



Review:

A review of the use of pteridophytes for treating human ailments^{*}

Xavier-ravi BASKARAN^{§1,2}, Antony-varuvel GEO VIGILA^{§3}, Shou-zhou ZHANG²,
 Shi-xiu FENG², Wen-bo LIAO^{†‡1}

¹State Key Laboratory of Biocontrol and Guangdong Key Laboratory of Plant Resources,
 School of Life Sciences, Sun Yat-sen University, Guangzhou 510275, China

²Shenzhen Key Laboratory of Southern Subtropical Plant Diversity, Fairy Lake Botanical Garden /
 Chinese Academy of Sciences, Shenzhen 518004, China

³Department of Zoology, St. Xavier's College, Palayankottai, Tamil Nadu 627002, India

[†]E-mail: lsslwb@mail.sysu.edu.cn

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Abstract: The aim of this review was to explore the pharmacological activity of early tracheophytes (pteridophytes) as an alternative medicine for treating human ailments. As the first vascular plants, pteridophytes (aka, ferns and fern allies) are an ancient lineage, and human beings have been exploring and using taxa from this lineage for over 2000 years because of their beneficial properties. We have documented the medicinal uses of pteridophytes belonging to thirty different families. The lycophyte *Selaginella* sp. was shown in earlier studies to have multiple pharmacological activity, such as antioxidant, anti-inflammatory, anti-cancer, antidiabetic, antiviral, antimicrobial, and anti-Alzheimer properties. Among all the pteridophytes examined, taxa from the Pteridaceae, Polypodiaceae, and Adiantaceae exhibited significant medicinal activity. Based on our review, many pteridophytes have properties that could be used in alternative medicine for treatment of various human illnesses. Biotechnological tools can be used to preserve and even improve their bioactive molecules for the preparation of medicines against illness. Even though several studies have reported medicinal uses of ferns, the possible bioactive compounds of several pteridophytes have not been identified. Furthermore, their optimal dosage level and treatment strategies still need to be determined. Finally, the future direction of pteridophyte research is discussed.

Key words: Pteridophyte; Fern; Alternative medicine; *Selaginella*; Human illness; Bioactive molecule
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1 Introduction

Medicinal plants have been the source of remedies for the treatment of several illnesses since earliest times, and people from all continents have practiced the use of botanicals for millenia. Despite the signif-

icant growth in synthetic organic chemistry in the 20th century, over 25% of approved drugs in industrialized countries are obtained directly or indirectly from plants (Newman et al., 2000). In recent years, the search for phytochemicals with antioxidant, antimicrobial, or anti-inflammatory properties has been on the rise due to their potential use for the treatment of various chronic and infectious diseases (Halliwell, 1996). Therapeutic plants may be an alternative source of antimicrobial agents with important bioactivity against pathogenic and transmissible microorganisms, with fewer side effects than synthetic antibiotics (Berahou et al., 2007). Plant extracts have numerous secondary metabolites, such as phenolic

[‡] Corresponding author

[§] The two authors contributed equally to this work

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ORCID: Wen-bo LIAO, <https://orcid.org/0000-0001-6839-9511>

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components, that enhance biological activity. Plant secondary metabolites are known to possess antimicrobial and antioxidant properties, and some of them are categorized as generally recognized safe substances (Proestos et al., 2005). With the growing interest in these compounds, phytochemicals from therapeutic plants with some biomedical activity are in great demand (Chen et al., 2008; Pesewu et al., 2008; Prachayasittikul et al., 2008).

Ferns and their allies are one of the oldest major divisions of the Pteridophyta, and comprise over 12000 species spread among 250 different genera (Chang et al., 2011). Traditionally, the biomedical system and Ayurvedic systems of medicine, named Sushruta (ca. 100 AD) and Charka (ca. 100 AD), suggested the use of some ferns in the *Samhita* texts. Pteridophytes are also used by physicians in the Unani system of medicine (Uddin et al., 1998). In the traditional Chinese system of medicine, several ferns are recommended by native doctors (Kimura and Noro, 1965). In more recent times, ethnobotanical and advanced pharmacological studies have been carried out on ferns and their allies by several investigators (Dhiman, 1998; Vasudeva, 1999; Reddy et al., 2001; Singh L et al., 2001; Gogoi, 2002; Singh M et al., 2008a, 2008b; Chen JJ et al., 2005; Chen K et al., 2005).

2 Phytochemicals of ferns and their distribution in other plant groups

The secondary metabolites, flavonoids, have anti-inflammatory properties through the inhibition of the cyclo oxygenase (COX) pathway (Liang et al., 1999). They were also found to have antioxidant, anti-cancer, and antimicrobial properties (Lin et al., 2008; Yoshida et al., 2008; Amaral et al., 2009; Lopez-Lazaro, 2009; Govindappa et al., 2011). Spider brake fern (*Pteris multifida*) has various bioactive flavonoids with heat-clearing, antipyretic, detoxification, antibiotic, anti-inflammatory, and antimutagenic activity (Lee and Lin, 1988). The entire plant of *P. multifida* contains various bioactive compounds including: luteolin-7-*O*-glucoside (Murakami and Machashi, 1985; Lu et al., 1999), 16-hydroxy-kaurane-2- β -D-glucoside (Liu and Qin, 2002), luteolin, palmitic acid, apigenin 4-*O*- α -L-rhamnoside (Lu et al.,

1999; Qin et al., 2006), quercetin, hyperin, isoquercitrin, kaempferol, rutin (Lu et al., 1999; Wang et al., 2010; Hoang and Tran, 2014), and apigenin-7-*O*- β -D-glucoside (Lu et al., 1999; Hoang and Tran, 2014). Also, the cytotoxic bioactive compounds, pterisin sesquiterpenes, have been isolated from *P. multifida* (Shu et al., 2012). Bioactive terpenoids, especially the monocyclic sesquiterpene α -caryophyllene, were found in an ethanolic extract of *Pteris tripartita* (Baskaran and Jeyachandran, 2010). Sesquiterpenes form a significant group of secondary metabolites and have a varied range of medicinal activity, including anti-cancer, anti-inflammatory, cytotoxic, plant growth-regulatory, and antimicrobial properties (Baruah et al., 1994).

The anti-inflammatory activity of fatty acids such as myristic, palmitic, stearic, oleic-linoleic, and eicosatrienoic acids are widely known (Bremner and Heinrich, 2002). Stearic acid has been shown to have both anti-inflammatory and hepatoprotective effects (Pan et al., 2010). Baskaran and Jeyachandran (2010) found octadecanoic acid (a stearic acid) in an ethanol extract of *P. tripartita*. *Pteridium aquilinum*, thought to be a fern with potent anti-cancer properties, contains *p*-coumaric, *p*-hydroxybenzoic, caffeic, ferulic, vanillic, and protocatechuic acids (Michael and Gillian, 1984). Hydroxycinnamic acid, anthocyanins, total polyphenols, and flavonoids have been quantified in *Stenochlaena palustris* (Chai et al., 2012). Some bioactive flavones such as amentoflavone, robustaflavone, biapigenin, hinokiflavone, podocarpusflavone A, and ginkgetin, in *Selaginella* sp. were reported to have antioxidant, antiviral, and anti-cancer activity (Ma et al., 2001; Shi et al., 2008; Liu et al., 2011; Li S et al., 2014). Both the whole plant and mature spores of *Lygodium japonicum* are used for medical purposes in traditional Chinese medicine. For over 2000 years, *L. japonicum* has been used in China for the treatment of gorge gall, skin eczema, enteritis diarrhea, nephritis dropsy, urine calculus, and infection (Wynne et al., 1998). The foremost phenolic components, namely 4-hydroxycinnamic acid (*p*-coumaric), 3-methoxy-4-hydroxycinnamic acid (ferulic), 3,4-dihydroxycinnamic acid (caffeic), 3-methoxy-4-hydroxybenzoic acid and 3-caffeoilquinic acid (chlorogenic), have been found in *Polypodium leucotomos* extracts (Gombau et al., 2006). The free radical scavenging bioactive principles viz. flavan-4-ol

glycosides, abacopterins, huperzine A, isoquercetin, di-*E*-caffeoyl-*meso*-tartaric acid, flavaspidic acid PB, flavaspidic acid AB, flavan-3-ol, kaempferol, A-type proanthocyanidins, and afzelechin, have been derived from a few ferns including *Abacopteris penangiana*, *Huperzia selago*, *Equisetum arvense*, and *Dryopteris crassirhizoma* (Lee et al., 2003; Staerk et al., 2004; Zhao et al., 2007; Mimica et al., 2008). Fig. 1 and Table 1 list the distribution of numerous bioactive compounds present in pteridophytes.

Marchantiophyta have a cellular oil body which produces numerous mono-, sesqui-, and di-terpenoids, aromatic compounds like bibenzyl, bis-bibenzyls, and acetogenins. Most sesqui- and di-terpenoids isolated from non-vascular plants (liverworts) are enantiomers of those present in vascular plants (Asakawa et al., 2013). Since 1960, studies have begun to identify triterpenoids in ferns too. Moreover, flavonoids are

present in more than one genus of ferns and also occur in fern allies (Berti and Bottari, 1968). Pteridophytes are known to produce proanthocyanidins which are present in a polymerized molecular form, as tannins. Proanthocyanidins in higher groups of plants are formed by dihydroflavonol-4-reductase (DFR) using dihydroflavonols as substrate. The DFR enzyme has not been described in pteridophytes, but the genomic characterization of ferns has begun. DFR has been obtained from duplicate genes linked with primary metabolism; in this instance, nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reductases are related to steroid metabolism (Baker and Blasco, 1992). Moreover, three divisions of the flavonoid pathway well-known in the bryophytes are also found in pteridophytes including procyanidins, prodelpinidins, and flavonols like kaempferol, quercetin, and myricetin (Markham, 1988). Acylphloroglucinol

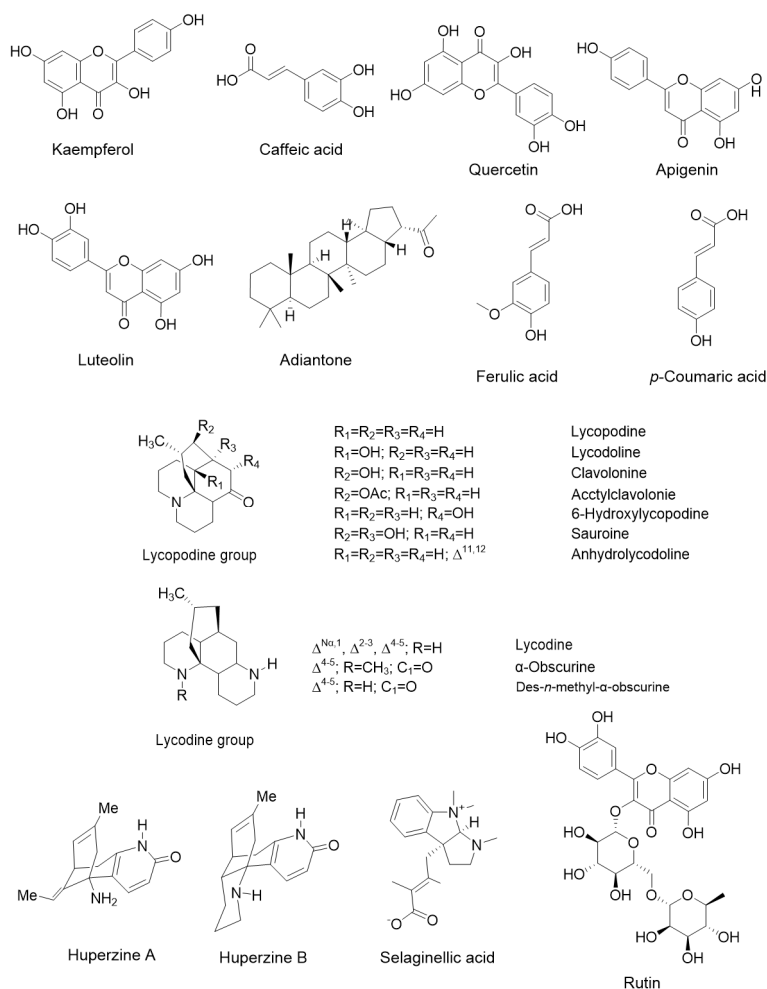


Fig. 1 Bioactive compounds in pteridophytes

Table 1 Distribution of bioactive compounds in pteridophytes

No.	Pteridophyte	Bioactive compounds	Source(s)
1	<i>Pteris multifida</i>	Luteolin-7- <i>O</i> -glucoside, 16-hydroxy-kaurane-2- β -D-glucoside, luteolin, palmitic acid, apigenin-4- <i>O</i> - α -L-rhamnoside, quercetin, hyperin, isoquercitrin, kaempferol, rutin, apigenin-7- <i>O</i> - β -D-glucoside, and pterisin	Murakami and Machashi, 1985; Lu et al., 1999; Liu and Qin, 2002; Qin et al., 2006; Wang et al., 2010; Shu et al., 2012; Hoang and Tran, 2014
2	<i>Pteris tripartita</i>	α -Caryophyllene and octadecanoic acid	Baskaran and Jeyachandran, 2010
3	<i>Abacopteris penangiana</i>	Flavan-4-ol, glycosides, and abacopterins	Zhao et al., 2007
4	<i>Pteridium aquilinum</i>	<i>p</i> -Coumaric acid, <i>p</i> -hydroxybenzoic acid, caffeic acid, ferulic acid, vanillic acid, protocatechuic acid, kaempferol, quercetin, and apigenin	Michael and Gillian, 1984
5	<i>Selaginella</i> sp.	Amentoflavone, robustaflavone, biapigenin, hinokiflavone, podocarpusflavone A, and ginkgetin	Ma et al., 2001; Shi et al., 2008; Liu et al., 2011; Li S et al., 2014
6	<i>Equisetum arvense</i>	Isoquercetin, quercetin 3- <i>O</i> -glucoside, quercetin 3- <i>O</i> -(6"- <i>O</i> -malonylglucoside), 5- <i>O</i> -caffeoyl <i>meso</i> -tartaric acid, monocaffeoyl <i>meso</i> -tartaric acid, mono-caffeoyl <i>meso</i> -tartaric acid, di- <i>E</i> -caffeoyl- <i>meso</i> -tartaric acid, hexahydrofarnesyl acetone, <i>cis</i> -geranyl acetone, thymol, and <i>trans</i> -phytol	Radulovic et al., 2006; Milovanovic et al., 2007; Mimica et al., 2008
7	<i>Polypodium leucotomos</i>	4-Hydroxycinnamic acid (<i>p</i> -coumaric), 3-methoxy-4-hydroxycinnamic acid (ferulic), 3,4-dihydroxycinnamic acid (caffeic), 3-methoxy-4-hydroxybenzoic acid, and 3-caffeoylquinic acid (chlorogenic)	Gombau et al., 2006
8	<i>Adiantum capillus-veneris</i>	Adiantone, adiantoxide, astragalol, β -sitosterol, caffeic acids, caffeoylgalactose, caffeoylglucose, campesterol, carotenes, coumaric acids, coumarylglucoses, diplopterol, epoxyfilicane, fernadiene, fernene, filicanes, hopanone, hydroxy-adiantone, hydroxy-cinnamic acid, isoadiantone, isoquercetin, kaempferols, lutein, mutatoxanthin, naringin, neoxanthin, nicotiflorin, oleananes, populnin, procyanidin, prodelphinidin, quercetins, querciturone, quinic acid, rhodoxanthin, rutin, shikimic acid, violaxanthin, and zeaxanthin	Taylor, 2003
9	<i>Dryopteris crassirhizoma</i>	Flaspidic acid PB and flavaspidic acid AB	Lee et al., 2003
10	<i>Cyathea gigantea</i>	β -Sitosterol	Woyengo, 2009
11	<i>Cibotium barometz</i>	Pterosins, terpenoids, sterides, flavones, glucosides, aromatic, and pyrone compounds	Wu et al., 2007; Xu et al., 2012
12	<i>Cyathea phalerata</i>	Kaempferol-3-neohesperidoside, 4- <i>O</i> - β -D-glucopyranosyl caffeic acid, 4- <i>O</i> - β -D-glucopyranosyl <i>p</i> -coumaric acid, 3,4-spyroglucopyranosyl protocatechuic acid, sitosterol β -D-glucoside, β -sitosterol, kaempferol, and vitexin	Hort et al., 2008
13	<i>Pteris vittata</i>	Rutin, kaempferol monoglycoside, kaempferol diglycoside, quercetin monoglycoside, and quercetin diglycoside	Salatino and Prado, 1998; Singh et al., 2008b
14	<i>Polypodium leucotomos</i>	3,4-Dihydroxybenzoic acid, chlorogenic acid, 4-hydroxybenzoic acid, chlorogenic acid, vanillic acid, caffeic acid, 4-hydroxycinnamic acid, 4-hydroxycinnamoyl-quinic acid, and ferulic acid	Garcia et al., 2006
15	<i>Angiopteris evecta</i>	Angiopterioside	Twentyman et al., 1989
16	<i>Onoclea sensibilis</i>	Kaempferol and quercetin	Harada and Saiki, 1955
17	<i>Matteuccia struthiopteris</i>	Kaempferol and quercetin	
18	<i>Equisetum ramoissimum</i>	Apigenin and luteolin	

To be continued

Table 1

No.	Pteridophyte	Bioactive compounds	Source(s)
19	<i>Lycopodium japonicum</i>	Lycopodine-type alkaloids	He et al., 2014
20	<i>Lycopodium sieboldii</i>	Sieboldine A	Hirasawa et al., 2003
21	<i>Lycopodium casuarinoides</i>	Huperzine B and <i>N</i> -demethylhuperzine	Shen and Chen, 1994
22	<i>Selaginella tamariscina</i>	Caffeic acid, ferulic acid, vanillic acid, syringic acid, adenosine, umbelliferone, and amentoflavone	Bi et al., 2004; Zheng et al., 2004; Woo et al., 2005
23	<i>Selaginella moellendorffii</i>	Moellenoside B and selaginellinic acid	Wang et al., 2009b; Feng et al., 2011
24	<i>Selaginella doederleinii</i>	Apigenin and hordenine	Chao et al., 1987; Chen et al., 1995
25	<i>Dicranopteris linearis</i>	Afzelin, quercitrin, isoquercitrin, astragalin, rutin, kaempferol 3- <i>O</i> -(4- <i>O</i> - <i>p</i> -coumaroyl-3- <i>O</i> - α -l-rhamnopyranosyl)- α -l-rhamnopyranosyl-(1 \rightarrow 6)- β -D-glucopyranoside, and (6S,13S)-6-[6- <i>O</i> -acetyl- β -D-glucopyranosyl-(1 \rightarrow 4)- α -l-rhamnopyranosyloxy]-13-[α -l-rhamnopyranosyl-(1 \rightarrow 4)- β -D-fucopyranosyloxy] cleroda-3,14-diene	Raja et al., 1995; Zakaria et al., 2008
26	<i>Psilotum nudum</i>	Quercetin, kaempferol, amentoflavone, hinokiflavone, vicenin-2 psilotin, and 3'-hydroxypsilotin	Cambie and Ash, 1994
27	<i>Huperzia selago</i>	Huperzine A	Staerk et al., 2004
28	<i>Huperzia serrata</i>	Alkaloids: huperzine A and B	Liu et al., 1986
29	<i>Pityrogramma tartarea</i>	2'6'-dihydroxy-4,4'-dimethoxydihydrochalcone, kaempferol 7-methyl ether, and apigenin 7-methyl ether	Star and Mabry, 1971
30	<i>Pityrogramma calomelanos</i>		
31	<i>Cheilanthes concolor</i>	7- <i>O</i> -Glycosides of apigenin, aglycone, 7- <i>O</i> -glycosides of luteolin, 7- <i>O</i> -glycosides of chrysoeriol, 3- <i>O</i> -glycosides of kaempferol, 3- <i>O</i> -glycosides of quercetin	Salatino and Prado, 1998
32	<i>Cheilanthes flexuosa</i>		
33	<i>Cheilanthes goyazensis</i>		
34	<i>Doryopteris ornithopus</i>		
35	<i>Pellaea cymbiformis</i>		
36	<i>Pellaea gleichenioides</i>		
37	<i>Pellaea pinnata</i>		
38	<i>Pellaea riedelii</i>		
39	<i>Pteris altissima</i>		
40	<i>Pteris angustata</i>		
41	<i>Pteris decurrens</i>		
42	<i>Pteris deflexa</i>		
43	<i>Pteris denticulata</i>		
44	<i>Pteris plumula</i>		
45	<i>Pteris podophylla</i>		
46	<i>Pteris splendens</i>		
47	<i>Pteris propinqua</i>		
48	<i>Cyrtomium fortunei</i>	Protocate chaldehyde, woodwardinsure methylester, physcion, pimpinellin, ursolic acid, sitost-4-en-3-one, betulin, 3',4',5-trihydroxy-3,7-dimethoxyflavone, woodwardinic acid, sutchuenoside A, kaempferol-3,7- <i>O</i> - α -l-dirhamnoside, (-)-epicatechin, (+)-catechin hydrate kaempferol, crassirhizomside A, and kaempferol-3- <i>O</i> -(3- <i>O</i> -acetyl- α -l-rhamnopyranoside	Yang et al., 2013

compounds are found only in the genus *Dryopteris*, which has been used in chemosystematic and phylogenetic studies (Widen, 1971; Widen and Britton, 1971a, 1971b). Flavonoids and phenolic compounds are the most general group of bioactive principles in plants, occurring in almost all plant parts, but mainly in photosynthesizing cells. These compounds are the main producers of the colors of blooming plants (Koes et al., 2005). In early studies, myricetin, quercetin, kaempferol, apigenin, luteolin, and gallic acid were reported in angiosperms including the Hamamelidaceae, Rutaceae, Eriocaulaceae, Lythraceae, and Velloziaceae (Grieve and Scora, 1980; Giannasi, 1986; Salatino et al., 2000). Several phenolic compounds, such as *p*-coumaric acid, caffeic acid, ferulic acid, protocatechuic acid, gallic acid, vanillic acid, and flavonoids like luteolin, apigenin, have also been identified in seagrasses (Subhashini et al., 2013). Apigenin, kaempferol, luteolin, myricetin, quercetin, and rutin were identified in some Iranian flowering plants from different families including the Leguminosae, Polygonaceae, Euphorbiaceae, Resedaceae, and Cyperaceae (Mitra, 2012). The bioactive flavonoids, kaempferol, luteolin, quercetin, quercitrin, isoquercitrin, hyperoside, and guaijaverin, have been derived from methanol extracts of *Hypericum brasiliense* (Rocha et al., 1995). In addition, kaempferol, myricetin, catechin, vitexin, orientin, isoquercitrin, hyperside, isovitexin, luteolin-7-glucoside, rutin, kaempferol-7-neohesperidoside, quercetin, luteolin, and apigenin have been identified in the angiosperm families Lythraceae, Acanthaceae, Chenopodiaceae, Caprifoliaceae, Euphorbiaceae, Verbenaceae, Zygophyllaceae, Moraceae, Asteraceae, Urticaceae, Scrophulariaceae, Verbenaceae, and Mimosaceae (Khan et al., 2012). The evolution of flavonoids in land plants has been discussed from an enzymatic point of view. In ferns and their allies, proanthocyanidin and NADPH reductase are present for flavonoid synthesis while anthocyanidin and pterocarpan synthase have been reported in gymnosperms and angiosperms. Moreover, at two different levels, chalcone synthase, chalcone isomerase, anthocyanidin synthase, flavonol synthase, isoflavone synthase, and NADPH reductase are also involved in flavonoid synthesis (Stafford, 1991). These studies show that all land plants are related based on the evidence of shared secondary metabolites. The genetic relationships among genes in response to phytochemical

synthesis in vascular and non-vascular plant groups should be studied further to understand their phytochemical evolution.

3 Activity of ferns

3.1 Antioxidant activity

Most of the pteridophytes are of great economic value, especially in medical, aesthetic, and food applications (Vasudeva, 1999). Table 2 summarizes the antioxidant activity of pteridophytes. The antioxidant activity has been reported for several fern species, namely *Polystichum semifertile*, *Nothoperanema hendersonii*, *Braomea insignis* (Chen K et al., 2005), some Chinese ferns (31 species) (Ding et al., 2008), *Selaginella* sp. (Gayathri et al., 2005), *Polyopodium leucotomus* (Garcia et al., 2006; Gombau et al., 2006), *E. arvense*, *Equesitum sylvaticum* (Milovanovic et al., 2007), *A. penangiana* (Zhao et al., 2007), *Drynaria fortunei*, *Pseudodrynaria coronans*, *Davallia divaricata*, *Davallia mariesii*, *Davallia solida*, *Humata griffithiana* (Chang et al., 2007b), *Marsilea quadrifolia* (Fig. 2c) (Ripa et al., 2009), *Cheilanthes anceps* Swartz (Chowdhary et al., 2010), *Pteris ensiformis* Burm. (Chen et al., 2007; Wei et al., 2007), *P. multifida* (Shyur et al., 2005; Wang et al., 2009a), *P. tripartita* (Baskaran and Jeyachandran, 2010), *Dicranopteris linearis* (Fig. 2d) (Zakaria et al., 2011), and *Drynaria quercifolia* (Fig. 2e) (Milan et al., 2013). Efficient antioxidant properties (0.02–0.12 mg/ml in 2,2-diphenyl-1-picrylhydrazyl (DPPH) activity and 0.03–0.22 mg/ml in activity of 2,2'-azino-bis-(3-ethyl benzthiazoline-6-sulphonie acid diammonium salt (ABTS) radical scavenging) of several fern genera like *Davallia*, *Hypolepis*, *Pteridium*, *Cyrtominum*, *Dryopteris*, *Polystichum*, *Dicranopteris*, *Lycopodium*, *Osmunda*, *Adiantum*, *Coniogramme*, *Polypodium*, *Pyrrosia*, *Pteris*, *Lygodium*, *Selaginella*, *Thelypteris*, *Athyrium*, *Matteuccia*, *Onoclea*, and *Woodsia* have also been reported (Shin, 2010). According to Shin and Lee (2010), scavenging effects on DPPH and ABTS radicals were higher in methanol extracts from rhizomes than in those from aerial parts of *Adiantum pedatum*, *Coniogramme japonica*, *D. mariesii*, *Cyrtominum fortunei*, *D. crassirhizoma*, *Polystichum polyblepharum*, *Polystichum lepidocaulon*, *Dryopteris nipponensis*, *Pteris cretica*, *P. multifida*, and *Polypodium nipponica*.

Table 2 Antioxidant potentials of pteridophytes

No.	Plant name	Family name	Methods used	Source(s)
1	<i>Polystichum semifertile</i>	Dryopteridaceae	Xanthine oxidase, lipoxygenase activity, and ABTS ⁺⁺ assay	Chen et al., 2005a
2	<i>Nothoperanema hendersonii</i>	Dryopteridaceae		
3	<i>Braomea insignis</i>	Blechnaceae		
4	<i>Blechnum orientale</i>	Blechnaceae	DPPH assay	Lai et al., 2010
5	<i>Selaginella</i> sp. (n=3)	Selaginellaceae	In vitro lipid peroxidation, hydroxyl radical scavenging activity	Gayathri et al., 2005
6	<i>Polypodium leucotomus</i>	Polypodiaceae	H ₂ O ₂ and FRAP assays	Garcia et al., 2006; Gombau et al., 2006
7	<i>Equisetum</i> sp. (n=5)	Equisetaceae	Total antioxidant capacity	Milovanovic et al., 2007
8	<i>Abacopteris penangiana</i>	Thelypteridaceae	Trolox equivalent antioxidant capacity (TEAC) assay	Zhao et al., 2007
9	<i>Marsilea quadrifolia</i>	Marsileaceae	DPPH assay	Ripa et al., 2009
10	<i>Cheilanthes anceps</i>	Sinopteridaceae	DPPH assay	Chowdhary et al., 2010
11	<i>Pteris ensiformis</i>	Pteridaceae	DPPH and TEAC assays	Chen et al., 2007; Wei et al., 2007
12	<i>Pteris multifida</i>	Pteridaceae	DPPH, superoxide scavenging activity	Shyur et al., 2005; Wang et al., 2009a
13	<i>Pteris tripartita</i>	Pteridaceae	DPPH, metal chelating activity, phosphomolybdenum assay	Baskaran and Jeyachandran, 2010
14	<i>Dicranopteris linearis</i>	Gleicheniaceae	DPPH assay	Milan et al., 2013
15	<i>Selaginella labordei</i>	Selaginellaceae	In vitro xanthine oxidase inhibition	Tan et al., 2009
16	<i>Diplazium polypodioides</i>	Athyriaceae	DPPH assay	Kshirsagar and Upadhyay, 2009
17	<i>Pteris vittata</i>	Pteridaceae	DPPH and ferric reducing power assays	Lai and Lim, 2011
18	<i>Adiantum radianum</i>	Pteridaceae		
19	<i>Acrostichum aureum</i>	Pteridaceae		
20	<i>Cyathea latebrosa</i>	Cyatheaceae		
21	<i>Cibotium barometz</i>	Dicksoniaceae		
22	<i>Drynaria quercifolia</i>	Polypodiaceae		
23	<i>Blechnum orientale</i>	Blechnaceae		
24	<i>Diplazium esculentum</i>	Athyriaceae		
25	<i>Nephrolepis biserrata</i>	Nephrolepidaceae		
26	<i>Dicranopteris linearis</i>	Gleicheniaceae		
27	<i>Dicksonia sellowiana</i>	Dicksoniaceae	In vitro and in vivo antioxidant assays	Bora et al., 2005; Rattmann et al., 2011; Oliveira et al., 2016
28	<i>Microgramma vacciniifolia</i>	Polypodiaceae	In vitro DPPH assay	Peres et al., 2009
29	<i>Polypodium leucotomos</i>	Polypodiaceae	In vitro H ₂ O ₂ assay	Gombau et al., 2006
30	<i>Davallia mariesii</i>	Davalliaceae	In vitro DPPH, ABTS ⁺⁺ , and total antioxidant assays	Shin, 2010; Delong et al., 2011
31	<i>Cyrtomium fortunei</i>	Dryopteridaceae		
32	<i>Dryopteris crassirhizoma</i>	Dryopteridaceae		
33	<i>Dryopteris nipponensis</i>	Dryopteridaceae		
34	<i>Polystichum lepidocaulon</i>	Dryopteridaceae		
35	<i>Polystichum polyblepharum</i>	Dryopteridaceae		
36	<i>Dicranopteris pedata</i>	Gleicheniaceae		
37	<i>Osmunda cinnamomea</i> var. <i>fokiensis</i>	Osmundaceae		
38	<i>Osmunda japonica</i>	Osmundaceae		

To be continued

Table 2

No.	Plant name	Family name	Methods used	Source(s)
39	<i>Adiantum pedatum</i>	Pteridaceae	In vitro DPPH, ABTS ⁺ , and total antioxidant assays	Shin, 2010; Delong et al., 2011
40	<i>Pyrrosia lingua</i>	Polypodiaceae		
41	<i>Lygodium japonicum</i>	Lygodiaceae		
42	<i>Thelypteris acuminata</i>	Thelypteridaceae		
43	<i>Athyrium niponicum</i>	Athyriaceae		
44	<i>Onoclea sensibilis</i> var. <i>interrupta</i>	Onocleaceae		
45	<i>Matteuccia struthiopteris</i>	Onocleaceae		
46	<i>Aleuritopteris flava</i>	Pteridaceae	DPPH, ABTS ⁺ , ferric reducing power, and metal chelating assays	Gupta et al., 2014
47	<i>Pteris scabristipes</i>	Pteridaceae		
48	<i>Adiantum edgeworthii</i>	Pteridaceae		
49	<i>Lindsaea odorata</i>	Dennstaedtiaceae		
50	<i>Microlepia rhomboidea</i>	Dennstaedtiaceae		
51	<i>Microlepia hallbergii</i>	Dennstaedtiaceae		
52	<i>Asplenium khasianum</i>	Aspleniaceae		
53	<i>Diplazium esculentum</i>	Athyriaceae		
54	<i>Athyrium filix-femina</i>	Athyriaceae	Oxygen radical absorbance capacity	Soare et al., 2012a
55	<i>Dryopteris affinis</i>	Dryopteridaceae		
56	<i>Dryopteris filix-mas</i>	Dryopteridaceae		
57	<i>Dryopteris cochleata</i>	Dryopteridaceae	DPPH, ABTS ⁺ , superoxide, nitric oxide, hydroxide, reducing power, ferrous chelating, and lipid peroxidation assays	Kathirvel et al., 2014

According to Kshirsagar and Upadhyay (2009), methanol extracts of *Diplazium polypodioides* and ethyl acetate or water extracts of *Blechnum orientale* show strong antioxidant capacity (Lai et al., 2010). Lai and Lim (2011) reported that *Pteris vittata*, *Cyathea latebrosa*, *Cibotium barometz* (Fig. 2f), *D. quercifolia*, *B. orientale* (Fig. 2g), *Adiantum radianum*, *Diplazium esculentum*, *Acrostichum aureum*, *Nephrolepis biserrata*, and *D. linearis* exhibited strong antioxidant activity ranging from 0.12 to 0.57 mg/ml. The presence of phenolics in extracts of *Dicksonia sellowiana* may contribute directly to its antioxidant properties (Duh et al., 1999; Bora et al., 2005). Ethanolic and ethyl acetate extracts showed good antioxidant action based on the DPPH radical scavenging assay in *Microgramma vacciniifolia* (Peres et al., 2009). According to Hort et al. (2008), the antioxidant activity and hepatoprotective potential of crude extracts are based on organic solvents of increasing polarity. Gombau et al. (2006) demonstrated that hexane and chloroform extracts of *P. leucotomos* had significant inhibitory activity/strong antioxidative properties, based on an H₂O₂ (hydrogen

peroxide) assay. The antioxidant properties of methanol extracts of rhizomes and fronds of *D. mariesii*, *C. fortunei*, *D. crassirhizoma*, *D. nipponensis*, *P. lepidocaulon*, *P. polyblepharum*, *Dicranopteris pedata*, *Osmunda cinnamomea* var. *fokiensis* (Fig. 3f), *Osmunda japonica*, *A. pedatum*, *Pyrrosia lingua*, *L. japonicum* (Fig. 2b), *Thelypteris acuminata*, *Athyrium niponicum*, *Matteuccia struthiopteris* (Fig. 3h), and *Onoclea sensibilis* var. *interrupta* were reported by Shin (2010) and Delong et al. (2011).

Methanol leaf extracts of *P. multifida* showed stronger antioxidant activity than ethanol extracts (Hoang and Tran, 2014). In a DPPH assay of *S. palustris*, antioxidant activity was higher in mature fertile (2.29 mg TE/mg GAE; TE: Trolox equivalent; GAE: gallic acid equivalent) and sterile (2.07 mg TE/mg GAE) fronds than in young fertile (1.99 mg TE/mg GAE) and sterile (1.80 mg TE/mg GAE) fronds. Moreover, significantly higher metal chelating activity was observed in young sterile fronds (101.22 µg EDTA/mg GAE; EDTA: ethylenediaminetetraacetic acid) and mature fertile fronds (176.37 µg EDTA/mg GAE) than in young fertile fronds (82.14 µg EDTA/mg

GAE) and mature sterile fronds (16.54 μg EDTA/mg GAE) (Chai et al., 2012). Methanol extracts from aerial plant parts of eleven different species of pteridophytes from Korea, namely *A. pedatum*, *C. japonica*, *D. mariesii*, *C. fortunei*, *D. crassirhizoma*,

P. polyblepharum, *P. lepidocolon*, *D. nipponensis*, *P. cretica*, *P. multifida*, and *P. nipponica* displayed significant DPPH scavenging activity ranging from 0.05 to 1.66 mg/ml while the activity of rhizome extracts ranged only from 0.02 to 4.99 mg/ml. Using ABTS

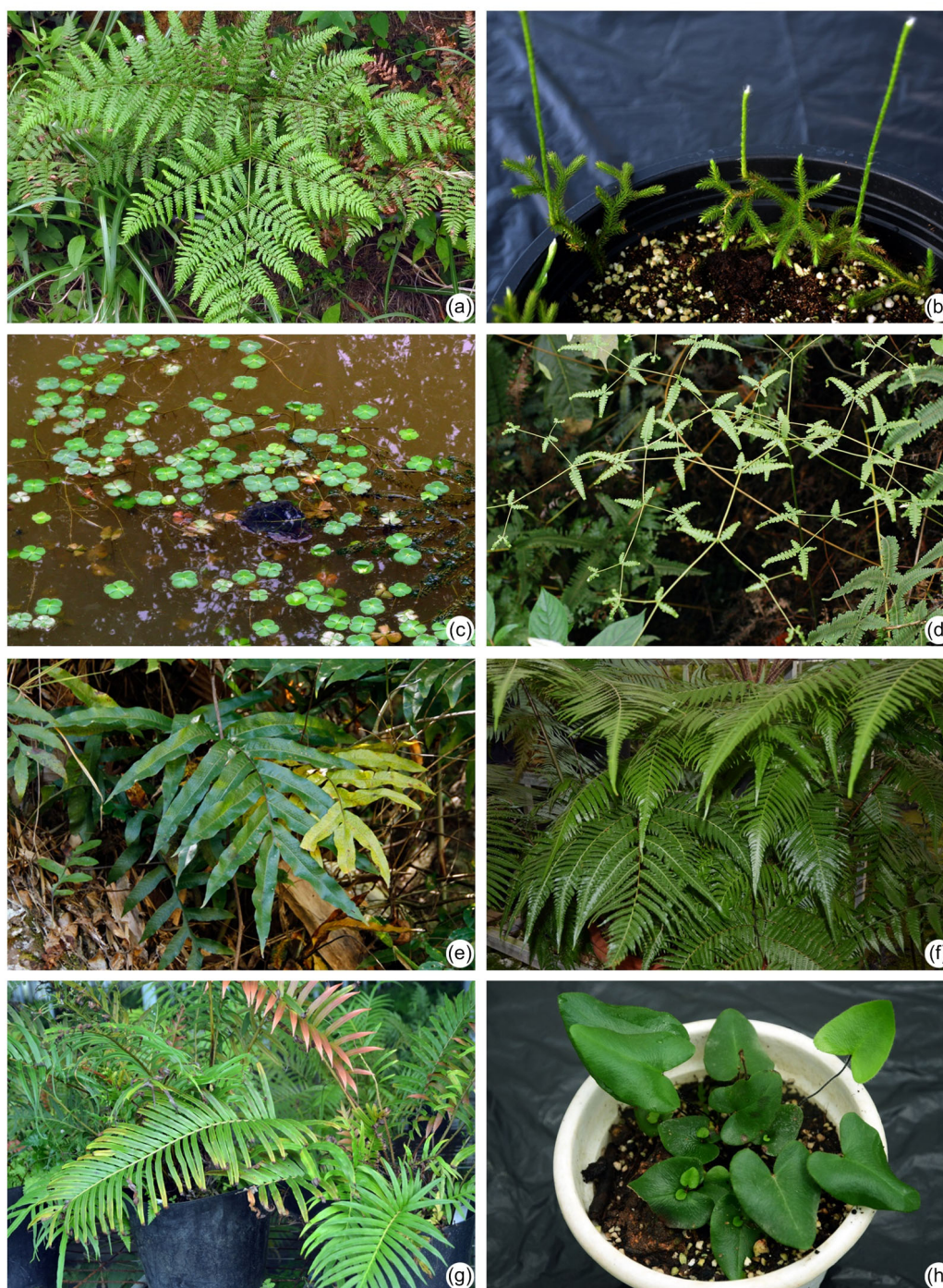


Fig. 2 Color illustrations of medicinal pteridophytes: (a) *P. aquilinum*; (b) *Lycopodium japonicum*; (c) *Marsilea quadrifolia*; (d) *Dicranopteris linearis*; (e) *Drynaria quercifolia*; (f) *Cibotium barometz*; (g) *Blechnum orientale*; (h) *Hemionitis arifolia*

Note: for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article

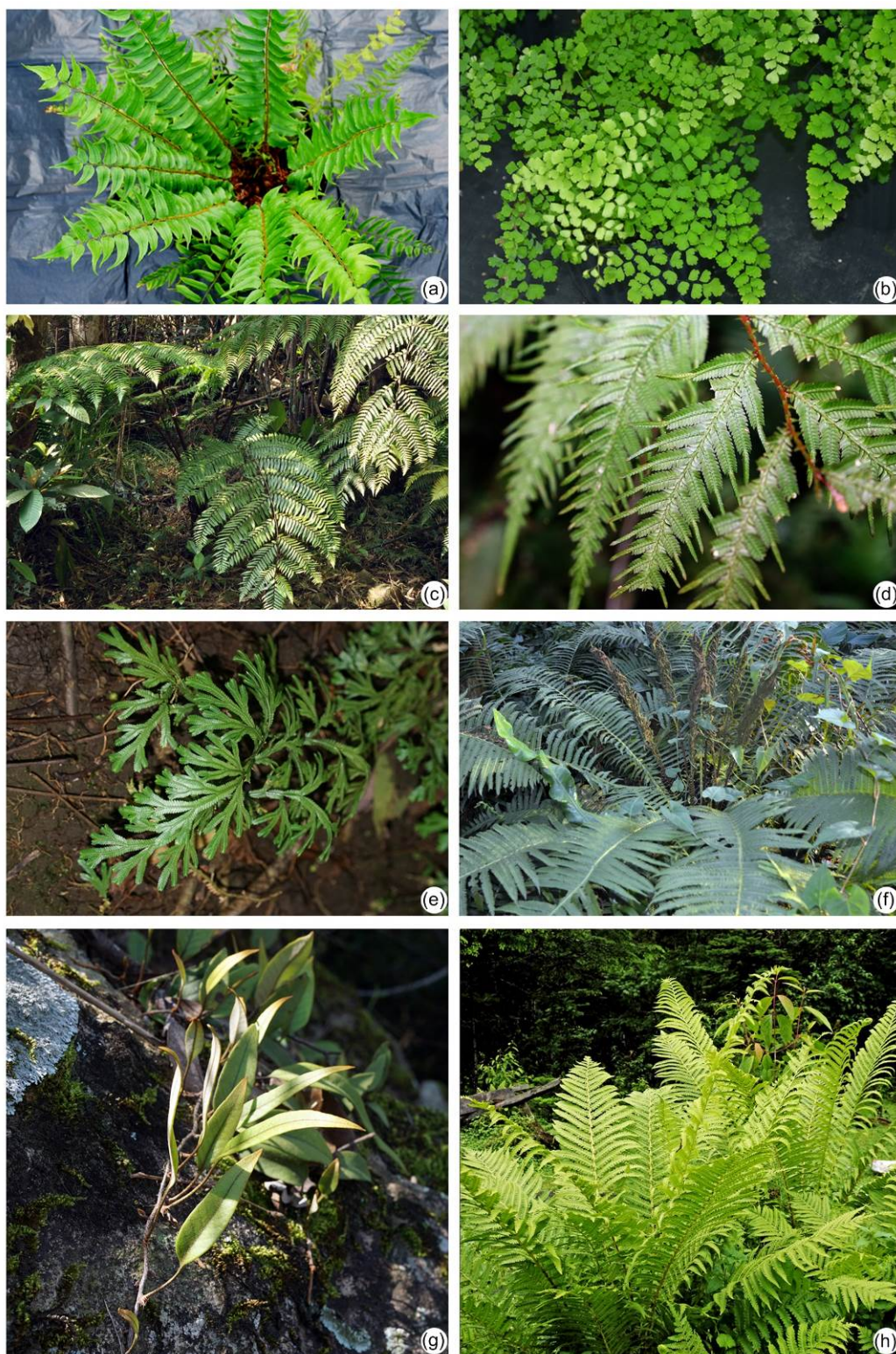


Fig. 3 Color illustrations of medicinal pteridophytes: (a) *Cyrtomium fortunei*; (b) *Adiantum capillus-veneris*; (c) *Cyathea gigantea*; (d) *Selaginella willdenowii*; (e) *Selaginella doederleinii*; (f) *Osmunda cinnamomea*; (g) *Pyrrosia lingua*; (h) *Matteuccia struthiopteris*

Note: for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article

assays, Zakaria et al. (2011) found 0.06 to 0.53 mg/ml of activity in methanol extracts from aerial plant parts and 0.03 to 1.24 mg/ml in rhizome extracts. In DPPH assays, methanol extracts from leaves of *D. linearis* exhibited higher antioxidant activity (20 µg/ml) (37.8%) than aqueous (29.3%) or chloroform extracts (13.3%). In *D. linearis*, superoxide scavenging activity was the highest in methanol extracts (84.2%), moderate in aqueous extracts (62.1%), and the lowest in chloroform extracts (23.2%) (Milan et al., 2013). Methanol extracts of *D. polypodioides* displayed only 5.87% antioxidant activity in DPPH assays (Kshirsagar and Upadhyay, 2009). The ethyl acetate, butanol, and water fractions of *B. orientale* revealed significant free radical scavenging activity (IC₅₀ 8.6–13.0 µg/ml) (Lai et al., 2010). Significant DPPH scavenging (0.12 to 0.14 mg/ml) and ferric reducing power (FRP) (963 to 1417 mg GAE/100 g) were observed in methanol extracts from leaves of *C. latebrosa*, *Cibotium barometz*, *D. quercifolia*, *B. orientale*, and *D. linearis*. *Adiantum raddianum* and *P. vittata* displayed the highest activity in DPPH scavenging (0.27 and 0.29 mg/ml, respectively) and FRP (842 and 578 mg GAE/100 g, respectively) (Lai and Lim, 2011).

3.2 Anti-cancer, antidiabetic, and antiviral activity

The anti-cancer activity of ferns is listed in Table 3, and their antidiabetic and antiviral activity in Table 4. Both ethanol and water extracts of *Hemionitis arifolia* (Burm.) Moore (Fig. 2h) showed hypoglycaemic and antidiabetic properties in rats (Ajikumar Nair et al., 2006; Kumudhavalli and Jaykar, 2012). The antihyperglycemic and analgesic activity of the leaves of *Christella dentata*, *Adiantum philippense*, and *Angiopteris evecta* has been studied by Paul et al. (2012), Tanzin et al. (2013), and Sultana et al. (2014). *Microsorium grossum* has been used to cure liver cancer (Petard and Raau, 1972; Defilpps et al., 1988). *Pteris polyphylla* (Lee and Lin, 1988) and *A. evecta* (Defilpps et al., 1988) also show anti-cancer activity. In the Chinese traditional medicine system, “Gusuibu” has been used for its anti-cancer and anti-inflammation activity. It is prepared from the rhizomes of various ferns, namely *D. fortunei* (Kze.) J. Sm., *P. coronans* (Wall. Ex Mett.) Ching, *D. divaricata* BL., *D. mariesii* Moore ex-Bak, *D. solida* (Forst.) Sw., and *H. griffithiana* (Hk.) C. Chr. (Cui

et al., 1990; Cai et al., 2004; ChPC, 2005; Chang et al., 2007a). *M. quadrifolia* has been used to treat human breast cancer, diabetes, and snake bites, and as an anti-inflammatory and diuretic (Uma and Pravin, 2013). The bear paw fern, *Phlebodium decumanum* has been used for anti-cancer, ulcer, and high blood pressure treatments (Punzon et al., 2003). The leaves and rhizomes of *H. arifolia* (Burm.) Moore and whole plants of *Adiantum capillus-veneris* L. were used by the tribes of the Valparai hills, Western Ghats, and Tamil Nadu (India) for their hypoglycaemic and anti-cancer activity (Santhosh et al., 2014). Both leaves and rhizomes of *A. capillus-veneris* L. have been used in the preparation of herbal drugs for treating diabetes in India and Europe. This fern has diverse phytochemical constituents: adiantone, adiantoxide, astragaline, β-sitosterol, caffeic acids, caffeylgalactose, caffeylglucose, campesterol, carotenes, coumaric acids, coumarylglucosides, diplopterol, epoxyfilicane, fernadiene, fernene, filicanes, hopenone, hydroxy-adiantone, hydroxy-cinnamic acid, isoadiantone, isoquercetin, kaempferols, lutein, mutatoxanthin, naringin, neoanthin, nicotiflorin, oleananes, populnin, procyanidin, prodelfphinidin, quercetins, querciturone, quinic acid, rhodoxanthin, rutin, shikimic acid, violaxanthin, and zeaxanthin (Taylor, 2003).

Pterosins, terpenoids, sterides, flavones, glucosides, aromatics, and pyrone compounds derived from *C. barometz* have antitumour properties (Wu et al., 2007; Xu et al., 2012). Plants in the polyploid genus *Pteris* contain many chemical compounds like apigenin-7-O-β-D-glucopyranosyl-4'-O-α-L-rhamnopyranoside, luteolin-7-O-β-D-glucopyranoside, apigenin-7-O-β-D-glucopyranoside, apigenin, luteolin, naringenin-7-O-β-D-neohesperidoside, apigenin-7-O-β-D-neohesperidoside, apigenin-4'-O-α-L-rhamnopyranoside, (2S,3S)-pterocin C, isovanillic acid, ferulic acid, 2β,16α-dihydroxy-ent-kaurane 2-O-β-D-glucoside, 2β,6β,15α-trihydroxy-ent-kaur-16-ene, 9-hydroxy-15-oxo-ent-kaur-16-en-19-oic acid, 19β-D-glucoside, 2β,14β,15α,16α,17-pentahydroxy-ent-kaurane, and 9-hydroxy-ent-kaur-16-en-19-oic acid (Gong et al., 2007; Ouyang et al., 2008). Extracts of *P. multifida* have anti-cancer activity (Wang and Zhang, 2008). Ethyl acetate, butanol, and water extracts of *B. orientale* (Linn.) show notable anti-cancer properties (Lai et al., 2010). The antithiamin substances in bracken, such as astragaline, isoquercitrin, rutin, caffeic acid, and tannic acid have

Table 3 Anti-cancer property of pteridophytes

No.	Plant name	Family name	Methods used	Source(s)
1	<i>Microsorium grossum</i>	Polypodiaceae	Traditional medicine	Petard and Raau, 1972; Defilpps et al., 1988
2	<i>Pteris polyphylla</i>	Pteridaceae	In vitro antimutagenic activity, traditional Chinese medicine	Lee and Lin, 1988; Wang and Zhang, 2008
3	<i>Pteris multifida</i>	Pteridaceae	In vitro MTT method; antimutagenic activity against picrolonic acid-induced mutation	
4	<i>Angiopteris evecta</i>	Marattiaceae	Traditional Chinese medicine	Defilpps et al., 1988
5	<i>Drynaria fortunei</i>	Polypodiaceae	Traditional Chinese medicine	Punzon et al., 2003; Cai et al., 2004; ChPC, 2005; Chang et al., 2007a
6	<i>Pseudodrynaria coronans</i>	Polypodiaceae	Traditional Chinese medicine	
7	<i>Phlebodium decumanum</i>	Polypodiaceae	In vitro tumour necrosis inhibition	
8	<i>Davallia mariesii</i>	Davalliaceae	Korea folk medicine	Cui et al., 1990; Cai et al., 2004; ChPC, 2005
9	<i>Davallia divaricata</i>	Davalliaceae	Traditional Chinese medicine	
10	<i>Davallia solida</i>	Davalliaceae		
11	<i>Humata griffithiana</i>	Davalliaceae		
12	<i>Marsilea quadrifolia</i>	Marsileaceae	In vitro cytotoxic activity on MCF-7	Uma and Pravin, 2013
13	<i>Hemionitis arifolia</i>	Pteridaceae	Traditional Indian medicine	Santhosh et al., 2014
14	<i>Adiantum capillus-veneris</i>	Pteridaceae		
15	<i>Blechnum orientale</i>	Blechnaceae	In vitro MTT assay against human colonic adenocarcinoma HT-29, human colonic carcinoma HCT-116, human breast adenocarcinoma MCF-7, human leukemia K562	Lai and Lim, 2010
16	<i>Polypodium nipponica</i>	Polypodiaceae	In vivo two-stage carcinogenesis test on mouse skin papillomas	Konoshima et al., 1996
17	<i>Polypodium formosanum</i>	Polypodiaceae		
18	<i>Polypodium vulgare</i>	Polypodiaceae		
19	<i>Polypodium fauriei</i>	Polypodiaceae		
20	<i>Polypodium virginianum</i>	Polypodiaceae		
21	<i>Dryopteris crassirizoma</i>	Dryopteridaceae		
22	<i>Adiantum monochlamys</i>	Pteridaceae	In vivo two-stage carcinogenesis test on mouse skin papillomas	
23	<i>Oleandra wallichii</i>	Oleandraceae		
24	<i>Cyrtomium fortunei</i>	Dryopteridaceae	In vitro MTT assay on MGC-803, PC3, A375 tumor cells	Yang et al., 2013
25	<i>Asplenium polyodon</i>	Aspleniaceae	Traditional Indian medicine	Singh, 1999; Santhosh et al., 2014
26	<i>Asplenium nidus</i>	Aspleniaceae		
27	<i>Adiantum capillus-veneris</i>	Pteridaceae		
28	<i>Ophioglossum gramineum</i>	Ophioglossaceae		
29	<i>Hemionitis arifolia</i>	Pteridaceae		
30	<i>Pteridium aquilinum</i>	Dennstaedtiaceae	Anticancer compounds identified	Nwiloh et al., 2014
31	<i>Pityrogramma calomelanos</i>	Pteridaceae	In vitro cytotoxicity against Dalton's lymphoma ascites tumour cells and Ehrlich ascites tumour cells	Sukumaran and Kuttan, 1991; Shin, 2010; Zakaria et al., 2011; Milan et al., 2013
32	<i>Drynaria quercifolia</i>	Polypodiaceae	Brine Shrimp lethality bioassay	
33	<i>Dicranopteris linearis</i>	Gleicheniaceae	In vitro MTT assay on MCT-7, HeLa, HT-29, HL-60, K-562, MDA-MB-231	

To be continued

Table 3

No.	Plant name	Family name	Methods used	Source(s)
34	<i>Selaginella willdenowii</i>	Selaginellaceae	In vitro cytotoxic activity on human cancer cell lines	Lee and Lin, 1988; Silva et al., 1995;
35	<i>Selaginella lepidophylla</i>	Selaginellaceae	In vitro MTT assay on human colon cancer cell line (HTB-38)	Sun et al., 1997; Lee et al., 1999; Lin et al., 2000; Su et al., 2000;
36	<i>Selaginella labordei</i>	Selaginellaceae	In vitro MTT assay on Bel-7402, HeLa, HT-29	Chen et al., 2005b;
37	<i>Selaginella moellendorffii</i>	Selaginellaceae	In vitro cytotoxic activity on human ovarian adenocarcinoma cells; in vitro MTT assay on cervical carcinoma (HeLa), foreskin fibroblast (FS-5), Bel-7402, HeLa, HT-29	Gao et al., 2007; Li J et al., 2014; Li S 2014; Elda et al., 2015
38	<i>Selaginella delicatula</i>	Selaginellaceae	In vitro cytotoxic activity on Raji and Calu-1 tumor cell lines; in vitro MTT assay on Bel-7402, HeLa, HT-29	
39	<i>Selaginella tamariscina</i>	Selaginellaceae	In vitro MTT assay; in vitro antiproliferative activity in leukemia cells, Bel-7402, HeLa, HT-29; in vivo single dose acute toxicity test	
40	<i>Selaginella doederleinii</i>	Selaginellaceae	Antimutagenic activity against picrolonic acid-induced mutation; in vitro anti-proliferative against human cancer cells	
41	<i>Selaginella uncinata</i>	Selaginellaceae	In vitro MTT assay on Bel-7402, HeLa, HT-29	
42	<i>Selaginella remotifolia</i>	Selaginellaceae		
43	<i>Selaginella pulvinata</i>	Selaginellaceae		
44	<i>Adiantum venustum</i>	Pteridaceae	Ehrlich ascites carcinoma in animal models, in vivo animal study	Woerdenbag et al., 1996; Li et al., 1998,
45	<i>Pteris semipinnata</i>	Pteridaceae	Human liver adenocarcinoma cell line (HePG II), human lung adenocarcinoma cell line (SPC-A-1), human gastric adenocarcinoma cell line (MGC-803), human nasopharyngeal carcinoma cells; in vitro MTT assay in HL-60 cells; in vivo anticancer activity	1999; Viral et al., 2011
46	<i>Pteris multifida</i>	Pteridaceae	In vitro MTT assay in Ehrlich ascites	
47	<i>Pteris vittata</i>	Pteridaceae	In vitro MTT assay on MCF-7 breast cancer cells	Chiu et al., 2009; Zhang et al., 2013; Tomsik, 2013; Kaur et al., 2014; Xia et al., 2014
48	<i>Pteridium aquilinum</i>	Dennstaedtiaceae	In vitro MTT assay	
49	<i>Davallia cylindrica</i>	Davalliaceae	In vitro MTT assay in A549 cells	
50	<i>Stenoloma chusanum</i>	Lindsaeaceae		
51	<i>Selaginella frondosa</i>	Selaginellaceae	In vitro MTT assay in A549 cells	
52	<i>Thelypteris torresiana</i>	Thelypteridaceae	In vitro MTT assay in lung cancer cell line H1299	
53	<i>Selaginella ciliaris</i>	Selaginellaceae	Potato disc-induced method	Sarker et al., 2011
54	<i>Marsilea minuta</i>	Marsileaceae		
55	<i>Thelypteris prolifera</i>	Thelypteridaceae		
56	<i>Trichomanes reniforme</i>	Hymenophyllaceae	In vivo growth inhibitory activity against ascitic fibrosarcoma in Swiss mice; in vitro cytotoxicity	Guha et al., 1996

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

Table 4 Antidiabetic, antiviral, anti-inflammatory, and wound healing activity of pteridophytes

Medicinal use	No.	Plant name	Family name	Methods used	Source(s)
Antiviral activity	1	<i>Hemionitis arifolia</i>	Pteridaceae	In vivo glucose tolerance test and alloxan-induced diabetic rats; in vivo glucose tolerance test in streptozotocin-induced diabetic rats; traditional Indian medicine	Ajikumaran Nair et al., 2006; Kumudhavalli and Jaykar, 2012; Santhosh et al., 2014
	2	<i>Christella dentata</i>	Thelypteridaceae	In vivo glucose tolerance test	Paul et al., 2012;
	3	<i>Adiantum philippense</i>	Pteridaceae	In vivo study in alloxan-induced diabetic rats	Tanzin et al., 2013; Sultana et al., 2014
	4	<i>Angiopteris evecta</i>	Marattiaceae	In vivo glucose tolerance test	
	5	<i>Adiantum capillus-veneris</i>	Pteridaceae	Traditional Indian medicine; traditional medicine in Amazon; in vivo glucose tolerance test	Jain and Sharma, 1967; Taylor, 2003; Santhosh et al., 2014; Neef et al., 1995
	6	<i>Angiopteris evecta</i>	Marattiaceae	In vivo glucose tolerance test	Miao et al., 1996;
	7	<i>Selaginella tamarascina</i>	Selaginellaceae	In vivo study in alloxan-induced diabetic rats	Nguyen, 2005
	8	<i>Asplenium polyodon</i>	Aspleniaceae	Traditional Indian medicine	Singh, 1999; Chand Basha et al., 2013; Santhosh et al., 2014
	9	<i>Asplenium nidus</i>	Aspleniaceae		
	10	<i>Adiantum capillus-veneris</i>	Pteridaceae		
	11	<i>Ophioglossum gramineum</i>	Ophioglossaceae		
	12	<i>Hemionitis arifolia</i>	Pteridaceae		
	13	<i>Actiniopteris radiata</i>	Pteridaceae	In vitro chromogenic DNSA method	
	14	<i>Blechnum orientale</i>	Blechnaceae	In vitro antiviral activity against hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and murine leukemia virus	Tsai and Hwang, 1999
	15	<i>Woodwardia orientalis</i>	Blechnaceae		
	16	<i>Woodwardia unigemmata</i>	Blechnaceae		
	17	<i>Athyrium acrostichoides</i>	Athyriaceae		
	18	<i>Sphaeropteris lepifera</i>	Cyatheaceae		
	19	<i>Cyrtomium fortunei</i>	Dryopteridaceae		
	20	<i>Dryopteris crassirhizoma</i>	Dryopteridaceae		
	21	<i>Osmunda japonica</i>	Osmundaceae		
	22	<i>Lygodium flexuosum</i>	Lygodiaceae	Traditional Indian medicine	Dhiman, 1998
	23	<i>Lygodium japonicum</i>	Lygodiaceae	In vitro antiviral activity against herpes simplex virus, Sindbis virus, and polio virus	Taylor et al., 1996
	24	<i>Asplenium adiantum-negrum</i>	Aspleniaceae	Traditional Indian medicine	Vasudeva, 1999
	25	<i>Microsorium membranifolium</i>	Polypodiaceae	Traditional Fijian medicine	Cambie and Ash, 1994
	26	<i>Pyrrosia lingua</i>	Polypodiaceae	In vitro antiviral activity against Herpes simplex virus	Zheng, 1990
	27	<i>Trichomanes reniforme</i>	Hymenophyllaceae	In vitro antiviral activity against HIV	Guha et al., 1996
	28	<i>Pteris glycyrrhiza</i>	Pteridaceae	In vitro antiviral activity against bovine herpesvirus type	McCutcheon et al., 1995
	29	<i>Polypodium vulgare</i>	Pteridaceae		Husson et al., 1986
	30	<i>Polypodium aureum</i>	Pteridaceae		

To be continued

Table 4

Medicinal use	No.	Plant name	Family name	Methods used	Source(s)
Antiviral activity	31	<i>Athyrium niponicum</i>	Athyriaceae	In vitro antiviral activity	Mizushina et al., 1998
	32	<i>Selaginella uncinata</i>	Selaginellaceae	In vitro antiviral activity against respiratory syncytial virus, parainfluenza type 3 virus	Ma et al., 2003
Anti-inflammatory activity	33	<i>Microsorium grossum</i>	Polypodiaceae	Traditional herbal medicine	Petard and Raau, 1972; Whistler, 1992
	34	<i>Drynaria quercifolia</i>	Polypodiaceae	Traditional Indian medicine	Dixit and Vohra, 1984
	35	<i>Microsorium scolopendria</i>	Polypodiaceae	Traditional herbal medicine in Tonga	Bloomfield, 2002
	36	<i>Polypodium leucotomos</i>	Polypodiaceae	Traditional herbal medicine in Bolivia	Lucca, 1992
	37	<i>Ophioglossum vulgatum</i>	Ophioglossaceae	Traditional Indian medicine	Vasudeva, 1999
	38	<i>Lygodium flexuosum</i>	Lygodiaceae		
	39	<i>Adiantum venustum</i>	Pteridaceae		
	40	<i>Adiantum caudatum</i>	Pteridaceae	Traditional medicine in Malay Peninsula	Burkill, 1996
	41	<i>Cheilanthes farinosa</i>	Pteridaceae	In vivo anti-inflammatory activity	Yonathan et al., 2006
	42	<i>Pteris ensiformis</i>	Pteridaceae	In vitro anti-inflammatory activity	Wu et al., 2005
	43	<i>Christella parasitica</i>	Thelypteridaceae	Traditional Indian medicine	Gogoi, 2002
	44	<i>Huperzia serrata</i>	Huperziaceae	Traditional Chinese medicine	Zangara, 2003
	45	<i>Selaginella tamarascina</i>	Selaginellaceae	In vitro anti-inflammatory activity	Woo et al., 2005
	46	<i>Selaginella bryopteris</i>	Selaginellaceae	Traditional Indian medicine	Dhiman, 1998
	47	<i>Dryopteris</i> sp	Dryopteridaceae	In vivo Carrageenan induced paw oedema method	Otsuka et al., 1972
48	<i>Blechnum occidentale</i>	Blechnaceae		Nonato et al., 2009	
49	<i>Alsophila gigantea</i>	Cyatheaceae	Traditional Indian medicine	Benjamin and Manickam, 2007	
50	<i>Cyathea gigantea</i>	Cyatheaceae	In vivo anti-inflammatory activity	Madhukiran and Ganga Rao, 2011	
51	<i>Phlebodium decumanum</i>	Polypodiaceae	In vitro anti-inflammatory activity	Punzon et al., 2003	
52	<i>Phyllitis scolopendrium</i>	Aspleniaceae	Traditional herbal medicine	Bonet and Valles, 2007	
53	<i>Dicranopteris linearis</i>	Gleicheniaceae	In vitro anti-inflammatory activity	Zakaria et al., 2008	
Wound healing activity	54	<i>Selaginella delicatula</i>	Selaginellaceae	Traditional Indian medicine	Santhosh et al., 2014
	55	<i>Dicranopteris linearis</i>	Gleicheniaceae		
	56	<i>Davallia solida</i>	Davalliaceae	Traditional medicine in Hawaii	Whistler, 1992
	57	<i>Polystichum pungens</i>	Dryopteridaceae	Traditional medicine in South Africa	Grierson and Afolayan, 1999
	58	<i>Angiopteris evecta</i>	Marattiaceae	Traditional medicine in Fijian	Cambie and Ash, 1994
	59	<i>Nephrolepis cordifolia</i>	Nephrolepidaceae	Traditional Indian medicine	Upreti et al., 2009
	60	<i>Ophioglossum reticulatum</i>	Ophioglossaceae		
	61	<i>Thelypteris arida</i>	Thelypteridaceae		
	62	<i>Phyllitis scolopendrium</i>	Aspleniaceae	In vivo method	Oniga et al., 2004
63	<i>Pityrogramma calomelanos</i>	Pteridaceae	Traditional medicine	de Feo, 2003	
64	<i>Polypodium</i> ssp.	Polypodiaceae	In vitro assay using platelet activating factor and leukotriene B(4)	Liu et al., 1998	

been identified as valuable natural constituents because of their antitumour or antioxidant properties (Kweon, 1986; Cai et al., 2004; Katsube et al., 2006). The ferns *P. nipponica*, *Polypodium formosanum*, *Polypodium vulgare*, *Polypodium fauriei*, *Polypodium virginianum*, *Dryopteris crassirizoma*, *Adiantum monochlamys*, and *Oleandra wallichii* have been shown to have anti-cancer activity (Konoshima et al., 1996). *A. evecta* and *Selaginella tamariscina* have been shown to have significant antidiabetic activity (Miao et al., 1996; Nguyen, 2005).

According to Singh (1999) and Lee et al. (2003), *Asplenium polyodon*, *Asplenium nidus*, *A. capillus-veneris*, *Ophioglossum gramineum*, and *H. arifolia* have anti-cancer, antidiabetic, and antiviral activity. Chloroform extracts of *Actiniopteris radiata* (Linn.) have significant antidiabetic activity as shown by the chromogenic DNSA (dinitrosalicylic) colorimetric method, and ethanolic extracts show strong in vitro antidiabetic properties when compared to *n*-hexane (Chand Basha et al., 2013). Both ethyl acetate and butanol extracts of the rhizome of *C. fortunei* (J.) Smith (Fig. 3a) exhibit anti-tumour activity (Yang et al., 2013). The phlorophenone derivatives in *Dryopteris* sp. (Kapadia et al., 1996) and *A. capillus-veneris* (Fig. 3b) that have anti-cancer activity have also been used as antidiabetic drugs in India and Europe (Jain and Sharma, 1967; Neef et al., 1995). β -Caryophyllene, linalool, geranial and γ -terpinene have also been isolated from the angiosperms *Citrus* and *Croton flavens*, revealing antitumour and antioxidant properties (Choi et al., 2000; Sylvestre et al., 2006). Moreover, anti-cancer compounds were detected in the essential oils of *P. aquilinum* L. Kuhn (Fig. 2a) (Nwiloh et al., 2014). Methanol extracts of *Pityrogramma calomelanos*, *D. quercifolia*, and *D. linearis* exhibit antitumour and cytotoxic activity (Sukumaran and Kuttan, 1991; Shin and Lee, 2010; Zakaria et al., 2011; Milan et al., 2013). Extracts of *Adiantum venustum* also have anti-cancer activity, as demonstrated by Viral et al. (2011). The lycophytes, *Selaginella willdenowii* (Fig. 3d), *Selaginella lepidophylla*, *Selaginella labordei*, *Selaginella moellendorffii*, *Selaginella delicatula*, *S. tamariscina*, and *Selaginella doederleinii* (Fig. 3e) were shown to have cytotoxic and antimutagenic effects due to the presence of bioflavonoids (Lee and Lin, 1988; Silva et al., 1995; Sun et al., 1997; Lee et al., 1999; Lin

et al., 2000; Su et al., 2000; Chen JJ et al., 2005; Gayathri et al., 2005; Woo et al., 2005; Gao et al., 2007; Shi et al., 2008; Tan et al., 2009), while *Pteris semipinnata* (Fig. 4c) and *P. multifida* have cytotoxic effects due to the presence of diterpenes (Woerdenbag et al., 1996; Li et al., 1998, 1999). Several authors have studied the anti-cancer potentials of ferns and lycopods, namely *P. aquilinum*, *Davallia cylindrical*, *Stenoloma chusanum*, *Selaginella frondosa*, *Thelypteris torresiana*, *P. vittata*, *Selaginella ciliaris*, *Marsilea minuta*, and *Thelypteris prolifera* (Chiu et al., 2009; Sarker et al., 2011; Tomsik, 2013; Zhang et al., 2013; Kaur et al., 2014; Xia et al., 2014).

According to Tsai and Hwang (1999), the hepatitis B virus (HBV) is a prominent infectious disease agent worldwide, especially in Asia and Africa, causing liver cirrhosis and cancer. Blechni rhizome, known for its antiviral (HBV) activity, is prepared from the roots and stems of various ferns including *B. orientale*, *D. crassirhizoma*, *O. japonica*, *Woodwardia orientalis* (Fig. 4d), *Woodwardia unigemmata* (Fig. 5b), *Athyrium acrostichoides*, *Sphaeropteris lepifera*, and *C. fortunei*. Likewise, an herbal mixture of *Woodwardia* species with some other flowering plants has shown anti-HIV-1 (human immunodeficiency virus) activity. *Lygodium flexuosum* (Dhiman, 1998) and *Asplenium adiantum-nigrum* (Vasudeva, 1999) have shown significant effects against viral disease and jaundice, while *Microsorium membranifolium* has shown activity against children's influenza (Cambie and Ash, 1994). The antiviral and anti-tumor activity shown by *Trichomanes reniforme* is due to the presence of mangiferin, which can kill cancer cells and has anti-HIV effects (Guha et al., 1996). The antiviral activity of *Pteris glycyrrhiza* (McCutcheon et al., 1995), *P. vulgare*, and *Polypodium aureum* (Husson et al., 1986) has been documented. A new antiviral compound, woodorien, was derived and identified by Xu et al. (1993). *A. niponicum* is reported to have anti-HIV properties (Mizushina et al., 1998), while Taylor et al. (1996) have shown that *L. japonicum* has antiviral effects against the Sindbis virus. Zheng (1990) revealed the antiviral activity of *P. lingua* (Fig. 3g) against the herpes simplex virus. *Selaginella uncinata* (Fig. 5c) displays antiviral activity against the respiratory syncytial virus (RSV) and parainfluenza type 3 virus (PIV3) (Ma et al., 2003).



Fig. 4 Color illustrations of medicinal pteridophytes: (a) *Equisetum ramosissimum*; (b) *Asplenium bulbiferum*; (c) *Pteris semipinnata*; (d) *Woodwardia orientalis*; (e) *Lygodium flexuosum*; (f) *Pteris ensiformis*

Note: for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article

3.3 Anti-inflammatory activity

In general, free radicals participate in numerous natural processes that are harmful to lipids, proteins, membranes, and nucleic acids, thereby contributing to a variety of diseases (Hadi et al., 2000; Lee et al.,

2005; Campos et al., 2006). Reactive oxygen species (ROS) contribute to both normal cell function and pathological ailments such as atherosclerosis, inflammatory injury, cancer, and cardiovascular disease. Inflammation is a typical defensive response to



Fig. 5 Color illustrations of medicinal pteridophytes: (a) *Selaginella delicatula*; (b) *Woodwardia unigemmata*; (c) *Selaginella uncinata*; (d) *Huperzia serrata*; (e) *Nephrolepis cordifolia*; (f) *Pittyrogramma calomelanos*; (g) *Selaginella involvens*; (h) *Psilotum nudum*

Note: for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article

cellular damage produced by physical distress (cuts, burns, or bruises), toxic chemicals, microbial agents, or autoimmune disease. Unfortunately, drugs currently available to treat pain and inflammation have numerous harmful side effects and low efficiency. Natural products are often easily available, with high clinical effectiveness and few side effects. The World Health Organization (WHO) estimates that 80% of the global population still depends on ethnomedicinal practices for treating their illnesses (Gurib-Fakim, 2006).

In inflammatory disorders, extreme stimulation of phagocytes and the production of O^{2-} (oxygen radicals), OH^- (hydroxide ions), and H_2O_2 (Gillham et al., 1997) are severely harmful to tissues, by their significant direct or indirect oxidizing action. Hydrogen peroxide and OH^- radicals formed from O^{2-} cause lipid peroxidation resulting in membrane destruction. In addition, tissue damage provokes an inflammatory response involving the production of mediators and chemotactic factors (Lewis, 1989). The free radical scavenging activity of plant products is primarily due to various bioactive compounds like phenolics, flavonoids, phenolic diterpenes, and tannins (Lee et al., 2004). Currently, steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) used to treat inflammatory disease frequently produce severely harmful effects (Vonkeman and van de Laar, 2010; Vijayalakshmi et al., 2011). Thus, there is abundant motivation to find new drugs with anti-inflammatory properties and fewer side effects, especially from plants used in folk medicine. Moreover, plant-derived natural products such as alkaloids, flavonoids, tannins, and terpenes have attracted significant attention recently due to their varied medicinal actions, including anti-inflammatory, analgesic, and antioxidant properties (Pandurangan et al., 2008). Traditional healers have defined the healing efficiencies of native medicinal plants for various diseases. Because bioproducts are a source of synthetic and traditional herbal medicines, which can potentially be used by modern health care systems, scientists have been urged to study these plants to identify their medicinal properties (Vimala et al., 2012).

Pteridophytes (the ferns and their allies) have an extensive geologic history as pioneer plants that have occupied various parts of our globe for millions of years. This group comprises a huge group of seedless vascular plants and occupies a significant place in

primary health care because of their cost effectiveness. Economic crises in developing countries mean that different fern species are presently used for various ailments (Ho et al., 2011). On the basis of antioxidant activity, ferns exhibit bioactivity such as anti-microbial, anti-viral, anti-inflammatory, anti-tussive, and anti-tumor activity (Chang et al., 2011). The Malasar tribes in the Valparai hills (Western Ghats, India) use both *S. delicatula* (Fig. 5a) and *D. linearis* for their wound healing activity (Santhosh et al., 2014). Table 4 shows the anti-inflammatory and wound healing activity of pteridophytes. In many studies, anti-inflammatory activity has been reported for many species of medicinal ferns, including *M. grossum* (Petard and Raau, 1972; Whistler, 1992), *D. quercifolia* (Dixit and Vohra, 1984), *A. aureum* (Defilpps et al., 1988), *Selaginella bryopteris* (Dhiman, 1998), *Ophioglossum vulgatum*, *L. flexuosum*, *A. venustum* (Vasudeva, 1999), *Adiantum caudatum* (Burkill, 1996), *Christella parasitica* (Gogoi, 2002), *Huperzia serrata* (Fig. 5d) (Zangara, 2003), *S. tamariscina* (Woo et al., 2005), *P. ensiformis* (Fig. 4f) (Wu et al., 2005), *P. multifida* (Lee and Lin, 1988), *Dryopteris* sp. (Otsuka et al., 1972), *Cheilanthes farinosa* (Yonathan et al., 2006), *Cyathea gigantea* (Fig. 3c) (Benjamin and Manickam, 2007; Madhukiran and Ganga Rao, 2011), *Blechnum occidentale* (Nonato et al., 2009), *D. mariesii* (Chang et al., 2007b), *Microsorium scolopendria* (Bloomfield, 2002), *Phyllitis scolopendrium* (Bonet and Valles, 2007), and *P. leucotomos* (Lucca, 1992). In addition, wound healing activity has been reported for many species of ferns such as *D. solida* (Whistler, 1992), *Polystichum pungens* (Grierson and Afolayan, 1999), *A. evecta* (Cambie and Ash, 1994), *Nephrolepis cordifolia* (Fig. 5e), *Ophioglossum reticulatum*, *Thelypteris arida* (Upreti et al., 2009), *P. scolopendrium* (Oniga et al., 2004), *P. calomelanos* (Fig. 5f) (de Feo, 2003), *Polypodium* spp. (Liu et al., 1998), and *P. decumanum* (Punzon et al., 2003).

3.4 Antimicrobial activity

There are many antibiotics currently available for the treatment of infection, including chloramphenicol, tetracycline, erythromycin, penicillin G, ampicillin, cephalosporin, ciprofloxacin, kanamycin, gentamicin, neomycin, amoxicillin, nystatin, amphotericin-B, and ketaconazole (Kaufman, 2000). Although there are numerous antibiotics for healing

bacterial and fungal infection, they are not always reliable against pathogenic organisms (Gearhart, 1994). Their use is restricted by several factors such as low potency, poor solubility, and drug toxicity (Fromtling and Rahway, 1987; Portillo et al., 2001). The development of resistance in pathogenic bacteria and fungi against most of the conventionally available drugs has been reported (Cuenca-Estrella et al., 2000). Confounding the issue further is the indiscriminate use of antibiotics, which leads to the loss of their effectiveness. Many of the pathogens, especially bacteria and fungi, have developed substantial resistance to the antibiotics (Darokar et al., 1998; Jones, 1998; Austin et al., 1999). Moreover, the widespread use of antibiotics has led to the decimation of sensitive organisms from the population with the consequence that there has been an increase in the number of resistant microorganisms. This situation has forced scientists to search for new bioactive compounds in traditional complementary medicines derived from plants (Kumar et al., 2006). Plant extracts have been widely used since ancient times for treating human illnesses. Numerous studies of the antimicrobial activity of different natural products have been reported (Bhattacharjee et al., 2006; Parekh and Chanda, 2006, 2007; Vaghasiya et al., 2008). Although the medicinal value of pteridophytes has been known to traditional cultures for more than 2000 years, they are used only on a small scale in modern chemotherapy. Studies of the bioactivity of pteridophytes are still in their early years compared with those of angiosperms.

The Greek botanist Theophrastus (ca. 372–287 BC) wrote about the medicinal value of pteridophytes. Dioscorides (ca. 50 AD) in his *de Materia Medica* also referred to a number of ferns, including *P. aquilinum* and *Dryopteris filix-mas*, as having medicinal values. In ancient Indian medicine systems, several ferns were used to cure a number of human ailments. Sushruta (ca. 100 AD) and Charaka (ca. 100 AD) recommended the medicinal use of some ferns in their samhitas. Several ferns have been used by Unani physicians in India and Western Asia (Banerjee and Sen, 1980). The antimicrobial activity of pteridophytes is summarized in Table 5. Several studies have been carried out to explore the antimicrobial activity of ferns such as *Nephrolepis acuminata* (Jimenez et al., 1979), *Davallia sodila*, *Lygodium reticulatum* (Cambie and Ash, 1994), *Marattia fraxinea* (de Boer et al., 2005), *Sphenomeris*

chinensis (Sengupta et al., 2002), *A. caudatum*, *Adiantum peruvianum*, *A. venustum*, *Adiantum incisum*, *Adiantum latifolium*, and *Ampelopteris prolifera* (Banerjee and Sen, 1980; Lakshmi et al., 2006; Lakshmi and Pullaiah, 2006; Singh et al., 2008a), *P. aquilinum* (Francisco and Driver, 1984), *Nephrolepis* sp. (Basile et al., 1997), *Adiantum lunulatum* (Reddy et al., 2001), *E. arvense* (Joksic et al., 2003; Radulovic et al., 2006), *S. tamariscina* (Woo et al., 2005), *A. capillus-veneris* (Guha et al., 2004, 2005; Besharat et al., 2008), *Athyrium pectinatum* (Parihar et al., 2006), *P. vittata* (Singh et al., 2008b), *P. multifida* (Hu et al., 2008; Hum et al., 2008), *Mecodium exsertum* (Maridass, 2009), *Selaginella involvens* (Fig. 5g), *S. inaequalifolia* (Haripriya et al., 2010), *S. pallescens* (Rojas et al., 1999), *Asplenium scolopendrium*, *Cystopteris fragilis*, *P. vulgare* (Soare et al., 2012b), *A. caudatum*, *A. evecata*, *Pteris confusa*, *P. argyreaea*, *Lygodium microphyllum* (Gracelin et al., 2012), *Pteris biaurita* (Dalli et al., 2007; de Britto et al., 2012), *D. crassirhizoma* (Lee et al., 2009), and various species (Maruzzella, 1961; McCutcheon et al., 1995). Furthermore, several studies (May, 1978; Dixit and Vohra, 1984; Dixit, 1992; Verma and Singh, 1995; Manandhar, 1996; Das, 1997; Singh, 1999; Benjamin and Manickam, 2007) have reported the antiviral, antibacterial, and antifungal activity of *Equisetum ramosissimum* (Fig. 4a), *A. aureum*, *D. quercifolia*, *Psilotum nudum* (Fig. 5h), *Parahemionitis arifolia*, *Helminthostachys zeylanica*, *O. gramineum*, *Tectaria caodunata*, *S. involvens*, *S. delicatula*, *Hypodematium crenatum*, *Leucostegia immersa*, and *Solvinia molusta*. Singh (1999) documented antibacterial and antifungal activity of *Botrychum lanuginosum*, *Dryopteris cochleata*, *N. cordifolia*, *Polystichum molluscens*, *Polystichum squarrosom*, *Salvinia radicata*, *Sphaerostephanos unitus*, *S. palustris*, *P. cretica*, and *P. vittata*. Although several studies have reported the antimicrobial activity of ferns, in-depth studies to estimate minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) have not yet been carried out for several ferns.

3.5 Activity against Alzheimer's disease and brain illness

Frequently, alkaloids act as stimulators of the nervous system, and occasionally as toxins. Cocaine (has an anaesthetic effect), atropine (affects motor

Table 5 Antimicrobial activity of pteridophytes

No.	Plant name	Family name	Methods used	Source(s)
1	<i>Nephrolepis acuminata</i>	Nephrolepidaceae	In vitro bioassay	Jimenez et al., 1979
2	<i>Davallia sodila</i>	Davalliaceae	Traditional Fijian medicine	Cambie and Ash, 1994
3	<i>Lygodium reticulatum</i>	Lygodiaceae		
4	<i>Marattia fraxinea</i>	Marattiaceae	In vitro antimicrobial assay	de Boer et al., 2005
5	<i>Sphenomeris chinensis</i>	Lindsaeaceae		Sengupta et al., 2002
6	<i>Adiantum caudatum</i>	Pteridaceae		Banerjee and Sen, 1980; Lakshmi and Pullaiah, 2006; Lakshmi et al., 2006; Singh et al., 2008a
7	<i>Adiantum peruvianum</i>	Pteridaceae		
8	<i>Adiantum venustum</i>	Pteridaceae		
9	<i>Adiantum incisum</i>	Pteridaceae		
10	<i>Adiantum latifolium</i>	Pteridaceae		
11	<i>Ampelopteris prolifera</i>	Thelypteridaceae		
12	<i>Pteridium aquilinum</i>	Dennstaedtiaceae		Francisco and Driver, 1984
13	<i>Nephrolepis</i> sp.	Nephrolepidaceae		Basile et al., 1997
14	<i>Equisetum arvense</i>	Equisetaceae		Joksic et al., 2003; Radulovic et al., 2006
15	<i>Athyrium pectinatum</i>	Athyriaceae		Parihar et al., 2006
16	<i>Adiantum lunulatum</i>	Pteridaceae		Reddy et al., 2001
17	<i>Adiantum capillus-veneris</i>	Pteridaceae		Guha et al., 2004, 2005; Besharat et al., 2008
18	<i>Pteris vittata</i>	Pteridaceae		Singh et al., 2008b
19	<i>Pteris multifida</i>	Pteridaceae		Hu et al., 2008; Hum et al., 2008
20	<i>Microsorium grossum</i>	Polypodiaceae	Traditional Polynesian medicine	Whistler, 1992
21	<i>Mecodium exsertum</i>	Hymenophyllaceae	In vitro antimicrobial assay	Maridass, 2009
22	<i>Selaginella involvens</i>	Selginellaceae		Rojas et al., 1999; HariPriya et al., 2010
23	<i>Selaginella inaequalifolia</i>	Selginellaceae		
24	<i>Selaginella pallescens</i>	Selginellaceae		
25	<i>Asplenium scolopendrium</i>	Aspleniaceae		Soare et al., 2012b
26	<i>Cystopteris fragilis</i>	Cystopteridaceae		
27	<i>Polypodium vulgare</i>	Polypodiaceae		
28	<i>Angiopteris evecta</i>	Marattiaceae		Gracelin et al., 2012
29	<i>Adiantum caudatum</i>	Pteridaceae		
30	<i>Pteris confusa</i>	Pteridaceae		
31	<i>Pteris argyraea</i>	Pteridaceae		
32	<i>Lygodium microphyllum</i>	Lygodiaceae		
33	<i>Pteris biaurita</i>	Pteridaceae		Dalli et al., 2007; de Britto et al., 2012
34	<i>Dryopteris crassirizoma</i>	Dryopteridaceae		Lee et al., 2009
35	<i>Equisetum ramosissimum</i>	Equisetaceae	Traditional Indian medicines	May, 1978; Dixit and Vohra, 1984; Dixit, 1992; Verma and Singh, 1995; Manandhar, 1996; Das, 1997; Singh, 1999; Benjamin and Manickam, 2007
36	<i>Drynaria quercifolia</i>	Polypodiaceae		
37	<i>Psilotum nidum</i>	Psilotaceae		
38	<i>Parahemionitis arifolia</i>	Pteridaceae		
39	<i>Acrostichum aureum</i>	Pteridaceae		
40	<i>Helminthostachys zeylanica</i>	Ophioglossaceae		
41	<i>Ophioglossum gramineum</i>	Ophioglossaceae		
42	<i>Tectaria caodunata</i>	Tectariaceae		
43	<i>Selaginella involvens</i>	Selaginellaceae		
44	<i>Selaginella delicatula</i>	Selaginellaceae		
45	<i>Hypodematum crenatum</i>	Woodsiaceae		
46	<i>Leucostegia immersa</i>	Davalliaceae		
47	<i>Solvinia molusta</i>	Salviniaceae		
48	<i>Marsilea quadrifolia</i>	Marsileaceae	Brine shrimp lethality bioassay	Ripa et al., 2009

nerve), and curare (used by South American natives to cause paralysis of prey), are all alkaloids (Kretovich, 1966). Even though several alkaloids are present in angiosperms, some specific groups of alkaloids, namely lycopodine and huperzine, are synthesized by the lower groups of plants, like club mosses. Some lycopodium alkaloids naturally present in *Lycopodium* sp. and other pteridophytes have some pharmacological activity. α -Onocerin and lycoperine A show acetylcholinesterase inhibition activity (Zhang et al., 2002; Hirasawa et al., 2006). Huperzine A obtained from *Huperzia* species and other members of the Lycopodiaceae, has been shown to improve memory in animals. *Huperzia quadrifariata* and *Huperzia reflexa* were also found to cure Alzheimer's disease (Ma and Gang, 2004; Ma et al., 2007; Singh and Singh, 2010; Konrath et al., 2012; Yang et al., 2012). Amentoflavone and ginkgetin, flavonoids found in *Selaginella*, display neurodefensive activity against cytotoxic stress, which suggests their promising usage to cure neurodegenerative diseases such as stroke and Alzheimer's (Kang et al., 2004). The neuromodulatory tendency of *S. delicatula* using in vivo models of chemically induced neurodegenerative diseases has been studied in rodent systems and *Drosophila*. Extracts of *S. delicatula* showed neuroprotective efficacy against Parkinson's disease, Huntington's disease, reduced glutathione levels, and acetyl cholinesterase inhibitory activity (Chandran and Muralidhara, 2014). The pteridophyte *Drynaria* is also used in traditional medicine in China to treat Alzheimer's disease. According to Yang (2005), 120 g of *Drynaria* (in decoction) produced significant improvement in Alzheimer's disease patients. Likewise, *Nephrolepis auriculata*, *S. bryopteris*, *H. zeylanica*, and *Lycopodium* were used to treat brain fever, headache, and unconsciousness, to improve vitality, and as a brain tonic and memory enhancer (Bai, 1993; Samant et al., 1998; Vasudeva, 1999; Kholia and Punetha, 2005).

4 Traditional uses of some pteridophytes

In India, the Gond communities of Badkachhar, Bariaam and Dapka ingest the juice of whole fresh plants to cure cough and diabetes mellitus. Leaves of *A. philippense* are used to cure fever, cough, asthma,

leprosy, and hair loss, while whole plants of *B. orientale* are used in anathematic and typhoid treatments. Fronds of *B. orientale* ground in cow's milk are used in the treatment of asthma, as antibacterials and anthelmintics, and to improve fertility in women. The whole plant of *H. zeylanica* is considered an intoxicant, anodyne, and is also used as an aphrodisiac. *L. flexuosum* (Fig. 4e) is used to cure skin diseases, rheumatism, sprains, scabies, eczema, cut wounds, and rheumatism, and as an expectorant. A paste made from the leaves of *N. cordifolia* is applied to wounds to stop bleeding. Whole plants of *S. bryopteris* are used as diuretics, and to treat gonorrhoea (Singh and Upadhyay, 2012). *A. capillus-veneris* is used for antifungal growth and to remove dandruff, and the juice of leaves is drunk to protect against infertility. In addition, *A. caudatum* is used to cure jaundice, scabies, abdominal pain, and constipation. The young fronds of *A. incisum* are used to treat malaria and bronchial diseases, while leaves and rhizomes of *A. venustum* are thought to cure diabetes, and are used to treat liver problems and circulatory disorders. Leaves of *Asplenium bulbiferum* (Fig. 4b) are applied externally to hemorrhoids, and fronds are taken for liver problems. Decoctions from the rhizomes of *P. aquilinum* are drunk as a herbal health tea, and the rhizomes of *W. unigemmata* are used to cure skin diseases. Leaf juices are used as a tea or bath for curing infertility in women, for abdominal pain, constipation and sore throats (Nwosu, 2002). A paste of leaves and rhizomes mixed with lukewarm milk for 30 d is used as an effective tonic. A paste of *P. vittata* was applied twice to glandular swellings for 15 d (Sharma, 2002). *M. grossum* is commonly used in Tahiti (Whistler, 1992), *H. serrata* in China (Zangara, 2003), and *S. bryopteris* in India (Dhiman, 1998) for their anti-inflammatory activity. A decoction of roots and fronds of *D. quercifolia* is used as a tonic for the bowels, and aqueous extracts of the rhizomes are applied to wounds and cuts (Anonymous, 1952, 1986; Singh, 1973; Islam, 1983; Jain, 1991). Dried rhizomes of *P. aquilinum* mixed with milk are used to relieve diabetic disorders, and tender fronds are used as vegetables. Green fronds are used as fodder, make a good soil binder, and are also used in the preparation of manure (Anonymous, 1972, 1986; Islam, 1983; Jain, 1991). A paste made from the rhizomes of *O. vulgatum* has been externally applied to wounds,

dropped in sore eyes as a detergent, and made into an antiseptic. Infusions can be taken internally for vulnery or to treat bleeding of the nose or mouth, and a decoction has been drunk to treat heart troubles (Anonymous, 1966, 1986; Islam, 1983). In Malaya, a rhizome paste of *A. aureum* is applied to wounds and boils, and in the Philippines, leaves of *A. caudatum* are used externally as remedies for skin disease and internally for diabetes. Rhizomes of *C. barometz* in the Philippines are used to treat wounds and ulcers. Roots and leaves of *Lygodium circinnatum* are applied to wounds in the Dutch East Indies (Quisumbing, 1951). Tribal people of the Palani hills from South India use *A. incisum*, *C. gigantea*, and *C. nilgirensis* to treat diabetes, while *N. cordifolia*, *H. arifolia*, and *Microsorium punctatum* are applied to cuts and wounds, or used as anti-inflammatories (Sathiyaraj et al., 2015). In the Similipal Biosphere Reserve of Orissa (India), *A. evecta*, *A. caudatum*, *B. orientale*, *Ceratopteris thalictroides*, *M. punctatum*, *P. biaurita*, and *P. cretica* are used to cure cuts, wounds, and inflammation (Rout et al., 2009).

5 Mechanisms of action of phytochemicals

In this review we have documented most of the pteridophytes evaluated for phytochemical composition and bioactivity. Tables 1–5 summarize the presence of phytochemicals and their medicinal uses in pteridophytes. Although there are more than 12000 species of pteridophytes distributed all over the world, few have been evaluated for their phytochemicals and their pharmacological properties. Most studies have reported only in vitro bioactivity, which suggests to investigate the pteridophytes could exert in vivo bioactivity. In general, phenolic compounds exist in both edible and non-edible plants and have proven bioactive. Phenolics are present in diverse groups of plants and show antimutagenic, anti-cancer, and antioxidant activity, which is beneficial to human life (Li et al., 2006). Due to synergistic effects, mixtures of bioactive compounds such as phenols, flavonoids, tannins, catechins, vitamins C and E, and β -carotene may give better protection/bioactivity than single phytochemicals (Bazzano et al., 2003). Phenolic compounds have been shown to have significant antioxidant effects (Newell et al., 2010). Phenols,

flavonoids, anthocyanins, and phenolic acids have been obtained from plants to attain an idyllic structural chemistry for scavenging free radicals. The antioxidant potential of polyphenols may arise from their great reactivity as hydrogen or electron donors. The polyphenol-derived radical stabilize and delocalize the unpaired electron (Chanda and Dave, 2009). The scavenging of DPPH and ABTS radicals may be associated with the hydroxyl groups in caffeic acid and chlorogenic acid. The radical scavenging activity of phenolic compounds is influenced by the number of hydroxyl groups on the aromatic ring (Lazarova et al., 2014). Both rutin and quercetin significantly chelate metal ions and have ferric reducing antioxidant power (Azuma et al., 1999). According to Kim et al. (2004), rutin and quercetin express their anti-inflammatory activity through modulation of the expression of pro-inflammatory genes such as cyclooxygenase-2 and inducible nitric oxide synthase, and via some vital cytokines. Based on these distinctive mechanisms, flavonoids are considered as plausible substances for anti-inflammatory activity. The presence of caffeic acid, chlorogenic acid, rutin, and quercetin has been reported in many pteridophytes, namely *P. multifida*, *P. vittata*, *P. aquilinum*, *P. leucotomos*, *Cyathea phalerata*, *S. tamariscina*, *O. sensibilis*, *M. struthiopteris*, *D. linearis*, *P. nudum*, *E. arvense*, and *A. capillus-veneris* (Table 1).

Free radicals are generated in cells where they accumulate and react with macromolecules, like lipids, proteins, and nucleic acids, thereby disrupting cellular functions. In addition, oxidative damage to cellular components results in alteration of membrane properties such as fluidity, ion transport, enzyme activity, and protein cross-linking, causing cell death (Chauhan and Chauhan, 2006). Bio-compounds containing antioxidant potential have the capacity to inhibit carcinogenesis (Wang et al., 2011; Firdaus et al., 2013). In earlier studies, apigenin, quercetin, and luteolin were shown to inhibit cancer cell proliferation (Mishra et al., 2013a, 2013b; Fotsis et al., 1997). Moreover, phenolics have been observed to postpone or inhibit the progression of various diseases by preventing peroxidation of lipid membranes (Kumar et al., 2013a, 2013b). Some bioactivity, such as lipoprotective, antiplatelet, and anti-inflammatory activity, is closely associated with antioxidative flavonoids (Kumar et al., 2012). Flavonoids have the

potential to be reducing agents and to scavenge free radicals, chelate metal ions and inhibit enzymatic systems (topoisomerases and kinases) responsible for free radical generation (Kumar and Pandey, 2013). Yang et al. (2013) reported the inhibition of cancer cell lines, such as stomach cancer, prostate cancer, malignant melanoma, and mouse fibroblasts, by crude extracts and several isolated compounds (Table 1) of *C. fortunei*. In addition, apigenin was found to induce apoptosis and suppress insulin-like growth factor I receptor signalling in human prostate cancer (Way et al., 2004; Shukla and Gupta, 2009). Some flavonoids, such as quercetin, apigenin, kaempferol, and rutin in *Murraya koenigii*, inhibit endogenous 26S proteasome activity in MDA-MB-231 cells (Noolu et al., 2016). Several authors have reported the presence of apigenin, kaempferol, and luteolin in following species, namely *P. multifida*, *P. aquilinum*, *Selaginella* sp., *A. capillus-veneris*, *C. phalerata*, *P. vittata*, *O. sensibilis*, *M. struthiopteris*, *Equisetum ramoissimum*, *S. doederleinii*, *D. linearis*, *P. nudum*, *Pityrogramma tartarea*, *P. calomelanos*, *Cheilanthes concolor*, *Cardamine flexuosa*, *Cardamine goyazensis*, *Pellaea cymbiformis*, *P. gleichenioides*, *P. pinnata*, *P. riedelii*, *Pteris altissima*, *Pteris angustata*, *Pteris decurrens*, *Pteris deflexa*, *Pteris denticulata*, *Pteris plumula*, *Pteris podophylla*, *Pteris splendens*, *Pteris propinqua*, and *C. fortunei* (Table 1). Synergism between several flavones and flavonols for antimicrobial activity was confirmed in an earlier study. Moreover, quercetin and naringenin were found to significantly inhibit bactericidal motility (Yilmaz and Toledo, 2004). The release of ROS from activated neutrophils and macrophages causes inflammation injury. Excessive production may lead to tissue injury by damaging macromolecules and lipid peroxidation of membranes (Winrow et al., 1993; Gutteridge, 1995). ROS inflammation stimulates the release of cytokines, such as interleukin-1, tumour necrosis factor- α , and interferon- α , which stimulate the production of extra neutrophils and macrophages. However, free radicals are the main mediators promoting the inflammatory process. By neutralizing free radicals, antioxidants can reduce inflammation (Delaporte et al., 2002; Geronikaki and Gavalas, 2006). Therefore, we urge biologists to focus on the mechanisms of action of bioactive compounds from

early tracheophytes (pteridophytes) in medicinal applications.

6 Conclusions

Several researchers have studied the phytochemical and medicinal uses of lycophytes and ferns in recent years. These studies have demonstrated the importance of ferns and their allies in plant science fields. We have listed here the medicinal uses of pteridophytes, specifically their antioxidant, anti-diabetic, anti-cancer, antiviral, anti-inflammatory, wound healing, antimicrobial, and anti-Alzheimer activity. No significant review papers on medicinal pteridophytes have been published recently, only a few articles with inadequate reports. The medicinal pteridophytes listed in this review belong to the following thirty families: Davalliaceae, Equisetaceae, Lygodiaceae, Ophioglossaceae, Polypodiaceae, Psilotaceae, Pteridaceae, Salviniaceae, Selaginellaceae, Tectariaceae, Woodsiaceae, Aspleniaceae, Athyriaceae, Blechnaceae, Cyatheaceae, Dennstaedtiaceae, Dicksoniaceae, Dryopteridaceae, Hymenophyllaceae, Lindsaeaceae, Thelypteridaceae, Marsileaceae, Nephrolepidaceae, Onocleaceae, Marattiaceae, Oleandraceae, Osmundaceae, Cystopteridaceae, Gleicheniaceae, and Huperziaceae. Our review might encourage an appreciation of the uses of pteridophytes beyond ornamental purposes and, in particular, promote their use and development for medicinal benefits.

7 Future directions

Pteridophytes comprise around 13000 species that belong to nearly 48 plant families, but only a small number of species from thirty families have been analyzed for their biological activity. Hence, we urge biologists to evaluate the medicinal uses of pteridophytes and their bioactive principles. Using biotechnological tools, the efficacy of bioactive compounds could be increased by studies of in vitro culture, biosynthetic pathways, modes of action, and genetic expression. In addition to studies of their biological activity, pharmacokinetics, and toxicological profiles, multidrug therapies should be developed

from early tracheophytes and pteridophytes. Furthermore, the genetic relationships among pteridophytes should be analyzed based on their secondary metabolite synthesis.

Compliance with ethics guidelines

Xavier-ravi BASKARAN, Antony-varuvel GEO VIGILA, Shou-zhou ZHANG, Shi-xiu FENG, and Wen-bo LIAO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题目: 蕨类植物治疗人类疾病的应用概况

概要: 蕨类植物全世界约 48 科 250 属 12000 种, 目前只有少数蕨类植物的生物学活性得到了研究, 这些研究已经证明蕨类植物的药用价值及其在植物科学领域的重要性。本文旨在总结关于蕨类植物的主要化学成分及药理活性, 特别是其抗氧化活性、抗肿瘤活性、抗糖尿病活性、抗病毒活性、抗炎活性、抗菌活性、抗老年痴呆症和脑疾病活性等, 可用于替代医学的各种人类疾病治疗。然而, 它们的最佳剂量和治疗策略仍需要进一步研究。

关键词: 蕨类植物; 替代医学; 卷柏属; 人类疾病; 生物活性分子