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**PHYTOCHEMISTRY, PHARMACOLOGICAL ACTIVITIES, AND
ETHNOMEDICINAL IMPORTANCE OF THE HIGHLY VALUABLE
ENDANGERED PLANT, *PODOPHYLLUM HEXANDRUM*; A
COMPREHENSIVE REVIEW**

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ABSTRACT

Podophyllum hexandrum, a highly valuable endangered medicinal plant, shows an enormous variety of secondary metabolites from its different parts. The plant parts have been in medicinal use since ancient times, and due to their vast therapeutic potential, *Podophyllum hexandrum* gained tremendous importance in various systems of medicine. The plant has been titled "divine drug" due to its antifungal, antioxidant, antibacterial, anticancer, antiviral, and insecticidal properties. In this review, the phytochemistry, pharmacological activities, and ethnomedicinal importance of this valuable plant have been comprehensively described.

Keywords: Podophyllotoxin, antitumor, teniposide, etopophos, etoposide

1. INTRODUCTION

Podophyllum hexandrum, a perennial rhizomatous herb belonging to Berberidaceae [1], is a precious endangered medicinal plant distributed at altitudes between 2000 and 4500 meters in the lower elevations of the

Himalayan zone [2]. The generic name of this plant, i.e., *Podophyllum*, has its origin in "podos" and "phylos" (Greek words), meaning "foot" and "leaf," referring to its leaf resemblance to a duck's foot, while as the six petals and stamens of this species had led to

its specific name, *hexandrum* [3].

Podophyllum hexandrum, commonly called 'Indian Mayapple' or 'Himalayan Mayapple,' is a cold-tolerant that propagates by seeds or rhizome divisions [4, 5]. The above-ground part of the plant is annual and emerges in mid-April with an erect and succulent stem of about 15 to 60cm tall bearing 1-3 (usually 2) alternate and often purple spotted leaves. Flowering occurs from May to August, and a large white or pale pink colored bisexual and cup-shaped flower is borne at the end of the stout stem, followed by the formation of an oval, fleshy, and red or orange berry fruit [6-8].

Phytochemical screening of the rhizome, seed, and leaf extracts of *Podophyllum hexandrum* has shown numerous secondary metabolites like tannins, flavonoids, alkaloids, terpenoids, glycosides, saponins, and amino acids [9, 10]. However, seed and leaf extracts are devoid of saponins. The essential secondary metabolite in *Podophyllum hexandrum* is an aryltetralin lignan known as "podophyllotoxin," present as the *Podophyllum* resin called Podophyllin. Podophyllin found its inclusion in US pharmacopeia in 1820 for the first time as a cathartic and Chalogogue. Though rhizomes are primarily used in medicine as a podophyllin resin source, about 7.8-9.7% of

resin is present in leaves also [5, 11].

Podophyllum hexandrum possesses the vast therapeutic potential and is essential in various systems of medicine. In Ayurveda (the Indian system of medicine), it has been described as a divine drug. The valuable drug, i.e., podophyllotoxin, for which *Podophyllum hexandrum* is famous worldwide, is cytotoxic, antitumor and used to develop crucial drugs for cancer, like teniposide, etopophos, and etoposide. *Podophyllum hexandrum* has antioxidant, antibacterial, antifungal, anticancer, antiviral, and insecticidal properties. It is used as a cholagogue, emetic, vermifuge, and tonic and controls skin diseases. In traditional medicine, *Podophyllum hexandrum* has been extensively used against brain, lung, and bladder cancer, skin allergy and inflammation, plague, constipation, burning sensation, colds, septic wounds, mental disorders, and erysipelas, Hodgkin's disease and non-Hodgkin's lymphoma [12-14]. In Kashmir, fresh fruits of *Podophyllum hexandrum* are eaten raw to cure a range of ailments. In Ladakh, the rhizome powder and fruit extract of *Podophyllum hexandrum* are combined with honey and ingested orally against intestinal infection [15]. Increased demand for *Podophyllum hexandrum* in national and international markets has led to

the considerable decline of the species due to heavy collection from the wild. About 37.3 tonnes of *Podophyllum hexandrum* rhizomes were uprooted in Himachal Pradesh from 1995 to 2000 [15]. Therefore, its over-exploitation poses a significant risk of its extinction. Thus, saving this excellent and essential medicinal herb becomes necessary.

2. MORPHOLOGY

Podophyllum hexandrum is an erect, glabrous, and somewhat fleshy or succulent perennial herb with creeping rootstock and attains a height of about 30-60 cm. The plant possesses a short and horizontally creeping grand nodose rhizome with many thick adventitious roots about 50 cm long. The stem is long, erect, terete, hollow, round, and naked below, with 1-3 alternate and long-stalked leaves about the middle. The leaves are large, palmate, umbrella-like, 6 to 10 inches in diameter, often purple-spotted, and deeply divided into three to five sharply toothed lobes. The leaves unfurl entirely after the plant has bloomed. At the onset of the spring season, large cup-shaped white or pale-pink-colored flowers are borne at the ends of stout stems. The flowers are bisexual, actinomorphic, and gamosepalous, bearing 3-6 petaloid sepals, 6 petals, 6 stamens, and many ovules [7, 16, 17]. The fruit is a large ovoid berry that ripens in August or

September with a bright orange or red color, is about 1 to 2.5 inches long, and bears many hard and deep red-colored seeds embedded in red pulp. The perennial root system possesses one aerial reproductive shoot and 4-5 vegetative shoots. Vegetative shoots bear a single leaf, while reproductive shoots generally have two and rarely three leaves [7].

3. PHOTOCHEMISTRY

Phytochemical profiling of *Podophyllum hexandrum* has revealed the presence of various secondary metabolites like tannins, terpenes, alkaloids, phenols, saponins, glycosides, and flavonoids in its root, leaf, and seed extracts [9, 18]. Podophyllin, a form of resin, constitutes the plant's belowground parts' active constituents [19]. In 1820, Podophyllin was included in pharmacopeia as a cholagogue and cathartic [20]. Podophyllin is an amorphous powder with a distinct odor and caustic and acrid taste. It is light brown to greenish-yellow or greenish-grey in color and is insoluble in cold water [21]. The amount of Podophyllin (resin) present in *Podophyllum hexandrum* is 7- 15%, while only 4-8% in its counterpart *Podophyllum peltatum* [22]. The resin possesses important lignans, flavonoids, 8.6% wax, mineral salts, and 3.7% essential oils responsible for the odor of Podophyllin [23]. The chemical composition of various parts of

Podophyllum hexandrum is shown in **Table 1**.

The different lignans isolated from rhizomes and roots of *Podophyllum hexandrum* [19, 24, 25] are:

- Podophyllotoxin
- Isopicropodophyllone
- 4'- demethylpodophyllotoxone
- 4'- demethylpodophyllotoxin
- Deoxypodophyllotoxin
- Podophyllotoxone
- β -peltatin
- 4'- demethyldeoxypodophyllotoxin
- α -peltatin
- 4'- demethylisopicropodophyllon.

The different flavonoids present in *Podophyllum hexandrum* are:

- Kaempferol-3- glucoside
- Kaempferol
- Podophyllotoxin glycoside
- Quercetin-3-glycoside
- Quercetin

Podophyllotoxin is the naturally occurring bioactive aryltetralin lignan with enormous medicinal uses. Podophyllotoxin is the most active and important lignan obtained from roots and rhizomes of *Podophyllum hexandrum*. In 1880, Podwysstzki isolated podophyllotoxin for the first time from

Podophyllum peltatum, the American counterpart of *Podophyllum hexandrum*. Higher concentrations of the lignan were later isolated from *Podophyllum hexandrum*. Podophyllotoxin's structure was initially determined in the 1930s and revealed four successive chiral centers with four fused planer rings [29]. Several oxygen-bearing functional groups like acetal, 3-methoxy groups, lactone, and alcohol are present in its structure.

Table 1: Chemical composition of various parts of *Podophyllum hexandrum* [5, 26-28]

Sr. No.	Part	Compound
1.	Roots	Aryltetralinlignans: 4'-demethylisopropodophyllone, 4'-demethylpodophyllotoxone, 4'-demethyldeoxypodophyllotoxin, isopropodophyllone, podophyllotoxone, deoxypodophyllotoxin, 4'-demethylpodophyllotoxin, podophyllotoxin, α -peltatin, and β -peltatin
2.	Resin	Lactone, podophyllotoxin, propodophyllin, podophyllic acid, quercetin, isorhamnetin, quercetingalactoside
3.	Rhizome	Aryltetrahydronaphthalene lignans such as podophyllotoxin-4-O-glucopyranoside, 4'-demethylpodophyllotoxin, podophyllotoxin, dehydropodophyllotoxin, podophyllotoxin-4-O-glucoside
4.	Fruit	Picropodophyllin, 4'-Demethylpodophyllotoxin
5.	Leaves	Epipodophyllotoxin, podophyllotoxone, 4-methylpodophyllotoxin, quercetin, kaempferol aryltetrahydronaphthalene lignans, 4-demethylpodophyllotoxin glycoside, quercetin-3-glycoside, podophyllotoxin glucoside and kaempferol-3-glycoside

3.1 Mode of action of podophyllotoxin

Podophyllotoxin is considered an anti-mitotic drug. It inhibits the microtubule assembly and arrests the cell cycle by binding to tubulin at the colchicine site [30, 31]. Podophyllotoxin's mode of action is similar to colchicine, which acts as spindle poison for its mode of action. Podophyllotoxin acts through cell protein attachment, accelerating amino acid incorporation into proteins and inhibiting the synthesis and incorporation of purines into RNA. The reduction of succinoxidase and cytochrome oxidase activity by podophyllotoxin impacts normal mitochondrial functioning [32]. The radioprotective exhibition of *Podophyllum hexandrum* has been explained through several mechanisms, like the stabilization of membrane potential, free radical scavenging, temporal apoptotic regulation, and manipulation of cell cycle leading to shielding of sub-cellular structures, including DNA [33-35]. The clinically applied podophyllotoxin semisynthetic derivatives, like etopophos, teniposide, and etoposide, function differently. These compounds

inhibit DNA topoisomerase II, a vital DNA replication and repair enzyme. The semisynthetic derivatives of podophyllotoxin stabilize the DNA topoisomerase II complex and prevent the sealing of the DNA strands. Consequently, the cells get arrested in the cell cycle's early G2 or late S phase [36-38]. Another derivative of Podophyllotoxin, Etopophos (Etoposide phosphate), is a prodrug of etoposide, and its significant advantage is that it has improved solubility in water. After administration, the human body hydrolyzes the phosphate group, yielding bioactive etoposide [39]. Because of its hydrophilic nature, etopophos is much easier to administer. NK611, another podophyllotoxin derivative, also blocks topoisomerase II and has improved water solubility [40].

4. PHARMACOLOGICAL ACTIVITIES

4.1 Antiviral activity

Podophyllotoxin and its derivatives can hinder viral replication because they can bind to tubulin and damage the cytoskeleton of cells. Additionally, synthetic analogs of

podophyllotoxin exhibit reverse transcriptase inhibition, which can be used to create anticancer medications against other retroviruses like HIV (Human immunodeficiency virus). Podophyllotoxin has been used as an antiviral drug against *Condyloma acuminatum*-causing HPV (Human Papillomavirus) [30]. Also, podophyllotoxin is the most effective inhibitor of herpes simplex type I virus and measles replication [21].

4.2 Antibacterial activity

A wide variety of bacterial species are affected by podophyllotoxin. On screening of various derivatives of podophyllotoxin, the findings showed that ethyl-2-(3-(3'-methyl-4-methoxybenzoyl)-3-(4"-dimethoxyphenyl)-cyclopropane-carboxylic acid and ethyl-2-(3'-methyl-4-methoxybenzoyl)-3-(4"-methoxyphenyl)-cyclopropane-1-carboxylic acid have substantial antibacterial activity against various strains of *E.coli*, *Salmonella typhi*, *Shigellasonnei*, *Streptococcus faecalis*, and *Pseudomonas aeruginosa*. The cup diffusion method determined antibiotic activity on a nutrient agar medium [41].

4.3 Radioprotective activity

The extract of *Podophyllum hexandrum* can act as a radioprotectant due to its property of arresting cell division. *Podophyllum hexandrum's* radioprotective efficacy against fatal radiation dosages has lately been examined in both in-vivo

and in-vitro models [33, 34, 42]. In mouse jejunum, pre-irradiation administration of *Podophyllum hexandrum* reduces severe radiation damage, while chloroform, hydro-alcoholic, and methanolic extracts of *Podophyllum hexandrum* provide 70-95% radioprotection in mice after 1-2 hours administration before entire body lethal 10Gy radiation [34]. Numerous explanations for the radioprotective manifestations have been put forth, including possible time-dependent apoptosis control, membrane stabilization, free radical scavenging, and modification of cell cycle activities that preserve DNA and other subcellular components [43]. Podophylloquercetin, a flavonoid found in *Podophyllum hexandrum* extract, is crucial in free radical scavenging and iron chelation [2].

4.4 Antifungal activity

Podophyllum hexandrum has also been shown to have antifungal properties. The antifungal effects of *Podophyllum hexandrum* were examined using disc diffusion techniques compared to pure cultures of clinical isolates of *Candida albicans* and *Aspergillus niger*. The extracts' minimum inhibitory concentration (MIC) was 16.66 mg/ml for *Aspergillus niger* and 25 mg/ml for *Candida albicans*. The findings supported the plant's antifungal ability [44]. Furthermore, *Allescheria boydii*, *Pleurotus ostreatus*, *Microsporium canis*, *Nigrospora oryzae*, *Epidermophyton floccosum*, and *Curvularia lunata* have all been shown to be

highly susceptible to lignans isolated from *Podophyllum hexandrum* [45].

4.5 Antioxidant activity

The antioxidant potential of several rhizome, leaf, and petiole extracts of *Podophyllum hexandrum* has been studied. The DPPH scavenging assay, H₂O₂ assay, superoxide assay, reducing power, and determining the antioxidant enzyme activities and glutathione levels in the liver tissue homogenate of albino rats were used to test the antioxidant activity of the *Podophyllum hexandrum* rhizome ethyl acetate extract. These techniques have shown that ethyl acetate extract outperforms the well-known antioxidants BHT and -tocopherol [46]. By preventing lipid peroxidation, enhancing antioxidant enzyme activity, and decreasing the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase, ethyl acetate extract of rhizome reduced the CCl₄-induced toxicity, notably hepatotoxicity (LDH). Petiole and rhizome ethanol and ethyl acetate extracts were also tested for antioxidant activity, with rhizome extracts demonstrating stronger antioxidant activity than extracts of petioles [47]. A methanolic extract of *Podophyllum hexandrum* also inhibits H₂O₂ lipid peroxidation. By boosting antioxidant defense capabilities, the aqueous extract of *Podophyllum hexandrum* has been shown to protect lung and kidney tissue from CCl₄-induced

oxidative stress [43].

4.6 Insecticidal activity

Podophyllum hexandrum dichloromethane extract exhibited insecticidal activity against *Drosophila melanogaster* larvae. The LC₅₀ value of podophyllotoxin against larvae of *Drosophila melanogaster* was 0.24 μmol/ml, and its LD₅₀ value against adults was 22 μg/adult [48]. Moreover, Deoxypodophyllotoxin is the vital compound responsible for toxic activity on insect larvae such as *Epilachnaspara*, *Culex pipiens*, and adult insects like *Blatella germanica*. The larvae of silkworm *Bombyx mori* are also affected by Deoxypodophyllotoxin [49].

4.7 Anti-inflammatory activity

Podophyllum hexandrum aqueous extract has anti-inflammatory potential [50].

4.8 Anticancer Activity

Several malignant illnesses have been effectively treated with podophyllotoxin, a naturally occurring aryltetralin lignan found in *Podophyllum hexandrum* and its derivatives, etoposide, teniposide, and etopophos (etoposide phosphate) [51]. Many diseases, including lung cancer, genital tumors, Wilms tumors, and various other lymphomas and tumors, are treated with podophyllotoxin. The podophyllin derivative etoposide is used to treat a variety of malignancies, including pancreatic, breast, small and large cell lung, germ cell, ovarian, rhabdomyosarcoma, and newly discovered glioblastoma multiforme [52].

Teniposide, a different podophyllotoxin derivative, cures brain and bladder tumors, acute refractory leukemia, and lymphomas [52]. Other podophyllotoxin derivatives with promising outcomes include NK611, TOP-53, GL331, and Tafluposide, which are anticipated to develop into potent anticancer medications. GL331, created by

substituting glycoside for an aniline group, is 40 times more effective than etoposide [53]. Etoposide and teniposide are outperformed by Nk611, which has a dimethylamino group at the D-glucose moiety regarding the anticancer activity.

Table 2: Semisynthetic derivatives of podophyllotoxin, their chemical names, and disease treatment [3, 30, 54-56]

Podophyllotoxin	Chemical name	Treatment
Etoposide (Vepeside)	Demethyl Epipodophyllotoxinethylidene glucopyranoside, epipodophyllotoxin or VP-16	It is a well-known and very effective anticancer drug, generally utilized in combination treatments for leucopenia and testicular cancers since it is effective against various tumor forms. This is the most effective treatment for ovarian cancer, kaposi sarcoma, rhabdomyosarcoma, Hodgkin's disease, acute myelogenous leukemia, neuroblastoma, histiocytosis, Ewing's sarcoma, brain tumors, small cell lung cancer, germ cell tumors, and newly diagnosed glioblastoma multiforma.
Etoposide Phosphate	Etophos	Treatment for many malignant conditions, water-soluble, concentrated to 20mg/ml, administered as a 5-minute bolus in large doses in tiny amounts as continuous infusion.
Teniposide	VM-26	Treatment of acute refractory leukemia lymphomas and brain and bladder tumors. It can be used in single drug therapy for induction of remission.
NK 611	-	NK 611 antitumor activity is comparable or superior to that of etoposide.
CPH 82	Reumacon	It can potentially treat rheumatoid, psoriatic arthritis, oligoarticular large joint arthritis, juvenile rheumatoid arthritis, and rheumatoid arthritis.

5. ETHNOMEDICINAL USES

In ancient times, *Podophyllum hexandrum* was known as Aindri (a divine drug) and its rhizomes have been used medicinally for centuries [43]. Native North American cultures employed the rhizome powder of *Podophyllum hexandrum* as a purgative, laxative, and anti-helminthic. Additionally, warts and tumorous skin growths were treated with a poultice produced from the powdered rhizome [5]. The herb has also been employed in ancient Kashmir's traditional medical system. Natives of the Himalayas have used an aqueous preparation of the plant's root to cure catharsis and ophthalmia for centuries [57]. In Ladakh, the rhizomes of *Podophyllum hexandrum* are called Ol-mo-se, which signifies women's health cures. They are used to treat various gynecological diseases in Ladakh and the Tibetan medical system [58]. Fruits are used to treat coughs, and tea made from roots prevents constipation. Also, roots treat jaundice, syphilis, fever, liver disorders, and cancer.

Podophyllum hexandrum is traditionally used in treating Hodgkin's disease and non-Hodgkin's lymphoma, constipation, colds, burning sensation, allergic and inflammatory conditions of the skin, septic wounds, mental disorders, erysipelas, plague, venereal warts, monocytoid leukemia, cancer of the bladder, lungs, and brain [26]. The rhizome possesses a hepatic stimulating effect and treats body pain and fever. The plant's root paste is used

topically to treat vaginal warts, genital herpes, and other sores and ulcers in Lawat Muzaffarabad [59].

6. SIDE EFFECTS

Despite enormous benefits, *Podophyllum hexandrum* has specific side effects, like oral *Podophyllum* causes severe stomach pain, bloody diarrhea, kidney failure, muscle paralysis, breathing failure, encephalopathy, and neuropathy. Some minor side effects of applying *Podophyllum hexandrum* on the skin include headache, confusion, irritation, nausea, vomiting, and low blood pressure [2]. The plant should only be utilized with prudence and under the guidance of a trained professional since it may sometimes be highly hazardous. Pregnancy should not be the time to utilize this herb [60].

REFERENCES

- [1] Kumar, R., Badere, R., and Singh, S.B. (2010). Antibacterial and antioxidant activities of ethanol extracts from trans Himalayan medicinal plants. *Pharmacognosy Journal* 2: 66-69.
- [2] Kumar, J., Sandal, P., Singh, A., Kumar, A., Arya, V., Devi, R., Sharma, B.P., and Verma, R. (2022). Conservation Status, Anticancer Compounds and Pharmacological Aspects of Royle: A Review *Podophyllum hexandrum*. *Indian J. Ecol.* 49: 1096-1102.
- [3] Qazi, P.H., Rashid, A., and Shawl, S.A. (2011). *Podophyllum hexandrum*: a versatile medicinal plant. *Int J Pharm Pharm Sci* 3: 261-268.

- [4] Sharma, A., and Sharma, P. (2018). The Himalayan May Apple (*Podophyllum hexandrum*): A review. *Asian J. Adv. Basic Sci* 6: 42-51.
- [5] Chaurasia, O., Ballabh, B., Tayade, A., Kumar, R., Kumar, G.P., and Singh, S. (2012). *Podophyllum L.*: An endangered and anticancerous medicinal plant—An overview. 11: 234-241.
- [6] Rather, M., and Amin, S. (2016). A comprehensive review on the phytochemical and pharmacological aspects of *Podophyllum hexandrum*: a high value medicinal plant. *Adv Biomed Pharma* 3: 216-226.
- [7] Airi, S. (1997). Population studies on *Podophyllum hexandrum* Royle—a dwindling, medicinal plant of the Himalaya. *Plant Genetic Resource Newsletter* 110: 29-34.
- [8] Shinwari, Z.K., and Gilani, S.S. (2003). Sustainable harvest of medicinal plants at Bulashbar Nullah, Astore (northern Pakistan). *J. Ethnopharmacol.* 84: 289-298.
- [9] Malik, M.A., Srivastava, P., and Ahmad, S.B. (2018). Quantitative estimation of phytochemicals and antimicrobial activity of *Podophyllum hexandrum*. *Int. J. Curr. Sci* 6: 1152-1155.
- [10] Kumar, J., and Dhillon, H. (2015). TLC profiling and phytochemical screening of *Podophyllum hexandrum* Royle—an endangered medicinal plant. *International Journal of Farm Sciences* 5: 56-61.
- [11] Hameed, I., Ullah, A., Murad, W., and Khan, S. (2014). *Podophyllum hexandrum* Royle. *Scholarly Journal of Agricultural Science* 4: 331-338.
- [12] Sagar, R.K., Chawla, R., Arora, R., Singh, S., Krishna, B., Sharma, R.K., Puri, S.C., Singh, P., Kumar, R., and Sharma, A.K. (2006). Protection of the hemopoietic system by *Podophyllum hexandrum* against gamma radiation-induced damage. *Planta Medica* 72: 114-120.
- [13] Beutner, K., and Von Krogh, G. (1990). Current status of podophyllotoxin for the treatment of genital warts. In 2. pp. 148-151.
- [14] Xu, H., Lv, M., and Tian, X. (2009). A review on hemisynthesis, biosynthesis, biological activities, mode of action, and structure-activity relationship of podophyllotoxins: 2003-2007. *Curr. Med. Chem.* 16: 327-349.
- [15] Nawchoo, I.A., and Buth, G. (1995). *Ethnobotany of Ladakh: studies on the traditional medicinal plants and their uses.* *Orient Sci* 1: 23-32.
- [16] Blatter, E., Wathen, G., and Walli, H.J. (1927). *Beautiful flowers of Kashmir.*
- [17] Hooker, J.D. (1875). *The flora of british India (L. Reeve).*
- [18] Wani, S.A., Ashfaq, M., Shah, K., and Singh, D. (2012). Phytochemical screening of methanolic extracts of *Podophyllum hexandrum* Royle and *Rheum emodi* Wall. *J Curr Chem Pharm Sci* 2: 125-128.
- [19] Husain, A. (1993). *Medicinal Plants and their cultivation (Central Institute of Medicinal and Aromatic Plants, Council of*

- Scientific ...).
- [20] Ayres, D.C., Ayres, D.C., and Loike, J.D. (1990). Lignans: chemical, biological and clinical properties (Cambridge university press).
- [21] Shah, Z., Gohar, U.F., Jamshed, I., Mushtaq, A., Mukhtar, H., Zia-Ui-Haq, M., Toma, S.I., Manea, R., Moga, M., and Popovici, B. (2021). Podophyllotoxin: History, Recent Advances and Future Prospects. *Biomolecules* 11. 10.3390/biom11040603.
- [22] Anju, T., Thakur, P., Dutt, V., and Thakur, C. (2010). Conservation of Podophyllum hexandrum through seeds. *Indian Journal of Plant Physiology* 15: 110-116.
- [23] Cheng, H., Qin, L., Lee, S., Fu, X., Richards, D.E., Cao, D., Luo, D., Harberd, N.P., and Peng, J. (2004). Gibberellin regulates *Arabidopsis* floral development via suppression of DELLA protein function. *Development* 131: 1055-1064. 10.1242/dev.00992.
- [24] Dewick, P.M., and Jackson, D.E. (1981). Cytotoxic lignans from Podophyllum, and the nomenclature of aryltetralin lignans. *Phytochemistry* 20: 2277-2280.
- [25] Krishnamurthi, A. (1969). The Wealth of India, Vol. VIII. Publication and Information Directorate. CSIR, New Delhi, Republic of India.
- [26] Chaudhari, S.K., and Yamin Bibi, M.A. (2021). 01. Podophyllum hexandrum: An endangered medicinal plant from Pakistan. *Pure and Applied Biology (PAB)* 3: 19-24.
- [27] Pandey, H., Kumar, A., Palni, L.M.S., and Nandi, S.K. (2015). Podophyllotoxin content in rhizome and root samples of Podophyllum hexandrum Royle populations from Indian Himalayan region. *Journal of Medicinal Plants Research* 9: 320-325.
- [28] Pandey, H., Nandi, S.K., and Palni, L.M.S. (2013). Podophyllotoxin content in leaves and stems of Podophyllum hexandrum Royle from Indian Himalayan region. *J Med Plant Res* 7: 3237-3241.
- [29] Borsche, W., and Niemann, J. (1933). Über Podophyllin. III. Justus Liebigs Annalen der Chemie 502: 264-272.
- [30] Ardalani, H., Avan, A., and Ghayour-Mobarhan, M. (2017). Podophyllotoxin: a novel potential natural anticancer agent. *Avicenna journal of phytomedicine* 7: 285.
- [31] Buss, A., Cox, B., and Waigh, R. (2003). Natural products as leads for new pharmaceuticals. *Burger's medicinal chemistry and drug discovery*: 847-900.
- [32] Ferguson, L.R., and Pearson, A. (1992). Chromosomal changes in Chinese hamster AA8 cells caused by podophyllin, a common treatment for genital warts. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis* 266: 231-239.
- [33] Goel, H., Prasad, J., Sharma, A., and Singh, B. (1998). Antitumour and radioprotective action of Podophyllum hexandrum. *Indian J. Exp. Biol.* 36: 583-587.
- [34] Gupta, D., Arora, R., Garg, A.P., and Goel, H.C. (2003). Radiation protection of

- HepG2 cells by Podophyllum hexandrum Royale. *Mol. Cell. Biochem.* 250: 27-40.
- [35] Gupta, D., Arora, R., Garg, A., and Goel, H. (2004). Radiation protection of mitochondrial system by Podophyllum hexandrum Royale in vivo. *Mol. Cell. Biochem.* 266: 65-77.
- [36] Schacter, L. (1996). Etoposide phosphate: what, why, where, and how? In 6 Suppl 13. pp. 1-7.
- [37] Stahblin, H. (1973). Activity of a new glycosidic lignan derivative (VP 16-213) related to podophyllotoxin in experimental tumors. *European Journal of Cancer* (1965) 9: 215-221.
- [38] Witterland, A., Koks, C., and Beijnen, J. (1996). Etoposide phosphate, the water soluble prodrug of etoposide. *Pharmacy World and Science* 18: 163-170.
- [39] Lewis, N.G., and Davin, L.B. (1999). Lignans: biosynthesis and function. *Comprehensive natural products chemistry* 1: 639-712.
- [40] Wei, J., Chen, J., Ju, P., Ma, L., Chen, L., Ma, W., Zheng, T., Yang, G., and Wang, Y.-X. (2019). Synthesis and biological evaluation of 4 β -n-acetylamino substituted podophyllotoxin derivatives as novel anticancer agents. *Front. Chem.* 7: 253.
- [41] Renouard, S., Lopez, T., Hendrawati, O., Dupre, P., Doussot, J., Falguieres, A., Ferroud, C., Hagege, D., Lamblin, F., and Laine, E. (2011). Podophyllotoxin and deoxypodophyllotoxin in *Juniperus bermudiana* and 12 other *Juniperus* species: Optimization of extraction, method validation, and quantification. *J. Agric. Food Chem.* 59: 8101-8107.
- [42] Nasution, H., Harahap, H., Dalimunthe, N.F., Ginting, M.H.S., Jaafar, M., Tan, O.O., Aruan, H.K., and Herfananda, A.L. (2022). Hydrogel and Effects of Crosslinking Agent on Cellulose-Based Hydrogels: A Review. *Gels* 8: 568.
- [43] Anand, U., Biswas, P., Kumar, V., Ray, D., Ray, P., Loake, V.I., Kandimalla, R., Chaudhary, A., Singh, B., and Routhu, N.K. (2022). Podophyllum hexandrum and its active constituents: Novel radioprotectants. *Biomedicine & Pharmacotherapy* 146: 112555.
- [44] Wani, S.A., Shah, K., and Ahmad, M.A. (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.
- [45] Sharma, A., Bhardwaj, G., Bhardwaj, P., and Cannoo, D.S. (2020). Medicinal Plants of the Trans-Himalayas: India. In *Natural Products of Silk Road Plants*, (CRC Press), pp. 73-103.
- [46] Ganie, S.A., Haq, E., Hamid, A., Qurishi, Y., Mahmood, Z., Zargar, B.A., Masood, A., and Zargar, M.A. (2011). Carbon tetrachloride induced kidney and lung tissue damages and antioxidant activities of the aqueous rhizome extract of Podophyllum hexandrum. *BMC complementary and alternative medicine* 11: 1-10.
- [47] Li, M., Zhou, L., Yang, D., Li, T., and Li,

- W. (2012). Biochemical composition and antioxidant capacity of extracts from *Podophyllum hexandrum* rhizome. *BMC complementary and alternative medicine* 12: 1-8.
- [48] Miyazawa, M., Fukuyama, M., Yoshio, K., Kato, T., and Ishikawa, Y. (1999). Biologically active components against *Drosophila melanogaster* from *Podophyllum hexandrum*. *J. Agric. Food Chem.* 47: 5108-5110.
- [49] Inamori, Y., Kato, Y., Kubo, M., Baba, K., Matsuyama, Y., Sakai, M., and KOZAWA, M. (1983). Mechanisms of insecticidal action of deoxypodophyllotoxin (Anthricin). I. Distribution of deoxypodophyllotoxin in tissues of the 5th instar larvae of silkworm, *Bombyx mori* Linne. *Chemical and Pharmaceutical Bulletin* 31: 4464-4468.
- [50] Prakash, H., Ali, A., Bala, M., and Goel, H.C. (2005). Anti-inflammatory effects of *Podophyllum hexandrum* (RP-1) against lipopolysaccharides induced inflammation in mice. *J Pharm Pharm Sci* 8: 107-114.
- [51] Kumar, D., Rajagopal, M., Akowuah, G.A., Lee, Y.-X., Chong, C.W., Gan, P.W., and Liew, J.C. (2022). Aryltetralin-type Lignan of *Podophyllum*: A Comprehensive Review. *The Natural Products Journal* 12: 19-28.
- [52] Deep, A., Kumar, D., Bansal, N., Narasimhan, B., Marwaha, R.K., and Sharma, P.C. (2023). Understanding mechanistic aspects and therapeutic potential of natural substances as anticancer agents. *Phytomedicine Plus* 3: 100418. <https://doi.org/10.1016/j.phyplu.2023.100418>.
- [53] Huang, T.-S., Lee, C.-C., Chao, Y., Shu, C.-H., Chen, L.-T., Chen, L.-L., Chen, M.-H., Yuan, C.-C., and Whang-Peng, J. (1999). A novel podophyllotoxin-derived compound GL331 is more potent than its congener VP-16 in killing refractory cancer cells. *Pharmaceutical Research* 16: 997-1002.
- [54] You, Y. (2005). Podophyllotoxin derivatives: current synthetic approaches for new anticancer agents. *Curr. Pharm. Des.* 11: 1695-1717.
- [55] Jagdish, S., Joginder, S., and Tewari, V. (2018). Screening and Evaluation of Superior Chemotypes of *Podophyllum hexandrum* Royle from Different Geographical Locations of North-west Himalayas. *Journal of Plant Chemical and Ecophysiology* 3: 1021.
- [56] Seegers, C.L., Setroikromo, R., Tepper, P.G., Horvatovich, P., Peters, R., and Quax, W.J. (2017). Methyl jasmonate treatment increases podophyllotoxin production in *Podophyllum hexandrum* roots under glasshouse conditions. *Plant Soil* 417: 117-126.
- [57] Bhat, M.N., Singh, B., Surmal, O., Singh, B., Shivgotra, V., and Musarella, C.M. (2021). Ethnobotany of the Himalayas: Safeguarding Medical Practices and Traditional Uses of Kashmir Regions. *Biology (Basel)* 10. 10.3390/biology10090851.
- [58] Ballabh, B., and Chaurasia, O.P. (2007).

Traditional medicinal plants of cold desert Ladakh—Used in treatment of cold, cough and fever. *J. Ethnopharmacol.* 112: 341-349.

<https://doi.org/10.1016/j.jep.2007.03.020>.

- [59] Ali, H., Sannai, J., Sher, H., and Rashid, A. (2011). Ethnobotanical profile of some plant resources in Malam Jabba valley of Swat, Pakistan. *J Med Plants Res* 5: 4676-4687.
- [60] Bown, D. (1995). *The Royal Horticultural Society encyclopedia of herbs & their uses* (Dorling Kindersley Limited).