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AN OVERVIEW OF THE TRADITIONAL USES, PHYTOCHEMICAL CONSTITUENTS, PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS OF *PERSICARIA HYDROPIPER* (L.) DELARBRE

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Review Article

ABSTRACT

Persicaria hydropiper (L.) Delarbre, an annual herb of the family *polygonaceae*, locally known as Patharua bihalagani in Assam (India), is reported as a traditional drug for birth control used by women in some parts of Assam. The current study presents the taxonomical description, geographical distribution, traditional uses, phytochemical composition, pharmacological and toxicological activities of *P. hydropiper*. The whole plant or part(s) like leaves, stems root etc have been traditionally used as herbal medicine for treatment of various ailments. Several bioactive components such as flavonoids, phenylpropanoids, essential oils, glycosides, phytosterols and sesquiterpenes among others were reported. The extracts and phytoconstituents of *P. hydropiper* possess antioxidant, anti-microbial, anti-inflammatory, cytotoxic, estrogenic, antifertility, neuroprotective activities, etc. Mutagenic activity and acute toxicity of *P. hydropiper* were also reported.

Keywords: *P. hydropiper*; polygonaceae; traditional uses; phytochemical constituents; pharmacological aspects.

1. INTRODUCTION

Healing with herbal plants is an antique process. Plants are the natural reservoirs of bioactive nutrient chemicals that may provide therapeutic health benefits to human or animals. According to the World Health Organization around 80 percent of the world's population depends mainly on traditional medicine; perhaps some two billion people are largely dependent on medicinal plants [1]. In 2002, the Food

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and Agriculture Organization estimated that over 50,000 medicinal plants are used worldwide [2]. In India, medicinal plants have remained the most abundant source of health care and life improvement since time immemorial. According to the National Medicinal Plant Board India, in India out of 17,000-18,000 species of flowering plants, 6000-7000 are known to have medicinal application in ancient medicinal systems such as ayurveda, siddha, unani, and homeopathy. Over the past two decades, there has been an enormous increase in the use of herbal medicine because of its minimal or no known side effects as compared with the modern synthetic drugs [3]. *P. hydropiper*, a member of the family *polygonaceae*, is one such medicinal plant that has been used in treating various ailments and has a wide range of pharmacological aspects. In this review we aimed to illustrate the taxonomic description, geographical distribution, phytochemical composition and ethno pharmacological profiles of *P. hydropiper*.

2. DESCRIPTION AND DISTRIBUTION OF *P. hydropiper*

The *polygonaceae* or commonly known as the knotweed family, are a family of flowering plants, comprising of about 1300 species grouped into 59 genera [4]. *Polygonaceae* derived its name from Greek, poly meaning 'many' and gony meaning 'knee' or 'joint' that refer to the many swollen nodes that the stems of some species have. Various species of *polygonaceae* are used either as ornamentals or as alternative medicine. Among them, *P. hydropiper* is tremendously popular because of its diverse phytochemistry and therapeutic uses. It is commonly known as Water Pepper, marsh-pepper or smartweed [5] and locally known by various names like patharua bihalagani in Assam, kesum in Malaysia etc [6]. It is an annual erect herb growing to a height of 0.8 m (Fig. 1). Roots are usually short (10 cm), often twined main root with several lateral roots. In case after flood, if the lower part of the stem becomes buried adventitious roots are formed at the nodes. The stems and branches are slender and glabrous with simple alternate, lanceolate leaves. Inflorescence terminal or axillary, usually lax, in raceme or filiform, each 3-5-flowered; flowers small pink or white. Petals 5, free, elliptic, densely glandular. Stamens 6; filaments filiform, white. Ovary unilocular with one ovule; style 2, filiform; stigma simple. Fruits trigonous, dull brown, minutely punctulate. It flowers in the month of July to September [7]. The plant is a native of Eurasia, widely distributed from the tropical region in the Northern hemisphere to the temperate zone including Western Asia, Caucasus, Siberia, Middle Asia, Russian Far East, China, Eastern Asia, Indian Subcontinent, Malaysia, Northern Europe, Middle Europe, East Europe, South eastern Europe, South western Europe, Northern Africa and Australia [5, 8]. In Assam, a state of India, the plant is commonly found in all the districts. It grows wildly in damp places and shallow waters, in marshes and swamps, in seasonally flooded areas and predominantly on agricultural land and on a wide variety of soils from clay to peat, whilst tolerating a wide range of pH [9]. *P. hydropiper* reproduces mainly by seed, although broken stems may grow into new plants if nodes are present.

Fig. 1. *P. hydropiper* (L.) Delarbre plant collected from Changsari area of Assam, India

3. TRADITIONAL USES OF *P. hydropiper* AS FOOD AND MEDICINE

Because of its strong peppery taste, *P. hydropiper* is commonly used as a hot-tasting spice, as flavoring agent and for garnishing various traditional dishes [10]. In Japan, young shoots are used as spice and garnished with raw fish such as "sashimi" for its peppery taste [11]. While the leaf extract is used as preservative for preserving pickles, dressing and cooked foods [12]. *P. hydropiper* has a long story of use in folk medicine for treatment of various ailments and its medicinal usage in Unani, Ayurveda, Siddha, and other traditional medicine is well-recognized. In Europe, this plant has been used to treat kidney problem and to regulate menstrual irregularities [13]. The whole plant decocted, either alone or mixed with other medicinal herbs, is used to treat diarrhoea, dyspepsia, itchiness, heavy and painful menstruation and haemorrhoids [14, 15, 16]. The seeds and leaves are used against cancer [13]. Bruised leaves of this plant are also reported to be used as a vesicant like mustard poultice [17]. In China, the plant is ingested to stop ovulation and unwanted pregnancy [18], while the root is used as stimulant, tonic, carminative, diuretic and anthelmintic [14]. The people of Vietnam use the stem and leaves for snake bite [19].

The tribal people of Tripura (India) and Bangladesh crushed the leaves with black peppers and taken through nose to cure headache [20]. In Bangladesh, the people of Garo tribe use the leaf juice to treat menstrual pain and for the relief of anxiety and insomnia, the leaf paste to terminate bleeding and the whole plant as pesticide for stored grains and in Rema Kalenga, the leaves are used for sedation and tranquilizers and to cure stomach pain [21, 22]. The leaf juice is taken to treat ailments like headache, toothache, liver enlargement, gastric ulcer, dysentery, anorexia and dysmenorrhea [23].

The Mishing women of Assam (India) take the dried root powder to check unwanted pregnancies which may lead to permanent infertility if consumed continuously for more than one year [24]. The Santal and Kumarikatas tribes of Kamrup district in Assam (India) are also reported to use leaf paste to get rid of body pains [25] while the people of Golaghat district of Asam use the entire plant as insect repellent and for curing pneumonia [26]. In Upper Siang area of Arunachal Pradesh and Assam dried plants and leaf extract are also used as insect repellent. Liquid extract of herb used as an oral contraceptive; infusion is used in uterine disorders [27], in colic pain [28] and as a hemostatic. The plant has also been reported to have bitter, emmenagogue, hemostatic and lithotripter properties [29] and exhibit anti-inflammatory potential [30], insecticidal properties [31], antioxidant, anticholinesterase [32], phytotoxic, anthelmintic [33], antiangiogenic, anticancer [34] and antimicrobial potential [35]. This plant is used in treating various health issues, including gastrointestinal upsets, neurological disorders, inflammation and diarrhoea [36].

4. PHYTOCHEMISTRY OF *P. hydropiper*

Till now, a large number of active phytochemicals of *P. hydropiper* has been identified, including flavonoids, phytosterols, terpenoids, anthraquinones, capsaicinoids, phenolics, glycosides etc (Table 1). Other bioactive compounds of this plant include catechins, procyanidins, condensed tannins [37]; gallic acid; ellagic acid; 3,30-di-O-methyl ether; aromatic 6-lactone; and flavonoids such as rutin, viscosumic acid, oxymethyl-anthraquinones, hyperin, quercetin, isoquercitrin, epicatechin, kaempferol, and isorhamnetin [38]; 4-methyloxazole, succinimide, pyrocatechol, farnesol, caryophyllene, myristic acid, arachidic acid, vanillic acid, methyl ester and capsaicin [35]. Phytochemical analysis also revealed the presence of alkaloid, polyphenols, sulfonyl urea, carboxylic acid, hydroxy ketone, such as theobromine, chlorpropamide, fumaric acid, gingerol respectively and many other constituents such as hypoxanthine, Erythrono-1,4-lactone, 2,4-Imidazolidinedione, L-Lyxose, 3,3-Dimethyl-1,2-dithiolane, N-Acryloylglycine, 6-Hydroxyluteolin 3'-methyl ether 7-sulfate and (6S)-dehydrovomifoliol [39]; hydropiperside, falccidine [40] etc. Besides, vanicoside B, vanicoside E, vanicoside F, 5,6-dehydrokawain, aniba-dimer-A, 6,6′-((1α,2α,3β,4β)-2,4-diphenylcyclobutane-1,3-diyl)bis(4-methoxy 2H-pyran-2-one), isalpinin, (+) ketopinoresinol, 3,7-dihydroxy-5,6-dimethoxy-flavone, cardamomin, pinosylvin, isorhamnetin, 2-desoxy-4-epi-pulchellin and β-sitosterol were also isolated from dichloromethane soluble portion of *P. hydropiper* [41]. Furthermore, 3,5-dihydroxy-4-methoxybenzoic acid, Galloyl quercetin-3-O-glucoside, Quercetin-3-O-glucoside, Quercetin, Kaempferol-3-O-glucoside, Galloyl kaempferol-3-O- glucoside, Apigenin-7-O-glucoside, Quercetin-3-O-rhamnoside, Galloyl quercetin-3-O-rhamnoside, Rhamnetin, Hydropiperoside, Vanicoside A, Vanicoside B, Vanicoside D, Kaempferol rutinoside from ethyl acetate fraction [42] while chlorogenic acid, ferulic acid, rutin, myricetin, dodecanal, caryophyllene, caryophyllene oxide, decanal, α-caryophyllene, citronellol, heptadecanal, linalool and phytol [43]; beta-sitosterol and stigmasterol [44] and two glycosides, cyanidin 3-O-galactoside (idaein) and quercetin 3-O-galactoside (hyperin) [45] were also isolated.

Table 1. List of bioactive compounds isolated from *P. hydropiper*

Class of compound	Name of compound	Part(s) used	Type of extract	References
Alkaloid	Theobromine	stem and leaves	Aqueous methanolic	[39]
Anthraquinone	oxymethyl-anthraquinones	Whole plant	Methanol (80%)	[38]
	Anthraquinone	Whole plant	Methanol (80%)	[38]
Capsaicinoids	Capsaicin	Aerial parts	Methanol (80%)	[35]
Carboxylic acid	Fumaric acid	stem and leaves	Aqueous methanolic	[39]
Essential oil.	Dodecanal	Leaves	Ethanol	[43]
	Caryophyllene	Leaves	Ethanol	[43]
	caryophyllene oxide	Leaves	Ethanol	[43]
	decanal, α-caryophyllene	Leaves	Ethanol	[43]
	Citronellol	Leaves	Ethanol	[43]
	Heptadecanal	Leaves	Ethanol	[43]
	Linalool	Leaves	Ethanol	[43]
	Phytol	Leaves	Ethanol	[43]
Flavonoids	Cardamomin	whole plant	Ethanol	[41]
	Rutin	Leaves	Ethanol	[43]
	Myricetin	Leaves	Ethanol	[43]
	Rutin	Whole plant	Methanol (80%)	[38]
	Viscosumic acid	Whole plant	Methanol (80%)	[38]
	Hyperin	Whole plant	Methanol (80%)	[38]
	Isoquercitrin	Whole plant	Methanol (80%)	[38]
	Epicatechin	Whole plant	Methanol (80%)	[38]
	Quercetin	Whole plant; Leaves	Methanol (80%) Ethyl acetate; Ethanol	[38]; [40]; [42]; [43]
	Kaempferol	Whole plant	Methanol (80%)	[38]
	Isorhamnetin	Whole plant	Methanol (80%); Ethanol	[38]; [41]
	6-Hydroxyluteolin 3'-methyl ether 7-sulfate	stem and leaves	Aqueous methanolic	[39]
	3,7-dihydroxy-5,6-dimethoxy-flavone	whole plant	Ethanol	[41]
	Isalpinin	whole plant	Ethanol	[41]
	Galloyl quercetin-3-O-glucoside	Leaves	Ethyl acetate	[42]
	Quercetin-3-O-glucoside	Leaves	Ethyl acetate	[42]
	Kaempferol-3-O-glucoside	Leaves	Ethyl acetate	[42]
	Galloyl kaempferol-3-O-glucoside	Leaves	Ethyl acetate	[42]
	Quercetin-3-O-rhamnoside	Leaves	Ethyl acetate	[42]
Flavonoids	Apigenin-7-O-glucoside	Leaves	Ethyl acetate	[42]
	Galloyl quercetin-3-O-rhamnoside	Leaves	Ethyl acetate	[42]
	Kaempferol rutinoside	Leaves	Ethyl acetate	[42]
	Rhamnetin	Leaves	Ethyl acetate	[42]
Glycosides	cyanidin 3-O-galactoside	Sprout	water or 70% Ethanol	[45]
	quercetin 3-O-galactoside	Sprout	water or 70% Ethanol	[45]
Others	aromatic 6-lactone	Whole plant	Methanol (80%)	[38]
	4-methyloxazole	Aerial parts	Methanol (80%)	[35]
	Succinimide	Aerial parts	Methanol (80%)	[35]
	Pyrocatechol	Aerial parts	Methanol (80%)	[35]

Class of compound	Name of compound	Part(s) used	Type of extract	References
	Caryophyllene	Aerial parts	Methanol (80%)	[35]
	vanillic acid	Aerial parts	Methanol (80%)	[35]
	arachidic acid	Aerial parts	Methanol (80%)	[35]
	methyl ester	Aerial parts	Methanol (80%)	[35]
	L-Lyxose, 3,3-Dimethyl-1,2-dithiolane	stem and leaves	Aqueous methanolic	[39]
	N-Acryloylglycine	stem and leaves	Aqueous methanolic	[39]
	Erythrono-1,4-lactone	stem and leaves	Aqueous methanolic	[39]
	(6S)-dehydrovomifoliol	stem and leaves	Aqueous methanolic	[39]
	Falccidine	whole plant	Methanol	[40]
	5,6-dehydrokawain	whole plant	Ethanol	[41]
	aniba-dimer-A	whole plant	Ethanol	[41].
	6,6′-((1α,2α,3β,4β)-2,4 diphenylcyclobutane-1,3-diyl)bis(4-methoxy2H-pyran-2-one)	whole plant	Ethanol	[41]
Phenol	Gingerol	stem and leaves	Aqueous methanolic	[39]
Phenolic acid	Chlorogenic acid	Leaves	Ethanol	[43]
	ferulic acid	Leaves	Ethanol	[43]
	gallic acid	Whole plant	Methanol (80%)	[38]; [39]
	ellagic acid 3,30-di-O-methyl ether	Whole plant	Methanol (80%)	[38]
	3,5-dihydroxy-4-methoxybenzoic acid	Leaves	Ethyl acetate	[42]
Phenylpropanoids	vanicoside B	Leaves; whole plant	Ethyl acetate	[41]; [42]
	vanicoside E	whole plant	Ethanol	[41]
	vanicoside F	whole plant	Ethanol	[41]
	Vanicoside D	Leaves	Ethyl acetate	[42]
	Vanicoside A	Leaves	Ethyl acetate	[42]
	Hydropiperoides A	Stems and leaves	Methanol	[46]
Phenylpropanoids	Hydropiperoides B	Stems and leaves	Methanol	[46]
Phytosterols	β-sitosterol	whole plant; Aerial parts	Ethanol; chloroform and ethyl acetate	[41]; [44]
	Stigmasterol	Aerial parts	chloroform and ethyl acetate	[44]
Sesquiterpenes and sesquiterpenoids	(+) ketopinoresinol	whole plant	Ethanol	[41]
	Polygodial	Top parts; Leaves and seeds	Petroleum; Diethyl ether	[11]; [47]
	Warburganal	Leaves and seeds	Diethyl ether	[11]
	Drimenol	Leaves and seeds	Diethyl ether	[11]
	Isodrimeninol	Leaves and seeds	Diethyl ether	[11]
	Isopolygodial	Leaves and seeds	Diethyl ether	[11]
	Confertifolin	Leaves and	Diethyl ether	[11]

Class of compound	Name of compound	Part(s) used	Type of extract	References
		seeds		
	Farnesol	Aerial parts	Methanol (80%)	[35]
Sphingoglycolipid	Hydropiperside	whole plant; leaves	Methanol; Ethyl acetate	[40]; [42]
Stilbenoid	Pinosylvin	whole plant	Ethanol	[41]
Sulfonyl urea	Chlorpropamide	stem and leaves	Aqueous methanolic	[39]
Terpenoid	2-desoxy-4-epi-pulchellin	whole plant	Ethanol	[41]
Triglycerides	Myristic acid	Aerial parts	Methanol (80%)	[35]
Xanthine	hypoxanthine, 2,4-Imidazolidinedione	stem and leaves	Aqueous methanolic	[39]

5. PHARMACOLOGICAL IMPORTANCE OF *P. hydropiper*

Pharmacological reports suggest that various parts of *P. hydropiper* possess antimicrobial, antioxidant, antinociceptive, cytotoxic, antidepressant, neuroprotective, anticholinesterase, anticancer and antifertility potentials which are described below:

5.1 Antioxidant activity of *P. hydropiper*

Because of the presence of conjugated ring structures and hydroxyl groups, phenolic compounds have the potentiality to function as antioxidants by scavenging the free radicals involved in oxidative processes [15]. 7,4'-dimethylquercetin and Isoquercitrin isolated from the methanolic extract of *P. hydropiper* leaves revealed potent antioxidative activity and were accounted for inhibition of lipid peroxidation using ferric thiocyanate (FTC) method. Yagi *et al*. (1994) studied the antioxidant activities of three sulphated flavonoids- quercetin3-sulphate, isorhamnetin-3,7-disulphate and tamarixetin3-glucoside-7-sulphate, extracted from the leaves. Among them, isorhamnetin-3,7-disulphate have the highest inhibition against lipid oxidation and generation of superoxide anions compared to α-tocopherol, a common natural antioxidant and quercetin, respectively [48]. Peng *et al*. (2003) also investigated the antioxidant potentials of 10 flavonoids, isolated from *P. hydropiper* leaves, showing Trolox equivalent antioxidant capacity (TEAC) values ranging from 1.39-6.14 against ABTS (2,2'-azino-bis(3-ethyl-benzo-thiazoline-6-sulfonic acid)) radicals and phenyl-tert-butyl nitrone (PBN) azo initiator (AI) [10]. Galloyl quercitrin was found to have exceptional antioxidative activity (TEAC- 6.14) compared to quercitrin (TEAC- 3.46) and its aglycone, quercetin (TEAC- 4.65). Moreover, Hydropiperoides B and vanicoside A also showed antioxidant activity in 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assay with half maximal scavenging concentration (SC_{50}) values of 23.4 and 26.7 µg/mL, respectively, compared to ascorbic acid (SC_{50} 22.0 µg/mL) [46]. Besides, the leaves and flower extracts of *P. hydropiper* also showed potent antioxidant activity as determined by using DPPH and ABTS [32, 39, 49].

5.2 Antimicrobial activity of *P. hydropiper*

Confertifolin, isolated from the essential oil of *P. hydropiper* leaves indicated moderate bactericidal activity against *Enterococcus faecalis* with minimum inhibitory concentration (MIC) of 31.25 µg/mL compared to streptomycin (MIC 25 µg/mL) and significant antifungal activity against *Scopulariopsis* sp, *Curvularia lunata*, *Epidermophyton floccosum* (7.81 µg/mL); *Trichophyton mentagrophytes*, *T. rubrum* (MTCC 296) (16.62 µg/mL); *Aspergillus niger*, *Botrytis cinerea* (31.25 µg/mL); *Magnaporthe grisea* (62.5 µg/mL); *T. simii* and *T. rubrum* (clinical isolate) (125 µg/mL) compared to fluconazole and ketoconazole (MIC<12.5 µg/mL)[50]. Polygodial showed potent antifungal activity against *Candida albicans* [51], whereas, moderate antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* upto 100 µg/mL and *Salmonella choleraesuis* upto 50 µg/mL [52]. Nasir *et al.*, 2021 reported strong antibacterial activities for both acetone and ethanol extracts of *P. hydropiper* stem and leaves against *E. coli*, *S. aureus*, *Klebsiella pneumoniae*, *Morganella morganii* and *Haemophilus influenzae*; but the leaves did not show antibacterial action against *E. coli* and *S. aureus* [49]. Hasan and his co-workers reported significant antibacterial activities of ethanol extract of *P. hydropiper* against *B. subtilis*, *B. megaterium*, *S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Shigella sonnei* at both 150 and 300 µg/disc ranging from 16 to 64 µg/mL MIC values and potent antifungal activities against *Aspergillus fumigatus*, *A. niger*, *A. flavus*, *C. albicans* and *Rizopus oryzae* [53]. Moreover, active compounds like vanicoside F, (+)-ketopinoresinol, isorhamnetin, cardamomin and pinosylvin, isolated from *P. hydropiper*, were found

active against *Trypanosoma brucei*, a unicellular bloodstream parasite transmitted by tsetse flies, with IC_{50} values ranging from 0.49-7.77 µg/mL, with the highest activity shown by Cardamomin (0.49 µg/mL) compared to their standards alpha-difluoromethylornithine (DFMO) (3.02 µg/mL) [41].

5.3 Anthelmintic activity of *P. hydropiper*

Ayaz *et al*., 2014 determined the anthelmintic potential of methanol extract (Ph.Cr) of *P. hydropiper* and its subsequent fractions: chloroform (Ph.Chf), ethyl acetate (Ph.EtAc), aqueous (Ph.Aq) and saponins (Ph.Sp) against *Pheretima posthuma* (earthworm) and *Ascaridia galli* (roundworm). Ph.Sp, Ph.Chf, Ph.EtAc and Ph.Cr fractions showed anthelmintic activity against *P. posthuma* with death time of 50.00, 64.67, 66.33 and 68.67 mins respectively and paralysis time of 11.00, 9.67, 12.67 and 17.00 mins respectively as compared to standard drugs albendazole (death time = 29.33 mins; paralysis time = 7.67 mins) and levamisole HCl (death time = 31.33 mins; paralysis time = 8.33 mins) at 10 mg/mL concentration. Ph.EtAc, Ph.Chf and Ph.Aq fractions showed anthelmintic activity against *A. galli* with average death time of 7, 9 and 10 mins respectively at 1 mg/mL when compared with standard drugs albendazole and levamisole HCl that killed *A. galli* in 10 and 9 mins, respectively [33].

5.4 Insecticidal activity of *P. hydropiper*

Ayaz and his co-workers (2016) carried out a study on the insecticidal potential of methanol extract of *P. hydropiper* and its fractions on adult insects of *Tribolium castaneum* (flour beetle), *Rhyzopertha dominica* (grain borer), *Anobium punctatum* (wood worm) and *Monomorium pharaonis* (Pharaoh ants). The ethyl acetate, saponins, chloroform and n-Butanol fractions showed potent insecticidal activity against *T. castaneum* and *R. dominica*. The saponin fraction, showing highest activity against *A. punctatum* and *M. Pharaonis* with LC_{50}< 0.01 mg/mL and 94.64, 96.00 and 100% lethality against *A. punctatum* and with LC_{50} of 12.5, 25 and 50 mg/mL and 93.30, 100.00 and 100% lethality against *M. pharaonis* at concentrations of 12.5, 25 and 50 mg/mL respectively. Larvicidal activity of methanol extract, chloroform and ethyl acetate fractions were also prominent with LC_{50} of 0.93, 1.16 and 6.35 mg/mL respectively. Chloroform fraction also caused 83.30, 86.65 and 96.65% death of *M. pharaonis* at concentrations of 12.5, 25 and 50 mg/mL with LC_{50}< 0.01 mg/mL [35]. Moreover, chloroform and ethyl acetate fractions of *P. hydropiper* plant extract exhibited remarkable residual effects on *T. castaneum* by decreasing the production of F1 progeny and/or by increasing mortality [54]. Bhattacharjee *et al*. (2019) reported insecticidal potentials of *P. hydropiper* leaf extract against *S. oryzae* adult [55]. The essential oils of *P. hydropiper* were reported toxic against second-instar larvae of *Plutella xylostella* (L.) after 72 hour of exposure (LC_{50}= 0.53µg/µL) [56].

5.5 Mosquitocidal activity of *P. hydropiper*

The mosquitocidal activity of essential oil and confertifolin, extracted from this plant, were bio assayed against larva of *Anopheles stephensi*, *Culex quinquefasciatus* [57] and *Aedes albopictus* L. [58]. The essential oil showed the LC_{50} values of 189 and 243 ppm; 217 and 242 ppm and 194.63 and 199.65 ppm; confertifolin showed the LC_{50} values of 2.40 and 3.09 ppm; 4.07 and 4.18 ppm and 2.02 and 3.16 ppm against the second and fourth instar larvae of *A. stephensi*, *C. quinquefasciatus* and *A. albopictus* L, respectively. Confertifolin showed ovicidal activity of 100, 98.60 and 86.40% against *A. stephensi* and 100, 100 and 75.20% against *C. quinquefasciatus* on 0-6, 6-12 and 12-18 hour old eggs and 100% on 0-6 hour old eggs against *A. albopictus*, respectively, at 10 ppm. The repellent activity lasted for 314.6, 319.0 and 320.6 mins; oviposition deterrent activity was 97.20, 99.00 and 98.51% and adulticidal activity was 100, 100 and 100% against *A. stephensi*, *C. quinquefasciatus* and *A. albopictus*, respectively.

5.6 Antinociceptive activity of *P. hydropiper*

The hexane, ethyl acetate and methanol extract of *P. hydropiper* whole plant administered to mice at doses of 250 and 500 mg/kg showed a significant activity on acetic acid-induced writhing. The ethyl acetate fraction showed the highest significant activity [59]. The ethanol extract at 150 mg/kg showed highest inhibition (32.57%) whereas, methanol extract at both 100 and 150 mg/kg showed inhibition of 31.6% as compared to the standard drug Diclofenac (29.32%) [60]. Antinociceptive activity of ethanolic leaf extract was also evaluated by observing the decrease in abdominal writhings in intraperitoneally administered acetic acid-induced pain model in mice [29, 61].

5.7 Anti-hyperglycemic activity of *P. hydropiper*

Ethanol leaf extract of *P. hydropiper* significantly reduced blood sugar level by 48.8, 51.5, 54.1, 58.2%, at the doses of 50, 100, 200 and 400 mg/kg body weight, respectively, performed by using oral glucose tolerance tests, suggesting its anti-hyperglycemic potential [61].

5.8 Antiadipogenic activity of *P. hydropiper*

Methanol extract of *P. hydropiper* and its active compounds- isoquercitrin (50 µM) and isorhamnetin (50 µM), activated the Wnt/β-catenin signalling in human embryonic kidney (HEK 293 TOP) cells, increased nuclear localization of β-catenin in 3T3-L1 adipocyte cells and inhibited adipocyte differentiation, indicating its potential usage as antiobesity agents and for associated disorders [62].

5.9 Anticholinesterase activity of *P. hydropiper*

Anticholinesterase activity of *P. hydropiper* was conducted by Ellman's assay using acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzyme [32, 63, 64]. Ayaz *et al*. (2014) reported that all fractions showed moderate to high AChE inhibitory activity as; Ph.Cr- 86.87% (IC_{50} 330 µg/mL), Ph.Hex- 87.49% (IC_{50} 35 µg/mL), Ph.Chf- 84.76% (IC_{50} 55 µg/mL), Ph.Sp- 87.58% (IC_{50} 108 µg/mL) and Ph.EtAc- 79.95% (IC_{50} 310 µg/mL) at 1 mg/mL. Furthermore, Ph.Hex, Ph.Chf, Ph.Aq and Ph.EtAc fraction also caused 90.30 (IC_{50} 40 µg/mL), 85.94 (IC_{50} 215 µg/mL), 87.62 (IC_{50} 3 µg/mL) and 81.01% (IC_{50} 395 µg/mL) BChE inhibition respectively [32]. Further studies by Ayaz and his co-workers [63] revealed that essential oils isolated from leaves and flowers of *P. hydropiper* caused 87.00% (IC_{50} 120 µg/mL) and 79.66% (IC_{50} 220 µg/mL) inhibition of AChE and 82.66% (IC_{50} 130 µg/mL) and 77.50% (IC_{50} 225 µg/mL) inhibition of BChE respectively at 1000 µg/mL concentration compared to standard drug galanthamine with IC_{50}-15 µg/mL for both AChE and BChE, suggesting its potential usage in the treatment of various neurodegenerative disorders.

5.10 Anti-inflammatory activity of *P. hydropiper*

Methanol leaf extract inhibited in vitro production of inflammatory mediators such as nitric oxide (NO), tumour necrosis factor (TNF)-α and prostaglandin (PG) E_2 in lipopolysaccharide induced RAW264.7 cells and peritoneal macrophages and mRNA levels of inducible NO synthase (iNOS) and cyclooxygenase (COX)-2 by suppressing the activation of Interleukin-1 receptor-associated kinase (IRAK), activator protein-1 (AP1), cAMP response element-binding (CREB) pathways and their upstream signalling enzymes Src/Syk/nuclear factor-kB (NF-kB) [30]. Another study investigated the anti-inflammatory effects of *P. hydropiper* stalks, administered orally at doses of 125, 250 and 500 mg/kg for 7 days to rats with intestinal inflammation induced by 2,4,6-trinitrobenzene sulphonic acid where the extract significantly protected the intestinal inflammation and played a potential role in inhibiting the NF-kB signalling pathways [65].

5.11 Gastroprotective potentials of *P. hydropiper*

P. hydropiper extract (50, 100 and 200 mg/kg) pre-treatment dose-dependently alleviated ethanol induced gastric mucosal injuries in rats mainly by increasing the antioxidant activity, decrease lipid peroxidation and inhibiting the formation of pro-inflammatory cytokines and inflammatory mediators to relieve inflammatory reactions by regulating NF-kB signalling pathways. Flavonoids might be the main effective components against gastric mucosal injury [66].

5.12 Anticancer activity of *P. hydropiper*

Methanol leaf extract of *P. hydropiper* (MPHL) had shown antitumour activity against Ehrlich ascites carcinoma (EAC) cells, inoculated intraperitoneally in albino mice [67]. The extract (25, 50 and 100 mg/kg body weight) significantly decreased body weight, tumour volume, packed cell volume and viable tumour cell count with a concomitant increase in non-viable tumour cell count dose-dependently as compared to EAC control group. The median survival time was also increased to 24.81 (% ILS = 33.21), 31.09 (% ILS = 50.28) and 37.21 (% ILS = 64.11) after administration of MPHL at a dose of 25, 50 and 100 mg/kg body weight respectively compared to the median survival time of 46.60 in the standard drug, bleomycin (% ILS = 85.81). Cytotoxic activity of ethanolic leaf and stem extract of *P. hydropiper* was determined using Brine shrimp (*Artemia salina*) cytotoxicity assay at different concentrations ranging from 10-45 µg/mL. LC_{50} values of the ethanol extract of leaves and stems were 16.22 µg/mL and 35.46 µg/mL when compared with the standard drugs Vincristine sulphate (0.288 µg/mL) and ampicillin (16.18 µg/mL) respectively [53, 61]. Two active components PH-1 (4-methyl-5-oxotetrahydrofuran-3-yl acetate) and PH-2 (methyl 4-hydroxy-3-methoxybenzoate) were tested for cytotoxic activity against cervical cancer cells (HeLA), breast cancer cells (MCF-7) and NIH/3T3 fibroblasts cells cultures using MTT assay [68]. Both PH-1 and PH-2 resulted in 87.50 (LD_{50} 60 µg/mL) and 82.33% (LD_{50} 160 µg/mL) cytotoxicity against MCF-7, 81.45 (LD_{50} 140 µg/mL) and 85.55% (LD_{50} 58 µg/mL) cytotoxicity against NIH/3T3 cells and 77.25 (LD_{50} 170 µg/mL) and 71.90% (LD_{50} 380 µg/mL) cytotoxicity against HeLA cells at 1 mg/mL concentration as compared to standard drug doxorubicin showing 88.53% (LD_{50} 11

µg/mL), 89.40 (LD_{50} 15 µg/mL) and 92.00% (LD_{50} 7 µg/mL) cytotoxicity against MCF-7 cell, NIH/3T3 and HeLA respectively. In anti-tumour assay, PH-1 and PH-2 exhibited 81.15 and 76.09% inhibitions with LD_{50} of 340 and 550µg/L respectively.

5.13 Anti-angiogenic activity of *P. hydropiper*

Anti-angiogenic activity of *P. hydropiper* extracts and saponins were demonstrated using chick embryo chorioallantoic membrane (CAM) assay. Ph.Chf, Ph.Sp, Ph.EtAc and Ph.Cr exhibited highest anti-angiogenic activity causing 78.63, 76.96, 69.43 and 65.33% inhibitions at 1000 µg/mL with IC_{50} of 28.65, 19.21, 88.75, and 461.53µg/mL, respectively [34]. Both PH-1 (4-methyl-5-oxotetrahydrofuran-3-yl acetate) and PH-2 (methyl 4-hydroxy-3-methoxybenzoate) also showed dose-dependent inhibition of blood vessels formation [68].

5.14 Anti-pyretic activity of *P. hydropiper*

In anti-pyretic test, ethanol (200 and 400 mg/kg body weight), methanol (400 mg/kg body weight) and chloroform (200 and 400 mg/kg body weight) leaf extracts of *P. hydropiper* showed considerable reduction of temperature within 1st hour of yeast induced pyrexia in albino mice when compared with standard drug paracetamol [69].

5.15 Sedative and anxiolytic activities of *P. hydropiper*

Methanol (150mg/kg) and chloroform (100mg/kg) extracts of *P. hydropiper* leaves significantly exerted immobile phase like Imipramine (10 mg/kg) indicating anti-depressant like effect of these extracts [60]. Further investigation at different doses (50, 200, 350 and 500 mg/kg) using open field, rota-rod and thiopental sodium-induced sleeping time test; elevated-plus maze, light-dark box, hole-board and marble-burying test in mice revealed its sedative and anxiolytic activities when compared against positive control, diazepam (1 mg/kg) that showed promising activities [70].

5.16 Anti-Alzheimer activity of *P. hydropiper*

In a recent study β-sitosterol, extracted from *P. hydropiper*, was tested for in vitro inhibitory potentials of β-sitosterol on Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) using Ellman's assay; behavioural studies using shallow water maze (SWM), Y-maze and balance beam tests and in vivo inhibitory potentials against cholinesterase's and free radicals in the frontal cortex (FC) and hippocampus (HC) to confirm its possibility as a potential anti-Alzheimer's agent. β-sitosterol presented an IC_{50} value of 55 and 50 µg/mL against AChE and BChE respectively. But activities of these enzymes were significantly low in FC and HC homogenates of transgenic animals. β-sitosterol significantly reduced free radicals load in the brain tissues and showed gradual improvement in working memory, spontaneous alternation behaviour and motor coordination as opposed to the transgenic saline treated groups, suggesting it as a promising component for the management of memory deficit disorders like Alzheimer disease [71].

5.17 Antifertility activity of *P. hydropiper*

P. hydropiper has been reported to possess antifertility activity (East, 1955; Chaudhury, 1966). East (1955) reported that the consumption of dried powder of *P. hydropiper* impaired fertility in both male and female mice and caused sterility in female guinea-pigs when included in the normal diet at a dose of 1 g/mouse/day and 9 g/guinea-pig/day. Alcoholic root extract showed encouraging result and its petroleum ether, petroleum ether+benzene (1:1 v/v) and benzene+chloroform (1:1 v/v) fractions prevented pregnancy in 8/10, 6/10 and 6/10 female albino rats respectively, when administered at a dose of 100 mg/kg body weight. Moreover, petroleum ether and petroleum ether+benzene fractions also caused resorption of implants by the completion of term [72, 73]. Earlier studies have shown that methanol root extract when administered orally at a dose of 1000 mg/kg body weight/day to both ovary-intact and ovariectomized albino rats for 12 consecutive days caused recruitment of ovarian follicles, promoted follicular atresia, induced endometrial hyperplasia and degeneration of endometrial glands [74]. This was confirmed by regulation of endometrial protein expression, supporting the steroidogenic activity of plant extract comparable to 17β-estradiol [75]. Further investigations have manifested that administration of steroid-containing fraction of *P. hydropiper* subcutaneously at a dose of 5 mg/kg body weight/day for 18 days increased proliferation of the endometrial tissue in both ovariectomized and ovary intact females and structural deformation of the cornified cells [76]. The chromatographic fraction also induced changes in the expression of uterine protein. It triggered expression of various uterine proteins in both ovary intact and ovariectomized rats but decreased expression of proteins in pregnant rats of day 5 to day 6 of gestation [77] followed by reduction in the expression of transforming growth factor-βI in the primary decidual zone of the implantation sites of rat uterus [78, 79]. Another study from this laboratory reported disruption of estrous cycle followed by

hormonal imbalance leading to antifertility effect [80].

6. TOXICOLOGY OF *P. hydropiper*

Kuroiwa *et al*. (2006) reported that ethanolic leaf extract of *P. hydropiper* having 7% polygodial showed positive mutagenic effect in Ames test using *Salmonella typhimurium* TA 100 and TA 98 and the chromosomal aberrations test using Chinese hamster-derived CHL/IU cells, but negative mutagenic activity in micronuclei test of bone marrow cells in mouse [81]. Moreover, review of previous literature reported that polygodial gave negative mutagenicity in the Ames test using TA 100, TA 98 and TA 2637 strains of *S. typhimurium* [82] and in the mammalian cell V79/HGPRT assay [83]. Acute toxicity study revealed that administration of aqueous methanolic extract of *P. hydropiper* to mice did not show any sign of toxicity, abnormal behaviour and mortality up to a dose of 4000 mg/kg [39, 69].

7. CONCLUSIONS

P. hydropiper has been used traditionally for ages, owing to its extensive pharmacological properties including antioxidant, antimicrobial, anthehelminthic, cytotoxicity, anti-neoplastic, anti-inflammatory, antinociceptive, estrogenic, antifertility etc. Whole plants or parts were used for treating various ailments. However, as this plant can cause skin irritation, it should be used cautiously [84]. Present-day research works have also focused on the potential usage of *P. hydropiper* as sedatives and in the treatment of anxiety, depression and neurological disorders such as Alzheimer's disease. Although the results observed are encouraging, but most of these research works are carried out using in vitro evaluation systems and in some studies very high doses of extracts were used in experimental animal models, which seems to be problematic. Literature review also revealed that *P. hydropiper* contained various pharmacologically active components like flavonoids, phenylpropanoids, essential oils, phytosterols, sesquiterpenes etc. So, further studies are required to exhibit the relationship between these active components, its traditional usage and reported pharmacological properties so that it can serve as a promising herbal medicinal candidate.

NOTE

The study highlights the efficacy of "traditional medicine" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

DISCLAIMER

Products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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