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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 zoneataltitudesrangingbetween2000to45000m. It is an herbaceous perennial plant and contain various pharmacologically importantsecondary metabolites amongwhich 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'aleaf. Name refers to the ressemblence of leaves to duck's foot. Plant is also known as Mayapple becauseof 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* Roylesyn *P. emodi* Wall. ex Hook.f. & Thomsis believed to be originated from Himalayan region. It isan important medicinal plant known for valuable drug podophylotoxin whichis effective against various diseases including warts and tumors growth of skinand 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 anti-oxidant, anti-inflammatory, antifungal, cytotoxic and radioprotection activity (Prakash *et al*., 2005; Ganie *et al*., 2010).*P. hexandrum* has been described as 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 inUnani, 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 highlightsthe phytochemistry, ethnomedicinal value and pharmacological activitiesof 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

*Podophyllumhexandrum*is nativeto the lower elevations of Himalayan region. Plant is distributed fromIndian Himalayas to Bhutan, Pakistan, Afganistan, 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 isgrown intheHimalayan regionsin 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).

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

Morphological description

*Podophyllum hexandrum*is anerect perennial herb 15-40 cm tall. It is low to the ground with glossygreen, grand nodose rhizome with many adventitious roots of length longer than 50cm. Stem is 30~90cm 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 splotched 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 hexandrummeaning six stamens.

Leaves are rounded in outline, 10-25 cm long, deeply cut into 3 ovate, toothed lobes, sometimes further lobed. Fruit isa large scarlet or reddish berrywith many seeds embedded in pulp. Seed weight is about 20.0g. 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 inAyurveda is bantrapushi or Giriparpat (Rawal *et al*., 2009; Dar, 2003; Phondani *et al*., 2010).

Active constituents of Podophyllum hexandrum

Rootof 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 hexundrum* also containa number of compounds withsignificant 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 metabolites 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).

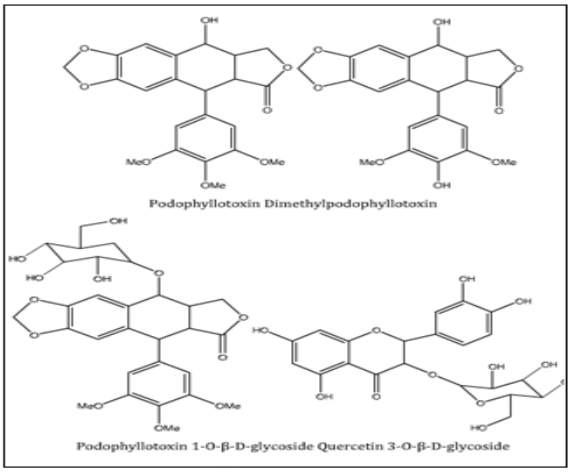

Fig. 4. Compounds isolated from *Podophyllum hexandrum* (Qazi *et al.,* 2011).

Three semisynthetic derivatives of podophyllotoxin etoposide, teniposide and etopophos are widely used as anticancer drugs and show good clinical effects against several types of neoplasms, including small cell lung cancers, lymphoma, leukemia, Kaposi's sarcoma, etc.Etoposide is used in combination therapy in refractory testicular lymphoid and myceloid leukemia and in stomach, ovarian, brain, breast, pancreatic, and both small- and large-cell lung cancers. Teniposide is used less often than etoposide and it is mainly used to treat lymphomas. The successful derivatization of podophyllotoxin into etoposide and teniposide has generated interest in structure optimization to produce new derivatives with a superior pharmacological profile and broader therapeutic uses (Uden *et al*., 1989; Qazi *et al*., 2011).
Some of the pharmacological properties of *P. hexandrum*, based on the active constituents, are given below:

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 antimiotic 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-picropodophyllotoxin 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 whoused rhizome powder asa laxativeoranagentthatexpelsworms (anthelmintic). A poultice of the powder was also used to treatwarts and tumorous growths on the skin. In Kashmir it has been used in traditional system of medicinefrom time immemorial and is locally known as Banwangun, 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'sdisease andnon-Hodgkin's lymphoma (Beutner and Vonkrough, 1990). In Lawat district Muzaffarabad, root paste is applied on ulcers, cuts wound 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 aperennial 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 inacoldframe but sometimes seed loses viability and poses problem in regeneration in natural habitat. Being an endangered species *P.hexandrum* needs study of itsvariability and population under different locations with scientificbasis and its ex-situ and in-situ conservation. National Medicinal Plant Board, India has initiatedefforts towards conservationof high value rare, endangered and threatened medicinal plants throughoutthe 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 1997-2002theexportof *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 thewild isprohibited forexport from India under CITES (Convention on InternationalTrade in Endangered Speciesof wild flora and fauna). Only cultivated/artificial ypropagated plants peciesis allowed for export under cover of CITES export permit and Legal Procurement Certificate (LPC) or certificate of cultivationfrom 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 climaticzonesof 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 noestablished variety either developedorunder development, therefore this is another areawhich need vital attention. Screeningofitschemotypes, diversity for morphological, biochemical and geneticlevelswillenabletheresearchers to realize the existing populationof *P. hexandrum* and hence useful in its conservation and sustainable utilization.

References

Ahmad R, Sharma VK, Rai AK, Shivananda BG. 2007. Production of lignans in callus culture of *Podophyllum hexandrum*. Tropical Journal of Pharmaceutical Research **6,** 803-808. http://dx.doi.org/10.4314/tjpr.v6i4.14661

Airi S, Rawal RS, Dhar U. 1997. Population studies on *Podophyllum hexandrum* Royle: a dwindling medicinal plant of the Himalaya. Plant

Genetic Resources News **110,** 20-34.

Archana GM, Lakshmi N. 2000. Production of podophyllotoxin from *Podophyllum hexandrum*: a potential natural product for clinically useful anticancer drugs. Cytotechnology **34,** 17-26. http://dx.doi.org/10.1023/a:1008138230896

Arora R, Chawla R, Singh S, Kumar R, Sharma AK, Puri SC, Sinha AK, Tripathi RP, Sharma RK. 2006. Radioprotection by himalayan high-altitude region plants. In: herbal drugs: a twenty-first century perspective. Jaypee Brothers Medical Publishing Limited, New Delhi. 301-325 p. http://dx.doi.org/10.5005/jp/books/10352

Arora R, Chawla R, Singh S, Sagar RK, Kumar R, Sharma A, Prasad J, Singh S, Gurudutta GU, Sharma RK. 2006. Bioprospection for radioprotective molecules from indigenous plants. In: recent progress in medicinal plants. Phytomedicine **16,** 179-219.

Beutner KR, Vonkrough G. 1990. Current status of podophyllotoxin for the treatment of genital warts. Seminars in Dermatology **9,** 148.

Board N. 2003. Herbs cultivation and their Utilization. Asia Pacific Business Press Kamal Nagar, Delhi, India. 329 – 333.

Bown D. 1995. Encyclopaedia of herbs and their uses. Dorling Kindersley, London. ISBN0-7513-020-31.

Canel C, Moraes RM, Dayan F, Ferreria D. 2000. Podophyllotoxin. Phytochemistry **54,** 115-120. http://dx.doi.org/10.1016/s0031-9422 (00)00094-7

Cassidy DE, Drewry J, Fanning JP. 1982. Podophyllum toxicity: a report of a fatal case and a review of the literature. Journal of Toxicology and Clinical Toxicology **19,** 35-44. http://dx.doi.org/10.3109/15563658208990364

Chattopadhyay S, Srivastava AK, Bhojwani SS, Bisaria VS. 2001. Development of suspension culture of *Podophyllum hexandrum* for the production of podophyllotoxin. Biotechnology Letters **23,** 2063 - 2066. http://dx.doi.org/10.1023/a:1013704116860

Chattopadhyay S, Srivastava AK, Bhojwani SS, Bisaria VS. 2002. Production of podophyllotoxin by plant cell cultures of *Podophyllum hexandrum* in Bioreactor. Journal of Bioscince and Bioengineering **93,** 215-220. http://dx.doi.org/10.1016/s1389-1723(02)80017-2

Chaudhari SK, Bibi Y, Arshad M. 2014. *Podophyllum hexandrum*: An endangered medicinal plant from Pakistan. Pure and Applied Biology **3,** 19-24.

Chaurasia OP, Ballabh B, Tayade A, Kumar R, Kumar GP, Singh SB. 2012. *Podophyllum* L.:An endergered and anticancerous medicinal plant–An overview. Indian Journal of Traditional Knowledge **11,** 234-241.

Chaurasia OP, Bhatt BB, Singh DV. 2000. Ethnobotany of Ladakh Himalaya, In::Ladakh: Past & Present, edited by PS Jina, (Gyan Publishing House, New Delhi).

Chawla R, Arora R, Kumar R, Sharma AK, Prasad J, Singh S, Sagar RK, Chaudhary P, Shukla S, Kaur G, Sharma RK, Puri SC, Dhar KL, Handa G, Gupta VK, Qazi GN. 2005. Antioxidant activity of fractionated extracts of rhizomesof high-altitude*Podophyllum hexandrum*: role in radiation protection. Molecular and Cellular Biochemistry **273,** 193-208. http://dx.doi.org/10.1007/s11010-005-0821-5

Chawla R, Arora R, Sagar RK, Singh S, Puri SC, Kumar R, Singh S, Sharma AK. 2005. 3-O-beta-D-Galactopyranoside of quercetin as an active principle from high altitude *Podophyllum hexandrum* andevaluation of its radioprotective properties.

Journal of Biosciences **60,** 728-738.

Chawla R, Arora R, Singh S, Sagar RK, Sharma RK, Kumar R. 2006. *Podophyllum hexandrum* offers radioprotection by modulating free radical flux: role of aryl-tetralin lignans. Evidence Based Complementary and Alternative Medicine **3,** 503-511.
http://dx.doi.org/10.1093/ecam/nel037

Chen SW, Wang YH, Yan J. 2007. Synthesis and anti-HIV-1 activities of novel podophyllotoxin derivatives. Bioorganic & Medicinal Chemistry Letters **17,** 2091-2095.
http://dx.doi.org/10.1016/j.bmcl.2006.11.070

Claus EP, Tyler VE, Brady LR. 1974. Pharmacognosy. 6th ed. Henry Kimpton publishers, London. 203–204 p.

Dar ME. 2003. Ethnobotanical uses of plants of Lawat district Muzaffarabad, Azad Jammu and Kashmir. Asian Journal of Plant Sciences **2,** 680-682.
http://dx.doi.org/10.3923/ajps.2003.680.682

Datt M, Sharma A. Vinblastine: podophylotoxin, a good mitotic agent for preparing embryonic chromosomes. Indian Journal of Animal Sciences **70,** 912–913.

Evans WC. 2002. Trease and evans pharmacognosy. 13th ed. Bailliere Tindall, London. 654-656 p.

Farkya S, Bisaria VS, Srivastava AK. 2004. Biotechnological aspects of the production of the anticancer drug podophyllotoxin. Applied Microbiology and Biotechnology **65,** 504-519.
http://dx.doi.org/10.1007/s00253-004-1680-9

Ganie SA, Haq E, Masood A, Zargar MA. 2010. Amelioration of carbon tetrachloride induced oxidative stress in kidney and lung tissues by ethanolic rhizome extract of *Podophyllum hexandrum* in Wistar rats. Journal of Medicinal Plant Research **4,** 1673- 1677.

Giri A, Narasu ML. 2000. Production of podophyllotoxin from *Podophyllum hexandrum*: a potential natural product forclinically useful anticancer drug. Cytotechnology **34,** 17-26.
http://dx.doi.org/10.1023/a:1008138230896

Goel HC, Arora R, Prasad J. 2000. A process for preparation of a radioprotective herbal extract - I and II. Indian Patent filed, Patent Office, New Delhi, India.

Goel HC, Arora R, Prasad J. 2001. A process for preparation of a radioprotective herbal formulation. Indian patent filed, Patent Office, New Delhi, India.

Goel HC, Prakash H, Ali A, Bala M. 2007. *Podophyllum hexandrum* modulates gamma radiation-induced immunosuppression in Balb/c mice: Implications in radioprotection. Molecular and Cellular Biochemistry **295,** 93-103.
http://dx.doi.org/10.1007/s11010-006-9277-5

Gordaliza M, Garcia PA, Miguel JM, Corral MA. 2004. Podophyllotoxin: distribution, sources, applications and new cytotoxic derivatives. Toxicon **44,** 441-459.
http://dx.doi.org/10.1016/j.toxicon.2004.05.008

Haq F, Ahmad H, Alam M. 2011. Traditional uses of medicinal plants of Nandiar Khuwarr catchment (District Battagram), Pakistan. Journal of Medicinal Plants Research **5,** 39-48.

Howes FN. 2001. Vegetable Gums and Resins. Reprint. Jodhpur, Scientific, 190.

Imbert TF. 1998. Discovery of podophyllotoxins. Biochimi **80,** 207-222.
http://dx.doi.org/10.1016/s0300-9084(98)80004-7

Jackson DE, Dewick PM. 1984. Aryltetralin lignans from *Podophyllum hexandrum* and *Podophyllum peltatum*. Phytochemistry **23,** 1147-1152.

http://dx.doi.org/10.1016/s0031-9422(00)82628-x

Kamil MW, Dewick PM. 1986. Biosynthesis of lignans alfa and beta- peltetin. Phytochemistry **25,** 2089-2092. http://dx.doi.org/10.1016/0031-9422(86)80071-1

Kaul MK, Sharma PK, Singh V. 1998. Crude drugs of Zanskar (Ladakh): Conservation Assessment and Management Plan Workshop – Kullu, HP.

Lerndal T, Svensson B. 2000. A clinical study of CPH 82 vs. methotrexate in early rheumatoid arthritis. Rheumatology (Oxford) **39,** 316. http://dx.doi.org/10.1093/rheumatology/39.3.316

Li W, Li M, Yang D, Xu R, Zhang Y. 2009. Production podophyllotoxin by root culture of *Podophyllum hexandrum* Royle. Electronic Journal of Biology **5,** 34-39.

Mahmood A, Malik RN, Shinwari ZK. Mahmood A. 2011. Ethnobotanical survey of plants from Neelum, Azad Jammu & Kashmir, Pakistan.Pakistan Journal of Botany **43,** 105-110.

Miyazawa M, Fukuyama M, Yoshio K, Kato T, Ishikawa Y. 1999. Biologically active components against *Drosophila melanogaster* from *Podophyllum hexandrum*. Journal of Agriculture and Food Chemistry **47,** 5108–5110. http://dx.doi.org/10.1021/jf9903509

Nadeem M, Palni LMS, Purohit AN, Pandey H, Nandi SK. 2000. Propagation and conservation of *Podophyllum hexandrum* Royle: an important medicinal herb. Biology Conservation **92,** 121–129. http://dx.doi.org/10.1016/s0006-3207(99)00059-2

Nasir E, Ali SI. 1972. Flora of West Pakistan. An annotated catalogue of the vascular plants of West Pakistan and Kashmir. R. R. Stewart, Stewart Herbarium, Gorden College, Rawalpindi, Department of Botany University of Karachi. 282.

Nautiyal MC, Nautiyal BP. 2004. Agrotechniques for High Altitude Medicinal and Aromatic Plants, (Bishen Singh, Mahendra Pal Singh, Dehradun).

Petersen M, Alfermann AW. 2001. The production of cytotoxic lignans byplant cell cultures. Applied Microbiology andBiotechnology **55,** 135–142. http://dx.doi.org/10.1007/s002530000510

Phondani PC, Maikhuri RK, Rawat LS, Farooquee NA, Kala CP, Vishvakarma SCR, Rao KS, Saxena KG. 2010. Ethnobotanical uses of plants among the Bhotiya tribal communities of Niti valley in Central Himalaya, India. Ethnobotany Research & Applications **8,** 233-244.

Prakash H, Ali A, Bala M, Goel HC. 2005. Anti-inflammatory effects of *Podophyllum hexandrum* (RP-1) against lipopolysaccharides indu. Journal of Pharmaceutical Sciences **8,** 107-114.

Qazi PH, Rashid A, Shawl SA. 2011. "*Podophyllum hexandrum*" – A versatile medicinal plant. International Journal of Pharmacy and Pharmaceutical Sciences **3,** 261-268.

Qi Y, Liao F, Chang Z, Yong L, Ming Z. 2005. Cytotoxicity, apoptosis induction, and mitotic arrest by a novel podophyllotoxin glucoside, 4DPG, in tumor cells1. Acta Pharmacologica Sinica **26,** 1000 –1008. http://dx.doi.org/10.1111/j.1745-7254.2005.00148.x

Rajesh M, Jeyaraj M, Sivanandhan G, Subramanyam K, Dev GK Ganapathi A. 2012. Adventitious root culture in *Podophyllum hexandrum* Royle (syn. P. emodi Wall. ex Hook.f. & Thomas): An important medicinal plant. Journal of Biotechnology and Biomaterials **2,** 6.

Rawal D, Sijapati SJ, Rana N, Rana P, Giri A, Shrestha S. 2009. Some High Value Medicinal Plants of Khumbu Region Nepal. Nepal Journal of Science and Technology **10,** 73-82. http://dx.doi.org/10.3126/njst.v10i0.2828

Tomlinson B, Chan TYK, Chan JCN, Critchley JA, But PPH. 2000. Toxicity of complementary therapies. An eastern perspective. Journal of Clinical Pharmacology **40,** 451–456. http://dx.doi.org/10.1177/00912700022009206

Uden WV, Pas N, Visser JF, Malingre TM. 1989. Detection and identification of podophyllotoxin produced by cell cultures derived from *Podophyllum hexandrum* Royle. Plant Cell Reports **8,** 165–168. http://dx.doi.org/10.1007/bf00716832

Wani SA, Shah KW, Ahmad MA. 2013. Antifungal activities of methanolic extracts of *Podophyllum hexandrum* and *Rheum emodi* against human pathogenic fungal strains. International Journal of Pharmaceutical Sciences Review and Research **19,** 56-59.

Wong SK, Tsui SK, Kwan SY, Su XL, Lin RC. 2000. Identification and characterization of *P. emodi* by API- LC/MS/MS. J. Mass Spectrum **35,** 1246-1251. http://dx.doi.org/10.1002/1096-9888(200011)35