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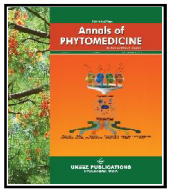

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A review on the importance of two medicinal plants of North East India: *Paris polyphylla* Smith and *Kaempheria parviflora* Wall. ex Baker

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Abstract

Paris polyphylla Smith and *Kaemperia parviflora* Wall ex Baker are two important medicinal plants, found mainly in the north eastern parts of India. These rhizomatic plants are in great demands and extracted injudiciously from the wild. The rhizome is the economic part which is used for its various medicinal properties. The present article gives an account of updated information on its phytochemical, pharmacological properties, its ethnomedicinal uses and their conservation aspects in the region. The review reveals that a wide numbers of phytochemical constituents have been isolated from these plants. The rhizomes of the several species of the genus Paris have been used as haemostatic and anti-inflammatory agent to treat traumatic injuries, snake bites, abscess, parotitis and mastitis. The rhizome of *K. parviflora* has several uses in treating various ailments including gastrointestinal disorders, fungal infections, allergies and alleviate male impotence, antiallergic, anti-inflammatory, antifungal, antiplasmodial, antimycobacterial, anti HIV-1, antispasmodic effects, *etc*. For the last few decades or so, extensive research work has been done to prove its biological activities and pharmacology of its extracts. Excessive injudicious collection and harvesting from the wild has pushed these species towards extinction. Domestication, cultivation and strict laws are the need of the hour to save these species from extinction.

1. Introduction

The traditional knowledge of utilization of plants and herbs as medicine is passed on from generations till today. The use of plants and herbs for medicinal purposes has been documented from many tribal communities. Plant and plant based traditional system of healthcare has been practiced in many parts of the world and the knowledge is slowly getting lost in the modern society (Aziz *et al*., 2016; Aziz *et al*., 2017; Mahmood *et al*., 2011). In India, the sacred Vedas give many references of medicinal plants used in our country for the last many centuries. Due to its fewer side effects as compared to allopathic drugs, there has been a tremendous increase in the demand of plant based health products in developing as well as developed countries, resulting in popularity of herbal products and medicine around the world. It is estimated that about 80% of the world population residing in the rural areas of the developing and under developed countries greatly rely mainly on medicinal plants and its extracts in the absence of affordable and accessible source of primary healthcare system (WHO, 2002). It is well known that plants play a significant role as a raw material source for various AYUSH-medicine formulations (https://main.ayush.gov.in). A more practical, productive and easily accessible source of medicine are the common medicinal herbs (Husain, 2021). Use of traditional herbs regularly improves immunity, fights many ailments, rejuvenates the body and age associated disorders. They have the potential to combat chronic conditions such as hypertension, high cholesterol, diabetes, AIDS, influenza, a persistent cold or cough, infections, chronic fatigue, and inflammatory conditions (Ansari and Ahmad, 2019). It is believed that many people still treat themselves with traditional medicines made from plants, herbs and spices. The WHO, which launched the traditional medicine strategy (2014-2023) with the goal of maintaining global population health by prioritizing the use of traditional and complementary medicines, has also acknowledged the importance of herbal medicine. Scientists are now conducting research on a variety of spices and herbs to provide a rational explanation for their use in the treatment and prevention of common illnesses (Mehrotra, 2021). Traditional medicine system of Ayurveda, Siddha and Unani has been existed in our country for centuries and plants are mentioned as a medicine in ancient texts like the Rig veda and the Atharva veda (2000 BC) (Warrier, 2021).

Many modern allopathic drugs and compounds are extracted from plants and also the modern medicine and pharmaceutical companies rely on plants for many important and novel drugs. The development

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of biomedicine, which has achieved wonders in medicine, has been greatly supported by the enormous advancements made by investigative biochemistry, electronics and other scientific fields. But, it also resulted into extra ordinary shoot up in costs of these advance medicines and putting it away from the grasp of the most of the world's population (Sharma, 2021). Many plants and plant products are evaluated and analysed based on their traditional uses for the development or discovery of new and novel drugs and compounds. Continuously unsustainable and injudicious extractions of these plants from their natural habitat have pushed some of the important species towards extinction. With the increase in world population and urbanization a rapid loss in medicinal plant species and knowledge seems to be inevitable in the near future. Citing an example, *Taxus wallichiana* Zucc., an important medicinal plant has pushed towards extinction due to unsustainable extraction from the wild after the discovery of its efficacy in cancer treatment. It contains a very important chemical, paclitaxel (taxol), one of the most effective drugs used for a variety of cancers (Cragg and donal, 1993; Goldspiel, 1997). In recognition of its anticancerous properties during 1980s the species has suffered large scale unsustainable extraction, which led to its present status (Paul *et al.*, 2013). IUCN has documented this plant as one of the most threatened species (Thomas and Farjon, 2011). Presently, many plant species comes under threatened and endangered category due over harvesting and injudicious collection from the wild. In this review, two endangered medicinal plant species; namely, *P. polyphylla* and *K. parviflora* found in North eastern part of India is taken up. *P. polyphylla* Smith and *K. parviflora* are two important medicinal plants found mainly in the north eastern parts of India (Gajurel *et.al.*, 2015; Devi *et. al.*, 2016). These plants are economically very important for the region and have high demand but they are very less documented.

2. *Paris polyphylla* Smith

P. polyphylla is a herbaceous plant belonging to Melanthiaceae family. The plant is found in many parts of Asia and Europe (two species). In Asia, it is mainly found in Indo-China region and South East Asia region and 24 species with 12 endemic species are reported to be found in China alone. Two species; namely, *P. polyphylla* and *P. thibetica* with about 6 intraspecific taxa are found in India (Liang and Soukup, 2000).

Several species of Paris as per World checklist of selected plant families (WCSP) are given below (Govaerts, 2011; Liang *et al.*, 2012).

- *P. polyphylla* var. *alba*
- *P. polyphylla* var. *chinensis*
- *P. polyphylla* var. *latifolia*
- *P. polyphylla* var. *nana*
- *P. polyphylla* var. *panxiensis*
- *P. polyphylla* var. *polyphylla*
- *P. polyphylla* var. *stenophyla*
- *P. polyphylla* var. *yunnanensis*

Five additional varieties were also identified by The flora of China, three of which are placed in different species by the WCSP:

- P. polyphylla var. *appendiculata=P. thibetica*
- *P. polyphylla* var. *brachystemon=P. polyphylla var. stenophyla*
- *P. polyphylla* var. *kwantungensis=P. polyphylla var. polyphylla*
- *P. polyphylla* var. *minor=P. delavayi*
- *P. polyphylla* var. *pseudothibetica=P. delavayi*

P. polyphylla is an erect, perennial, herbaceous plant with unbranched shoot. The shoot contains a single stem-like structure and 2 to 3 whorls of leaves. The underground part is a rhizome with nodes. The flowering period starts in April and May last up to three months. It has odd flowers with long yellow radiating anthers (Shah *et al.*, 2012). The stems are smooth and 50-100 cm in height with a diameter of 1-2.5 cm in diameter. The leaves are simple and arranged in whorls; petiolate, lanceolate and reticulate with 3 primary veins. The flowers are solitary and hermaphrodite borne at the axial terminal. The flowers are yellowish green in colour and the outer sepaloid is larger than the inner with 3-5 tepals. The androecium is free containing 6-11 stamens. The gynoecium contains only one pistil and 3-5 carpels; syncarpous and superior, ovary. The seeds are reddish orange in colour and a mature fruit contains about 50-60 seeds (Puwein and Thomas, 2020). In North East region the flowers start blooming in the month of April and lasts upto 3 months.

Figure 1: *P. polyphylla* plant and rhizome.

P. polyphylla is a shade loving plant which grows luxuriously under the forest canopy of more than 80% shade at an altitude of 1200-3000 msl. Its natural habitats are mainly thick moist forest understory (Liang *et al.*, 2000). Germination is very slow in this species and usually needs 7-8 months to sprout from the seed. It is best suited in humus rich and well drained soil and waterlogging detrimental for this plant. The seeds failed to germinate or grow well or failed to flower or set seed when tried to grow in other environment out of the natural habitat. The growth of this plant is very slow and takes many years (5-7 years) to have mature and economical rhizomes. The slow growth nature of the plant makes it vulnerable to extinction from its natural habitat.

2.1 Ethnomedicinal uses

This plant has many traditional medicinal uses in many countries. This plant is very popular in China and Nepal for its medicinal properties. Some of the traditional uses are as analgesic, diphtheria, boils, removes heat, antispasmodic, depurative stomach ache, appendicitis, Japanese B encephalitis, snake bites, antitussive, ulcers, insect bites, tonsillitis, *etc.* ((Farooquee *et al.*, 2004; Maity *et al.*, 2004; Tiwari *et al.*, 2010; Jamir *et al.*, 2012; Lalsangluaii *et al.*, 2013; Pfoze *et al.*, 2013; Mir *et al.*, 2014; Sharma and Samant 2014). In North East India, the leaves and rhizome is used for treating diabetes, stomachache, stomach worms and as tonic.

2.2 Pharmacology

Numerous pharmacological studies showed that compounds and extracts from this plant have a wide range of pharmacological effects, including antitumor, cytotoxic, antimicrobial, antifungal, hemostatic and anti-inflammatory properties. According to the evaluations of toxicity, *Rhizome paridis* may cause mild liver damage (Ding *et.al.*, 2021).

2.2.1 Antitumour activity

Polyphyllin D, which is a steroidal saponin from *P. polyphylla* is a potential drug for breast cancer treatment (Lee *et al.*, 2005). Treatment of MCF-7 and MDA-MB-231 cells with polyphyllin D resulted in the inhibition of viability and induction of apoptosis. It was reported that main steroidal saponin of *P. polyphylla i.e.* {Diosgenin-3-a-L-arabinfuranosyl (1-4)-[a-L-rhamnopyanosyl (1-2)]-ß-D-Glycopyranoside} is found to have cytotoxicity and caused typical apoptosis (Yan *et al.*, 2009). Anticancer activity against lung adenocarcinoma cell lines were observed when treated with *Rhizoma paridis* saponins, both *in vivo* and *in vitro*. It was also found that *P. polyphylla* showed inhibitory effect on all the cell lines with IC_{50} values ranging from 10/µg/ml to 30/µg/ml which shows its effectiveness against digestive cancer (Sun *et al.*, 2007). Wang *et al.* (2007) isolated antitumour constituents from *P. polyphylla* var. yunanensis by column chromatography with silica gel which are given below:

i. Diosgenin-3-O- a -L- arabinofuranosyl (1-4) ß-D-glycopyranoside
ii. Pennogenin-3-O-a -L- arabinofuranosyl (1-4) ß-D-glycopyranoside
iii. Isorhamnetin-3-O- ß -D- glycopyranoside
iv. Ethyl - a -D-fructofuranoside
v. Pennogenin-3-O-a-L-rhamnopyranosyl(1-4)[a-L-rhamnopyranosyl(1-2)]ß-D-glycopyranoside
vi. Pennogenin-3-O-a-L-rhamnopyranosyl (1-4)[a -L- rhamnopyranosyl (1-4)] a -L-[a -L-
vii. Rhamnopyranosyl (1-2)] b-D-glycopyranoside

2.2.2 Immunostimulating properties

It was reported that the compounds (1) 3 -O- a -1 - rhamnopyranosyl (1-4) - a -1-rhamnopyranosyl (1-4)-[a-1-rhamnopyranosyl (1-2)- a -d-glucopyranoside, (2) Diosgenin-3-O-a-1- rhamnopyranosyl (1-2)- a -1-arabinofuranosyl- b- d-glucopyranoside and (3) Diosgenin from *P. polyphylla* showed phagocytic activity, respiratory burst and no production in RAW 264.7 (Zhang *et al.*, 2007).

2.2.3 Antibacterial action

The rhizomes of *P. polyphylla* have antibacterial action against various bacteria like *Bacillus dysentery, B. typhi, B. paratyphi, E. coli, Staphylacoccus aureas, Haemolytic streptococci* and *Meningococci* (Anon, 2002). Mayirnao and Bhat (2017) found that the rhizome extract of *P. polyphylla* species had significant antimicrobial activity. At a concentration of 5 mg/ml of the sample, 95-97% of *E. coli, S. aureus* and *A. niger* growth were inhibited, while 74% of *T. reesei* were found to be inhibited. *Bacillus dysentery, B. paratyphi, B. typhi, Staphylacoccus aureas, Escherichia coli, Haemolytic streptococci* and *Meningococci* were found to be inhibited by the rhizomes of *P. polyphylla* (Sharma *et al.*, 2015).

2.2.4 Spermicidal action

Plant extract of *P. polyphylla* was found to be effective as spermicidal. The application of the plant's extract (100 mg/ animal) on vagina prevented pregnancy upto 60% on the tested subjects (Devkota, 2005). Effective spermicidal activity was demonstrated by the plant extracts of *P. polyphylla* against rat and human sperm. When tested on rabbits, it prevented pregnancy by as much as 60% (Pande *et al.*, 2007).

2.2.5 Antifungal

Antifungal activity of *P. polyphylla* saponin has been reported effective against *Cladosporium cladosporioides* and Candida species (Deng *et al.*, 2008). *P. polyphylla* var. *yunnanensis* was effective against *Candida albicans*, *Cladosporium cladosporioides* and *Saccharomyces cerevisiae* Meyen ex E.C. Hansen (Sharma *et al.*, 2015). Others a-paristypnin extracted from *P. polyphylla* is found to have a depressant action on carotid pressure, myocardium and respiratory movements. It also affects vasodilation in the spleen and limbs, vasoconstriction in kidney and stimulation in the intestines (Devkota *et al.*, 2005).

2.3 Chemical composition

Devkota *et al.* (2005) had isolated 6 (six) compounds from *P. polyphylla* collected from Parbat district of Nepal. The compounds are:

i. Przewalskinone B
ii. Polyphyllin C
iii. Polyphyllin D
iv. Saponin-1
v. Stigmasterol
vi. Stigmasterol-3-O- ß -D-glucoside.

A new saponin, Saponin-polyphyllin A-H has been isolated from the rhizome of *P. polyphylla* (Rastogi and Mehrotra, 1993). A novel steroidal saponin along with the 12 known compounds from *P. polyphylla* var. chinensis was also separated from *P. polyphylla* (Yun *et al.*, 2007).

i. Diosgenin
ii. Pennogenin
iii. Diosgenin-3-O-a-L-rhamnopyranosyl (1 → 2)-b-D-glucopyranoside
iv. Pennogenin-3-O-a-L-rhamnopyranosyl(1 → 2)-b-D-glucopyranoside
v. Diosgenin-3-O-a-L-rhamnopyranosyl (1 2)[a-Larabinofuranosyl (1 → 4)]-b-D-glucopyranoside
vi. Pennogenin-3-O-a-Lrhamnopyranosyl (1 → 2)-[a-Larabinofuranosyl (1 → 4)]-b-D-glucopyranoside
vii. Diosgenin-3-O-a -L-rhamnopyranosyl (1 → 2) [b-Dglucopyranoside (1 → 3)]-b-D-glucopyranoside

viii. Diosgenin-3-O-a-L-rhamnopyranosyl (1 → 4)-a-Lrhamnopyranosyl (1 4)[a-L-rhamnopyranosyl (1 → 2)]-b-D-glucopyranoside

ix. Pennogenin-3-O-a-Lrhamnopyranosyl (1 → 4)-a-Lrhamnopyranosyl (1 → 4) [a-L–rhamnopyranosyl (1 → 2)]-b-D-glucopyranoside

x. 3-O-a-Larabinofuranosyl(1 4)[a-Lrhamnopyranosyl (1 → 2)]-b-D-glucopyranoside

xi. b-D-chacotriosyl-26-O-b- D-glucopyranoside

xii. 2b,3b,14a,20b,22a,25b hexahydroxycholest- 7-en-6-one, and

xiii. 2b,3b,14a,20b,24b,25b hexahydroxycholest-7-en-6-one

2.4 Propagation

P. polyphylla grows best in moist humus rich soil under partial or complete shade as in jungle understory. Propagation by seed is a big problem due to its long seed dormancy and slow germination. The best way to propagate this plant is by rhizome or rhizome cuttings. Rhizomes from the wild are collected and used for propagation as well as for medicinal purposes. This leads to a great decline of the herb population. Excessive illegal harvesting and collection for many years has pushed this species towards extinction (Zhang *et al*., 2011). Matured rhizomes can only be harvested economically after 5-7 years and which is one of the main reasons for the shortage of this plant. Fully economical plant can only be harvested after growing for 5-7 years, which aggravates the shortage of its resources (Wen *et al*., 2012). In order to conserve this species from extinction, a successful propagation method is the need of the hour (Jianjun *et al*., 2013). There is an urgent need to discover alternate ways to produce propagules and cultivation methods. A systematic domestication and cultivation method on large scale is really needed for conserving this species and a sustainable supply of this plant material in the market. Rhizome cuttings and tissue cultured planting materials are the prospective methods of propagation of this threatened species.

2.5 Conservation

P. polyphylla is one of the medicinal plants listed as vulnerable by the IUCN (Madhu *et al.*, 2010). This plant has a long seed dormancy period and the germination of the seed takes lots of time. There is difficulty in germination of the seeds under laboratory conditions with different treatments. The growth of the rhizome is very slow and takes almost a year to increase its node number. In addition to its slow growth rate and long dormancy period, the fate of this precious plant is sealed with the increase in its demand, overharvesting, unsustainable collection of rhizomes, harvesting of plants before seed maturity and the increase in urbanization and construction of roads, rail tracks and deforestation. The whole plant, either matured or immature, is often uprooted at the time of harvesting, thereby killing the whole plant. This unsustainable harvesting practice, combined with illegal/cross-border trades of rhizome, deforestation and loss of habitat are common as a result the species is vanishing day-by-day. Market driven collection has pushed to a greedy and unsustainable collection and habitat degradation. Cultivation of the species coupled with *in situ* conservation could be a solution to address the escalated herbal demand (Cunningham *et al*., 2018).

The College of Horticulture and Forestry, Central Agricultural University, Pasighat, Arunachal Pradesh, India has started the work on micropropagation of this plant species by tissue culture method for the conservation of this vulnerable species. Tissue cultured plants are produced from rhizomes in the laboratory of College of Horticulture and Forestry, Pasighat, Arunachal Pradesh. The plants will be planted in the wild that it can flourish and increases its population in nature away from human disturbance.

3. *Kaemperia parviflora* Wall. ex Baker

K. parviflora commonly known as 'Black galingale', is an important herbaceous plant which is rhizomatous in nature. It belongs to Zingiberaceae family and it has high medicinal value (Techaprasan *et al.*, 2010). The rhizomes are the economical part and it is mainly cultivated for its various medicinal properties. They have been widely used in traditional medicines to cure fevers, hypertension, metabolic disorders, inflammation, urinary tract infections, coughs, erectile, dysfunction, abdominal and gastrointestinal ailments, asthma, wounds, rheumatism, epilepsy, and skin diseases (Abdelsamed *et al.*, 2019). More than 60 species of Kaempferia species are distributed from India to Southeast Asia, whereas, Thailand has the richest Kaempheria biodiversity with more than 20 different species (Sirirugsa, 1992; Larsen and Larsen *et al.*, 2006). The rhizomes are popularly added as a flavoring agent in local cuisine and also used as traditional medicine for a wide range of ailments in Thailand (Sutthanut *et al.*, 2007; Konkumnerd *et al.*, 2010). The genus *Kaempferia* is subdivided into two sub-genera: *K. subgen. Kaempferia* and subgen. *Protanthium* (Horan.) Baker based on the positioning of the inflorescence. *Kaempferia* subgen. *Kaempferia* produces terminal inflorescences while the subgen. *Protanthium* produces the inflorescences directly from the rhizome (Saensouk *et al.*, 2021).

It is a perennial herb with reddish black rhizome. It has thin ovate green leaves with a dimension of 13.5-23.2 cm × 9.3-13.5 cm. The petioles are 9-10 cm in length. The inflorescence is pedunculate and 5.1-5.4 cm in length. The flowers are sessile and white with purple tinged colour. The bracts are lanceolate and slightly greenish in colour measuring 1.4-1.7 × 3- 3.5 cm in size. Calyx is white (2.4 × 0.7 cm) and corolla lobes are linear white (1.5 cm). Staminodes are lateral, linear, white in colour measuring 1.1 × 0.3 cm. Labellum is white tinged with purple at the base and lip is lilac in colour, obovate, cuneate, bifid and 1.2 × 0.8 cm in size. Anthers are sessile, crested and 0.4 × 0.1 cm long. Stigma is 4.2 cm in size and the ovary is velutinous, trilocular and elliptic in shape (Devi *et al.*, 2016).

Figure 2: *K. parviflora* plant and rhizome.

In Thailand, the rhizomes of this plant are widely used as a flavoring agent and as a traditional medicine for a wide range of ailments (Sutthanut *et al.,* 2007; Konkumnerd *et al.,* 2010). *K. parviflora* is also used as an aphrodisiac, to treat colic disorder, peptic and duodenal ulcers, to lower blood glucose levels, improve blood circulation and to increase vitality (Yenjai *et al*., 2004, Akase *et al.,* 2011). Numerous pharmacological studies have been prompted by the recognition of high potential of this plant for the development of various health products (Chivapat *et al.,* 2010).

3.1 Pharmacology

K. parviflora has many medicinal uses and found to be effective against knee osteoarthritis, inhibition of a breast cancer resistance protein (BCRP), wound healing, antidrug resistant strains of *Mycobacterium tuberculosis*, neuroprotective, antinociceptive, human immunodeficiency virus type-1 (HIV-1) inhibitory activity, *in vitro* antiallergenic, and larvicidal activity against *Aedes aegypti* are some of the pharmacological properties of this plant. The following is a list of some of the reported biological activities of *Kaempheria* plant and its extracts (Ekor, 2013; Techaprasan *et al.,* 2010; Wutythamawech, 1997; Yenjai *et al.,* 2004; Akase *et al.,* 2011; Nakao *et al.,* 2011; Sivarajan and Balachandran, 1994; Hidaka *et al*., 2017).

3.1.1 Anticancer activity

The ethanol extract of *K. parviflora* suppresses the PI3K/AKT and MAPK signalling pathways, which in turn promotes cell apoptosis in HeLa cells from cervical cancer patients. HeLa cell invasion and migration are also prevented by *K. parviflora*. This could have something to do with the inhibition of MMP-2 expression. It has been demonstrated that the ethanol extract of *K. parviflora* has an effect on human cholangiocarcinoma cell lines (HuCCA-1 and RMCCA-1) with CC_{50} values of 46.1 g/ml and 62.0 g/ml, respectively. During cancer treatment, the ATP-binding cassette (ABC) protein P-glycoprotein (P-gp) extrudes multiple chemotherapeutic agents, resulting in multidrug resistance. It was discovered that the ethanol extract of *K. parviflora* and compound-1 increased the accumulation of rhodamine 123 and daunorubicin, which are the substrates of P-gp (Patanasethanont *et al.,* 2007). Multidrug resistance may also be caused by the multidrug resistance associated proteins (MRPs), such as MRP-1, -2, and -3.Unlike the usual P-gp inhibitor, verapamil, MRPs inhibitors can significantly increase the accumulation of calcerin, a MRPs substrate. By inhibiting MRP functions, it was discovered that the ethanol extract of *K. parviflora* and the methoxyflavones increased the dose-dependent accumulation of calcein and doxorubicin in A549 cells. Doxorubicin accumulation in A549 cells is stimulated most strongly by compound 6.On the other hand, it would appear that 5-hydroxy-methoxyflavones are not associated with these stimulatory effects (Saranyapin *et al.,* 2017).

3.1.2 Antiobesity activity

K. parviflora extracts were tested against obesity-induced dermatopathy system. Ethanolic extract, a polymethoxyflavonoid-rich fraction (PMF), and a polymethoxyflavonoid-poor fraction from *K. parviflora* were used in the experiment. It was found that the ethanolic extract reduced the body weight of the mouse and the thickness of the subcutaneous fat layer more effectively (Hidaka *et al*., 2017).

3.1.3 Antiinflammatory activity

The ethanol extract of *K. parviflora* had a significant effect on PGE2 inhibition. It was also reported that the plant extract and 3',4',5,7-tetramethoxyflavone (86) both inhibited iNOS-mRNA expression in a dose-dependent manner. In addition, rat paw oedema was reduced by the soluble subfractions of H_2O, C_2H_5OH, $C_4H_8O_2$, $CHCl_3$ and n-hexane, which demonstrated excellent *in vivo* antiinflammatory activity (Sae-wong *et al*., 2009). Ethanol extract of 80 per cent was found to have antioxidative activity of polyphenolics against the oxidizing effects of UV radiation (Lee *et al*., 2018). The methoxylated flavones in the 60% ethanol and ethyl acetate soluble fraction of the 100% methanol extracts of *K. parviflora* likely contributed to the reduction in knee osteoarthritis (Kobayashi *et al*., 2018). Methoxylated flavonoids were isolated from *K. parviflora*; namely, 5-hydroxy-3,7,3',4'-tetramethoxyflavone (96), 5-hydroxy-7,4'-dimethoxyflavone (93), and 5-hydroxy-3,7,4'-trimethoxyflavone (95) which has IC_{50} values of 16.1 M, 24.5 M. They described methoxyflavones 96, 93, and 95 from a hexane extract of K. parviflora rhizomes were active against NO release in RAW264.7 cells (Tewtrakul *et al*., 2009).

3.1.4 Anticholinesterase activity

Thirteen known methoxyflavones (1-13) were isolated from K. parviflora and their structures were completely elucidated based on NMR analysis. 5,7,4'-trimethoxyflavone (6) and 5,7-dimethoxyflavone (7) were the highest potential cholinesterase inhibitors towards AChE and BChE. The compounds bearing 5,7-dimethoxy groups and a free substituent at C-3 had a significant inhibitory effect at a concentration of 0.1 mg/ml, but those bearing a 5-hydroxyl group reduced the inhibitory potency. Significant finding in the treatment of Alzheimer's disease was that a methanol extract as well as compounds (86-87) isolated from *K. parviflora* rhizomes inhibited acetylcholinesterase and butyryl cholinesterase more effectively than (86) (Sawasdee *et al*., 2009).

3.1.5 Antimutagenicity activity

Soluble CH_2Cl_2 and ethyl acetate fractions of *K. parviflora* exhibited antimutagenicity and glucosidase inhibitory activity. With IC_{50} values of 0.40, 0.40, 0.42, and 0.47 nmol/plate, respectively, isolated methoxylated compounds from these extracts (86, 97, 84, and 92) demonstrated potent activity. With IC_{50} values of 20.4 M, 54.3 M, and 64.3 M, respectively, compounds 88, 87, and 91 also demonstrated significant activity (Azuma *et al*., 2011)

3.1.6 Effect on cytochromes

It was found that continuous consumption of compound (88) isolated from *K. parviflora* lowers liver CYP3A expression, which raises levels of CYP3A-metabolized substances like midazolam. K. parviflora extract significantly induced CYP1A1, CYP1A2 enzyme activities following short-term treatment (Ochiai *et al*., 2018). CYP2B enzyme activities were markedly increased by all *K. parviflora* extract treatment, whereas *K. parviflora* extract significantly enhanced CYP2E1 activity only after long-term treatment (Mekjaruskul *et al*., 2012).

3.1.7 Adaptogenic activity

K. parviflora extracts made from hexane, chloroform, methanol and ethanol had more adaptogenic properties than the reference's crude

ginseng root powder. In humans, the whole-body potential expenditure was increased by a single oral dose of *K. parviflora* rhizome (60 per cent ethanol extract) (Pripdeevech *et al*., 2012). Improvement in physical fitness and health was observed when treated *K. parviflora* (Wattanathorn *et al*., 2012).

3.1.8 Xanthine oxidase inhibitory activity

With IC_{50} values of 0.9 and >4 mM, respectively, of the isolated methoxylated flavonoids from *K. parviflora* (87 and 86) inhibit xanthine oxidase activity (Nakao *et al*., 2011).

3.1.9 Allergenic activity

In addition to H_2O, CH_2Cl_2, ethyl acetate and isolated polymethoxyflavones from *K. parviflora* (86,97) antiallergenic activity was observed highest with compounds (92) and (94) extracted from *K. parviflora* (Kobayashi *et al*., 2015).

3.1.10 Neurological activity

By increasing levels of serotonin, norepinephrine, and dopamine in the rat hippocampus, a methanolic extract of *K. parviflora* (95 per cent methanol) exhibited neuroprotective activity (Plaingam *et al*., 2017). Tonsomboon *et al.* (2021) found out that in HT-22 cells, co-treatment of glutamate with *K. parviflora* extract significantly inhibited glutamate-mediated cytotoxicity and decreased intracellular ROS production. Additionally, the glutamate-induced apoptosis and apoptotic-inducing factor (AIF) translocation were blocked by *K. parviflora* extract co treatment. Western blot analysis also demonstrated that *K. parviflora* extract significantly diminished extracellular signal-regulated kinase (ERK) phosphorylation induced by glutamate, and brain-derived neurotrophic factor (BDNF) was recovered to the control. Moreover, this *K. parviflora* extract treatment prolonged the lifespan of *C. elegans*. Altogether, this study suggested that *K. parviflora* extract possesses both neuroprotective and longevity-inducing properties, thus serving as a promising candidate for development of innovative health products.

3.1.11 Effects on sexual performance

7-methoxyflavones (86, 87, 89, 91, 93-95) from *K. parviflora* rhizomes were found to increase male sexual activity by inhibiting PDE5, with 86 being the most effective. According to Temkitthawon *et al.* (2011), methoxyls at positions C5 and C752 were responsible for the activity. In healthy men, standardized *K. parviflora* rhizome extracts of 5% DMF also improve erectile function (Stein *et al*., 2018). In addition to boosting testosterone production, *K. parviflora* extract and 5,7-dimethoxyflavones reduce age-related diseases and hypogonadism (Horigome *et al*., 2016). When streptozotocin (STZ)-induced diabetic rats were given *K. parviflora* extract (aqueous with 1% Tween-80) 49, their testosterone levels, sperm count and sexual performance are all increased (Lert-Amornpat *et al*., 2017).

Miscellaneous

In mice, the rhizome extract of *K. parviflora* (95 per cent ethanol) reduced obesity by inhibiting adipogenesis, lipogenesis and muscle atrophy (Lee *et al*., 2018). *K. parviflora* derivatives of the 5-hydroxy-7-methoxyflavone, on the other hand, cause skeletal muscle hypertrophy (Ono *et al*., 2019). Plant extract of *K. parviflora* (95 per cent ethanol) has activity against propioni bacteria, sebostatics, and inflammation and as a potential acne treatment (Jin and Lee, 2018). In a study for rheumatoid arthritis, ethanol extract significantly reduced the levels of gene expression for matrix-degrading enzymes, inflammatory mediators, and pro-inflammatory cytokines, it did not alter the cell cycle or induce apoptosis. Without interfering with the NF-B pathway, they also reported that the alcoholic extract inhibits cell migration, reduces the mRNA expression of cadherin-11, and selectively reduces the phosphorylation of signal transducers, activators of transcription 1 (STAT1), and STAT3 signaling molecules (Kongdang *et al*., 2019).

3.2 Chemical composition

14 compounds, including two polyoxygenated cyclohexanes (1 and 2), eleven flavonoids (3-13), and sitosterol (14), were identified through phytochemical analysis of *K. parviflora* extract. The primary methoxyflavones in *K. parviflora* have been identified structurally, according to phytochemical analysis (Kim *et al*., 2007 and Sutthanut *et al*., 2007). Five coumpounds including 5,7-dimethoxyflavone (1), 3,5,7-trimethoxyflavone (2), di-O-methylpinocembrin (3), bisdemethoxycurcumin (4), aloe-emodin (5) were isolated from the n hexane extract of *K. parviflora* rhizomes (Tri *et al*., 2021). Structure-activity relationship (SAR) studies of *K. parviflora* methoxyflavones reveal that methoxylation at position 5 and vicinal methoxylation at positions 3' and 4' play crucial roles in promoting this activity in order to investigate the antiallergic activity in inhibiting degranulation (Azuma *et al*., 2008; Okabe *et al*., 2014). It has been demonstrated that compounds 4 and 6 have the greatest inhibitory effects on the activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). According to the SAR study, hydroxylation at position 5 reduces the inhibitory effects on AChE and BChE, while dimethoxylation at positions 5 and 7 is required for these effects to occur. Another study demonstrates that PDE-5 inhibition relies heavily on the methoxyl group at position 5 in 7-methoxyflavones. Methoxylation at position 4', on the other hand, has no effect on PDE inhibition (Temkitthawon *et al*., 2011). Additionally, B16 melanoma 4A5 cells are less cytotoxic to methoxyflavones when methylated at position 5. As a result, compound-11 is more cytotoxic than compound-359. KP methoxyflavone structural modifications have been investigated. Compound-6's various oxime derivatives are synthesized and found to be cytotoxic to HepG2 and T47D cell lines (Sutthanut *et al*., 2007). For the purpose of examining the characteristics of pharmacokinetics, three methoxyflavones, 3,5,7,3',4'-pentamethoxyflavone (compound 1), 5,7,4'-trimethoxyflavone (compound 4) and compound 6, were chosen. Within 1 to 2 h of oral administration to rats, they quickly reach their peak concentration. However, they exhibit a very low bioavailability of one to four per cent. Pitakpawasutthi *et al*. (2018) reported that *K. parviflora* oil contains a copaene,dauca 5, 8 diene, camphene, b pinene, borneol, and linalool as major components.

3.3 Conservation

K. parviflora is one of the important medicinal plants which has high demand but has not been domesticated or grown extensively in the region. The plant is highly sought after due to its high medicinal value. It is difficult for the plant to survive and reproduce in its natural environment when it is collected from the wild in an uncontrolled and unwise manner. Currently, this crop is being grown on a large and small scale in the region. The application of tissue culture to the large-scale multiplication of this crop has been taken up by our Institute at the College of Horticulture and Forestry. In order for the tissue-cultured plants to grow and multiply in the wild

without being harmed by human activities, they were relocated to their natural or similar habitats. The species can be preserved and its population can grow in this way. The availability of *K. parviflora* materials in the market and the prevention of its extinction will be aided by strict forest policies, wild collection policies, and cultivation subsidies.

4. Conclusion

P. polyphylla and *K. parviflora* are two important medicinal plants that are found in the North-eastern part of India. Both of these plants are under threat from overexploitation and a lack of cultivation efforts. Numerous ailments can be treated with the help of these two plants. These plants are very expensive in the market because there are fewer of them in the wild and there are fewer of them available from cultivation. At present, the marketing of these species are not organized yet and there is a huge collection of these species from the wild and traded illegally. Unsustainable and injudicious harvesting from the wild along with illegal trading of these species push them towards extinction. *P. polyphylla* typically thrives in temperate climates at high altitudes as a forest understory. The propagation of this species takes a long time in its natural habitat and with long seed dormancy period makes it difficult to multiply and propagate in nature as well. The species is illegally taken from the wild and causes a decline in population as a result of its high demand on the global market. The IUCN classifies this species as a threatened species. Since *K. parviflora* can easily be grown from its rhizomes, many people have started cultivating this species. In addition, there is a significant market demand for this plant, many of which can be met through cultivation. Before it's too late, scientists and policymakers need to develop conservation policies and conduct research on these two species.

Conflict of interest

The authors declare that there are no conflicts of interest relevant

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