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Review article

PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS OF *PERSICARIA HYDROPIPER* (L.) DELARBRE OF BANGLADESHI MEDICINAL PLANT USED BY FOLK MEDICINE PRACTITIONERS

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ABSTRACT

Persicaria hydropiper (L.) Delabre is a member of Polygonecea family, which is a weed commonly found in the temperate regions such as Bangladesh, China, Malaysia and Japan. It is also called marsh weed or smart weed. It has been proven as a useful herb as medicinally. recently we completed studies of its pharmacology, toxicology and traditional uses of this plant. All parts of the plant have uses as medicines. Flavinoids are the major group of phytochemical components followed by drimane type sesquiterpenes and sesquipenoids, as well as phenylpropanoids. It shows several diffent properties such as antioxidant, antibacterial, antifungal, antihelminth, antifeedant, cytotoxicity, anti-inflammatory, antinociceptive, oestrogenicity, antifertility, antidipogenecity and neuroprotection. Reports have confirmed mutagenicity and subchronic toxicity yet the plant is under research to improve its medicainal properties.

Key words: Argyreia nervosa, Argyreia speciosa, Antibacterial Activity, Acetic acid induced writhing, Analgesic activity.

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INTRODUCTION

Description and Distribution of Plant Botanical

Persicaria hydropiper (L.) delabre belongs to the family of Polygonaceae. The synonyms for this species are *Persi-saria hydropiper* (L.) Spach, *P.hydropiper* (L.) Opiz, *P.hydropiper* (L.) H. Gross, *Polygonum hydropiper* L and P.hydropiper var. projectum Stanford (Huq AKMM *et al.*, 2014). They are also called marsh-pepper smartweed, marsh-knotweed, smartweed or water pepper and is also known as la liao in China, bishkatali or pakarmul in Bangladesh and daun senahun in Malaysia (Burkill IH et al., 1966).

According to Flora of North America and Flora of China, P.hydropiper grows upto 40-70 cm tall.

It has ascending or erect branches and glabrous stem. The leaves are lanceolate or elliptic lanceolate i.e about 0.4 to 0.25 cm and glabrous with petiole about 0.1 to 0.8 cm. it has cuneate base,

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acuteto acuminate apex, ciliated margin, and sessile attachment with stipule. The terminal and axillary inflouresences are (0.3-0.18*0.5-0.9)cm and are either erect or nodding with glabrous peduncle 0.1 to 0.5 cm, acending pedicels, and 3-5 flowers. The flowers have greenish proximal and white or pink distal perianth, obovate tepals, 6-8 stamens and 2-3 styles.

Figure 1. Persicaria hydropiper (L.) delabre Plant

P.hydropiper is found wordwide in countries with a temperate climate including tropical Asia, western Asia, Caucaus, Siberia, Middle-East, Russian far East, China, Eastern Asia, Europe, Australia and Africa. The plant usually grows in wet area at watersides and in marshes (Loi DT *et al.*, 2000) and is usually predominant in agricultural fields (Miyazawa M *et al.,* 2007). It is also found in highland sites with highly organic, moist or silty areas.

TRADITIONAL USES

Persicaria hydropiper has a strong peppery taste and is com- monly used as a hot-tasting spice, food flavor, and garnish for a variety of traditional dishes (Peng ZF *et al.,* 2003). The Japanese people use the young shoot as spice and garnish with raw fish such as "sashimi" for its pungent taste (Fukuyama Y *et al.,* 1980). While the water or ethanol leaf extract served as a food additive to preserve pickles, dressing, and cooked foods. In Southeast Asia, the Chinese and Malays use the leaves in traditional laksa dishes (Peng ZF *et al.,* 2003). A situation in which use of, or exposure to, a violate product is not likely to cause adverse health consequences (Hasan MM *et al.,* 2016).

Most importantly, P. hydropiper also has a wide range of traditional uses for medicinal purposes. In Europe, the plant has been used as diuretic and emmenagogue (Stuart GA *et al.,* 1979) and to regulate menstrual irregularities. In addition, decoction of the whole plant, either alone or mixed with other medicinal plants, is also given for diarrhea, dyspepsia, itching skin, excessive menstrual bleeding, and hemorrhoids .The leaves and seeds are used in a folk medicine against cancer (Hartwell LJ *et al.,* 1070). The Romanian people in Oltenia utilized infusion of the aerial part as astringent and cicatrising, as well as for gastric, pulmonary problems, and uterine hemorrhages .The use of bruised leaves and seeds as vesicants has also been reported (Moerman D *et al.,* 1998).

In India, the Mishing women in Assam take the dried root powder of P. hydropiper for termination of pregnancy and it may lead to permanent sterility if taken continuously for more than a year (Hazarika A *et al.,* 2006). Leaf's juice is consumed for uterine disorders (Choudhary RK *et al.,* 2011). In Arunachal Pradesh, the whole plant extract and ground plant paste are used as fish poisons (Choudhary RK *et al.,* 2011), whereas the leaf infusion is used to relieve colic pain .The plant has also been utilized as natural dyes (Mahanta D *et al.,* 2005).

In Bangladesh, the Garo tribe uses the leaf juice for menstrual pain, the leaf paste to stop bleeding, and the whole plant as pesticide for stored grains .Another tribe of Tripura uses the mixture of crushed P. hydropiper leaf with black pepper for headache. In a district of Sylhet, the crushed plant helps to arrest hemorrhage and in Rema- Kalenga, the leaves are used for stomach pain. The leaf juice has been given for treating many health problems like headache, pain, toothache, liver enlargement, gastric ulcer, dysentery, loss of appetite, and dysmenorrhea, while the roots are used as stimulant and their juice is applied to wounds, skin diseases, and painful carbuncles. For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration (Hasan MM *et al.,* 2016).In Vietnam, the stems and leaves are taken for snake-bite and as diuretic and anthelmintic (Loi DT *et al.,* 2000). In China, the plant is consumed to prevent ovulation and cease pregnancy (Xiao PG *et al.,* 1991). While the root is used as stimulant, diuretic, carminative, tonic, and anthelmintic (Duke A *et al.,* 1985). This plant has been found to be toxic to pigs and sheep (Akamatsu K *et al.,* 1970).

PHARMACOLOGICAL PROPERTIES:

Several reports on pharmacological properties of *P. hydropiper* are available to support the ethnomedicinal uses of the plant including antioxidant, antibacterial, antifungal, antihelminth, antifeedant, cytotoxicity, anti-inflammatory, antinociceptive, oestrogenicity, anti-fertility, anti-adipogeni- city, anticholinesterase, and neuroprotection. Toxicological effects of *P. hydropiper* are also described.

Antioxidant Activity (Haraguchi H *et al.,* 1992):

Flavonoids are powerful antioxi- dants that can protect the human body from free radicals. Isoquercitrin and 7, 4' -dimethylquercetin isolated from the methanol extract of P. hydropiper leaves were found to inhibit lipid peroxidation using ferric thiocyanate (FTC) method with ID50 of 0.6 and 1.5 ppm, respectively also studied the antioxidant activity of quercetin-3-sulphate, isorhamnetin-3,7-disulphate, and tamarixetin- 3-glucoside-7-sulphate isolated from the methanol leaf extract. Amongst the sulphated flavonoids, isorhamnetin- 3,7-disulphate gave the strongest inhibition against lipid peroxidation even compared to α-tocopherol and quercetin and the formation of superoxide anion and xanthine oxidase, compared to quercetin, investigated the antioxidant properties of 10 flavonoids isolated from the leaves of P. hydropiper, that is, quercitrin, kaempferol-3-glucoside, 6-hydroxyapigenin, gal-loyl kaempferol-3-glucoside, scutillarein, 6-hydroxyluteolin, 6-hydroxyluteolin 7-O-β-D-glucopyranoside, quercetin 3-O-β-D-glucuronide, galloyl quercitrin, and quercetin, show- ing Trolox equivalent antioxidant capacity (TEAC) values of 1.39–6.14 against 2,2'-azinobis (3-ethyl-benzothiazoline-6- sulphonic acid (ABTS) radicals. Galloyl quercitrin was the most powerful antioxidant found in the study (TEAC = 6.14) compared to quercitrin (TEAC = 3.46) and its aglycone, quercetin (TEAC = 4.65).

Hydropiperoides B and vanicoside A isolated from the P. hydropiper methanol leaf extract demonstrated antioxidant activity in 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical- scavenging assay with half maximal scavenging concen- tration (SC50) values of 23.4 and 26.7 μg/mL, respectively, compared to ascorbic acid (SC50 22.0 μg/mL) also reported the antioxidant activity of ethyl acetate fraction of methanol leaf extract against DPPH free radicals with IC50 value of 13.30 μg/mL, whereby the 3,5-dihydroxy-4-methoxybenzoic acid (IC50 8.08 μg/mL), quercetin (IC50 11.14 μg/mL), and quercetin-3-O-rhamnoside (IC50 18.46 μg/mL) were found to be most active as compared to vitamin C (IC50 6.80 μg/mL).

Antibacterial Activity (Duraipandiyan V *et al.*, 2010):

Confertifolin isolated from the leaf essential oil of P. hydropiper showed strong/good anti-bacterial activity against Enterococcus faecalis (MIC 31.25 μg/mL) as compared to a positive standard, streptomycin (MIC 25 μg/mL), but did not inhibit the growth of *Bacillus subtilis*, *Erwinia* sp., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *and S. epidermidis*. On the other hand, reve- aled that polygodial had moderate bactericidal action against Bacillus subtilis (minimum bactericidal concentration, MBC 100 μg/mL), *Staphylococcus aureus* (MBC 100 μg/mL), *Escherichia coli* (MBC 100 μg/mL), and *Salmonella choleraesuis* (MBC 50 μg/mL).

Antifungal Activity:

Confertifolin isolated from the leaf essential oil was also found to have potent antifungal activity against *Epidermophyton floccosum, Curvularia lunata, and Scopulariopsis sp*. (MIC 7.81 μg/mL) and moderate activ- ity against *Aspergillus niger*, *Botrytis cinerea, Magnaporthe grisea, Trichophyton mentagrophytes, Trichophyton rubrum* (MTCC 296 and clinical isolate) and Trichophyton simii (MIC 16.62–125 μg/mL) as compared to fluconazole (MIC < 12.5–100 μg/mL) and ketoconazole (MIC < 12.5 μg/mL) **(** Duraipandiyan V et al., 2010).

Polygodial was also reported to inhibit *Candida albicans, C. utilis, C. krusei*, *Cryptococcus neoformans, Saccharomyces cerevisiae*, *Epidermophyton floccosum, Trichophyton menta-grophytes, T. rubrum* and *Penicillium marneffei* (Malheiros A *et al.,* 2005). It showed potent fungicidal activity against *C. albicans*. In another studies, polygodial isolated from Warburgia species and *P. hydropiper* showed fungicidal activity against *S. cerevisiae* , via several mechanisms such as decreasing cytoplasmic and mitochondrial glutathione and increasing production of reactive oxygen species and inhibition of mitochondrial ATPase (Lunde C *et al.,* 2000). Later, (Fujita KI *et al.,* 2005) revealed that polygodial, a nonionic surfactant, denatured the lipid-protein conformation of the cell membrane and interacted with L-cysteine containing cytoplasmic materials such as glutathione.

Anthelmintic Activity (Raihan MO *et al.,* 2012):

Methanol (99%) extract of P. hyd- ropiper aerial plant part (50 mg/mL) displayed anthelmintic activity against adult earthworms, Pheretima posthuma, in vitro with time of paralysis and death of 12.44 and 18.19 min, respectively, compared to the positive standard, piperazine citrate (10 mg/mL, time of paralysis = 24.00 min, time of death = 38.00 min) .

Antifeedant Activity (Asakawa Y *et al.,* 1988):

Hot water extract of P. hydropiper leaves (10% w/v) was significantly effective against the bean aphids, Aphis craccivora, with 87.6–94.5% mortality (P <0.01) 7 days after the application of spray at 227 L/ha. Warburganal was previously reported to have strong antifeedant activity against *African armyworms, Spodoptera exempta* and aphids.

Polygodial was found to be active antifeedant against a variety of aphids (*Aphis craccivora, Myzus persicae* and *Rhopalosiphum padi*), African or Egyptian cotton leafworm (*Spodoptera littoralis*) and whiteflies (*Bemisia tabaci*).

Cytotoxic Activity (Anke H *et al.,* 1991):

Various fractions of P. hydropiper herb and root methanol extracts were tested for antiproliferative activity against cervical epithelial adenocarcinoma (HeLa), skin epidermoid carcinoma (A431), and breast epithelial ade- nocarcinoma (MCF7) cells; only hexane fraction of the root methanol extract (30 μg/mL) was found to inhibit HeLa cell proliferation (54.75% inhibition) . Polygodial exhibited cytotoxicity against Ehrlich ascites tumor cells and mouse lymphocytic leukemia-derived L1210 cells.

An in vivo study performed showed that the methanol (99%) extract of P. hydropiper aerial part had antiproliferative activity against Ehrlich Ascites Carcinoma (EAC) cells inoculated intraperitoneally (i.p.) in Swiss-Webster albino male mice. The extract at a dose of 50 mg/kg/day (i.p.) significantly (P < 0.001) inhibited (84.54%) EAC cell growth, decreased tumor weight to 7.85 g, and improved mean survival time (68.0% increase of life span) of EAC bearing mice, as compared to the positive standard, bleomycin (0.3 mg/kg, i.p.) with values of 98.55%, 7.05 g, and 94.66%, respectively.

Anti-Inflammatory Activity (Sayah ME *et al*., 1998):

Methanol (99%) leaf extract of P. hydropiper inhibited production of inflammatory medi- ators in vitro such as nitric oxide (NO), tumor necrosis factor (TNF)-α, and prostaglandin (PG) E2 in lipopolysaccharide- induced RAW264.7 cells and peritoneal macrophages by suppressing the activation of Src/Syk/NF-kB and IRAK/AP-1/CREB pathways. The anti-inflammatory property of polygonolide isolated from methanol extract of P. hydropiper root by inhibiting reversed passive Arthus reaction. A dose of 100 mg/kg polygonolide administered orally 1 hour before induction of inflammation on the rat skin was able to inhibit 39.2% (P < 0.05) of the acute inflammation.

Polygodial, a major compound previously isolated from the barks of Drimys winteri, was reported to be responsi- ble for inhibiting guinea-pig ileum and tracheal contrac- tility in vitro induced by several mediators associated with asthmatic and allergic responses, including acetylcholine, histamine, bradykinin, KCl, 9,11-dideoxy-9α, 11α-methano- epoxy prostaglandin F2α , substance P, and tachykinin NK2 receptor . It also showed inhibitory effect of ovalbumin- sensitized and compound 48/80-stimulated contraction of guinea-pig trachea , revealed that polygodial had anti-inflammatory and antiallergic properties in vivo via various mechanisms of actions including inhi- bition of mice paw oedema induced by prostaglandin E2 (ID50 107 μmol/kg at 180 min), bradykinin (ID50 86 μmol/kg at 60 min), substance P (ID50 83 μmol/kg at 180 min), dextran (ID50 17 μmol/kg at 60 min), platelet activating factor (58% inhibition at 60 min), carrageenan (ID50 32 μmol/kg), and ovalbumin (80% inhibition at 240 min); mice ear oedema was stimulated by arachidonic acid (ID50 141.3 μmol/kg), cap- saicin (ID50 169 μmol/kg), and croton oil (44% inhibition), pleurisy was induced by substance P and histamine, and anaphylactic shock was stimulated by ovalbumin.

Antinociceptive Activity (Rahman E *et al.,* 2002):

Ethyl acetate extract of P. hydropiper whole plant exhibited significant dose-dependent antinociceptive activity in Swiss albino mice (42.86% inhi- bition at 250 mg/kg and 54.95% at 500 mg/kg, P < 0.001) as compared to aminopyrine (73.62% at 50 mg/kg) by acetic acid-induced writhing method, suggesting its analgesic potential. It isolated polygodial from the barks of D. winteri and found that it (0.1 to 10 mg/kg, administered by intraperitoneal injection) was able to inhibit mice abdominal contractions induced by acetic acid (ID50 0.8 mg/kg), zymosan (ID50 2.1 mg/kg,) and kaolin (ID50 2.6 mg/kg).

Polygodial also demonstrated distinct systemic, spinal, and supraspinal antinociceptive effect on mice, mainly preventing the formalin- and capsaicin-induced neurogenic pain, via several mechanisms including binding to the k and d subtypes of opioid receptors, activation of pertussis toxin-sensitive Gi/Go-protein, binding to 1 - adrenoceptors and serotonin-ergic system. Neurogenic antinociceptive and thermal antihyperalgesic effects were observed in neonatal treatment of rats.

Oestrogenic and Antifertility Activity (Goswami P *et al.,* 2009):

First reported the antifertility activity of ethanol extract of *P. hydropiper* root on female albino rats. Recently, the methanol root extract administered orally to ovary-intact and ovariectomized adult albino rats at a dose of 1000 mg/kg body weight/day for three consecutive oestrous cycles (12 days) was found to induce endometrial proliferation and follicular growth that

was evidenced by the regulation of endome- trial protein expression, suggesting its oestrogenic property comparable to estradiol-17β . Further investigations have demonstrated that the steroid-containing fraction of P. hydropiper methanol root extract, administered subcuta- neously at a dose of 5 mg/kg/day, stimulated proliferation of uterine epithelium of ovariectomized adult albino rats . The fraction also stimulated expression of various uterine proteins in ovary intact (molecular weight ≈150000, ≈90000,≈82000, ≈56000, ≈43000, and ≈38000) and ovariectomized (≈38000) rats but reduced expression of proteins (≈65000 and ≈38000) in pregnant rats of 5-6 days after implantation .The latter was indicated by the suppressed expression of estrogen-sensitive transforming growth factor-βI in the primary decidual zone of the implantation sites during day 6 of gestation, suggesting the antifertility activity .

Antiadipogenic Activity (Lee SH *et al.,* 2011):

Methanol extract of P. hydro- piper whole plant (1 μg/mL) and its flavonol components, iso-quercitrin (50 μM) and isorhamnetin (50 μM), were shown to activate the Wnt/β-catenin signaling in HEK 293 cells containing pTOPFlash reporter gene, increase nuclear local- ization of β-catenin in 3T3-L1 adipocyte cells, and inhibit adipocyte differentiation, suggesting its potential application as antiobesity agents and for associated disorders [84].

Anticholinesterase Activity:

Cholinesterase assays using acetylcholinesterase and butyrylcholinesterase enzymes were conducted on P. hydropiper. However, the methanol extract, fractions (hexane, dichloromethane, ethyl acetate, butanol, and aqueous) and changweikangic acid A did not exhibit anticholinesterase activity.

Neuroprotective Activity (Ma CJ et al., 2010):

Persicarin was discovered as a component of the P. hydropiper methanol leaf extract .As a matter of fact, it reported that persicarin isolated from the stems and leaves of *Oenanthe javanica* demonstrated significant neuroprotective activity (40.8–74.5% protection at 10.0 μM, $P < 0.001$) in glutamate-induced neurotoxicity of rat cortical cells by inhibition of intracellular calcium influx, intracellular nitric oxide production, and cellular peroxide formation, as well as by increasing the antioxidant activities of superoxide dismutase, glutathione reductase and glutathione peroxidase. Depending on the amount of persicarin in *P. hydropiper*, its extract could potentially possess neuroprotective activity.

TOXICOLOGY

Kuroiwa K *et al.,* (2006) stated that the *P. hydropiper* ethanol leaf fraction containing 7.0% polygodial gave positive mutagenicity in two tests, that is, the Ames test using *Salmonella typhimurium* TA 100 and TA 98 and the chromosomal aberrations using Chinese hamster-derived CHL/IU cells, but it was negative for micronuclei in mouse bone marrow cells. It was also previously reported that polygodial was negatively mutagenic in the Ames test using TA 100, TA 98, and TA 2637 strains of *S. typhimurium* and in the mammalian cell V79/HGPRT assay (Morales P et al., 1992). Acute toxicity in Swiss-Webster albino male mice was conducted by, in which methanol (99%) extract of *P. hydropiper* aerial part (20–600 mg/kg) was injected intraperitoneally. After 24 hours, no mortality was observed up to 400 mg/kg, but 100% mice died at 600 mg/kg, suggesting the LD50 of the extract to be 500 mg/kg (i.p.). (Kuroiwa K *et al.,* 2006) also investigated the subchronic toxicity of WPE in male and female F344/DuCrj rats given ad libitum for 13 weeks. The no observed-adverse effect was found with 1000 ppm ethanol leaf fraction containing 7.0% polygodial (57.4 and 62.9 mg/kg/day for males and females, resp), whereby there were no obvious clinical signs and no significant changes in food consumption, hematology and serum biochemistry, body and organ weights, and histopathology of organs of the tested rats. The aerial parts cause blister of the skin upon repeated handling that could be due to the skin irritant polygodial (Clapham AR *et al.,* 1952) Polygodial isolated from the bark of *D. winteri* was found to increase extracellular glutamate concentrations via concurrently inhibiting glutamate uptake by rat astrocytes and slices of cortex, striatum, and hippocampus and increasing glutamate release by synaptosomes, suggesting possible neurotoxic effect of polygodial (Martini LH *et al.,* 2006).

CONCLUSION

The wide spectrum of uses have encouraged scientist to study more about this plant. The dicussions on this paper have given us a perception about pharmacology and its different traditional properties such as antibacterial, cytotoxicity, anti-inflammatory, antin ociceptive, oestrogenicity, anti-fertility, anti-dipogenecity and neuroprotection, anti-oxidant, anti-bacterial, anti-fungal, anti-helminth, anti-feedant etc. This plant has evidence of containing several pharmacologically active compounds. Warburganal acted as anti-feedant, confertifolin had antibacterial and anti-fungal activities, persicarin demonstrated neuroprotective, isoqurcities, quercetin, quercitin 3-O-rhamnoside,

7,4-dimethylquercetin, galloyquercitin, isorhamnetine 3,7-disulphate, 3,5-dihydroxy-4-methoxybenzoic acid, hydropiperoside B and vanicoside A showed antioxidant properties, while isoquertrin and isohamnetin were antidipogenic. Oral consumption of ethanol leaf containing 7% polygodial was found to be safe in vivo.

Thus, we can say that this plant serves us with its various and useful properties in curing diseases and alleviate several microbial infections, inflammation, pain, allergy, uterine disorders, fertility, obesity and improvement of memory.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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