

Phytochemical and Pharmacological Potential of Genus *Drynaria* (Bory) J. Sm.: A Comprehensive Review

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Abstract

The genus *Drynaria* (Bory) J. Sm. (Polypodiaceae) comprises approximately 32 species distributed across Africa, Asia and the Pacific Islands, representing diverse ecological and climatic zones. This genus has long been utilized in traditional medicine systems, where species are prescribed for the treatment of osteoporosis, bone fractures, tinnitus, inflammation, hyperlipidemia, arteriosclerosis and rheumatism. Phytochemical investigations have revealed the presence of diverse bioactive compounds including flavonoids, phenols, triterpenoids, phytosterols, chromones, furanocoumarins, lignans, tocopherols, fatty acid derivatives, phenylpropanoids and terpenoids. These constituents are associated with a wide range of pharmacological activities, such as analgesic, anti-arthritic, anticancer, anti-HIV, anti-inflammatory, antimicrobial, antioxidant, antipyretic, hepatoprotective, immunomodulatory, nephroprotective, neuroprotective, osteogenic, thrombolytic, cytotoxic and anti-obesity effects. This systematic review integrates ethnomedicinal knowledge with modern phytochemical and pharmacological evidence, highlighting the therapeutic relevance of *Drynaria* species and underscoring their potential for future drug discovery.

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INTRODUCTION

The genus *Drynaria* has been extensively utilized in traditional medicine, particularly for the treatment of bone-related disorders, inflammatory conditions, infections and bacterial diseases (Chen et al., 2021). Phytochemical studies have identified a wide spectrum of bioactive compounds, including flavonoids, triterpenoids, tannins and phenolic acids, which contribute to the genus's diverse pharmacological activities (Chen et al., 2021; Trinh et al., 2015). Recent pharmacological investigations have demonstrated the therapeutic potential of *Drynaria* species, highlighting their anti-inflammatory, analgesic, antimicrobial, osteoprotective, neuroprotective and hepatoprotective properties (Irudayaraj and Senthamarai 2004; Jeong et al., 2005; Anuja et al., 2010; Wang, 2018; Huang et al., 2023). This systematic review aims to synthesize current evidence on the medicinal value of *Drynaria*, with a focus on its phytochemical composition and pharmacological activities, thereby providing deeper insights into its potential applications in both traditional and modern medicine.

MATERIALS AND METHODS

Ethnobotanical and pharmacological data concerning the genus *Drynaria* were compiled through a systematic review of several well-established online resources, including Web of Science, Scopus, PubMed, Google Scholar, ResearchGate, Wiley Online Library, ScienceDirect, the Global Biodiversity Information Facility (GBIF) and Plants of the World Online (POWO). Information regarding phytochemicals and bioactive compounds was extracted from PubChem and the Royal Society

of Chemistry's ChemSpider database. The molecular structures of key constituents were drawn and analyzed using ChemSketch (Freeware Edition, ACD/Labs), which provides precise tools for structural representation and molecular modelling. This integrated methodology strengthened the accuracy, reproducibility and reliability of the phytochemical and pharmacological information assembled for *Drynaria*.

Taxonomy:

Drynaria is a distinct genus, best recognized by the peculiar frond dimorphism *Drynaria*, commonly known as 'Basket ferns' or 'Oak leaf ferns.' The fern genus *Drynaria* belongs to family Polypodiaceae. There are 33 species in the genus *Drynaria* (Christenhusz, 2015). In India it is represented by 6 species (Rawat and Deroliya, 2024). *Drynaria coronans*, *D. propinqua* and *D. quercifolia* are cultivated in gardens. According to Rawat and Deroliya (2024) these ferns thrive well in temperate to tropical climates rich in moisture, often flourishing along watercourses with gentle sunlight exposure. Known for their elegant, green basket like fronds, they are popular for ornamental use and natural landscaping.

Drynaria (Bory) J. Sm. in Hook. Journ. Bot. 4: 60. 1841; Nayar, Bull. Nation. Bot. Gard. Lucknow no. 56.9. 1961. nom. cons., *Polypodium* subgenus *Drynaria* Clarke, Trans. Linn. Soc. Lond. II (Bot.) 1: 555 (1825); Hope, J. Bombay nat. Hist. Soc. 15: 89 (1903).

Type species: *Drynaria quercifolia* (L.) J. Sm. in Hook. Journ. Bot. 3: 398. 1841.

Distribution: Africa, Australia, China, India, Indonesia, Malaysia, Philippines, Thailand, Singapore and Sri Lanka



Figure 1: A, B. Habit of *Drynaria* C. Vegetative frond D. Reproductive frond E. enlarged reproductive frond.

Ethnobotany

Species of the genus *Drynaria* have been traditionally employed as medicinal remedies across the world, with widespread use in Southeast Asia and China. Among the different plant parts, the rhizome is particularly valued in folk medicine for the treatment of bone fractures, osteoporosis, tinnitus, rheumatic pain and

respiratory ailments such as cough and tuberculosis. In addition to these ethnomedicinal applications, pharmacological investigations have revealed that *Drynaria* species possess a broad spectrum of bioactivities. A detailed account of the traditional uses of the genus is presented in **Table 1**.

Table 1: Traditional Uses of *Drynaria* Species

Name of the plant	Plant Part	Local Name	Preparation Method	Traditional use	References
<i>D. bonii</i> Christ	Rhizome	-	Decoction	Used for the treatment of osteoporosis, bone fractures and tinnitus.	Pham et al., 2015
	Rhizome	-	-	Used to heal bone fractures, stimulate hair growth and treat tinnitus or deafness.	Trinh et al., 2015
<i>D. fortunei</i> (Kunze) J. Sm	Rhizome	Gusuibu	Decoction	Used as a traditional Chinese medicine for bone healing.	Liu et al., 2001
	Rhizome	Gol-Se-Bo	Decoction	Demonstrates therapeutic potential in managing inflammation, hyperlipidemia, arteriosclerosis, rheumatism, osteoporosis, and bone resorption	Jung., 2007
	Rhizome	Gu sui bu	-	In China it used from thousands of years to treat the kidney, strengthen bones, promote fracture healing and relieve pain.	Liu et al., 2012
	Rhizome	-	Paste	Traditional Chinese medicine for treating injuries and bone fractures from falling and beating.	Zhao., 2024
	Rhizome	-	-	Used to heal bone fractures, stimulate hair growth, treat tinnitus, deafness, chronic diarrhea, low back pain and odontopathy.	Benskey and Gamble, 1996
	Rhizome	Gurar	Decoction	Used to treat cough, tuberculosis and typhoid fever	Khan et al., 2007a
<i>D. quercifolia</i> (L.) J.Sm.	Rhizome	Gurar	-	Used to treat tuberculosis, loss of appetite, cough, and fever.	Bhattacharya., 1990; Kirtikar and Basu., 1994
	Rhizome	Mudava atukkal	Soup	Used to treat rheumatic complaints.	Saravanan et al., 2013
	Rhizome	Bandor shoal	-	Treats typhoid, fever, cough, indigestion, jaundice, diabetes,	Chaity et al., 2016

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				tuberculosis, and throat infections.	
	Fronds	Mudava atukkal	Soup	The fronds are traditionally used by Indian tribal communities to treat typhoid, jaundice, headache, cough, cholera, and skin diseases.	Modak et al., 2021

Phytochemistry

The genus *Drynaria* exhibits a rich diversity of bioactive phytochemicals, most of which are derived from the rhizomes, as reported in species such as *D. fortunei* (Kunze) J. Sm., *D. propinqua* (Wall. ex-Mett.) J. Sm. ex Bedd., *D. bonii* H. Christ., *D. quercifolia* (L.) J. Sm., and *D. roosii* Nakaike. A smaller proportion of compounds have been isolated from aerial parts, particularly the leaves. In China, the rhizome of *D. fortunei* is widely recognized in local herbal medicine under the names *D. rigidula* and *Rhizome Drynariae*. To date, approximately 190 phytochemicals have been isolated and classified according to their structural classes. Among them, flavonoids and flavone derivatives represent the most abundant group, followed by phenols and phenolic acids. Species-specific distribution has also been noted: *D. fortunei* contains the highest number of flavonoids and phenols, *D. quercifolia* is particularly rich in fatty acids and triterpenoids, while *D. bonii* and *D. propinqua* also yield flavonoids, phenols and triterpenoids. Notably, *D. roosii* contains five liglaurates, which are associated with cytotoxic activity.

Pharmacological studies on isolated compounds have demonstrated diverse biological activities,

including anti-inflammatory, neuroprotective, acetylcholinesterase inhibitory, antioxidant, antibacterial, cell proliferation-promoting and anti-osteoporotic effects (Ramesh et al., 2001; Wang et al., 2016; Xu et al., 2018; Liang, 2011a; Liu et al., 2020; Trinh et al., 2020; Zhang et al., 2022; Ahn et al., 2023). Extraction of plant material has been conducted using solvents such as ethanol, methanol and petroleum ether, while compound isolation and characterization have been achieved through chromatographic and spectrometric techniques, including silica gel chromatography, Sephadex LH-20, gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography (HPLC). Frequently identified bioactives include naringin and neoericiotin (in *D. fortunei* and *D. quercifolia*) and β -sitosterol (in *D. propinqua*). Furthermore, several novel structures, such as Drynaether A and Drynachromosides A, highlight the unique phytochemical profile of the genus. Collectively, these findings emphasize the therapeutic potential of *Drynaria* species, particularly for their anti-inflammatory, antioxidant and anticancer properties. A detailed list of phytochemicals is presented in **Table 2**.

Table 2: Phytochemical compounds of genus *Drynaria*

Species	Plant Part	Class	Compounds	Biological activity	Reference
<i>D. bonii</i>					
1.	Rhizome	Flavonoids	Kaempferol	Osteoblast	Trinh et al., 2016
2.			Nobiletin	Antifungal, Antioxidant	Trinh et al., 2015
3.			Drynaether A	Osteoblast	Trinh et al., 2016
4.			5-Hydroxymethylfurfural	Osteoblastic	Trinh et al., 2020

5.		Phenol	Protocatechuic acid	Antifungal, Antioxidant Osteoblastic	Trinh et al., 2015; Trinh et al., 2016; Trinh et al., 2020
6.			Rutin	Osteoblastic, Antifungal, Antioxidant	Trinh et al., 2015; Trinh et al., 2020
7.			Nicotiflorin	Osteoblastic, Antifungal, Antioxidant	Trinh et al., 2015; Trinh et al., 2020
8.			Protocatechualdehyd e	Antifungal, Antioxidant	Trinh et al., 2015
9.			Isoliquiritigenin	Antifungal, Antioxidant	Trinh et al., 2015
10.			3-(5-hydroxymethyl) furan-2-yl)-2- phenylacrylaldehyde	Antifungal, Antioxidant	Trinh et al., 2015
11.			Chrysophanol	Antifungal, Antioxidant	Trinh et al., 2015
12.			Linocaffein	Antifungal, Antioxidant	Trinh et al., 2015
13.		Triterpeno id	24-Methylen- cycloartan-3 β -ol	Osteoblastic	Trinh et al., 2020
14.			Triphyllol	Osteoblastic	Pham et al., 2015; Trinh et al., 2020
15.			24- Methylencycloartan- 3 β -olt	-	Pham et al., 2015
<i>D. fortune</i>					
16.	Rhizome	Chromone	5,7- Dihydroxychromone- 7-O- neohesperidoside	-	Ahn et al., 2023
17.			5,7-Dihydroxy-2- methyl chromone		Han et al., 2015
18.			5,7-Dihydroxy-2- hydroxymethyl chromone		Han et al., 2015
19.			Drynachromoside C		Han et al., 2015
20.			Drynachromoside D		Han et al., 2015
21.			Drynachromoside B	Osteoblast	Shang et al., 2013; Han et al., 2015
22.			Drynachromoside A	Osteoblast	Shang et al., 2013
23.			Schumannioside A		Han et al., 2015
24.			5-Hydroxy-2- methylchromone-7- O-rutinoside		Han et al., 2015

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25.		Flavonoid	Eriodictyol	Osteoblastic activity, Cytotoxicity	Liang, 2011a; Wang et al., 2016; Xu et al., 2018; Liu et al., 2020; Zhang et al., 2022
26.			Kaempferol 3-O-rhamnoside 7-O-glucoside	-	Ahn et al., 2023
27.			Kaempferol 3-O-glucopyranoside-7-O-arabinofuranoside	-	Ahn et al., 2023
28.			Neoeriodictin	Neuropharmacological, Cytotoxicity	Li et al., 2009; Liang, 2011a; Liu et al., 2012; Wang et al., 2018; Liu et al., 2020; Dang et al., 2022; Ahn et al., 2023
29.			Naringin	Neuropharmacological, Cytotoxicity, Osteoblastic	Liang, 2011a; Liu et al., 2012; Wang et al., 2016; Xu et al., 2018; Wang et al., 2018; Liu et al., 2020; Dang et al., 2022; Zhang et al., 2022; Ahn et al., 2023
30.			Hesperidin	-	Ahn et al., 2023
31.			Luteolin-7-O- β -D-glucoside	Cytotoxicity	Xu et al., 2018; Liu et al., 2020
32.			Astragalin	Cytotoxicity	Xu et al., 2018, Liu et al., 2020
33.			Luteolin	Neuropharmacological, Cytotoxicity, Osteoblastic	Liang, 2011a; Xu et al., 2018; Wang et al., 2018; Liu et al., 2020; Zhang et al., 2022
34.			Naringenin	Neuropharmacological, Osteoblastic	Xu et al., 2018; Liu et al., 2020; Zhang et al., 2022
35.			Naringenin chalcone	Osteoblastic	Zhang et al., 2022
36.			Kaempferol	Neuropharmacological, Cytotoxicity, Osteoblastic	Xu et al., 2018; Wang et al., 2018; Liu et al.,

					2020. Zhang et al., 2022
37.			2',4'-Dihydroxydihydrochalcone	-	Liang, 2011a
38.			Nobiletin	Osteoblastic	Zhang et al., 2022
39.			Luteolin 7-O- β -D-glucopyranoside	-	Liang, 2011a; Sui et al., 2015
40.			Kaempferitrin	Osteoblastic	Zhang et al., 2022
41.			Cianidanol	Osteoblastic	Zhang et al., 2022
42.			Luteolin-7-glucuronide	Osteoblastic	Zhang et al., 2022
43.			Quercetin	Osteoblastic	Zhang et al., 2022
44.			Isorhamnetin	Osteoblastic	Zhang et al., 2022
45.			Dehydrodiisoeugenol	Osteoblastic	Zhang et al., 2022
46.			Eriodictyol 7-O- β -D-glucopyranoside	-	Liang, 2011a
47.			Luteolin 8-C- β -D-glucopyranoside	-	Liang, 2011a
48.			Epicatechin	-	Dang et al., 2022
49.			Cymaroside	-	Dang et al., 2022
50.			Drynaether A	Osteoblast	Trinh et al., 2016
51.			5,7,3',5'-Tetrahydroxyflavanone	Osteoblast	Shang et al., 2013
52.			5,7,3',5'-Tetrahydroxyflavanone-7-O- β -D-glucopyranoside	Osteoblast	Shang et al., 2013
53.			5,7,3',5'-Tetrahydroxyflavanone-7-O-neohesperidoside	Osteoblast	Shang et al., 2013
54.			(+)-Afzelechin	-	Liang et al., 2011b
55.			(+)-Catechin	-	Liang et al., 2011b
56.			(-)-Epiafzelechin		Wu and Zhao, 2005; Liang et al., 2011b
57.			4 α -Carboxymethyl-(+)-catechin methyl ester	-	Liang et al., 2011b

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58.			4 β -Carboxymethyl- (-)-epiafzelechin methyl ester	-	Liang et al., 2011b
59.			4 β -Carboxymethyl- (-)-epiafzelechin	-	Liang et al., 2011b
60.			(+)-Afzelechin-3-O- β -allopyranoside	-	Liang et al., 2011b
61.			(+)-Afzelechin-6-C- β -glucopyranoside	-	Liang et al., 2011b
62.			(-)-Epicatechin-3-O- β -D-allopyranoside	-	Liang et al., 2011b
63.			(+)-Epicatechin-3-O- β -D-allopyranoside	-	Liang et al., 2011b
64.			(-)-Epicatechin-8-C- β -D-glucopyranoside	-	Liang et al., 2011b
65.			(-)-Epiafzelechin-5-O- β -D-glucopyranoside	-	Liang et al., 2011b
66.			(-)-Epiafzelechin-3-O- β -D-allopyranoside	-	Wu and Zhao, 2005; Liang et al., 2011b;
67.			(-)-Epiafzelechin-(4 β \rightarrow 8)-4 β -carboxymethyl- (-)-epicatechin methyl ester	-	Liang et al., 2011b
68.			(-)-Epiafzelechin-(4 β \rightarrow 8)-4 α -carboxymethyl- (-)-epiafzelechin ethyl ester	-	Liang et al., 2011b
69.			Epiafzelechin-(4 β \rightarrow 8)-4 β -carboxymethyl-epiafzelechin methyl ester		Liang et al., 2011b
70.			Epicatechin-(4 β \rightarrow 8)-epicatechin		Liang et al., 2011b
71.			(-)-Epiafzelechin-(4 β \rightarrow 8)- (-)-epiafzelechin-(4 β \rightarrow 8)-4 β -carboxymethyl- (-)-epiafzelechin methyl ester		Liang et al., 2011b
72.			(-)-Epiafzelechin-(4 β \rightarrow 8,2 \rightarrow O \rightarrow 7)-epiafzelechin-(4 β \rightarrow 8)-epiafzelechin		Liang et al., 2011b
73.			5-Hydroxymethylfurfural		Ahn et al., 2023

74.		Phenol	4-Hydroxybenzoic acid		Ahn et al., 2023
75.			Gallic acid		Liang et al., 2010b; Ahn et al., 2023
76.			Protocatechuic acid	-	Liang et al., 2010b; Sui et al., 2015; Dang et al., 2022; Ahn et al., 2023
77.			Caffeic acid 4-O- β -D-glucopyranoside	-	Liang et al., 2010b; Liu et al., 2012; Ahn et al., 2023
78.			4,4'-Dihydroxy-3,3'-imino-di-benzoic acid	-	Liang et al., 2010b
79.			p-Hydroxybenzoic acid	-	Liang et al., 2010b
80.			(E)-Caffeic acid	-	Liang et al., 2010b
81.			Ethyl trans-3,4-dihydroxycinnamate (First-time)	-	Liang et al., 2010b
82.			p-Coumaric acid 4-O- β -D-glucopyranoside	-	Liang et al., 2010b
83.			Coumaric acid 4-O- β -D-glucopyranoside		Ahn et al., 2023
84.			Lavandoside		Ahn et al., 2023
85.			Trans-p-sinapoyl- β -D-glucopyranoside		Ahn et al., 2023
86.			23(S)-12-O-Caffeoyl-12-hydroxyllauric acid glycerol ester	-	Liang et al., 2010b
87.		Triterpenoid	Fern-9(11)-ene	-	Liu et al., 1999
88.			Hop-22(29)-ene	-	Liu et al., 1999
89.			Cyclolaudenol	-	Liu et al., 1999
90.			20 β -Hydroxychiratan-22-one	Cytotoxicity	Liang et al., 2010a
91.		Sterol	β -Sitosterol	Cytotoxicity	Wu and Zhao, 2005; Liang, 2011a; Wang et al., 2018
92.			Daucosterol	Osteoporosis	Liang, 2011a
<i>D. propinqua</i>					
93.		Flavonoid	(-)-Epiafzelechin-3-O- β -D-allopyranoside	-	Liu et al., 1994
<i>D. quercifolia</i>					
94.		Flavonoid	Naringin	Antibacterial	Ramesh et al., 2001

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95.			5-Hydroxymethylfurfural	Anti-inflammatory	Modak et al., 2021
96.		Fatty Acid	Decanoic Acid		Ragavan and Srinivasan, 2024
97.			Dodecanoic acid	Anti-inflammatory	Modak et al., 2021; Ragavan and Srinivasan, 2024
98.			Benzene-propionic Acid		Ragavan and Srinivasan, 2024
99.			Acetate		Ragavan and Srinivasan, 2024
100.			Eicosyl Acetate		Ragavan and Srinivasan, 2024
101.			Methyl Stearate		Ragavan and Srinivasan, 2024
102.			Palmitic Acid		Ragavan and Srinivasan, 2024;
103.			Stearic Acid		Ragavan and Srinivasan, 2024
104.			Propanoic Acid		Ragavan and Srinivasan, 2024
105.			Succinate		Ragavan and Srinivasan, 2024
106.			Tetradecanoic Acid		Ragavan and Srinivasan, 2024
107.		Triterpenoid	Friedelin	Antibacterial	Ramesh et al., 2001
108.			Epifriedelinol	Antibacterial	Ramesh et al., 2001
109.			β -Amyrin	Antibacterial	Ramesh et al., 2001
110.					
111.		Sterol	β -Sitosterol	Antibacterial,	Ramesh et al., 2001
112.			β -Sitosterol 3- β -D-glucopyranoside	Antibacterial	Ramesh et al., 2001
<i>D. rigidula</i>					
113.	leaves	Flavonoid	Kaempferitrin		Nugraha et al., 2019
114.		Sterol	Kaempferol-7-O- α -l-rhamnopyranosyl-4'-O-glucopyranoside		Nugraha et al., 2019
115.			β -Sitosterol		Nugraha et al., 2019
116.			Campesterol		Nugraha et al., 2019
117.			Stigmasterol		Nugraha et al., 2019

<i>D. roosii</i>					
118.	Rhizome	Liglaurates	Liglaurates A to E	Cytotoxicity	Wufuer et al., 2022
Other					
<i>D. bonii</i>					
119.			Ethyl β -D-fructopyranoside	-	Pham et al., 2015
120.			Drybonioside	-	Pham et al., 2015
121.			α -Tocopherol	-	Pham et al., 2015
122.			4'-Hydroxy-7-methoxyflavan	Osteoblast	Trinh et al., 2016
123.			Uracil	Osteoblast	Trinh et al., 2016
124.			Indole-3-carboxylic acid	Osteoblast	Trinh et al., 2016
<i>D. fortune</i>					
125.			(7'R,8'S)-Dihydrodehydrodiconiferyl alcohol 4'-O- β -D-glucopyranoside		Liang, 2011a
126.			Lariciresinol 4'-O- β -D-glucopyranoside		Liang, 2011a
127.			(-)-Secoisolariciresinol 4-O- β -D-glucopyranoside		Liang, 2011a
128.			12-O-caffeoyl-12-hydroxydodecanoic acid methyl ester	-	Sui, 2015
129.			p-Hydroxybenzenepropanoic acid	-	Sui, 2015
130.			Caffeic acid	-	Sui, 2015
131.			3,4-Dihydroxyphenyl ethyl 8-O- β -D-allopyranoside	-	Sui, 2015
132.			5,7-Dihydroxychromone-7-neohesperidoside	Cytotoxicity	Wang et al., 2018
133.			Psoralen	Cytotoxicity	Sui, 2015; Wang et al., 2018
134.			(E)-4-O- β -D-glucopyranosyl caffeic acid	Cytotoxicity	Wang et al., 2018
135.			Protocatechoic acid	Cytotoxicity	Wang et al., 2018
136.			E-4-O- β -D-glucopyranosyl caffeic acid	-	Li et al., 2009
137.			5,7-Dihydroxychromone-7-O-rutinoside	-	Liu et al., 2012

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138.			Maltol 3-O-β-D-glucopyranoside	-	Liang, 2011a
139.			Trans-cinnamic acid	Neuropharmacological	Wang et al., 2018
140.			P-coumaric acid	Neuropharmacological	Wang et al., 2018
<i>D. quercifolia</i>					
141.	Rhizome		Vitamin E	Anti-inflammatory	Modak et al., 2021
142.			Silane, ethenylethoxydimethyl-	Anti-inflammatory	Modak et al., 2021
143.			4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	Anti-inflammatory	Modak et al., 2021
144.			Catechol	Anti-inflammatory	Modak et al., 2021
145.			Benzeneacetic acid	Anti-inflammatory	Modak et al., 2021
146.			Beta-D-Ribopyranoside, methyl, 3-acetate	Anti-inflammatory	Modak et al., 2021
147.			Benzenepropanoic acid, 4-hydroxy-, methyl ester	Anti-inflammatory	Modak et al., 2021
148.			1,3,4,5-Tetrahydrocyclohexanecarboxylic acid	Anti-inflammatory	Modak et al., 2021
149.			1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	Anti-inflammatory	Modak et al., 2021
150.			n-Pentadecanol	Anti-inflammatory	Modak et al., 2021
151.			Hexadecanoic acid, methyl ester	Anti-inflammatory	Modak et al., 2021
152.			2-Hydroxycyclopentadecanone	Anti-inflammatory	Modak et al., 2021
153.			Dibutyl phthalate	Anti-inflammatory	Modak et al., 2021
154.			n-Hexadecanoic acid	Anti-inflammatory	Modak et al., 2021
155.			Alpha-D-Glucopyranoside, methyl	Anti-inflammatory	Modak et al., 2021
156.			n-Nonadecanol-1	Anti-inflammatory	Modak et al., 2021
157.			9,12-Octadecadienoic acid (Z, Z)-, methyl ester	Anti-inflammatory	Modak et al., 2021

158.			6-Octadecenoic acid, methyl ester, (Z)-	Anti-inflammatory	Modak et al., 2021
159.			cis-9-Hexadecenal	Anti-inflammatory	Modak et al., 2021
160.			Octadecanoic acid	Anti-inflammatory	Modak et al., 2021
161.			4,8,12,16-Tetramethylheptadecan-4-olide	Anti-inflammatory	Modak et al., 2021
162.			1-Heptacosanol	Anti-inflammatory	Modak et al., 2021
163.			Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	Anti-inflammatory	Modak et al., 2021
164.			Bis(2-ethylhexyl) phthalate	Anti-inflammatory	Modak et al., 2021
165.			9,12-Octadecadienoic acid (Z, Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester	Anti-inflammatory	Modak et al., 2021
166.			Squalene	Anti-inflammatory	Modak et al., 2021
167.			Gamma-Tocopherol	Anti-inflammatory	Modak et al., 2021
168.			A'-Neogammacer-22(29)-ene	Anti-inflammatory	Modak et al., 2021
169.			1-Phenanthrenecarboxylic acid, 7-ethyl-..., methyl ester	Anti-inflammatory	Modak et al., 2021
170.			Ergost-5-en-3-ol, (3 β ,24R)	Anti-inflammatory	Modak et al., 2021
171.			Cholest-5-en-3-ol, 4,4-dimethyl-, (3 β)	Anti-inflammatory	Modak et al., 2021
172.			Cholest-5-en-3-ol, 4,4-dimethyl-, (3 β)-	Anti-inflammatory	Modak et al., 2021
173.			Ergosta-8,24(28)-dien-3-ol, 4,14-dimethyl-, (3 β ,4 α ,5 α)	Anti-inflammatory	Modak et al., 2021
174.			Stigmast-5-en-3-ol, (3 β)	Anti-inflammatory	Modak et al., 2021
175.			9,19-Cyclolanost-24-en-3-ol, (3 β)-	Anti-inflammatory	Modak et al., 2021
176.			9,19-Cyclolanost-25-en-3-ol, 24-methyl-, (3 β ,24S)-	Anti-inflammatory	Modak et al., 2021
177.			Dimethylhexyl-tetramethyl-	Anti-inflammatory	Modak et al., 2021

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			benzo[cyclohepta]indene derivative		
178.			Cyclopropa[5,6]-33-norgorgostan-3-ol derivative	Anti-inflammatory	Modak et al., 2021
179.			9,19-Cyclolanostan-3-ol, 24-methylene-, (3 β)-	Anti-inflammatory	Modak et al., 2021
180.			5-(7a-Isopropenyl-4,5-dimethyloctahydroinden-4-yl)-3-methylpent-2-en-1-ol	Anti-inflammatory	Modak et al., 2021
181.			9,19-Cyclolanostan-3-ol, 24-methylene-, (3 β)-	Anti-inflammatory	Modak et al., 2021
182.			Indole		Ragavan and Srinivasan, 2024
183.			Acetamide		Ragavan and Srinivasan, 2024
184.			Butylated Hydroxytoluene		Ragavan and Srinivasan, 2024
185.			Sucrose	-	Liu et al., 1992
186.			(-)-epiafzelechin-3-O-beta-Dalloypyranoside	-	Liu et al., 1992
187.			4-O- β -D-glucopyranosyl caffeic acid	-	Liu et al., 1992
188.			Beta-sitosterol-3-O- β -D-glucopyranoside	-	Liu et al., 1992
<i>D. quercifolia</i>					
189.	Rhizome		3,4-dihydroxybenzoic acid	Antibacterial, Cytotoxicity	Khan et al., 2007b
190.			acetyl lupeol	Antibacterial, Cytotoxicity	Khan et al., 2007b

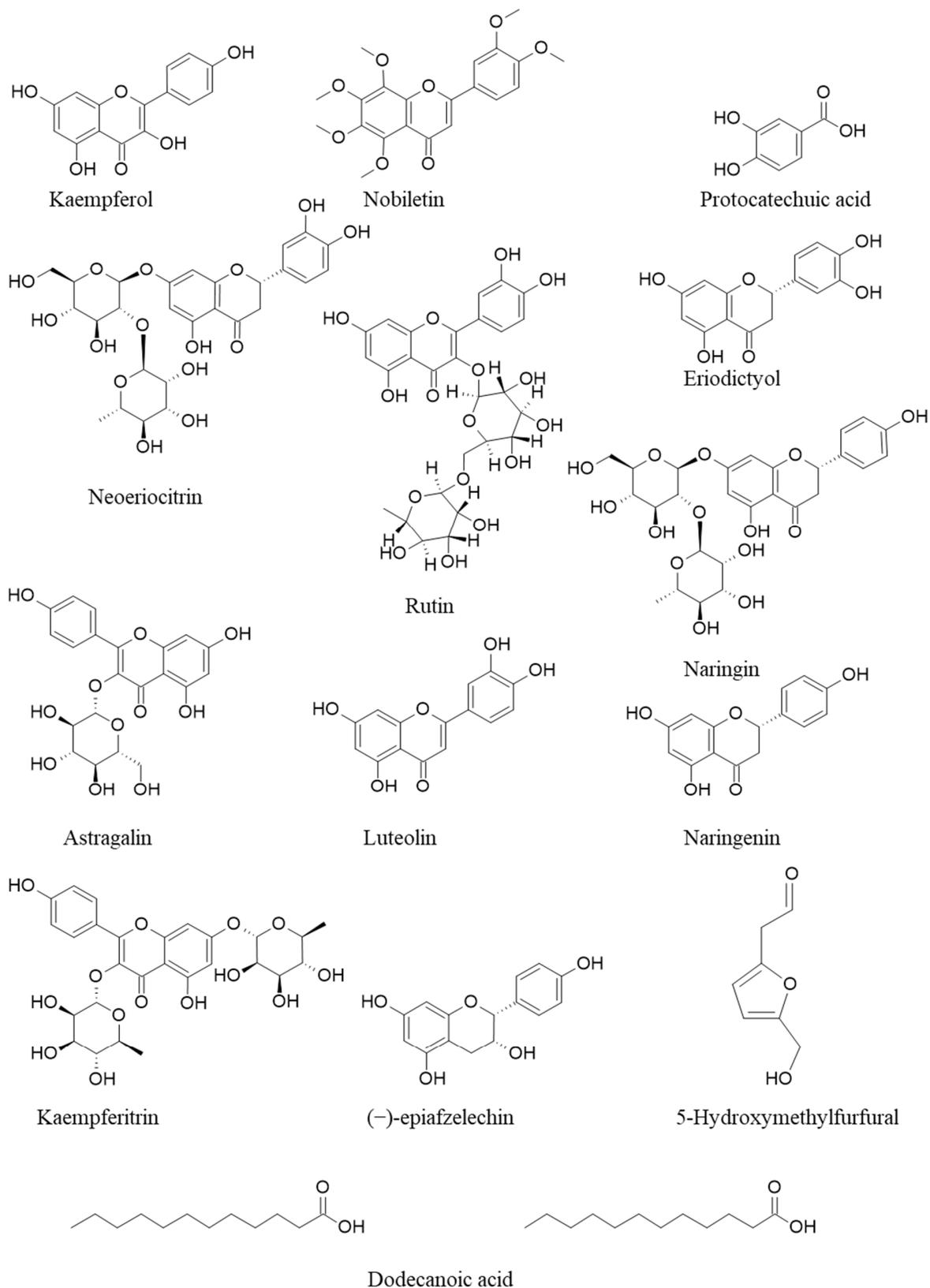


Figure 2: Chemical compounds from *Drynaria* species.

Pharmacology

Drynaria exhibits various pharmacological activities presented in Figure 3 as below.

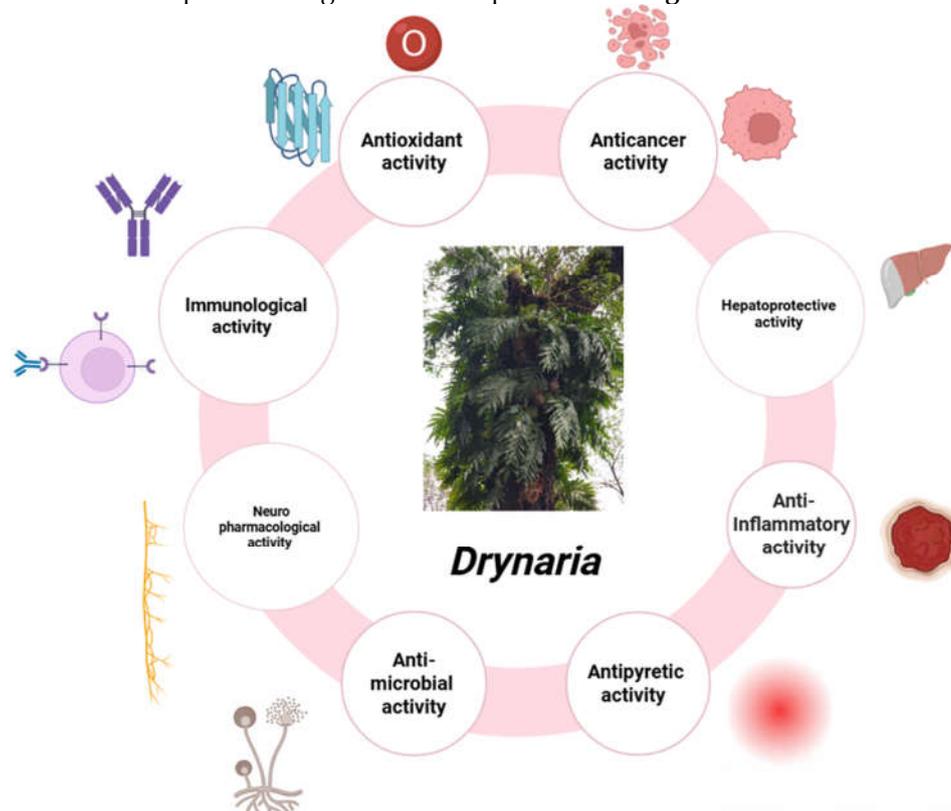


Figure 3: Pharmacological activity of *Drynaria*.

Anti-microbial activity:

The antimicrobial potential of *Drynaria* species has been widely reported across multiple extracts, plant parts and target pathogens. The methanolic rhizome extract of *D. quercifolia* demonstrated significant, dose-dependent antibacterial activity against both Gram-positive and Gram-negative bacterial strains, as assessed by the agar well diffusion assay. The strongest inhibition was observed against *Pseudomonas aeruginosa* (29 mm at 50 mg/mL), followed by *Salmonella typhi* (26 mm) and *Aeromonas hydrophila* (25 mm), while other bacterial strains showed moderate inhibition (Ramesh et al., 2001). In a related study, chloroform and *n*-butanol fractions of *D. fortunei* root demonstrated the strongest activity against oral pathogens (MIC: 0.0078–0.3125 mg/mL; MBC: 0.019–0.625 mg/mL), outperforming methanol and ethyl acetate fractions. However, the activity was relatively weak against *Streptococcus criceti*, *Aggregatibacter actinomycetemcomitans* and

Fusobacterium nucleatum (MIC/MBC: 1.25–5 / 1.25–10 mg/mL) (Jung, 2007). Bioactive compounds have also been identified as contributing to antimicrobial activity. For example, 3,4-dihydroxybenzoic acid, isolated from the ethanolic extract of *D. quercifolia* rhizome, exhibited significant antibacterial effects against both Gram-positive and Gram-negative bacteria using disc diffusion and serial dilution assays, with MIC values ranging from 8–32 µg/mL for Gram-positive strains and 16–64 µg/mL for Gram-negative strains (Khan et al., 2007b). Consistent with this, different extracts of *D. quercifolia* rhizome displayed antibacterial activity in the order: ethanol (80%) > methanol (70%) > benzene (50%) > chloroform (40%), as assessed by the agar diffusion method (Kandhasamy et al., 2008). The antibacterial efficacy of acetone and ethanol extracts of *D. quercifolia* rhizome was further validated against urinary tract pathogens using the disc diffusion method, with amikacin serving as a standard.

The acetone extract was effective against *Enterococcus faecalis* (8 mm) and *Streptococcus pyogenes* (MZOI: 22 mm vs. 23 mm for amikacin), whereas the ethanol extract showed notable inhibition of *P. aeruginosa* (Mithraja et al., 2012). Similarly, methanolic extract of *D. quercifolia* rhizome displayed significant antibacterial activity against Gram-positive bacteria (*S. aureus*, *B. subtilis*, *S. pyogenes*; MIC: 0.31–1.25 mg/mL) and Gram-negative bacteria (*E. coli*, *P. aeruginosa*; MIC: 0.62–2.5 mg/mL), with *S. flexneri* being the least sensitive (Pandhy and Dash, 2015). Extending to other species, phytochemicals isolated from the ethanolic extract of *D. bonii* rhizome, including chrysophanol, nobiletin, protocatechualdehyde, isoliquiritigenin, rutin and drynaran, exhibited only minimal antimicrobial effects against fungi (*Fusarium oxysporum*, *Saccharomyces cerevisiae*, *Candida albicans*, *Aspergillus niger*) and bacteria (*B. subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli*) with a MIC of 50 µg/mL (Trinh et al., 2015). In contrast, chloroform fractions of *D. fortunei* root showed stronger activity against periodontal pathogens (*Prevotella intermedia* and *Porphyromonas gingivalis*) in MIC/MBC checkerboard dilution and time-kill assays, with MIC/MBC values ranging from >39 to 2,500/5,000 µg/mL. The activity, although less potent than ampicillin or gentamicin (MIC/MBC: 0.25–64/0.25–64 µg/mL and 0.5–256/1–512 µg/mL, respectively), still highlighted significant antibacterial potential (Cha et al., 2017). Beyond antibacterial activity, *D. baronii* rhizome extracts, rich in flavonoids and phenolics, exhibited anti-HIV activity by inhibiting viral replication and key enzymes associated with HIV progression. The extract showed a CC₅₀ of 263 µg/mL, an EC₅₀ of 57 µg/mL and a selectivity index (SI) of 5, indicating mild anti-HIV potential and moderate protection against HIV-induced cytopathic effects (Chu et al., 2009).

Thrombolytic activity

The thrombolytic activity of various extracts of *Drynaria quercifolia* rhizome and fertile foliage was assessed using an *in vitro* clot lysis assay with human blood. Among the tested extracts, the methanolic extract of the rhizome exhibited the highest thrombolytic activity (38.34%), followed by the aqueous extract with moderate activity (33.32%). Fertile foliage extracts also

demonstrated moderate thrombolytic potential (>25%), while the chloroform extract showed moderate activity in both rhizome and foliage (Chaity et al., 2016).

Antipyretic activity

Antipyretic activity of *Drynaria* species has been demonstrated in several experimental models. Petroleum ether and ethyl acetate fractions of *D. quercifolia* rhizome produced significant ($p < 0.05$) antipyretic effects in Wistar albino rats, reducing elevated rectal temperature after 3 hours by $38.5 \pm 0.15\%$ and $37.03 \pm 0.16\%$ at 40 mg/kg and by $88.9 \pm 0.23\%$ and $84.6 \pm 0.20\%$ at 80 mg/kg, respectively. These results were comparable to the standard drug aspirin ($96.3 \pm 0.10\%$) (Khan et al., 2007a). Similarly, methanolic extract of *D. quercifolia* rhizome exhibited dose-dependent antipyretic activity at 100, 250 and 500 mg/kg in Brewer's yeast-induced pyrexia in Wistar albino rats, with effects comparable to the standard drug paracetamol (200 mg/kg; 37.24°C) (Janaranjani et al., 2014).

Anti-Inflammatory activity

The anti-inflammatory potential of *Drynaria* species has been extensively investigated through both *in vivo* and *in vitro* studies. Ethanolic extract of *D. quercifolia* rhizome demonstrated significant activity in Wistar albino rats, effectively inhibiting carrageenan-induced paw oedema and cotton pellet-induced granuloma formation in a dose-dependent manner, with inhibition rates of 80.00%, 83.53% and 85.88%, while the indomethacin-treated group exhibited maximum inhibition (88.24%) (Anuja et al., 2010). Similarly, methanolic extract of *D. quercifolia* rhizome produced notable anti-inflammatory effects at 2.5 hours, with paw oedema inhibition of 21%, 33% and 58% at doses of 100, 250 and 500 mg/kg b.w., respectively, compared to 40% inhibition observed with the standard drug dexamethasone (200 mg/kg b.w.) (Janaranjani et al., 2014). In another study, aqueous and methanolic extracts of *D. quercifolia* rhizome significantly reduced carrageenan-induced oedema in a dose-dependent manner ($p < 0.05$ and $p < 0.01$), with methanolic extract showing the highest activity at 150 mg/kg (Das et al., 2014). Further, methanolic extract of *D. quercifolia* demonstrated both *in vivo* and *in vitro* efficacy, with paw oedema reduction over 21

days (low and high dose groups recording 60.44 ± 1.44 mm and 58.39 ± 1.72 mm, respectively) and protein denaturation inhibition of $29 \pm 6.34\%$, $39.6 \pm 6.46\%$ and $51.2 \pm 4.41\%$ at concentrations of 600, 800 and 1000 $\mu\text{g/ml}$ (Modak et al., 2021). Beyond *D. quercifolia*, ethanolic extract of *D. fortunei* rhizome has also been evaluated for anti-inflammatory potential (Mani et al., 2024). Studies in RAW264.7 macrophages and SW1353 human chondrocytes revealed inhibition of 5-LO (85.78%) and COX-2 (56.64%), suppression of NO, LTB₄ and PGE₂ production, and downregulation of MMP-3 and MMP-9 in IL-1 β -stimulated chondrocytes. These findings suggest a cartilage-protective effect, highlighting its potential application in osteoarthritis management (Lee and Kang, 2023).

Hepatoprotective activity

Total flavonoids of *D. fortunei* (TFRD, 125 mg/kg; Rutin 97.82%) demonstrated significant hepatoprotective activity against aflatoxin B₁ (AFB₁)-induced liver toxicity in chickens. Treatment with TFRD reduced intestinal permeability, enhanced villus height and goblet cell maturation by 59% and restored gut microbiota composition. Moreover, it protected hepatic tissue by modulating bile acid metabolism, while simultaneously suppressing oxidative stress, hepatic lipid accumulation and ferroptosis-related gene expression, thereby conferring protection against AFB₁-induced hepatotoxicity (Huang et al., 2023).

Nephroprotective activity:

The flavonoid fraction (FF) of *Drynaria fortunei* (10 mg/kg) demonstrated significant nephroprotective activity in murine models of renal injury. In gentamicin- and mercuric chloride-induced acute renal failure as well as in 5/6-nephrectomized mice, FF treatment markedly reduced blood urea nitrogen (17.1 ± 1.0 vs. 22.7 ± 3.8 mg/dL) and serum creatinine levels (0.58 ± 0.09 vs. 0.68 ± 0.05 mg/dL). Moreover, it significantly improved survival time (116.8 ± 36.3 vs. 40.8 ± 6.9 days) and promoted tubular regeneration, indicating both functional and structural renal recovery (Long et al., 2005).

Neuropharmacological activity

The neuropharmacological potential of *Drynaria* species has been extensively investigated.

Petroleum ether and ethyl acetate fractions of *D. quercifolia* rhizome exhibited significant central nervous system (CNS) depressant activity in mice, as evidenced by prolonged diazepam-induced sleep, delayed nikethamide-induced death, increased time spent in the dark, and enhanced immobility in a dose-dependent manner (50–200 mg/kg). Among the two, the petroleum ether fraction demonstrated greater potency, with no mortality observed even at 800 mg/kg, highlighting a favorable safety profile (Khan et al., 2009). An aqueous extract of *Drynaria fortunei* rhizomes was found to reverse A β _{25–35}-induced axonal atrophy in cultured mouse cortical neurons (Yang et al., 2015). In a controlled cortical impact (CCI) rat model of traumatic brain injury (TBI), a decoction of *D. fortunei* rhizome (20 mg/kg, orally for 14–28 days) reduced brain damage by ~40%, improved memory and motor performance by ~35%, and alleviated anxiety and depression. The extract also modulated immune responses by downregulating pro-inflammatory IL-6 (~45%), upregulating anti-inflammatory IL-10 (~50%), restoring immune cell balance and attenuating pathological brain cell activation, with eriodictyol identified as a major bioactive constituent (Wang et al., 2016). Furthermore, fractions of *D. fortunei* rhizome were evaluated for acetylcholinesterase inhibitory activity through bio-guided fractionation using UPLC-MS/MS. The n-butanol fraction exhibited the strongest inhibitory effect ($\text{IC}_{50} = 5.62 \pm 0.23$ $\mu\text{g/ml}$), outperforming petroleum ether (35.48 ± 9.93 $\mu\text{g/ml}$) and aqueous fractions (36.31 ± 3.68 $\mu\text{g/ml}$). Isolated flavonoid aglycones, including naringenin, eriodictyol, kaempferol and luteolin, showed markedly stronger inhibition (IC_{50} as low as 3.81 ± 0.21 μM for naringenin) compared to their glycosidic counterparts, such as astragaloside, luteolin-7-O- β -D-glucoside, naringin and neoeriocitrin (Liu et al., 2020).

Immunological activity

The immunomodulatory potential of *Drynaria fortunei* was demonstrated through both cellular and humoral immune assays. In a delayed-type hypersensitivity (DTH) model, the extract produced a dose-dependent enhancement of immune responses in mice sensitized with sheep red blood cells (SRBC) and oxazolone. Humoral immunity was also stimulated, as evidenced by a

significant elevation in circulating antibody in SRBC-immunized mice. Hematological analysis revealed an increase in total WBC counts, further supporting its immunostimulatory activity. Moreover, in a cyclophosphamide-induced immunosuppression model, *D. fortunei* treatment effectively restored immune function, counteracting the suppressive effects of cyclophosphamide (Jeong et al., 2005).

Anti- obesity

The aqueous extract of *Drynaria fortunei* rhizome was evaluated for its anti-obesity potential in male C57BL/6 mice. After six weeks of treatment, the extract significantly reduced body weight, with a final mean weight of 31.85 ± 1.95 g compared to 35.50 ± 2.76 g observed in the high-fat diet (HFD) control group, demonstrating a notable weight-lowering effect (Gil et al., 2023).

Haematological studies

Haematological effects of *Drynaria* have also been investigated. Intraperitoneal administration of 3,4-dihydroxybenzoic acid, isolated from the ethanol extract of *D. quercifolia* rhizome, was evaluated in Swiss albino rats. The compound did not produce any significant alterations in haematological parameters compared to the control group. Specifically, RBC counts remained within normal ranges (control: 5.08 ± 0.07 – 5.16 ± 0.09 ; experimental: 5.10 ± 0.08 – 5.37 ± 0.12), while WBC counts were similarly unaffected (control: 5.86 ± 0.32 – 6.04 ± 0.28 ; experimental: 6.08 ± 0.21 – 6.19 ± 0.22). Platelet levels also showed no significant variation (Khan et al., 2007b).

Anti- arthritic activity

Species such as *Drynaria quercifolia* and *Drynaria fortunei* have demonstrated significant anti-arthritic potential through mechanisms involving the reduction of inflammation, protection of cartilage and promotion of bone repair. The ethanolic flavonoid extract of *D. fortunei* rhizome was evaluated in a Collagen-Induced Arthritis (CIA) model in Wistar rats, established via subcutaneous injection of bovine type II collagen. The treatment resulted in a significantly higher trabecular area percentage and trabecular number, along with a significantly reduced resolving power in comparison to the control group ($P < 0.05$) (Gao et al., 2013). Similarly, the aqueous extract of *D. quercifolia* (100 and 200

mg/kg body weight) produced a dose-dependent reduction in elevated enzyme levels ($P < 0.05$ to $P < 0.001$) relative to arthritic controls. Notably, this effect was comparable to indomethacin (2 mg/kg) in a model of arthritis induced by 0.1 ml of Freund's Complete Adjuvant (Sigma-Aldrich) (Saravanan et al., 2013).

Osteoblastic activity

Ethanolic extract of *Drynaria bonii* rhizome, fractionated into hexane, chloroform, ethyl acetate and methanol, demonstrated stimulatory effects on MG-63 osteoblastic cell proliferation, with the methanol fraction showing the highest activity, increasing proliferation by 6.16% at 0.01 mg/mL (Trinh et al., 2016). Subsequently, Trinh et al., (2020) isolated 24-methylen-cycloartan-3 β -ol, triphyllol and protocatechuic acid from *D. bonii* rhizome, which enhanced MG-63 proliferation by 7.68–11.18% at 100 μ g/mL in MTT assays. In parallel, flavonoid fractions of *D. fortunei* significantly promoted bone defect healing in rat bone marrow stromal cells (BMSCs) via the p38 MAPK pathway, with medium-dose treatment ($0.22 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) achieving optimal bone repair. This was evidenced by higher X-ray scores (~ 8 – 10 vs. ~ 4 – 5 in controls), BV/TV ratios (~ 40 – 50% vs. ~ 20 – 25%), 2–3-fold increases in osteoblast counts, ~ 70 – 80% reduction in fibrous tissue and marked upregulation of BMP-2 (~ 3 – 4 -fold) and RUNX-2 (~ 2.5 – 3 -fold). Enhanced BMSC proliferation, alkaline phosphatase (ALP) activity and mineralized nodule formation (~ 1.5 – 3 -fold increases) further confirmed strong osteogenic potential (Sun et al., 2021). Total flavonoids of *D. fortunei* (TFDR) ameliorated glucocorticoid-induced osteoporosis (GIOP) in rats by significantly improving femoral bone mineral density ($0.300 \pm 0.023 \text{ g/cm}^2$, $p < 0.01$) and bone microarchitecture through upregulation of OC, OPG, BMP-2 and PINP (Zhang et al., 2022). Likewise, TFRD and its major flavonoids—neeriocitrin, naringin and naringenin—enhanced IDG-SW3 cell viability by 20–30%, suppressed RANKL and SOST expression by 40–50% and improved trabecular bone parameters (BV/TV $\uparrow 15$ – 25% , Tb.Th $\uparrow 10$ – $20 \mu\text{m}$, Tb.Sp $\downarrow 15$ – $20 \mu\text{m}$), along with 10–12% increases in bone mineral density, without hepatic or renal toxicity in osteoporotic rats (Jin et al., 2022). Supporting these results, TFRD (0.22 g/kg/day) significantly

improved bone remodeling in rat femoral defect models, promoting continuous bone formation, cortical bone reconstruction and increased expression of BMP-2, VEGF and CD31, thereby enhancing both osteogenesis and angiogenesis (Zhao et al., 2022). Combination therapy of TFRD with metformin in ovariectomized rats further improved bone quality, with ~15–20% increases in BMD, ~25% rise in BV/TV, ~20% increase in Tb.N and ~15% decrease in Tb.Sp, accompanied by ~30% elevation of serum PINP, ~35% reductions in CTX-1 and TRAP and ~20% improvement in femoral strength (Jiang et al., 2023). Most recently, TFRD was shown to enhance cranial bone repair in rat defect models, validated through micro-CT, histological, and ELISA analyses, with network pharmacology and molecular assays implicating TGF- β -mediated osteogenesis. Serum profiling identified 27 active compounds, while *in vitro* studies confirmed enhanced BMSC proliferation and differentiation (Zhao et al., 2024). Collectively, these findings highlight *D. bonii* and *D. fortunei* flavonoids as potent stimulators of osteoblast proliferation, osteogenesis and bone regeneration, supporting their potential as therapeutic agents for osteoporosis and bone defect repair.

Antioxidant activity

An aqueous extract of *Drynaria fortunei* rhizome was evaluated for its antioxidant potential against reactive oxygen species (ROS) in rat osteoblasts using a cytometric assay. The extract significantly reduced intracellular ROS levels in a concentration-dependent manner, showing reductions of 35% at 10 $\mu\text{g}/\text{mL}$ ($p = 0.003$) and 50% at 100 $\mu\text{g}/\text{mL}$ ($p = 0.001$) (Liu et al., 2001). Similarly, Chang et al., (2012) investigated the antioxidant activity of methanolic extract of *D. fortunei* rhizome using multiple *in vitro* assays. In the HRP-Luminol- H_2O_2 system, the extract exhibited strong activity with an IC_{50} of 2.9 ± 0.3 $\mu\text{g}/\text{mL}$. In contrast, moderate activity was observed in the CuSO_4 -Phen-Vc- H_2O_2 assay ($\text{IC}_{50} = 27.7 \pm 1.0$ $\mu\text{g}/\text{mL}$) and the Luminol- H_2O_2 assay ($\text{IC}_{50} = 9.2 \pm 2.5$ $\mu\text{g}/\text{mL}$). In another study, Das et al., (2014) evaluated the antioxidant activity of methanolic and aqueous extracts of *D. quercifolia* rhizome using superoxide scavenging, DPPH radical scavenging and reducing power assays. The methanolic and aqueous extracts

exhibited IC_{50} values of 42.93 μg and 67.20 μg for superoxide scavenging, 53.60 μg and 66.20 μg for DPPH radical scavenging and 42.83 μg and 41.05 μg for reducing power, respectively. Both extracts demonstrated dose-dependent activity, although their efficacy was lower compared to the standard ascorbic acid ($\text{IC}_{50} = 4.30$ μg). Furthermore, the methanolic extract of *D. quercifolia* rhizome demonstrated significant free radical scavenging activities. It showed potent DPPH ($\text{EC}_{50} = 18.54 \pm 0.70$ $\mu\text{g}/\text{mL}$) and ABTS ($\text{EC}_{50} = 29.80 \pm 0.70$ $\mu\text{g}/\text{mL}$) scavenging activity, along with notable hydroxyl radical ($\text{EC}_{50} = 37.60 \pm 0.41$ $\mu\text{g}/\text{mL}$), nitric oxide ($\text{EC}_{50} = 42.40$ $\mu\text{g}/\text{mL}$) and hydrogen peroxide ($\text{EC}_{50} = 32.80 \pm 1.89$ $\mu\text{g}/\text{mL}$) scavenging effects. These results were comparable to the standard antioxidant butylated hydroxytoluene (BHT) (Jinu et al., 2014). Consistently, Trinh et al., (2015) investigated the antioxidant potential of isolated compounds from the ethanolic extract of *D. bonii* rhizome using the DPPH radical scavenging assay. Protocatechuic acid, protocatechualdehyde and rutin exhibited strong antioxidant activities, with SC_{50} values of 13.12, 4.87 and 25.00 $\mu\text{g}/\text{mL}$, respectively. Prasanna and Anuradha (2015) demonstrated that the methanolic extract of *D. quercifolia* rhizome exhibited a dose-dependent antioxidant effect. In the DPPH radical scavenging assay, maximum inhibition of $49.58 \pm 0.03\%$ was observed at 150 μL , with lower activities of $22.71 \pm 1.00\%$ and $17.13 \pm 0.16\%$ at 100 μL and 50 μL , respectively. Similarly, the ferric reducing antioxidant power (FRAP) assay confirmed a concentration-dependent response, with the highest reducing activity at 300 μg (2.78 ± 0.01 $\mu\text{M}/\text{mg}$), followed by 200 μg (0.44 ± 0.005 $\mu\text{M}/\text{mg}$) and 100 μg (0.27 ± 0.01 $\mu\text{M}/\text{mg}$). Moreover, Tan and Lim (2015) investigated the antioxidant activities of methanolic extracts of rhizomes and fronds from *D. quercifolia*, *D. rigidula* and *D. sparsisora*. Among the tested samples, *D. quercifolia* fronds exhibited the highest total phenolic content (TPC: 2939 ± 469 mg GAE/100 g), free radical scavenging activity (FRS: $\text{IC}_{50} = 0.09$ mg/mL) and ferric reducing power (FRP: 17.5 mg GAE/g). In contrast, *D. sparsisora* rhizomes outperformed its fronds in FRS, while lipid peroxidation inhibition (LPI) remained comparable across all extracts ($\geq 50\%$). The ferrous ion chelating (FIC) assay, however, revealed weak secondary antioxidant

activity in all species. Chaity et al., (2016) evaluated the antioxidant activity of methanolic and aqueous extracts from the rhizome and fertile foliage of *D. quercifolia*. In the DPPH assay, the aqueous rhizome fraction showed the highest activity ($IC_{50} < 15 \mu\text{g/mL}$) with an antioxidant activity index (AAI) of 1.77. In the H_2O_2 scavenging assay, the aqueous fractions of rhizome and foliage exhibited IC_{50} values of 77.36 ± 2.2 and $90.33 \pm 4.1 \mu\text{g/mL}$, respectively. The ABTS assay revealed the strongest activity in the aqueous rhizome fraction ($IC_{50} = 23.29 \pm 1.85 \mu\text{g/mL}$), while the FRAP assay confirmed the highest reducing capacity in the same fraction ($42.36 \pm 1.36 \mu\text{mol Fe}^{2+}/\text{g}$). Chu et al., (2009) evaluated the antioxidant activity of a herbal extract of *D. baronii* using electron-spin resonance spectroscopy. The extract demonstrated effective superoxide ion scavenging ($IC_{50} = 40 \mu\text{g/mL}$) and moderate hydroxyl radical scavenging ($IC_{50} = 1500 \mu\text{g/mL}$). Interestingly, it also enhanced the superoxide scavenging capacity of vitamin C.

Anticancer activity

The anticancer potential of *Drynaria* species has been explored through in vitro studies. An herbal extract of *D. baronii* exhibited weak cytotoxicity ($CC_{50} > 400 \mu\text{g/mL}$) against normal cell lines (HGF, HPC, HPLF) and tumor cell lines (HSC-2, HSC-3, HSC-4, Ca9-22, NA, T98G, HL-60), showing only slight tumor specificity. Its primary activity appeared to be free radical scavenging, as demonstrated by superoxide ($IC_{50} = 40 \mu\text{g/mL}$) and hydroxyl radical ($IC_{50} = 1,200 \mu\text{g/mL}$) inhibition, as well as enhanced synergistic scavenging with vitamin C. In addition, the extract displayed weak anti-HIV activity ($SI = 5$), suggesting that radical scavenging rather than direct cytotoxicity underlies its antitumor effect (Chu et al., 2009). Complementing these findings, an aqueous extract of *D. fortunei* rhizome demonstrated antiproliferative activity against breast cancer cells. Using CellTiter-Glo assay and cell cycle analysis, the extract dose-dependently reduced MDA-MB-231 cell viability, with maximum inhibition observed at $1,000 \mu\text{g/mL}$. It further suppressed colony formation in soft agar at concentrations of $100\text{--}5,000 \mu\text{g/mL}$ and induced G1-phase cell cycle arrest at $300\text{--}800 \mu\text{g/mL}$, highlighting its potential to inhibit cancer cell proliferation and tumorigenic capacity (Telang et al., 2024).

Cytotoxicity

The *Drynaria* genus has been extensively investigated for its cytotoxic and anticancer potential, with extracts and isolated compounds exhibiting apoptosis induction, proliferation suppression, and modulation of cancer-related pathways. Notably, the flavonoid fraction of *D. fortunei* protected against gentamycin-induced ototoxicity in guinea pigs by decreasing inner hair cell damage (2%, $p < 0.05$) and maintaining auditory thresholds comparable to controls (Long et al., 2004). Similarly, *D. fortunei* enhanced the proliferation of human osteo precursor cells (OPC-1) at concentrations of $10\text{--}120 \mu\text{g/mL}$, with maximal stimulation observed at $120 \mu\text{g/mL}$, although higher doses were inhibitory (Jeong et al., 2005). Acute toxicity assessments of *D. quercifolia* rhizome fractions (petroleum ether and ethyl acetate) revealed no mortality up to 800mg/kg , supporting their safety profile (Khan et al., 2009). In cancer models, the isolated compound 20 β -hydroxychiratan-22-one from *D. fortunei* exhibited strong cytotoxicity against HeLa, PC-13 and HepG2 cells with IC_{50} values of 2.92, 1.08 and $2.45 \mu\text{M}$, respectively (Liang et al., 2010a). Furthermore, nine compounds from *D. fortunei* rhizome, including naringin, neoeriocitrin, kaempferol, luteolin and protocatechuic acid, demonstrated neuroprotective effects by promoting PC12 cell proliferation under $\text{A}\beta_{25\text{--}35}$ -induced injury without exerting cytotoxicity (Wang et al., 2018). Likewise, ethanolic extracts of *D. fortunei* rhizome exhibited no cytotoxicity in RAW264.7 macrophages and SW1353 chondrocytes, maintaining $>90\%$ viability even at $100 \mu\text{g/mL}$ (Lee and Kang, 2023). In contrast, ethanolic extracts of *D. roosii* rhizome displayed notable cytotoxicity against multiple cancer cell lines (A549, HeLa, HepG2, MCF-7, HCT-116), with superior potency against HeLa cells (IC_{50} $0.06\text{--}0.34 \mu\text{M}$), surpassing the standard drug adriamycin (IC_{50} $1.49 \mu\text{M}$) and optically pure (+)-1 and (+)-2 enantiomers showing enhanced activity (Wufuer et al., 2022). Additionally, methanolic extracts of *D. quercifolia* leaves, fractionated into petroleum ether, carbon tetrachloride, chloroform and aqueous fractions, exhibited moderate cytotoxicity in the brine shrimp lethality assay, with LC_{50} values ranging from 7.61 to $15.83 \mu\text{g/mL}$ compared to the standard vincristine sulfate (Runa et al., 2013).

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Collectively, these findings underscore the anticancer potential of *Drynaria* species, while also highlighting their selective cytotoxicity and favorable safety margins.

CONCLUSION

The *Drynaria* genus, predominantly distributed across Southeast Asia, particularly in China and India, comprises mostly epiphytic species thriving in warm and humid forest ecosystems. Traditionally, members of this genus have been employed in ethnomedicine for the treatment of osteoporosis, bone fractures, tuberculosis, rheumatic disorders and as stimulants for hair growth, often administered as decoctions or soups prepared from rhizomes and fronds. Phytochemical investigations reveal that *Drynaria* species, especially *D. fortunei*, *D. quercifolia* and *D. bonii*, are rich in flavonoids, phenols, triterpenoids, fatty acids, chromones, and sterols, with flavonoids being the major bioactive constituents. These compounds largely underpin the reported pharmacological properties, including anti-inflammatory, antioxidant, neuropharmacological, anticancer, cytotoxic and osteogenic effects. Importantly, *Drynaria* species have demonstrated a relatively safe therapeutic profile in preclinical studies, supporting their potential as candidates for herbal drug development. However, further clinical investigations are imperative to validate their efficacy, optimize dosage regimens and establish standardized formulations for human use. With growing global interest in natural medicine, *Drynaria* holds promise as a valuable source of effective phytotherapeutics for diverse health conditions.

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Author contributions

AVL was responsible for writing, data collection and compilation. SPD critically reviewed and

revised the manuscript as required. SBP and PVP, MMA, SMP reviewed the manuscript. SAD provided supervision, technical guidance and final editing. All authors read and approved the final version of the manuscript.

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Declarations

Ethical statement

This study did not involve any experiments on human participants or animals conducted by the authors

Conflict of interest

All authors declare that they have no conflict of interest.

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