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Paris polyphylla Smith – A critically endangered, highly exploited medicinal plant in the Indian Himalayan region

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ABSTRACT

India, consisting of 15 agro climatic zones, has got a rich heritage of medicinal plants, being used in various folk and other systems of medicine, like Ayurveda, Siddha, Unani and Homoeopathy. However, in growing world herbal market India's share is negligible mainly because of inadequate investment in this sector in terms of research and validation of our old heritage knowledge in the light of modern science. *Paris polyphylla* Smith, a significant species of the genus, has been called as 'jack of all trades' owing its properties of curing a number of diseases from diarrhoea to cancer. The present paper reviews the folk and traditional uses of the numerous varieties *Paris polyphylla* along with the pharmacological value. This may help the researchers especially in India to think about the efficacy and potency of this wonder herb. Due to the importance at commercial level, the rhizomes of this herb are illegally traded out of Indian borders. This illegal exploitation of the species poses a grave danger of extinction of its population if proper steps are not taken for its conservation. Both *in situ* and *ex situ* effective conservation strategies may help the protection of this species as it is at the brink of its extinction.

KEY WORDS: *Paris polyphylla* Smith, Himalayan region, Medicinal, Endangered, Anticancer.

1. INTRODUCTION

Since time immemorial, plant usage has played an important role in the development of mankind and its culture (Petrovska, 2012; Hassan, 2012). Tribal healers used plants for medicinal purposes, either as a whole or extracts. Many plants (including food crops like mint, garlic, turmeric, etc.) are used directly and indirectly as medicines and long term practice leads to the progressive growth of modern medicines, though early uses of treatments are still prevalent today (Tapsell, 2006). Nonetheless, it is no longer limited to indigenous or non-industrialized societies but intensified due to urbanization and globalization in recent few decades. Moreover, non-urbanized folk cultures gained knowledge about its usage and practical implications through steady interactions with the biotic environment. Throughout human history, plants play basic role in medical treatments and such folk medicines are still predominant (Fabricant and Farnsworth, 2001). Indigenous practice has major advantage over modern drugs as it is cost effective in collection and plantations. A large population depends on plant-derived drugs; around 7000 medicinal compounds listed in preparation of modern medicines and drugs are obtained from plants (Caufield, 1991).

Medicinal plants designed to produce new drugs are mostly due to the characteristic effects of secondary metabolites present in plants (Meskin, 2002). Isolation, purification, identification and structure of distinguished chemical compounds found in plants, known as phyto chemistry, specifically describe its secondary metabolites (Doughari, 2012). It includes terpenoids, alkaloids, saponins, polysterols, amines, glucossinolates, flavonoids, cyanogenic glycosides, phenolics, etc. (Sasidharan, 2011). Indefinite number of the pharmaceuticals currently available like aspirin, digoxin, quinine and opium are derived from plants (viz: *Filipendula ulmaria*, *Digitalis purpurea*, *Cinchona officinalis* and *Papaver somniferum*) that have millennia-long history drug information of use as folk herbalism (Swain, 1972).

The Species *Paris polyphylla* Smith: *Paris polyphylla* Smith has manifold local names like *Singpan* by Manipuris, *Satwa* by Garhwalis of Uttarakhand, *Satuwa* by Nepalese is an important member of the genus Paris. It is a perennial herb belonging to the family Melanthiaceae of order Liliales (Stevens, 2001). The word "Paris" is a Latin origin, "pars" which means consistency, often referred to the uniform arrangement of flower and leaves and the word 'polyphylla' poly-many and phyla-leaves (Shah, 2012).

The plants belonging to this species are 10-100 cm tall and are distributed in an altitudinal range between 100-3500 masl (Fig.1). Rhizome 1-2.5 cm thick. Leaves 5-10 (-22); petiole 1-6 cm; leaf blade variable, usually oblong to lanceolate, 6-15(-30) × 0.5-5 cm, base rounded to cuneate. Peduncle 5-24 (-65) cm. Outer tepals (3 or) 4-6 (or 7), green or yellow-green, narrowly ovate-lanceolate to lanceolate, (3-) 4.5-7 (-11) × 1-4 cm; inner ones usually yellow-green, narrowly linear, shorter or longer than outer ones, 1-1.5 (-5) mm wide. Stamens 2 ± as many as outer tepals, (6-) 8-12 (-14) or sometimes more; filaments 4-10 mm; anthers 5-12 mm; free portion of connective usually 0.5-4 mm. Ovary subglobose, ribbed, 1-loculed, sometimes tuberculate. Short style, base enlarged, purple to white; stigma lobes (4or) 5. Capsule globose, sometimes tuberculate. Seeds enveloped by red, succulent aril. Fl. and Fr. Mar-Nov.

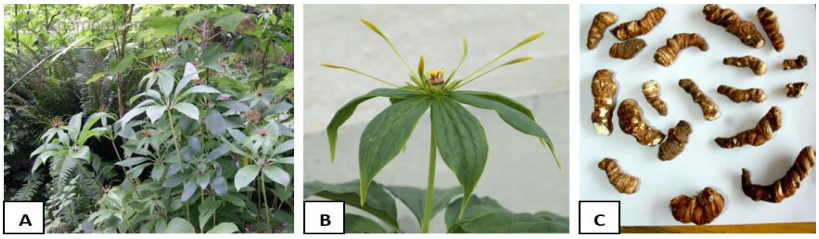

Fig.1. *Paris polyphylla*: (A) Habit, (B) Flower and (C) Rhizome

In recent times, *Paris polyphylla*, was in news in the state of Manipur, India for illegally exporting to China and other South East Asian countries through Myanmar. The local gazette; The Sangai Express and Poknapham reported the massive trading of the rhizome through Indo-Myanmar border by the local traders in the name of 'Zinseng' without knowing its properties and medicinal uses (Shah, 2012; Mao, 2009). A research team working under Natural Resource Data Management System (NRDMS), Department of Science & Technology (DST) witnessed smuggling of the rhizomes in huge quantities in and around Senapati District of Manipur (Imotomba and Devi, 2011).

Habitat and Distribution: *Paris polyphylla* plants are usually found inside deep forests where human interference is minimal. The herb grows well in areas with moist, well-drained soil and usually on slope areas, also, that are usually covered with dry and decayed organic matters and humus rich soil under canopy of forest in full shade to partial shade (Jamir, 2015). It has been found that, in soils, which are rich in nutrients like organic matter, nitrogen and phosphorus the plants of *Paris polyphylla* flourished well. But the potassium content of soil was found to be just the opposite (Madhu, 2010).

The genus is found growing in Europe, East Asia and Himalayan regions (Fig.2). The center of diversity of *Paris* is the Yunnan-Guizhou Plateau, China (Ji, 2006). *Paris polyphylla* is native to China and India. The species is growing in China, Bhutan and Nepal. There are widely known subspecies and varieties of *P. polyphylla* distributed in Bhutan, Laos, Myanmar, Thailand and Vietnam as well (Liang and Soukup, 2000). In India, the species have been recorded from Arunachal Pradesh, Himachal Pradesh, Jammu and Kashmir, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim and Uttarakhand of Indian-Himalayan region (Paul, 2015). In Manipur, where the species is found in abundance, it is found growing in Hengbung, Maram, Purul and Makui regions of Senapati district and Puilong in Tamenglong district.

Fig.2. Distribution of *Paris polyphylla*

Bioactive Compounds: The main chemical constituents of *P. polyphylla* responsible for its huge medicinal properties are the Paris saponins which accounts for more than 80% of the total compounds. These compounds, among them, major part is played by diosgenin. Paris saponin II (diosgenin3-O-α-rha-(1-4)-α-L-rha-(1-4)-[α-L-rha-(1-2)]-β-Dglu), Paris saponin III, diosgenin and C22-methoxy-protodioscin, C22-hydroxyprotodioscin, C22-methoxy-protopolyphyllin I, C22-hydroxyprotopolyphyllin I, C22-methoxy- protopolyphyllin II (Wu, 2004), polyphyllin VI, and polyphyllin VII are other important compounds found in this plant along with Paris saponin I (diosgenin 3-O-α-L-rha-(1-2)-[α-L-arab-(1-4)]-β-D-glu) (Sharma, 2015).

While studying antityrosinase and antileishmanial constituents of *P. polyphylla*, 4 compounds were isolated from its rhizome. Compound I namely 1,5-dihydroxy-7-methoxy-3-methylanthraquinone was reported form the first time (Devkota, 2007).

Polyphyllin A-H are some new saponins isolated from the rhizome of *Paris polyphylla* (Rastogi and Mehtotra, 1993). Out of these, first six are spirostanol steroidal saponins and remaining two are furastanol steroidal saponins. Analysis of polyphyllin group I, II, VI and VII by specific LC-MS-MS technique in the plasma of beagle dog after oral administration of Rhizoma Paridis extracts (RPE), which had recovery, precision, high sensitivity, accuracy and reproducibility (Yina, 2013).

A study to determine the content of minerals in *P. polyphylla* var. *yunnanensis* was carried out. The study proposed that the plant is a worthy source of mineral elements. They reported the presence of 9 mineral elements in the species in order of Ca > K >Mg > Fe > Na > Cu > Mn > Zn > Cr. The minerals might have a relationship with this plant's physiology (Zhang, 2011).

A novel steroidal saponin together with the 12 known compounds from *Paris polyphylla* var. *chinensis* was extracted (Yun, 2007). The novel compound was attained as an amorphous solid and spectral data including two dimensional NMR showed the structure as 3b,21-dihydroxypregnane-5-en-20S-(22,16)-lactone-1-O-a-L-rhamnopyranosyl(1®2)-[b-D-xylopyranosyl(1®3)]-b-D-glucopyranoside. The 12 known compounds are identified steroids and their structures were recognized by 13C NMR spectrum (in pyridine-d5). These compounds were named as:

a) Diosgenin,
b) Pennogenin,
c) Diosgenin-3-*O*-a-L-rhamnopyranosyl(1→2)-b-D-glucopyranoside,
d) Pennogenin-3-*O*-a-L-rhamnopyranosyl(1→2)-b-D-glucopyranoside,
e) Diosgenin-3-*O*-a-L-rhamnopyranosyl(1→2)-[a-L-arabinofuranosyl(1→4)]-b D-glucopyranoside,
f) Pennogenin-3-*O*-a-Lrhamnopyranosyl(1→2)-[a-L-arabinofuranosyl(1→4)]-b D-glucopyranoside,
g) diosgenin-3-*O*-a -L-rhamnopyranosyl(1→2)-[b-D-glucopyranoside(1→3)]-b-D-glucopyranoside,
h) Diosgenin-3-*O*-a-L-rhamnopyranosyl(1→4)-a-L-rhamnopyranosyl(1→4)-[a-L-rhamnopyranosyl(1→2)]-b-D-glucopyranoside,
i) pennogenin-3-*O*-a-L-rhamnopyranosyl(1→4)-a-L-rhamnopyranosyl(1→4)-[a-L-rhamnopyranosyl(1→2)]-b-D-glucopyranoside,
j) 3-*O*-a-L-arabinofuranosyl(1→4)-[a-L-rhamnopyranosyl(1→2)]-b-D-glucopyranoside-b-D-chacotriosyl-26-*O*-b-D-glucopyranoside,
k) 2b,3b,14a,20b,22a,25bhexahydroxycholest-7-en-6-one, and
l) 2b,3b,14a,20b,24b,25bhexahydroxycholest-7-en-6-one

Recently, a total of ten chemical compounds have been reported from the aerial parts of *P. polyphylla* var. *chinensis* (Yin, 2015). The compounds were identified as: β-sitosterol; ergosta-7, 22-dien-3-one; β-ecdysone; kaempferol; daucosterol; luteolin; calonysterone; luteolin-7-O-glucoside; quercetin; and 3β, 5α, 9α-trihydroxyergosta-7, 22dien-6-one.

Compounds 2, 6 and 10 were isolated from *Paris polyphylla* var. *chinensis* for the first time.

Quite recently, two new highly oxygenated spirostanol saponins from *P. polyphylla* var. *stenophylla* have been reported (Jin, 2016). These two compounds, namely paristenoside A and paristenoside B were isolated from the rhizome of the species together with seven other known compounds.

Phytomedicinal Properties:

Anti-cancer (Table.1)**:** The extracts of rhizome induce apoptosis, affect cell cycle distribution, inhibit angiogenesis and regulate immune function.

Table.1. Some reports on the various anti cancerous uses of *Paris polyphylla* Sm.

Type of disease	Description	Reference
Cervical cancer	*Paris* saponin I had more potent and selective cytotoxic effects on tumor cell lines promoting dramatic apoptosis in SKOV3 cells in a time- and dose-dependent manner.	Xiao, 2009; Zhang, 2014
Ovarian cancer	Polyphyllin D has *in vitro* cytotoxicity against ovarian cancer cells. This enhances the effect of cisplatin, and its activity is influenced by the expression of CLDN4 genes.	Al Sawah, 2015; Yang, 2015
Glial cell cancer	Polyphyllin D inhibit U87 glioma cell proliferation and reduces cell viability.PolyphyllinD downregulateBcl-2 protein expression and upregulateBax and caspase-3 protein expression which leads to induction of apoptosis in U87 glioma cells.	Yu, 2014
Chondrosarcoma	Methanol extracts of *P. polyphylla* showed particular potential as anticancer agents, demonstrating effective apoptosis induction activity on human chondrosarcoma SW 1353 cells, while normal chondrocytes show less effect.	Ruamrungsri, 2016
Nasopharyngeal carcinoma	Tri-terpenoid saponins from rhizomes of *Paris polyphylla* show cytotoxic activities against human nasopharyngeal carcinoma epithelial cells. These compounds exhibited inhibitory effects on nasopharyngeal carcinoma epithelial cells growth with IC50 values of 16.53, 16.77, and 12.69 μm, respectively.	Wu, 2012; 2013
Gastric cancer	The 12 isolated steroidal compounds from rhizome of *P. polyphylla* show cytotoxic activity on human gastric cancer cell lines HepG2, SGC7901, BxPC3.	Sun, 2007; Shah, 2012

Colon adenocarcinoma	*P. polyphylla* showed a predominant inhibitory effect on human colon adenocarcinoma cell lines (LoVo and SW-116) with IC50 values ranging from 10µg/ml to 30µg/ml in ethanol extract.	Sun, 2007
Esophageal cancer	*P. polyphylla* extract inhibited the growth and proliferation on esophageal cancer ECA109 cells.	Sun, 2007; Li, 2012
Leukemia	Two new furo-stanolsaponins and one new spiro-stanolsaponin isolated from the rhizome of *P. polyphylla*var. *yunnanensis* together with18 known steroidal saponins showed high cytotoxicity against HL-60 human promyelocytic leukemia cells.	Zhao, 2008; Wu, 2014; Yang, 2016
Breast cancer	Apoptosis through mitochondria dysfunction has also been reported to be carried out by Polyphyllin D. Daily dosage of polyphyllin D (2.73 mg/kg body weight) through ten days in nude mice efficiently lessened tumor growth for 50% without any significant toxicity in liver and heart to the host.	He, 2015; Sharma, 2015
Osteosarcoma	Polyphyllin I down-regulates integral proteins involved in epithelial-mesenchymal transition (Vimentin, Snail, Slug) and up-regulates E-cadherin resulting in apoptosis of osteosarcoma cells.	Chang, 2015
Lung cancer	*Paris polyphylla* steroidal saponin inhibit lung cancer cell adhesion, migration and invasion, the mechanism underlying was attributed to attenuation of the activity and expression of MMP-2 and MMP-9.	He, 2014; Kumar, 2014; Li, 2013; Lin, 2015; Zhang, 2015
Liver cancer	Avoiding of drug resistance and apoptosis in liver cancer HepG2, R-HepG2, cells by Polyphyllin D and dioscin has also been reported.	Cheung, 2005; Sun, 2007; Gao, 2011; Zhu, 2011; Han, 2015; Man, 2015; Zhang, 2016

Anti-Leishmania: The extracts, compounds and fractions of *Paris polyphylla* showed mild to moderate anti-leishmanial activities (Devkota, 2007; Atta-ur-Rahman, 2008; Shah, 2012).

Haemostatic activity: A study on the comparative haemostatic, cytotoxic and haemolytic activity of six *Paris* species (*P. polyphylla* var. *yunnanensis*, *P. delavayi* var. *delavayi*, *P. fargesii* var. *fargesii*, *P. bashanensis*, *P. polyphylla*var. *minora*, and *P. polyphylla* var. *pseudothibetica*) reported that all species except *P. fargesii* var. *fargesii* exhibited the haemostatic activity in a wider range. He concluded that *P. delavayi* var. *delavayi* and *P. bashanensis* could be used as the resources of hemostatic drugs and *P. fargesii* var. *fargesii* as the antitumor medicine (Liu and Ji, 2012).

Anthelmintic: *In vitro* anthelmintic activity of steroidal saponins from the rhizomes of *Paris polyphylla* was reported for the first time in 2010 (Wang, 2010). The extract and the isolated compounds are potential natural agents for the control of *Dactylogyrus intermedius* infestation. Formosanin C and polyphyllin VII showed significant anthelmintic activity against serious infection caused by *Dactylogyrus* (Li, 2013).

Alzheimer's disease: Exogenous stimulator, diosgenin, activates very critical signaling target for anti-Alzheimer's disease therapy, the 1,25D3-MARRS pathway. Diosgenin is a memory-enhancing drug and its administration increased the object detection memory deficit and reduced several signs of neuronal degeneration including presynaptic disintegration combined with amyloid plaques in the cortex, axonal degeneration associated with amyloid plaques in the cortex, hippocampus and cortex and PHF-tau expression associated with and distal to amyloid plaques in the cortex and hippocampus (Tohda, 2012).

Immuno-stimulating properties: Diosgenyl saponins having the presence of glucoside moieties is needed for the commencement of immunological reactions, particularly during the period of oxygen expenditure such as in the process including microbial activity and inflammation although diosgenin could only stimulate the macrophages phagocytosis including elimination of foreign or denatured matter. The three diosgenyl saponins isolated from *P. polyphylla* stimulates the activities of phagocytosis, respiratory burst, and nitric oxide production. These saponins with sugar moiety possess immunomodulatory activities (Zhang, 2007).

Anti- tyrosinase activity: *Paris polyphylla* is used for the treatment of some skin-related disorders associated with melanin hyper pigmentation. It has been reported that activity of enzyme tyrosinase was inhibited by chloroform, ethyl acetate, and butanol extracts of the plant (Devkota, 2007).

Anti-bacterial action: Volatile oils present in *Paris polyphylla* show strong inhibitory effects on *Micrococcus, Xanthomonas, Aerobacter* and *Brevibacterium* (Zhao, 2009; Liu, 2014). The roots have shown anti-bacterial action against *Bacillus* spp., *B. typhi, B. paratyphi, E. coli, Staphylacoccus aureas, Haemolytic streptococci, Meningococci,*

etc. (Sharma, 2015). It has been reported that 25 compounds are present in stem and leaves of *P. polyphylla.* Out of these 25, 11 compounds showed potent antibacterial activity against *Propionibacterium acnes* (Qin, 2012).

A study carried out on antibacterial activity of *P. polyphylla* reported that extracts of the aerial parts are active against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *E. coli* and *Salmonella flexinerai* whereas, rhizome extract was active only against *S. aureus* (Chhetri, 2012).

Spermicidal action: The plant extract showed effective spermicidal activity against rat and human sperms. The vaginal application of the plant's extract (100mg/animal) prevented pregnancy upto 60% of the rabbits tested (Pande, 2007). Rhizome extract of the various species of *Paris* showed significant spermicidal activity (Zhang, 2012).

Anti-Fungal: A new steroidal saponin along with two other known compounds isolated from the rhizomes of *P. Polyphylla* showed antifungal activity against *Cladosporium cladosporioides, Magnaporthe oryzae* and various strains of *Candida albicans* (Deng, 2008; Zhang, 2011). The three pennogenin steroidal saponins isolated from the plant exhibit moderate antifungal activities against *Saccharomyces cerevisiae* and *Candida albicans* (Zhu, 2011).

Antiviral: A study on *in vitro* activity of *P. polyphylla* against Enterovirus 71 (EV71) and Coxsackie virus B3 (CVB3) was carried out (Wang et al., 2011). They reported the prevention of viral infection, viral inactivation, and anti-viral replication effects of the species extract in 95% ethanol against both EV71 and CVB3. The anti-viral replication effect was found to be more perceptible (Wang, 2016).

Antiviral activity of *Paris polyphylla* saponin I on influenza A virus both *in vitro* and *in vivo* has also been reported (Pu, 2015). It was further revealed that *P. polyphylla* saponin I, at a dose of 5 and 10 mg/kg, prolonged the survival rate of mice, infected with influenza A virus, from 8 to 13 days.

Uterine contractile activity: Abnormal uterine bleeding (AUB) is one of the major fields of concern for gynecologists worldwide. Some spirostanol glycosides representing a new type of contractile agonist were recently isolated from *Paris polyphylla*.

The total steroidal saponins from the rhizome extract of *Paris polyphylla* var. *yunnanensis* shows uterotonic activity justifying their usage in the therapy of AUB. It was reported that Pennogenin-3-*O*-α-L-arabinofuranosyl (1→4)[α-L-rhamnopyranosyl(1→2)]-β-D-glucopyranoside (PARG), identified in TSSP, was responsible for the stimulation of myometrial contractions (Guo, 2008).

2. CONCLUSION

The IUCN and CAMP listed *Paris polyphylla* Sm. as vulnerable medicinal plant (Anonymous, 2001). Seed viability has been found to be low and the seeds did not germinate in laboratory conditions even under different chemical treatments. People living in areas where this plant grows should be apprehended the value of its product (Madhu, 2010). Random collection by uprooting the young or mature plant which sprouted from either from seeds or fragmented rhizomes is one of the key factors for downsizing the population of *P. polyphylla* (Jamir, 2015).

With so much of work and researches done on the different aspects and potentials of *Paris polyphylla* in China, not many works pertaining to the medicinal properties and other, of this plant has been reported from India. Since the seed viability of the plant is very low, almost nil, the tissue culture studies should be taken for this medicinal herb. We have already started to work on the micro-propagation of this plant using different explants. The need of the hour is for the scientific community to draw their attention to this wonder herb.

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