dar, 2003). Rhizome is considered as hepatic stimulant, purgative, emetic, fever and body pain in district Battagram, Pakistan (Haq et al., 2011).

Podophyllum hexandrum is used to cure small tumors and its powder is an antiseptic for the healing wounds (Mahmood et al., 2011).

Other uses
Fruit of plant is edible but these must be eaten when...
fully ripe. Powdered root of plant is used to increase yield of butter (Dar, 2003).

**Side effects**
The side effects of oral *Podophyllum* may include: Bloody diarrhea, severe stomach pain, hallucinations, muscle paralysis, kidney failure, breathing failure, neuropathy and encephalopathy while other less side effects from using Podophyllum on the skin may include: confusion, headache, irritation at the site of application, low blood pressure, nausea and vomiting (Cassidy et al., 1982; Tomlinson et al., 2000). This plant is highly poisonous and should only be used under the supervision of a qualified practitioner. It should not be prescribed for pregnant women (Bown, 1995).

**Conservation and management**
*P. hexandrum* is a perennial plant and habitats in scrub forests and alpine meadows associating with other plants, usually in humus rich soil. It is a very important medicinal plant but now a day it is regarded as a rare and threatened species mainly due to the large scale removal of its underground parts which is rich in active constituent, podophyllotoxin, used for the treatment of cancer. *Podophyllum* can be cultivated through seeds while sown as soon as it is ripe in acoldframe but sometimes seed loses viability and poses problem in regeneration in natural habitat.

Being an endangered species *P. hexandrum* needs study of its variability and population under different locations with scientific basis and its ex-situ and in-situ conservation. National Medicinal Plant Board, India has initiated efforts towards conservation of high value rare, endangered and threatened medicinal plants throughout the country after its formation in the recent past (Nautiyal and Nautiyal, 2004; Kaul et al., 1998). Under schedule2-appendix 2 of Export and Import Policy 1997-2002 the export of *Podophyllum* parts and its derivatives and extracts as such obtained from the wild, except the formulations made there from, is prohibited. Exploitation of *Podophyllum* from the wild is prohibited for export from India under CITES (Convention on International Trade in Endangered Species of wild flora and fauna). Only cultivated/artificially propagated plants species is allowed for export under cover of CITES export permit and Legal Procurement Certificate (LPC) or certificate of cultivation from the designated authorities. Certain other attempts regarding the conservation of plant have also been made to conserve this plant through invitro propagation and artificial breaking of seed dormancy. Moreover, the biotechnological production of Podophyllotoxin using plant cell culture derived from *P. hexandrum* may be an attractive alternative. Podophyllotoxin content are prone to changes due to environmental factors of different ecoregions and stage of harvest. These changes could be controlled by in-vitro culture of *Podophyllum hexandrum* for the synthesis of lignan Podophyllotoxin (Rajesh et al., 2012; Nadeem et al., 2000).

**Conclusion**
*P. hexandrum* is an endangered but highvalue medicinal plant from temperate and cold climatic zones of world. Plant has immense importance because of its efficacy towards cancer and other serious diseases. It’s over exploitation poses serious threat towards its extinction. There is an urgent need to take steps towards its conservation. Sustainable harvesting methods are urgently required. There is no established variety either developed or under development, therefore this is another area which need vital attention. Screening of its chemotypes, diversity for morphological, biochemical and genetic levels will enable the researchers to realize the existing population of *P. hexandrum* and hence useful in its conservation and sustainable utilization.

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