

Review Article

A REVIEW ON THE PHYTOPHARMACOLOGICAL PROPERTIES, UNANI AND MODERN PHARMACOLOGY OF *BISFAYEJ* (*POLYPODIUM VULGARE* LINN)

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ABSTRACT

Different herbs and their constituents are used for medicinal purposes by approximately 80 percent of the world population, which is evidenced by the rapidly growing global and national markets of herbal drugs. This review is aimed at presenting an overview of the medicinal properties of *P. vulgare*, its phytoconstituents and diverse pharmacological activities. To retrieve the information related to this drug, a thorough literature survey was undertaken using the various classical Unani and Herbal literature books viz., Al-Qānūn fi'l Tibb, Makhzan al-Mufradat, Kanzul Advia Mufradah, Ilmul Adwiya Nafisi, Taj al-Mufradat, Indian Materia Medica, Indian Medicinal Plants among others. Further, for other traditional uses, phytoconstituents, pharmacological activities and research studies of the drug, various online bibliographic databases like Pub Med, Google Scholar, Science Direct, Web of Science and Scopus were meticulously searched. The keywords used for the search included "*Polypodium vulgare*", "*Bisfayej*", "*Polypody* root and rhizome", "Phytoconstituents of *Polypodium vulgare*". *P. vulgare* is proven to possess neuro-psycho-pharmacological, CNS depressant and anti-epileptic activity through its anti-cholinesterase and 5-hydroxytryptamine (5-HT) stimulatory effect. Various clinical researches validate the use of *P. vulgare* in the management of conditions such as Epilepsy, Arthritis, Leprosy, Melancholy and Alzheimer's disease. Further studies are needed to unravel its other pharmacological activities.

Keywords: *Polypodium vulgare* Linn, Bisfayej, Anti-spasmodic, Anti-epileptic, Melanagogue, Phlegmagogue

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INTRODUCTION

Polypodium vulgare Linn is a small, wintergreen, perennial fern that belongs to the Polypodiaceae family [1]. It is one of the most widely distributed fern species in the world [2]. The Latin name Polypodium derived from the word poly (many) and podos (feet) has arisen from the particular shape of its rhizomes, branching like feet [1]. The plant usually ranges from 10 to 30 cm in height, having a scaly stem. The stem scales are variable in size, usually 4 mm long, narrowly triangular, and red-brown colour [3]. It has slender knotty rhizomes and curving fronds that are dotted with brown spores on the lower surface. The rhizome is fibrous, having a dark brownish color on the outside and greenish color within [4-7]. It is covered with cavernous suckers like those on the arms of the polypus or centipede [4, 5, 7].

A record of the medicinal applications of *Polypodium vulgare* in the primitive period

Polypodium vulgare has been used for its various properties since the ancient Greek era [8]. The medicinal and therapeutic uses of the drug are thoroughly documented in old classical texts. The renowned Greek philosopher Dioscorides, in his classical texts from 1st century AD has opined the purgative properties of the *polypody* root and mentioned its use to purge phlegm. He also stated its use as an ingredient of a plaster applied to dislocated fingers and to sores that occurred between the fingers [9]. The thick stems were earlier used as a remedy for diseases of the air passages, such as cough, cold, adenoids and multiple other purposes [5, 10]. Its tea or decoction was used by the Indians for the treatment of pleurisy, hives, stomachache and inflammations. According to an ancient source in Telemark, Norway, it is believed that *P. vulgare* grew for the first time at a rock cleft where Virgin Mary squirted some of her breast milk. Hence, in folk medicine, the name "Mariebregne" (Mary fern) is used for this drug [1]. Its rhizome was also used as a sweetener. It is considered as an important drug for liver ailments, pleurisy and intestinal worms [1].

Habitat

Polypodium vulgare Linn is native to Europe, Africa and Eastern Asia, mostly in northern or upland areas [10, 11]. It is a common specie

found throughout Scandinavia [10]. The plant grows to a maximum during the months of October and November. It has only one branch with small leaves and does not bear any flowers [4, 5, 12]. It can grow to an average height of 30 cm and is well tolerant to successive dry periods [8]. This fern is often encouraged to grow as a garden plant but does not acclimatize easily [13]. In India, the root of *Bisfayej* is procured from other countries [7, 11].

General description of the drug in the classical Unani texts

Bisfayej is known by various names in different parts of the world, "*Azrasul Kalb*" "dog's tooth," in allusion to the toothed appearance of the leaves, "*Kathirul Arjil*" "many-footed," and "*Thakibul Hajar*" "penetrating stones" [7, 14].

On the basis of its geographical location and traditions, it has different therapeutic applications in different regions. The rhizome having fibrous projections and appearing grassy green or dark brown in colour is used as a drug. It has been observed that the fresh root, which is grassy green in colour becomes darker when kept for a long period [5, 6]. The grassy green fresh root is considered best for medicinal purposes [6, 7]. *Polypody* root is used both fresh and dried, however, the leaves are also sometimes used for its medicinal value [15]. The rhizome of the size of the little finger, that appears fresh and having taste like cloves is considered of best quality [5, 6, 16]. The surface is hard, hairy, rugous and longitudinally fissured. The upper surface presents several horn-like tubercles or scaly projections of suckers. Each projection is curved, 0.5 inches long and fissured. Due to these projections the drug is named as "*Kathirul Arjil*" resembling the legs of a centipede [4, 6, 8]. Regarding the temperament (Mizaj) of *P. vulgare* Linn., different authors have different opinions. Most of the Unani physicians are of the view that it is hot in the second degree [7, 11, 12, 16, 17] and dry in the third-degree [12].

Ethnobotanical description

P. vulgare is a small, terrestrial or epiphytic fern that grows into large colonies, with a creeping, densely hairy or scaly rhizome bearing fronds at intervals along its length. The fern is rather thick, creeping and ramifying, having scaly stems and long stalk, usually 10-30 cm. The stem scales are narrowly triangular, red-brown in colour, variable

in size, usually up to 4 mm long [10]. The dried rhizome is flattened to round in cross-section and yellowish-brown to dirty brown externally and slightly lighter at the cut ends. The drug is characterized by a ferry odour, sweet, astringent and nauseous taste and moderately hard and brittle in fracture [11]. It has long, glabrous, dull green, deeply pinnatifid leaves having various crests arranged alternately in 2 rows. The leaves and petioles are above the ground. The pinnae have entire or crenate margins, more deeply serrate. The veinlets usually divide 2-3 times [6, 10, 11]. It has brown, brownish-yellow to rusty brown sori in two rows on the dorsal side, on each side of the midrib, mainly in the upper half of the blade [10].

According to an assessment report on *Polypodium vulgare* L (2008), the more accurate description of the *P. vulgare* part used medicinally should be rhizome and not root. It states that "a rhizome is typically a horizontally oriented underground stem that may outwardly appear root-like but has definite nodes and internodes" [1].

Under a microscope, the transverse section of the rhizome is somewhat oval to round in shape. The rhizome is seen to consist of a delicate cellular structure containing much starch and green granular matter. It is traversed by large bundles of scalariform vessels [11].

Phytoconstituents of *P. vulgare* and their possible mechanism of action

Important groups of phytochemicals that have been isolated from *P. vulgare* are alkaloids, tannins, flavonoids and phenolic compounds [18]. 20-hydroxyecdysone is the most abundant ecdysteroid isolated from the rhizomes. Minor amounts of other phytoecdysteroids, such as polypodine B (5,20E) and the parent ecdysone (E) have also been found. However, variability in its contents has been reported as a possible influence of microclimate due to geographic location as well as the season of collection. Part of the plant examined and the age of the field-collected material is also said to give rise to such differences [2, 19].

Table 1: Phytoconstituents of *polypodium vulgare* linn

Compound groups	Active phytoconstituents	References
Alkaloids, Flavonoids, Tannins, Phenolic compounds	-	[18]
Ecdysteroids	Ecdysone, 20-Hydroxyecdysone, Polypodine B, Inokosterone, Pterostemne, 24-Hydroxyecdysone, Abutasterone, 5-Hydroxyabutasterone	[2, 19]
Phytoecdysteroids	Polypodine B (5 β -hydroxy ecdysterone), parent Ecdysone (E)	[2, 19]
Volatile oil, 8% fixed oil	-	[19]
Saponins	Osladin Polypodosaponin	[20]
Other compounds: Butyric, hexoic, lauric and succinic acids, methyl salicylate, butyric, isovaleric and α -methyl butyric esters, glucoside samambain, Cyclolanostanic triterpenes-cyclolaudenol	-	[20]

Table 2: Macro-, Micromorphological and cytological characters of *Polypodium vulgare* L

Character	<i>P. vulgare</i>	Reference
Leaves	Lanceolate	[20]
Leaf length/width ratio	2.2-4.3 (average 3.1)	
Pinnae	Obtuse	
Sori	Orbicular	
Indurated annulus cells	12-16	
Ripe annulus	reddish brown	
Basal cells	0-2 (average 1)	
Spore length (μ m)	56-68	
Mean stomata length (μ m)	56.3 \pm 8.4	

Medicinal properties of *Polypodium vulgare* in Unani traditional medicine

Dāfi'-i-Qūlanj (antispasmodic); Dāfi'-i-Istisqā' wa Waja' al-Mafasil (antiarthritic); Dāfi'-i-Tashannuj (anticonvulsant) [5, 7, 16, 17] Hādīm (digestive); Kāsir-i-Riyāh (carminative); Mudirr-i-Bawl (diuretic); [7] Mufarrih-i-Qalb (exhilarant); Muqawwī-i-Qalb (cardiotonic); Dāfi'-i-Mālanikhūliya (melancholia); Musaffi-i-Dam (blood purifier); Mushil-i-Balgham wa Sawdā' (melanagogue and phlegmagogue) [5-8, 11, 12, 16, 21-24].

Pharmacological actions and therapeutic implications of *P. vulgare*

The traditional use of *polypody* rhizome has been documented in several handbooks and in the scientific literature.

Dāfi'-i-Qulanj (antispasmodic)

P. vulgare has been used as an antispasmodic agent and has been found effective in various types of colics. Along with some other drugs like *Anisoon* (Aniseed) and *Multi* (Liquorice) [16], it is useful in cough and *Dama* (asthma) as it relieves bronchospasm [5, 16].

Dāfi'-i-Tashannuj (anti-convulsant)

The drug has been found to be effective in epileptic disorders along with *Amaltas* (Cassia fistula L).

Hazim (digestive)

It assists in the digestive processes and helps in the digestion of milk, causing first its precipitation and later followed by its dissolution and purges out phlegm from the stomach [5, 6, 16, 25].

Kāsir-i-Riyah (carminative)

It relieves the patient of *Nafkh al-Shikam* (flatulence) and dyspepsia as it has *Kāsir-i-Riyah* property [5-7, 11, 12, 16, 17, 22, 25].

Muqawwī-i-Qalb (cardiotonic)

It purifies the heart muscles from the toxic effects of black bile and hence improves the functioning of the heart [5, 6, 17, 23, 25]. It is useful in *Amrad-i-Qalb* (cardiac disorders) [26].

Mushil-i-Balgham wa Sawda (melanagogue and phlegmagogue)

Bisfayej has a wide application in various *Amrad-i-Balghami wa Sawdawī* (Black bile diseases) such as *Sar'* (epilepsy), *Waja' al-Mafasil* (arthritis) [5, 7, 8, 16, 17] *Judhām* (leprosy) and *Mālanikhūliya* [5, 6, 11, 16, 17, 25, 26] when used with decoction form because it purges out *Sawda*, *Safra* and *Balgham* without causing gripes [16, 25].

Scientific studies of *P. vulgare*

Analgesic activity

The aqueous extract of *Polypodium vulgare* was found to possess analgesic activity by increasing the reaction time in rat's post-administration [27].

Antimicrobial activity

The methanol extract of *P. vulgare* was screened for antimicrobial activity by measuring the minimum bacterial concentration (MBC) and minimum inhibitory concentration (MIC) values against the gram-negative and gram-positive bacteria named

Staphylococcus aureus and Escherichia coli by standard assay. It is indicated that *P. vulgare* ferns have the highest antibacterial activity and it is the most suitable source for the discovery of antibiotic drug [28].

Antioxidant property

The phenolic compounds present in rhizome have antioxidant properties and also have a protective chemical barrier against environmental stresses [26].

Cholinesterase inhibitory activity

The rhizome of *Polypodium vulgare* Linn. was evaluated for its cholinesterase inhibitory activity and has been recommended for the treatment of Alzheimer's disease symptoms [29].

CNS depressant and anti-epileptic activity

The rhizome of *P. vulgare* has been found to possess a protective effect in drug-induced catalepsy in swiss mice, thus suggesting that it enhances the transmission of dopamine in CNS and possibly acts as a D2 receptor agonist. Hence, it can be explored for various psycho-neurological disorders [30]. The rhizome extract was found to possess CNS depressant and anti-epileptic activity [27].

Ma'jun Najah and its two developed dosage forms, hydro-alcoholic extract and sugar-free granules in mice were found to have anticonvulsant activity, thereby possessing a protective role against epilepsy [31].

Effect on 5-hydroxytryptamine (Serotonin-5HT)

Authors of the study on *Sharbate-Ahmed Shah* (SAS), discussed that this compound formulation (containing *Bisfayej*) increased the

availability of tryptophan in blood and brain and hence increases 5-hydroxytryptamine (Serotonin: 5HT) in the brain. It was concluded that SAS contains some active principles which increase the availability of neurochemicals (tryptophan and 5HT) and decrease the 5HT turnover rate thus causes antidepressant and anxiolytic effects in experimental animals [32].

Hypotensive effect

Aqueous extract of the roots of *P. vulgare* (PV) produced CNS depressant effect. It decreased the spontaneous motor activity, prolonged the pentobarbitone-induced hypnosis, reduced body temperature and increased the reaction time to pain stimuli. In anesthetized dogs, the *Polypodium vulgare* extract at low dose produced a fall in blood pressure and which in short duration is rapid at the onset. However, with a high dose, there was a rise in blood pressure and then it suddenly fell down due to β -adrenoceptor agonist activity and vasodilation. *Polypodium vulgare* showed the hypotensive effect that is caused due to catechins [27].

Neuro-psychopharmacological activity

The aqueous extract of the *P. vulgare* linn showed neuro-psychopharmacological activity. Its administration showed decreased alertness, mild passivity and decreased locomotor activity in mice and rats [30].

Smooth muscle relaxation effect

P. vulgare has a dual receptor block mechanism that arbitrates smooth muscle relaxation effect. A study demonstrated the uses of *P. vulgare* in smooth muscle's contraction and also described its applications to *in vivo* and *in vitro* experimental techniques with its possible underlying mechanisms [33].

Table 3: Scientific studies on the clinical efficacy of *P. vulgare*

S. No.	Title of the study, author name with year	Journal name	Comments	References
1.	Antioxidant, antimicrobial and anti-inflammatory activities of flavonoids and tannins extracted from <i>Polypodium vulgare</i> L., Sofiane S., 2015	Asian Journal of Biochemical and Pharmaceutical Research	The findings of the study revealed high antioxidant and antifungal capacities of flavonoids and tannins of <i>P. vulgare</i> , but weak anti-inflammatory activities and affirmed harmful above 100 $\mu\text{g/ml}$	[18]
2.	<i>In vitro</i> cholinesterase inhibitory activity of some plants used in Iranian traditional medicine. Saeedi M. 2017	Natural Product Research	The rhizome of <i>Polypodium vulgare</i> Linn. was evaluated for its cholinesterase inhibitory activity and has been recommended for the treatment of Alzheimer's disease symptom.	[29]
3.	Effect of rhizome extract of <i>Bisfayej</i> (<i>Polypodium vulgare</i> L.) on chemically induced catalepsy in mice. Dar PA. 2012	International Journal of Institutional Pharmacy and Life Sciences	The rhizome of <i>P. vulgare</i> has been found to possess a protective effect in drug-induced catalepsy in swiss mice, thus suggesting that it enhances the transmission of dopamine in CNS and possibly acts as a D2 receptor agonist	[30]
4.	Pharmacodynamic studies on <i>Polypodium vulgare</i> (Linn.) Mannan A-1989	Indian J Exp Biol.	The aqueous extract of <i>P. vulgare</i> rhizome was found to possess to possess CNS depressant and anti-epileptic activity	[27]
5.	Antibacterial evaluation and preliminary phytochemical screening of selected ferns from Iran. Bahadori MB-2015	Research Journal of Pharmacognosy	It was indicated that <i>P. interjectum</i> ferns have the highest antibacterial activity and it is the most suitable source for the discovery of antibiotic drug when the methanol extract of <i>P. interjectum</i> was screened for antimicrobial activity	[28]
6.	<i>Bisfayej</i> (<i>Polypodium vulgare</i> L.): A review on medicinal importance of rhizome with Unani prospective and modern pharmacology. Kalam MA-2017	International Journal of Unani and Integrative Medicine	The phenolic compounds present in rhizome have antioxidant property and also have a protective chemical barrier against environmental stresses.	[26]
7.	Decreased brain serotonin turnover rate following administration of <i>Sharbat-e-Ahmed Shah</i> produces antidepressant and anxiolytic effect in rats. Ahmed M-2017	Metabolic Brain Disease	It was concluded that <i>Sharbate-Ahmed Shah</i> contains some active principles which increase the availability of neurochemical (tryptophan and 5HT) and decrease the 5HT turnover rate, thus causes antidepressant and anxiolytic effects in experimental animals	[32]
8.	Preliminary Screening of a Classical Unani Formulation <i>Majoon Najah</i> for Anticonvulsant Activity. Afrin Z-2019	International Journal of Pharmaceutical Research	<i>Majoon Najah</i> and its two developed dosage forms, hydroalcoholic extract and sugar-free granules in mice, were found to have anticonvulsant activity, thereby possessing protective role against epilepsy.	[31]

Table 4: Herbal preparations containing *Bisfayej* with known therapeutic activity

S. No.	Compound Unani preparations	Constituents	Actions	Therapeutic activity	Dose	Reference
1.	<i>Majun Najah</i>	<i>Post-e-Halela Kabli, Post-e-Balela, Aamla, Halela Siyah, Turbud, Bisfayej, Aftimoon, Ustukhuddus</i>	<i>Musaffi-e-Dam, Muqawwi-e-Asab</i>	Malikhuliya, Qulanj, Ikhtinaq-ur-Rahem	5-10 g	[34] [NFUM-part-I]
2.	<i>Majun Chobchini</i>	<i>Chobchini, Khusyat-us-Salab, Khulanjan, Gul-e-Gaozaban, Behman Safaid, Behman Surkh, Shaqaq-ul-Misri, Abresham, Mughas, Jadawar Sana, Sandal Surkh, Sandal Safaid, Misri, Abresham, Mughas, Jadawar</i>	<i>Musaffi-e-Dam</i>	<i>Falij, Wja-ul-Mafasil, Hikka, Jarab</i>	5-10 g	[34] [NFUM-part-I]
3.	<i>Majun Ushba</i>	<i>Chobchini, Gul-e-Surkh, Darchini, Kababchini, Gaozaban, Aftimoon, Bisfayej, Ushba, Post-e-Balela, Sumbul-ul-Teeb, Halela Siyah, Post-e-Halela Zard</i>	<i>Mulaiyin</i>	<i>Jarab, Waja-ul-Mafasil, Hikka</i>	5-10 g	[34] [NFUM-part-I]
4.	<i>Habb-e-Aftimoon</i>	<i>Aftimoon, Ghariqoon, Turbud, Raughan-e Zard, Ustukhuddus, Bisfayej, Aab-e-Badiyan</i>	<i>Munaqqi-e-Dimagh, Mulaiyin</i>	<i>Malikhuliya, Waswas</i>	5 to 10 g	[34] [NFUM-part-II]
5.	<i>Majun Musaffi-e-Azam</i>	<i>Barg-e-Shahtara, Post Halela Zard, Post Halela Kabli, Post Balela, Aamla Khushk, Halela Siyah, Barg-e-Sana, Gul-e-Surkh, Maweez Munaqqa, Bisfayej Fistaqi, Aftimoon, Turbud</i>	<i>Musaffi-e-Dam, Mukhrij-e-Mawad-e-Fasida, Waram-e-Mafasil</i>	<i>Busoor, Damameel, Kharish, Aatishak, Waj-ul-Mafasil,</i>	6 g with 50 ml Araq-e-Musaffi Murakkab or with water twice daily	[34] [NFUM-part VI]

Adverse effects as per Unani classical text

In classic Unani literature, *Bisfayej* is considered harmful for the lungs and kidneys [5, 6, 8, 16]. Also, it sometimes causes nausea on ingestion [5, 8].

Studies illustrating the adverse events

The *polypody* rhizome may cause a skin rash when applied externally [9]. Also, it was found to cause a rash after its ingestion which was reportedly harmless. Nevertheless, it is not established by any scientific literature [35]. A minor adverse reaction in form of a mild laxative effect is noted when *polypody* root is used as a traditional indication in cough and cold. *Polypody* rhizome is not recommended during pregnancy, breastfeeding and in children younger than 12 y of age due to lack of available scientific data [1].

Conclusion and future potential

The extensive survey of literature revealed that *P. vulgare* has been traditionally used worldwide since ancient times due to its diverse medicinal properties and pharmacological activities. The overall ethnobotanical, ethno-pharmacological and phytochemical studies of *P. vulgare* L were well emphasized in this review article. Since time immemorial, it has played a significant role in the area of medicine and various clinical studies have confirmed that it has a wide application in the management of various diseases such as Epilepsy, Arthritis, Leprosy, Melancholy and Alzheimer's disease. However, further evaluation needs to be carried out in order to explore the concealed areas and its practical clinical applications, which can be used for the welfare of mankind.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

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