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Review Article

Integrative Insights into the Medicinal Potential of *Bisfayej* (*Polypodium vulgare* Linn.)

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ABSTRACT

Approximately 80% of the global population relies on herbs and their constituents for medicinal purposes, as reflected in the rapidly expanding global and national markets for herbal remedies. Medicinal properties can be derived from the whole plant in its crude or extract form, or specific plant parts such as roots, fruits, seeds, flowers, and storage structures like rhizomes, bulbs, stamens, and tubers. Various natural organic and inorganic active compounds extracted from plants are widely utilized in medicine across many countries. Additionally, crude plant-based drugs are often considered safer for use compared to their isolated phytochemical counterparts. This review is aimed at presenting an overview of the medicinal properties of *Polypodium vulgare* Linn., its phytoconstituents and diverse pharmacological activities. A thorough literature survey was undertaken using the various classical Unani and Herbal literature books, as well as various online bibliographic databases, which were meticulously searched. P. vulgare is found to possess various medicinal and therapeutic properties and has a wide application in diseases such as arthritis, epilepsy, leprosy, melancholy and Alzheimer's disease symptoms. Nevertheless, the concealed areas need to be evaluated to explore the practical clinical applications of *P. vulgare* roots.

INTRODUCTION

The use of traditional medicine and medicinal plants for maintaining health has grown significantly in developing countries, where about 80% of the population depends on them for primary healthcare. Medicinal plants also serve as valuable sources of bioactive compounds for modern drug discovery and development (Gleńsk et al., 2019). India officially recognizes six systems of medicine: Ayurveda, Siddha, Unani, Yoga, Naturopathy, and Homoeopathy. Globally, and particularly in India, rural populations depend heavily on these traditional medicine systems for healthcare. The Unani system, introduced to India by the Arabs, originated in Greece and follows the "humoral theory," which attributes disease to an imbalance of humors (Kumar, 2014). Unani medicine, also known as Unani Tibb, is a traditional system of healing rooted in ancient Greek medical principles and later enriched by Persian, Arab, and Indian scholars. It emphasizes the balance of the body's four humors blood, phlegm, yellow bile, and black bile and incorporates a holistic approach to health, focusing on physical, mental, and spiritual well-being. This system employs natural remedies, including herbal formulations, dietary regulations, and therapeutic techniques like cupping and massage, to restore harmony in the body (Husain & Sofi, 2010; Sultana et al., 2016)

Botany, the scientific study of plants, plays a crucial role in Unani medicine and Unani relies heavily on the therapeutic properties of plants, emphasizing the balance of the body's humors to maintain health. Botany plays a pivotal role in Unani medicine, as plants form the backbone of its pharmacopoeia. By understanding the morphology, physiology, and biochemical

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properties of medicinal plants, botanists contribute to the identification and cultivation of species used in Unani remedies. Common plants such as winter cherry, neem, and fennel are integral to Unani formulations, offering treatments for ailments ranging from digestive issues to skin disorders. This synergy between botany and Unani underscores the importance of natural resources in holistic health practices. Medicinal herbs are carefully studied for their properties, such as temperament (hot, cold, moist, or dry) and their effects on the body's humoral balance. Botanists and herbalists collaborate to identify, cultivate, and preserve plants with medicinal value, ensuring sustainable use and efficacy. By harnessing the therapeutic potential of plants, Unani medicine continues to contribute to preventive healthcare and the treatment of chronic and acute conditions(Perveen et al., 2020).

Ferns (phylum Pteridophyta) have long been used in traditional medicine to treat conditions such as wounds and disorders of the stomach, lungs, and urinary tract. Their ability to resist pathogens has drawn scientific interest, indicating potential natural antibiotic properties(Contreras Cárdenas et al., 2016). *Polypodium vulgare* L., commonly known as *Bisfayej*, is a small, evergreen perennial fern belonging to the Polypodiaceae family [1]. It is among the most widespread fern species globally. The genus name *Polypodium*, derived from the Greek words *poly* (many) and *podos* (feet), refers to the distinctive foot-like branching pattern of its rhizomes (Sultana et al., 2022). This plant is also referred to by various traditional names worldwide, such as "*Azrasul Kalb*" (dog's tooth), referencing the leaf shape; "*Kathirul Arjil*" (many-footed); and "*Thakibul Hajar*" (stone penetrator)(Hakim, 2002).

The purpose of this review is to provide an overview of India's recognized traditional medicine systems, with a specific focus on Unani medicine on *P. vulgare*. The context for this review emphasizes the importance of medicinal plants in Unani practices and their contribution to holistic health. *P. vulgare* is to provide an overview of this medicinal plant, emphasizing its significance within Unani medicine. It highlights its botanical characteristics, traditional applications, and global distribution. This review establishes as an important therapeutic agent and sets the stage for a detailed exploration of its traditional uses, phytochemical constituents, and pharmacological properties through a blend of classical Unani knowledge and modern scientific research.

METHODOLOGY

The methodology aims to describe the systematic approach taken to gather information on *P. vulgare,* a medicinal plant used in Unani medicine. It details the extensive literature survey conducted across classical Unani texts, herbal literature, and modern research databases. This method ensures a comprehensive understanding of the plant's traditional uses, phytochemical composition, pharmacological properties, and scientific validation, providing a robust foundation for further research. To retrieve the information related to this drug, a thorough literature survey was undertaken using the various classical Unani and Herbal literature books. Twenty-five classical texts were searched for the information Research. *Al-Qānūn fi'l Tibb, Makhzan al-Mufradat, Kanzul Advia Mufradah, Bisfayej Ilmul Adwiya Nafisi, Taj al-Mufradat,* Indian Materia Medica, Wealth of India, and Indian Medicinal Plants books had information regarding this plant. Further for other traditional uses, phytoconstituents, pharmacological activities and research studies of the drug, various online bibliographic databases were meticulously searched. The keywords used for the search included "*Polypodium vulgare*", "*Bisfayej*", "Polypody root and rhizome", and "Phytoconstituents of *Polypodium vulgare*". Research and review 50 papers were retrieved and only full-length papers were included.

RESULTS

Ethnobotanical description

P. vulgare is a small terrestrial or epiphytic fern that forms large colonies, with a creeping, densely hairy or scaly rhizome from which fronds emerge at intervals. The plant has thick, creeping, branched stems with scaly, red-brown triangular scales, typically up to 4 mm in length, and long petioles, usually measuring 10-30 cm (Prajapati, ND and Kumar, 2005). The species is characterized by thin, knotted rhizomes and arching fronds that bear brown spores on their undersides. The rhizome has a fibrous texture, with a dark brown exterior and a greenish interior (Dar PA; Sofi G; Jafri M A., 2012; Dymock W, Warden CJH, 1890; Marhaba, 2023). The dried rhizome is flattened to round in cross-section, yellowish-brown to dirty brown on the outside, and lighter at the cut ends. It has a faint odour and a sweet, astringent, and slightly nauseous taste, with a moderately hard and brittle texture (Anonymous, 1992). The rhizome of *P. vulgare*, about the size of a little finger, is considered of the highest quality when fresh and has a clove-like taste (Kabir-al-Din, 2007). Its surface is hard, covered in hair, rugged, and longitudinally fissured. The upper surface features horn-like tubercles or scaly projections, each curved, around 0.5 inches long, and fissured. The fern's leaves are long, glabrous, and dull green, deeply pinnatifid, with alternate crests arranged in two rows. The pinnae have entire or crenate margins, sometimes more deeply serrate, and the veinlets typically divide 2-3 times. On the dorsal side, there are brown to rusty brown sori arranged in two rows along the midrib, mostly in the upper half of the blade (Dar PA; Sofi G; Jafri M A., 2012). Native to Europe, Africa, and Eastern Asia, especially in northern and upland regions, it is commonly found across Scandinavia. The plant grows most actively in October and November, reaching up to 30 cm in height. It features a single stem with small leaves, does not produce flowers, and is well adapted to dry conditions (Anonymous, 1992; Dar PA; Sofi G; Jafri M A., 2012) Though often cultivated as a garden fern, it does not adapt easily (Farràs et al., 2021). In India, the root known as Bisfayej is typically imported(Kalam et al., 2017). A 2008 report clarifies that the medicinally used part of *P. vulgare* is the rhizome, not the root. It describes the rhizome as a horizontally oriented underground stem with distinct nodes and internodes, often resembling a

root". Microscopically, the transverse section of the rhizome is oval to round, with a delicate cellular structure containing starch and green granular matter, and large scalariform vascular bundles (Anonymous, 1992). Regarding its temperament (*Mizaj*), opinions among Unani physicians vary, but most classify it as hot in the second degree and dry in the third degree (Ghani, 2001; MA, 2018).

Ethnomedicinal properties of P. vulgare in Unani medicine

The properties of *P. vulgare* is summarised in Table 1. (Baitar, 2003; C.P, 2007; Ghani, 2001; Hakim, 2002; Mahboubi & Mahboubi, 2021; Nadkarni KM, 2004).

Table 1. Ethnomedicinal Properties of *P. vulgare*

Ethnomedicinal Properties (Unani)	Ethnomedicinal Properties (English)	References
Dāfi'-i-Qūlanj	Antispasmodic	(Ghani, 2001; Hakim, 2002; MA, 2018)
Dāfi'-i-Istisqā' wa Waja' al-Mafasil	Antiarthritic	(Ghani, 2001; Hakim, 2002; MA, 2018)
Dāfi'-i-Tashannuj	Anticonvulsant	(Ghani, 2001; Hakim, 2002; MA, 2018)
Mufarrih-i-Qalb	Exhilarant	(Ghani, 2001; Hakim, 2002; MA, 2018)
Muqawwī-i-Qalb	Cardiotonic	(Ghani, 2001; Hakim, 2002; MA, 2018)
Dāfi'-i-Mālankhūliya	Melancholia	(Baitar, 2003; Hakim, 2002; Kalam et al., 2017; Nadkarni KM, 2009)
Musaffī-i-Dam	Blood purifier	(Baitar, 2003; Hakim, 2002; Kalam et al., 2017; Nadkarni KM, 2009)
Mushil-i-Balgham wa Sawdā'	Emmenagogue and Phlegmagogue	(Baitar, 2003; Hakim, 2002; Kalam et al., 2017; Nadkarni KM, 2009)

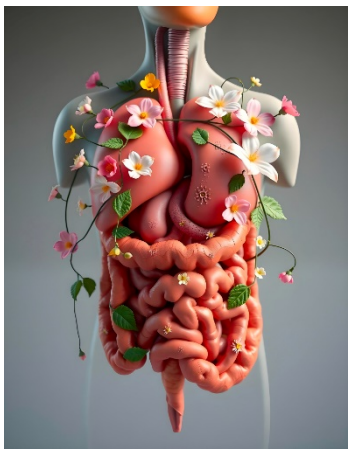
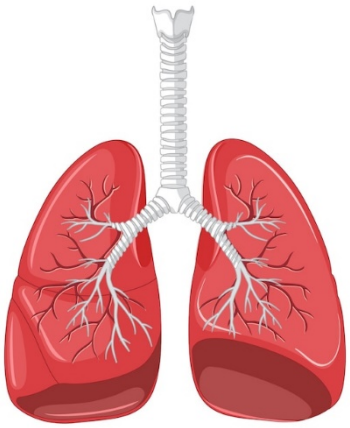
Ethnomedicinal therapeutic uses

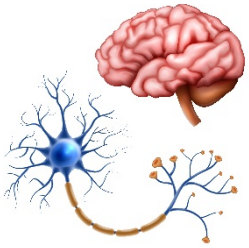
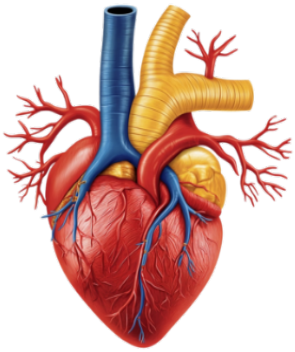
P. vulgare has been utilized for its various medicinal properties since ancient Greece, with its therapeutic applications extensively recorded in classical texts (Darr PA, Sofi G, Parray S, 2012). The therapeutic uses of *P. vulgare* vary by region, influenced by its geographical location and local traditions. The Greek physician Dioscorides, in his 1st-century writings, noted the purgative effects of the polypody root, particularly its ability to expel phlegm. He also described its use as a component in plasters for dislocated fingers and sores between the fingers (Chevallier, 2001). The plant's thick stems were traditionally used to treat respiratory conditions such as cough, cold, and adenoids, among others. Indigenous peoples of North America brewed it into tea or decoctions to address issues like pleurisy, hives, stomachaches, and inflammations. According to an ancient source from Telemark, Norway, *P. vulgare* was believed to have first grown at a rock cleft where the Virgin Mary is said to have spilled some of her breast milk, leading to its folk name "Mariebregne" (Mary Fern) (Mannan et al., 1989). The rhizome of *P. vulgare* has traditionally been used as a sweetener and is valued for its medicinal properties, particularly in treating liver disorders, pleurisy, and intestinal worms (Marhaba, 2023). The rhizomes of *P. vulgare* were traditionally eaten as snacks or famine food and used to sweeten beverages like coffee and tea due to their natural sweetness. In traditional Polish medicine, infusions of the rhizome served as expectorants and diuretics, mainly for chronic kidney ailments, nephrolithiasis, and promoting the breakdown of kidney stones(Gleńsk et al., 2019). It is noted that the fresh, grassy green root darkens over time, with the fresh root being considered most effective for medicinal purposes. Both fresh and dried polypody roots are used, though the leaves are occasionally utilized for their medicinal properties as well (Anonymous, 1992; Darr PA, Sofi G, Parray S, 2012; Farràs et al., 2021; Kalam et al., 2017).

Therapeutic implications of P. vulgare in Traditional Unani Medicine:

The traditional use of polypody rhizome has been documented in several handbooks and the Unani classical literature. Its diverse applications showcase its broad therapeutic potential across multiple body systems, making it a versatile herb in traditional medicine. Its antispasmodic, digestive, anti-convulsant, carminative, cardiotonic, and detoxifying actions highlight its comprehensive medicinal value. **Table 2** summarizes the diverse therapeutic actions of *P. vulgare* across various body systems, providing a concise view of its traditional uses and effectiveness.

Table 2. Diverse therapeutic actions of *P. vulgare*

S. No.	Body System	Action	Therapeutic Use	References
1	**Gastrointestinal System** 	***Hazim* (Digestive Aid)**	*P. vulgare* has significant digestive benefits. It assists in the breakdown of milk, initially causing its precipitation, followed by dissolution, and subsequently helps in purging excess phlegm from the stomach. This makes it particularly effective in treating digestive disturbances, especially those related to phlegm accumulation and milk digestion.	(Baitar, 2003; Hakim, 2002)
		***Kasir-i-Riyāh* (Carminative)**	It is recognized for its ability to relieve *Nafkh al-Shikam* (flatulence) and dyspepsia. Its carminative properties help in the expulsion of gas from the digestive tract, providing relief from bloating and discomfort caused by excessive gas build-up.	(Baitar, 2003; C.P, 2007; Ghani, 2001; Hakim, 2002; Mahboubi & Mahboubi, 2021; Nadkarni KM, 2004)
2	**Respiratory System** 	***Dāfi'-i-Qūlanj* (Antispasmodic)**	It has long been used as an antispasmodic agent, particularly for alleviating different types of colic. When combined with other herbs like Aniseed (*Pimpinella anisum*) and Liquorice (*Glycyrrhiza glabra*), it is particularly useful for relieving bronchospasms in conditions like cough and asthma. The plant's antispasmodic action helps in reducing the contraction of smooth muscles, thus easing symptoms of respiratory distress	(Hakim, 2002)
3	**Nervous System**	***Dāfi'-i-Tashannuj* (Anti-convulsant)**	It is effective in managing epileptic disorders, particularly when combined with *Cassia fistula*. It has anticonvulsant properties that help in managing seizures, demonstrating its importance in treating neurological disorders such as epilepsy	(Hakim, 2002)

				
	Cardiovascular System			
4		***Muqawwī-i-Qalb* (Cardiotonic)**	One of the prominent effects of *P. vulgare* is its ability to support heart health. It acts as a cardiotonic, purifying the heart muscles from the toxic effects of black bile, thus improving the heart's overall function. This makes it useful in treating *Amrad-i-Qalb* (cardiac disorders), such as heart disease, and in strengthening the heart's ability to perform under st	(Baitar, 2003; C.P, 2007; Ghani, 2001; Hakim, 2002; Mahboubi & Mahboubi, 2021; Nadkarni KM, 2004), (Afsahul Kalam, et al., 2021).
	General Health & Detoxification			
6		***Mushil-i-Balgham wa Sawdā'* (Melancholic & Phlegm-Removing Agent)**	It is beneficial in treating conditions associated with black bile (Sawda), bile (Safra), and phlegm (Balgham). It is particularly useful in a range of diseases associated with excess black bile, such as Sar'(epilepsy), Waja' al-Mafasil (arthritis), Judhām (leprosy), and Mālankhūliya (melancholia). When used in decoction form, it helps expel these substances from the body without causing the discomfort commonly associated with purgative treatments. Its properties as a phlegmagogue and melanagogue make it effective in purging toxins and excess fluids, promoting overall wellness	(Baitar, 2003; C.P, 2007; Ghani, 2001; Hakim, 2002; Mahboubi & Mahboubi, 2021; Nadkarni KM, 2004)

Images: Freepik.com

Compound formulations

The compound formulations used in traditional Unani medicine are as follow

***Majun Najah*:** This formulation contains *Post-e-Halela Kabli, Post-e-Balela, Aamla, Halela Siyah, Turbud, Bisfayej, Aftimoon,* and *Ustukhuddus*. It acts as a blood purifier (*Musaffi Dam*) and nervine tonic (*Muqawwi-e-Asab*), traditionally used for managing melancholia (*Malankhuliya*), colic (*Qulanj*), and hysteria (*Ikhtinaq-ur-Rahim*). The recommended dose is 5–10 g (Anonymous, 2006).

The anticonvulsant activity of the classical Unani formulation *Majoon Najah* (MN) and its two modern form, hydroalcoholic extract (HEMN) and sugar-free granules (GMN) was evaluated in mice using Increased Current Electroshock and Pentylenetetrazole-induced seizures. All three formulations significantly increased seizure threshold and delayed seizure onset without causing motor incoordination. These results

suggest that *Majoon Najah* and its derivatives are effective and safe alternatives for managing epilepsy (Afrin et al., 2019).

Majun Chobchini: Composed of *Chobchini, Khusyat-us-Salab, Khulanjan, Gul-e-Gaozaban, Behman Safaid, Behman Surkh, Shaqaq-ul-Misri, Abresham, Mughas,* and *Jadawar*, this preparation functions primarily as a blood purifier. It is indicated for hemiplegia (*Falij*), joint pain (*Waja al-Mafasil*), and scabies (*Hikka Jarab*), with a dose range of 5–10 g.

***Majun Ushba*:** This formulation includes *Sana, Sandal Surkh, Sandal Safaid, Chobchini, Gul-e-Surkh, Darchini, Kababchini, Gaozaban, Aftimoon, Bisfayej, Ushba, Post-e-Balela, Sumbul-ul-Teeb, Halela Siyah,* and *Post-e-Halela Zard*. It acts as a resolvent and laxative (*Mulaiyyin*) and is used for treating scabies, joint pain, and Hikka, administered at 5–10 g.

***Habb-e-Aftimoon*:** Containing *Aftimoon, Ghariqoon, Turbud, Raughan-e-Zard, Ustukhuddus, Bisfayej,* and *Aab-e-Badiyan,* this preparation serves as a brain tonic (*Munaqqi-e-Dimagh*) and laxative. It is traditionally used for mental disorders such as insanity, at a dose of 5–10 g.

***Majun Musaffi-e-Azam*:** Comprising *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,* and *Turbud*, this formulation functions as a blood purifier and expels putrid matter (*Mukhrij-e-Mawad-e-Fasida*). It is traditionally used for acne (*Busoor)*, syphilis (*Aatishak*, *Kharish, Damameel*), and joint inflammation, administered at 6 g with 50 ml of Araq-e-Musaffi Murakkab or water twice daily (Anonymous, 2006).

Phytoconstituents

P. vulgare is rich in diverse phytochemicals, contributing to its wide range of medicinal applications. Key groups of bioactive compounds identified in the plant include alkaloids, flavonoids, tannins, and phenolic compounds (Sofiane et al., 2015). The presence and concentration of these compounds are known to vary depending on several factors, including geographic location, microclimatic conditions, season of collection, the part of the plant examined, and the age of the material collected (Afrin et al., 2019). Among its most significant constituents are ecdysteroids, particularly 20-hydroxyecdysone, which is the most abundant in the rhizomes. Smaller quantities of other ecdysteroids such as polypodine B, ecdysone (parent compound), inokosterone, pterostemne, 24-hydroxyecdysone, abutasterone, and 5-hydroxyabutasterone have also been detected (Hršak, 2000). In addition to ecdysteroids, *P. vulgare* contains volatile oil and approximately 8% fixed oil (Dar PA; Sofi G; Jafri M A., 2012; Hršak, 2000; Sofiane et al., 2015) also produces saponins, notably osladin and polypodosaponin, which are associated with its sweet taste and potential therapeutic effects (**Figure 1**). Other notable constituents include organic acids such as butyric, hexoic, lauric, and succinic acids; methyl salicylate; various esters like butyric, isovaleric, and α-methyl butyric esters; the glucoside samambain; and cycloartenol, a cyclolanostanic triterpene (Sofiane et al., 2015; Thiem et al., 2017) .

The term "ecdysteroids" is derived from the Greek word "ecdysis," meaning the shedding of the outer skin. These compounds were initially recognized as steroid hormones that regulate insect molting and metamorphosis (Das et al., 2021). Phytoecdysteroids are plant-derived compounds structurally related to insect hormones such as ecdysone and 20-hydroxyecdysone (20E). Some plants, like *P. vulgare*, accumulate high levels of 20E (about 25 mg per 2.5 g of rhizome). These cholesterol-derived molecules share structural similarities with other plant steroids such as withanolides, cucurbitacins, and polyhydroxysterols. True ecdysteroids are polyhydroxylated steroids characterized by a cis A/B ring junction (5β-H), a 7-en-6-one chromophore, and a 14α-hydroxyl group, typically containing 19–29 carbon atoms (Marion-poll et al., n.d.). Five phytoecdysteroids, previously unreported in *P. vulgare*, were isolated from methanol extracts of in vitro prothalli cultures. Among these, two compounds had been identified in other plants, while 24-hydroxyecdysone and 5-hydroxyecdysone were described for the first time in this species. Their structures were determined using 1H and 13C NMR and thermospray-HPLC-MS analyses, including stereochemical assignment at C-24, which was found to be 24S for all compounds based on 13C NMR studies of 22,22-benzylidene derivatives(Coll et al., 1994). Ecdysteroids exhibit multiple beneficial biological effects. They enhance protein synthesis in various mammalian systems, demonstrating anabolic activity. Additionally, they possess adaptogenic, antidepressive, tonic, and restorative properties, which improve the body's ability to cope with stress and reduce fatigue. Their anti-diabetic effects include lowering blood glucose levels, promoting glycogen synthesis in the liver, enhancing tissue glucose utilization, and supporting cholesterol metabolism, contributing to hypocholesterolemic and anti-atherosclerotic outcomes. Ecdysteroids also promote wound healing by stimulating keratinocyte differentiation, indicating potential applications in treating superficial wounds, burns, and psoriasis. It has also demonstrated immunomodulatory and anti-inflammatory effects in animal models and humans (Al Naggar, 2017; Das et al., 2021).

This complex phytochemical profile underlines the pharmacological potential of *P. vulgare* in traditional and modern medicine.

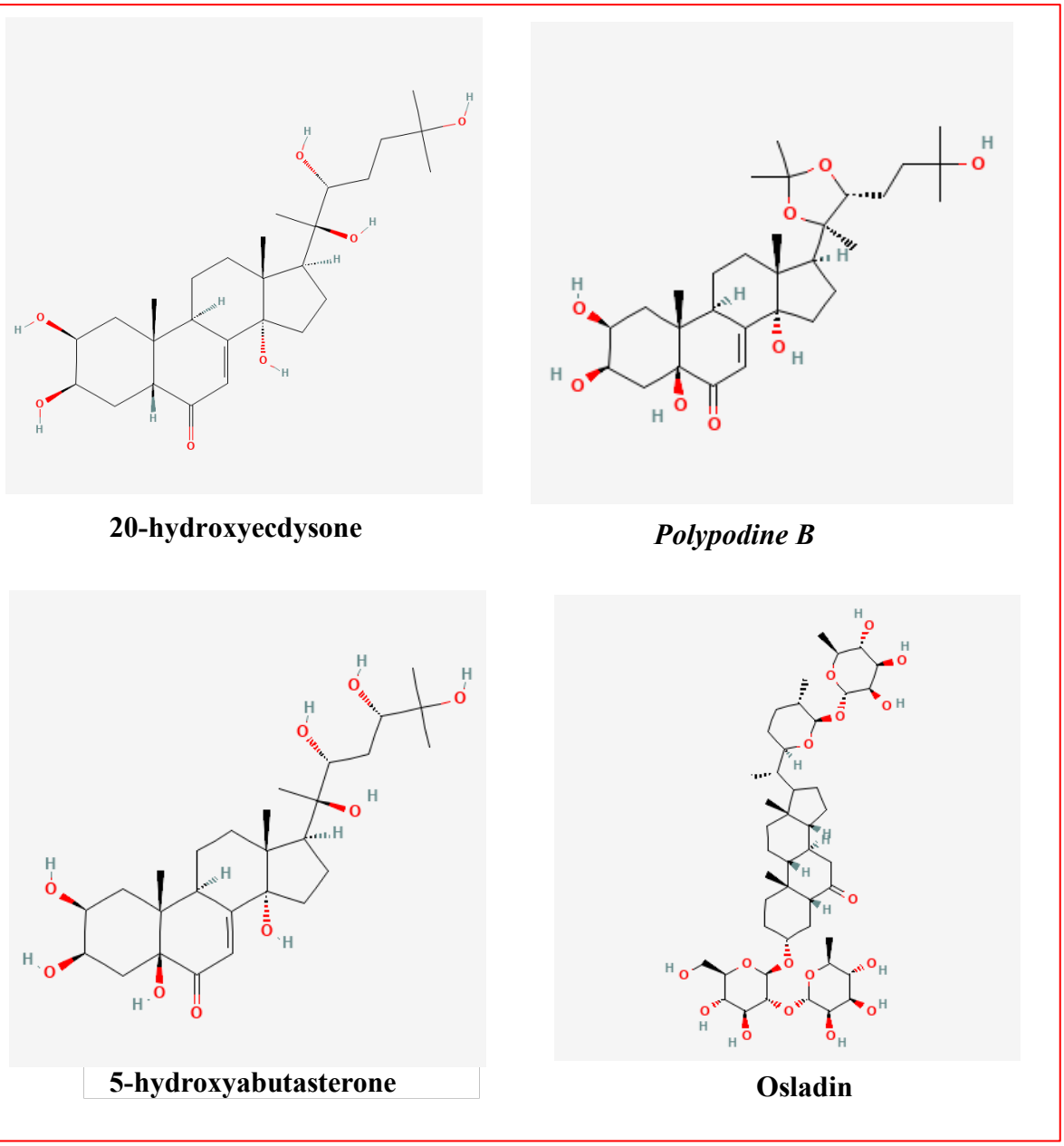


Figure 1. Structure of bioactive compounds present in *P. vulgare* (Source: Pubchem)

Pharmacological studies of P. vulgare:

This fern exhibits a wide spectrum of pharmacological activities, including analgesic, antimicrobial, antibiofilm, antioxidant, cholinesterase inhibitory, CNS depressant, anti-epileptic, neuropsychopharmacological, hypotensive, and smooth muscle relaxant effects. Its rhizomes and fronds, rich in phenolics, flavonoids, and phytoecdysteroids, contribute to pain modulation, antimicrobial and antibiofilm activity, neuroprotection, enhancement of serotonergic and dopaminergic neurotransmission, and cytoprotective antioxidant effects. Comprehensive details are summarized below (**Figure 2**)

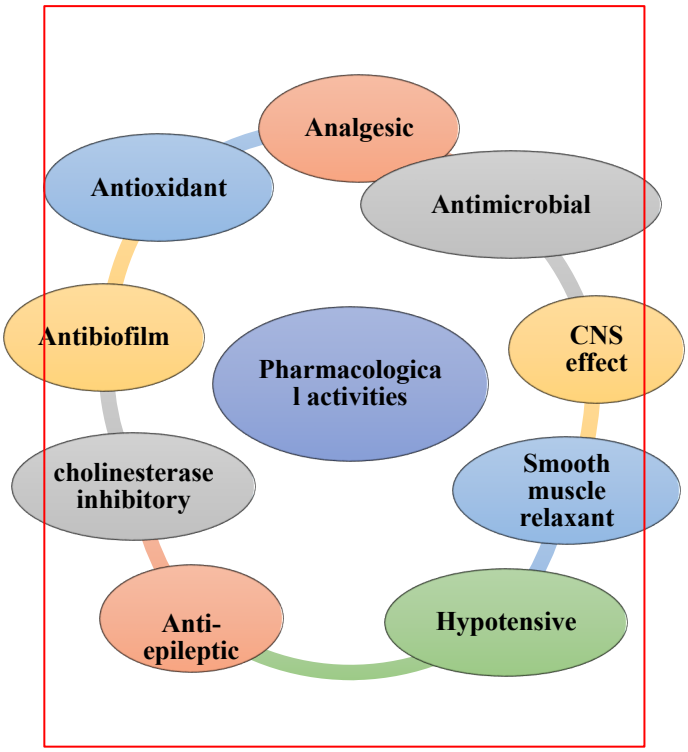


Figure 2. Pharmacological activities of *P. vulgare*

1. ***Analgesic activity:*** The aqueous extract of *P. vulgare* has demonstrated significant analgesic activity in rodent models, as evidenced by increased reaction time to nociceptive stimuli. This suggests that the extract may modulate pain pathways through central nervous system mechanisms and neurochemical interactions. Its analgesic effects are likely mediated by multiple factors, including modulation of neurotransmitter systems such as the adrenergic, GABAergic, and opioid pathways, as well as the action of phytochemicals like flavonoids and phytoecdysteroids. Additionally, the extract's antioxidant properties may contribute by reducing oxidative stress, which can sensitize pain pathways. Together, these mechanisms support the traditional use of *P. vulgare* in pain management and highlight the need for further studies to identify the active compounds responsible for its analgesic effects.to possess analgesic activity by increasing the reaction time in rats, post-administration (Mannan et al., 1989). This suggests modulation of pain pathways, potentially through central mechanisms or neurochemical interactions.

2. ***Antianxiety activity:*** The methanolic extract of *P. vulgare* roots, rich in flavonoids and phenolics, was tested for antianxiety effects using the elevated plus maze (EPM) in rats. At 400 mg/kg, the extract showed significant anxiolytic activity comparable to the standard drug. Among its fractions, only the ethyl acetate fraction (100 mg/kg) demonstrated similar efficacy, enhancing open arm entries and time. These results suggest flavonoids and phenolics are likely responsible for the observed antianxiety effects (Kaur et al., 2025).

3. ***Antimicrobial activity:*** The methanol extract of *P. vulgare* L. has been evaluated for its antimicrobial properties against both Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* bacteria. Standard assays determined the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the extract. The MIC represents the lowest concentration of the extract that inhibits visible bacterial growth, while the MBC is the lowest concentration that kills 99.9% of the bacterial population. These findings suggest that *P. vulgare* possesses significant antibacterial activity, indicating its potential as a source for developing new antibiotic agents. In addition to its antibacterial effects, the methanol extract of P. vulgare has demonstrated antioxidant properties. This dual activity supports its traditional use in herbal medicine and highlights its potential for therapeutic applications (Bahadori et al., 2015; Kalam et al., 2017). Another study evaluated the antioxidant potential of *P. vulgare* L. using DPPH and reducing power assays, and its antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*) and *Salmonella typhimurium*), and fungi (*Aspergillus niger*, *Aspergillus flavus* and *Candida albicans*). Results demonstrated significant antioxidant capacity, supporting its potential as a medicinal resource (Shaker et al., 2024).

4. ***Anti-inflammatory, Antimicrobial and Antioxidant Activity:*** A study evaluated the antioxidant, antimicrobial, and anti-inflammatory activities of flavonoids and tannins isolated from *P. vulgare* L. Antioxidant potential was measured using the DPPH radical scavenging assay. Antimicrobial effects were tested against bacterial strains (*Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhimurium*) and fungal strains (*Aspergillus niger*, *Aspergillus flavus*, and *Candida albicans*). Anti-inflammatory activity was assessed via protein denaturation inhibition. The results demonstrated significant antioxidant capacity, strong antifungal activity, but indicated a potentially pro-inflammatory effect (Sofiane et al., 2015).

5. ***Antibiofilm activity:*** The bacteriostatic and antibiofilm activities of *P. vulgare* rhizome extract and its active component, osladin, were assessed using time-kill and biofilm assays against uropathogenic *Escherichia coli* strains. Both the aqueous extract and osladin inhibited bacterial growth and biofilm formation, with the extract showing greater biofilm suppression and complete inhibition at 48 and 72 hours in clinical and CFT073 E. coli strains ($p < 0.05$). Traditionally used for urinary tract infections, *P. vulgare* demonstrated moderate antimicrobial but strong antibiofilm potential. Although osladin exhibited higher antibacterial activity, the extract's superior antibiofilm effect suggests synergism among its phytoconstituents (Gleńsk et al., 2019). Another study evaluated that *P. vulgare* extract (PvE) ability to enhance the efficacy of ciprofloxacin and photodynamic therapy (PDT) against uropathogenic *Escherichia coli*. Using UHPLC-MS for extract analysis and chlorin e6 as a photosensitizer, the study assessed bacterial survival, biofilm formation, and morphological changes.

Combined treatments (PvE + CIP and PvE + PDT) significantly reduced bacterial viability and biofilm production, indicating that PvE can potentiate antibiotic and PDT effects, offering a promising strategy against drug-resistant bacterial infections (Tichaczek-Goska et al., 2021).

6. ***Anticancer activity:*** A study explored the anticancer potential of *P. vulgare* ethanolic extract against A375 melanoma cells. Treatment with 0.123 mg/ml of the extract significantly induced cell death, oxidative stress (via increased ROS and lipid peroxidation), and cytochrome c release, indicating activation of apoptosis pathways. Importantly, the extract showed no cytotoxic effects on normal AGO-1522 fibroblast cells, suggesting it may offer a selective and safer alternative for melanoma treatment (Tabeshpour et al., 2023).

7. ***Antioxidant property:*** A study investigated the polar constituents of *P. vulgare* fronds to validate traditional uses. The methanolic extract of fronds was analyzed by high-performance liquid chromatography with diode-array detection to determine its polyphenolic profile, and its cytotoxicity, phototoxicity, reactive oxygen species production, and protective effects against oxidative stress were assessed in vitro using 3T3 fibroblasts, HaCaT keratinocytes, HeLa, HepG2, MCF-7, and A549 cell lines. Oxidative stress was induced in 3T3 and HaCaT cells using hydrogen peroxide and ultraviolet A radiation, and antioxidant activity was measured via reactive oxygen species assays. The extract contained significant amounts of shikimic acid, caffeoylquinic acid derivatives, and flavonoids such as catechin and epicatechin. It was non-cytotoxic at physiological concentrations and showed cytoprotective and repair-promoting effects in fibroblasts, likely due to its high polyphenol content. These results support the traditional wound-healing use of *P. vulgare* fronds and highlight their potential for further pharmacological exploration (Farràs et al., 2021).
The rhizomes of *P. vulgare* are rich in phenolic compounds, which play a crucial role in the plant's defense mechanisms. These compounds exhibit strong antioxidant activity, neutralizing reactive oxygen species and thereby protecting cells from oxidative damage. Beyond their free radical scavenging properties, phenolic compounds also form a protective chemical barrier that helps the plant withstand various environmental stresses, this dual function antioxidant defense and environmental protection highlights the importance of phenolic constituents in both the physiological resilience of the plant and their potential therapeutic benefits when used in medicinal applications (Farràs et al., 2019).

8. ***Anticonvulsant activity:*** Epilepsy affects over 1% of the global population, and *Polypodium vulgare* L. has shown potential antiepileptic effects. A study assessed the anticonvulsant activity of its hydroalcoholic extract in a pentylenetetrazole (PTZ) induced epilepsy model in rats, aiming to determine the optimal dose for delaying seizure onset and reducing severity. Male Wistar rats were divided into control, reference, and experimental groups receiving varying doses of the extract (150–500 mg/kg). PTZ was administered intraperitoneally to induce seizures. Analysis revealed that the 300 mg/kg dose significantly delayed seizure onset and reduced seizure severity, outperforming higher doses and standard sodium valproate. These findings indicate that the hydroalcoholic extract of *P. vulgare* L. holds promise as a potential antiepileptic agent (Shaker et al., 2024).

9. ***Cholinesterase inhibitory activity:*** *P. vulgare* L., rhizome has been evaluated for its cholinesterase inhibitory activity, indicating potential therapeutic applications in managing Alzheimer's disease symptoms. Alzheimer's disease is characterized by a decline in acetylcholine levels due to the increased activity of cholinesterase enzymes, leading to cognitive impairments. The inhibition of these enzymes can help maintain acetylcholine levels, thereby supporting neurotransmission and improving cognitive functions. In vitro studies have demonstrated that extracts from various plants, including *P. vulgare*, possess cholinesterase inhibitory properties. The cholinesterase inhibitory activity of *P. vulgare* rhizome suggests that it may offer a natural alternative or adjunct to conventional treatments for Alzheimer's disease. These findings underscore the importance of exploring traditional medicinal plants for potential therapeutic agents in neurodegenerative diseases (Marhaba, 2023; Mottay & Neergheen-Bhujun, 2016; Saeedi et al., 2017) .This mechanism is vital in addressing Alzheimer's disease symptoms by improving cognitive function and memory.

10. ***CNS depressant and anti-epileptic activity:*** The rhizome of *P. vulgare* L. has demonstrated notable neuroprotective and psychoactive properties in preclinical studies. It has been shown to reduce drug-induced catalepsy in Swiss mice, suggesting that the extract may enhance dopaminergic transmission in the central nervous system, potentially through agonistic effects on D2 dopamine receptors (Dar PA; Sofi G; Jafri M A., 2012). This mechanism indicates its possible therapeutic application in psycho-neurological disorders that involve dopaminergic dysfunction, such as Parkinson's disease and other movement disorders. Additionally, the rhizome extract exhibits central nervous system depressant and anti-epileptic activities (Mannan et al., 1989), further supporting its neuroprotective potential. Studies on Ma'jun Najah, a formulation containing *P. vulgare,* along with its hydroalcoholic extract and sugar-free granules, have demonstrated anticonvulsant effects in mice, indicating a protective role against epileptic seizures (Afrin et al., 2019). The combined activities enhancement of dopamine signaling, CNS depressant effects, and anticonvulsant properties highlight the rhizome's potential for managing various neuropsychiatric and neurological conditions, warranting further investigation to elucidate the underlying mechanisms and active compounds.

11. ***Effect on 5-hydroxytryptamine (Serotonin-5HT):*** The study on *Sharbat-e-Ahmed Shah* (SAS), a traditional compound

formulation containing Bisfayej, investigated its effects on neurochemical balance and behavior in experimental animals. The authors reported that administration of SAS significantly increased the availability of tryptophan in both blood and brain tissues. Tryptophan, being a precursor of serotonin (5-hydroxytryptamine, 5-HT), led to elevated serotonin levels in the brain. Additionally, SAS was found to reduce the turnover rate of serotonin, which implies slower degradation and sustained activity of this neurotransmitter. These neurochemical changes correlated with observable behavioural outcomes in the experimental animals, including reduced anxiety-like behaviour and alleviation of depressive-like symptoms. The study concluded that the bioactive constituents in SAS enhance serotonergic neurotransmission by both increasing serotonin synthesis and limiting its breakdown, thereby producing measurable antidepressant and anxiolytic effects. These findings provide a mechanistic basis for the traditional use of SAS in improving mood and reducing anxiety (Ahmed & Azmat, 2017). Increases blood and brain tryptophan availability, elevating serotonin (5-HT) levels. This reduces 5-HT turnover, yielding antidepressant and anxiolytic effects.

12. ***Central nervous system depressant and hypotensive effect:*** The aqueous extract of *P. vulgare* L. roots has been shown to exert notable central nervous system (CNS) depressant effects. In experimental studies, administration of the extract led to a marked reduction in spontaneous motor activity, suggesting sedative properties. It also prolonged pentobarbitone-induced hypnosis, indicating potentiation of CNS depressant activity, and decreased body temperature, reflecting an influence on thermoregulatory mechanisms. Additionally, the extract increased the reaction time to painful stimuli, demonstrating analgesic potential likely linked to CNS modulation. Cardiovascular studies in anesthetized dogs revealed a dose-dependent effect on blood pressure. At low doses, the extract caused a rapid yet transient hypotensive response, whereas higher doses initially produced a rise in blood pressure followed by a sudden decline. This biphasic response is thought to result from β-adrenoceptor agonist activity coupled with vasodilation, suggesting complex modulation of vascular tone. The hypotensive effects are primarily attributed to the presence of catechins and other bioactive compounds within the extract, which may act synergistically to influence both cardiac and vascular function (Marhaba, 2023; Ulbricht et al., 2006). Overall, these findings highlight the potential of *P. vulgare* for managing CNS-related disorders and cardiovascular conditions, warranting further investigation into its mechanisms and therapeutic applications.

13. ***Neuro-psychopharmacological activity:*** The aqueous extract of Polypodium vulgare Linn has demonstrated notable neuro-psychopharmacological effects in preclinical studies involving mice and rats. Administration of the extract resulted in decreased alertness, reduced locomotor activity, and mild behavioral passivity, indicating a central nervous system–depressant effect. These observations suggest that the extract may modulate neuronal activity and neurotransmitter systems involved in arousal, mood, and motor control. The findings support the traditional use of P. vulgare in managing conditions related to stress, anxiety, and mood disturbances, aligning with descriptions of melancholia in the Unani system of medicine. The behavioral effects observed in animal models provide a pharmacological basis for its potential applications in neuropsychiatric disorders, warranting further investigation to isolate the active constituents responsible for these effects (Bhat et al., 2023; Dar PA; Sofi G; Jafri M A., 2012).

14. ***Smooth muscle relaxation effect:*** *P. vulgare* exhibits smooth muscle relaxant properties through a dual receptor blockade mechanism. Experimental studies, employing both in vivo and in vitro models, have demonstrated that the extract can effectively relax smooth muscles, suggesting its potential utility in conditions associated with excessive smooth muscle contraction. The dual receptor blockade likely involves modulation of multiple signaling pathways that control muscle tone, contributing to its spasmolytic effects. These findings provide a pharmacological basis for the traditional use of *P. vulgare* in managing disorders related to smooth muscle hyperactivity, such as gastrointestinal or vascular spasms (Naz et al., 2016). By employing a dual receptor block mechanism, *P. vulgare* relaxes smooth muscles. Experimental studies validate its potential in managing smooth muscle contraction-related conditions.

15. ***Wound healing activity:*** In a study using 32 Balb-c mice, topical application of *Polypodium vulgare* and *Centella asiatica* extracts significantly improved wound healing, showing enhanced vascularization, epidermal regeneration, and granulation tissue formation. Both groups had stronger PDGF staining, while VEGF and collagen staining were notably higher only in the CAE group. *P. vulgare*, with its antioxidant and antimicrobial properties, may support wound healing as an adjunct treatment (Batur et al., 2020).

Clinical Trial

Premenstrual syndrome: *P. vulgare* L. *(Bisfayej)* was evaluated in a randomized, placebo-controlled trial for its efficacy and safety in women with premenstrual syndrome (PMS). Sixty participants received 1000 mg twice daily or placebo for three menstrual cycles. The treatment group showed significant reductions in PMS severity and duration, measured by the Premenstrual Syndrome Scale, and improvements in EQ-5D-5L scores compared to placebo ($p < 0.001$). No adverse effects were reported. These findings indicate that *P. vulgare* is a safe and effective option for alleviating PMS and enhancing health-related quality of life.

Adverse Effects and Safety Profile of P. vulgare: Classical Unani texts describe *P. vulgare* as potentially harmful to the lungs and kidneys (NajmulGhani, n.d.), and ingestion may occasionally induce nausea (Tariq, 2010). Traditional practice recommends the use of *Musleh* (corrective agents) such as *Halela Zard, Gul-e-Surkh*, and *Hansraj* to mitigate these effects, while *Badal*

(substitute agents) include *Aftimoon*, *Sana*, and *Qurtum*. The traditionally prescribed dosages vary according to form: powdered rhizome (3–10 g) and decoction (10–15 g) (Kabir-al-Din, 2007; NajmulGhani, n.d.). Contemporary observations indicate that topical application of polypody rhizome may occasionally result in mild skin rashes, while oral consumption can sometimes induce minor laxative effects (Chevallier, 2001). These reactions are generally considered mild and self-limiting, although robust scientific studies confirming these outcomes are lacking. Due to insufficient safety data, the use of *P. vulgare* is not recommended during pregnancy, lactation, or in children under 12 years of age. These findings underscore the importance of cautious administration and the need for further toxicological and safety evaluation.

Implication of P. vulgare: It demonstrates a broad spectrum of pharmacological activities, supported by both traditional use and experimental studies. Its rhizomes and fronds exhibit analgesic, antimicrobial, antibiofilm, antioxidant, cholinesterase inhibitory, central nervous system (CNS) depressant, anti-epileptic, neuropsychopharmacological, hypotensive, and smooth muscle relaxant effects. The analgesic activity is linked to modulation of neurotransmitter systems and antioxidant properties, while the methanol and aqueous extracts show antibacterial and antibiofilm effects against pathogens such as *Escherichia coli* and *Staphylococcus aureus*. The extract also enhances serotonergic and dopaminergic neurotransmission, demonstrating antidepressant, anxiolytic, and neuroprotective potential. Antioxidant activity, mediated by phenolic compounds, flavonoids, and phytoecdysteroids, supports cellular protection and wound-healing effects. Additionally, the rhizome exhibits cholinesterase inhibitory activity, suggesting potential benefits in neurodegenerative disorders such as Alzheimer's disease, and the CNS depressant and anticonvulsant properties indicate its relevance in managing neuropsychiatric and epileptic conditions. Cardiovascular studies show dose-dependent hypotensive effects, while smooth muscle relaxation is mediated through a dual receptor blockade mechanism. Additionally, *P. vulgare* promotes wound healing, exhibits anti-diabetic, adaptogenic, and anabolic effects, and protects against oxidative and environmental stress. These combined activities support its traditional use in managing pain, infections, neuropsychiatric and neurodegenerative disorders, cardiovascular dysfunction, and smooth muscle-related conditions, highlighting its therapeutic versatility and potential for further drug development.

Despite these therapeutic potentials, classical Unani texts and contemporary observations highlight certain adverse effects. The plant may affect the lungs and kidneys and occasionally induce mild nausea. Topical application can cause skin rashes, and minor laxative effects may occur upon oral ingestion. Traditional guidelines recommend corrective (*Musleh*) and substitute (*Badal*) agents to mitigate adverse effects, and caution against use in pregnancy, lactation, and in children under 12 years due to limited safety data.

DISCUSSION

Authors' Opinion: Considering the wide-ranging pharmacological properties of *P. vulgare*, it holds significant promise as a source of bioactive compounds for therapeutic applications. However, the presence of mild adverse effects and limited clinical safety data necessitate careful standardization, dosage optimization, and further preclinical and clinical studies. Integrating traditional knowledge with modern pharmacological research could help validate its efficacy and safety, potentially leading to novel treatments in pain management, neuropsychiatric disorders, cardiovascular health, and infectious diseases.

Strengths: The strength of this review lies in highlighting the multi-target therapeutic potential of *P. vulgare* L., which is attributable to its diverse range of bioactive compounds, including phenolics, flavonoids, phytoecdysteroids, and catechins. These compounds act synergistically to produce a wide spectrum of pharmacological effects, encompassing analgesic, antioxidant, antimicrobial, neuroprotective, CNS-modulating, hypotensive, and smooth muscle relaxant activities. Notably, the review bridges traditional knowledge from Unani medicine with modern scientific evidence, demonstrating that the historical use of *P. vulgare* in managing conditions such as epilepsy, melancholy, arthritis, and urinary tract disorders is substantiated by contemporary experimental findings. The dual ability of the plant to exert both central nervous system stimulant and depressant effects underscores its versatility in modulating neurological and psychological functions, offering potential applications in mood disorders, neurodegenerative diseases, and seizure management. Furthermore, the identification of both individual active constituents and the synergistic effects of the whole extract provides a scientific rationale for its broad therapeutic applications and supports further pharmacological and clinical investigations.

Limitations: Despite extensive pharmacological evidence supporting the therapeutic potential of *P. vulgare* L., several important gaps remain. The precise molecular targets and signaling pathways through which its bioactive compounds such as flavonoids, phenolics, catechins, and phytoecdysteroids exert their effects are not yet fully elucidated. This limits our understanding of the mechanistic basis of its analgesic, neuroprotective, antioxidant, antimicrobial, and other pharmacological activities. Furthermore, the phytochemical composition of *P. vulgare* is influenced by geographical origin, environmental conditions, harvest time, and processing methods, which creates considerable variability in bioactive constituent content and complicates efforts toward standardization of extracts. Most existing evidence derives from in vitro studies or animal models, with only a few well-designed clinical trials in humans. This scarcity of clinical data restricts the translation of preclinical findings into evidence-based therapeutic applications. Comprehensive studies are therefore needed to identify active constituents, clarify molecular mechanisms, establish standardized extract formulations, and evaluate efficacy and safety in larger human populations.

***Future Research Gaps*:** The future research gaps are the elucidation of molecular pathways involved in the anti-inflammatory, antispasmodic, and antioxidant actions of *P. vulgare*. Besides comprehensive clinical trials to validate its

efficacy and safety in humans. Investigation of potential drug-herb interactions, especially given its diverse bioactive profile. Development of standardized formulations with defined active constituents for targeted therapeutic uses.

CONCLUSION

P. vulgare is a small, wintergreen, perennial fern with a creeping, densely hairy or scaly rhizome that grows into large colonies. A large number of medicinal applications of *P. vulgare* from the primitive period have been variedly described in different traditional medicines. 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 phytopharmacologically it has *Dāfi'-i-Qūlanj, Dāfi'-i-Istisqā' wa Waja' al-Mafasil*, *Dāfi'-i-Tashannuj, Hādim*, *Kāsir-i-Riyāh*, *Mudirr-i-Bawl*, *Mufarrih-i-Qalb Muqawwī-i-Qalb, Dāfi'-i-Mālankhūliya* (melancholia), and *Musaffī-i-Dam* properties. Various scientific studies have proven that it possesses neuro-psycho-pharmacological, CNS depressant and anti-epileptic activity through its anti-cholinesterase and 5-hydroxytryptamine (5-HT) stimulatory effect. It has a wide application in diseases such as epilepsy, arthritis, leprosy, melancholy and Alzheimer's disease symptoms. However, further, evaluation needs to be carried out to explore the concealed areas and their practical clinical applications, which can be used for the welfare of mankind.

P. vulgare L. is a small, perennial, wintergreen fern with a creeping, densely hairy or scaly rhizome that forms extensive colonies. Traditionally, it has been valued in various medicinal systems worldwide for its diverse therapeutic properties. Classical Unani texts describe it as having *Dāfi'-i-Qūlanj* (carminative), *Dāfi'-i-Istisqā' wa Waja' al-Mafasil* (diuretic and joint pain reliever), *Dāfi'-i-Tashannuj* (antispasmodic), *Hādim* (digestive), *Kāsir-i-Riyāh* (flatulence reliever), *Mudirr-i-Bawl* (diuretic), *Mufarrih-i-Qalb* (cardiac tonic), *Muqawwī-i-Qalb* (heart-strengthening), *Dāfi'-i-Mālankhūliya* (antidepressant for melancholia), and *Musaffī-i-Dam* (blood purifier) properties. Modern pharmacological investigations have corroborated many of these traditional claims, demonstrating that *P. vulgare* exhibits neuro-psychopharmacological, central nervous system depressant, anti-epileptic, cholinesterase inhibitory, antioxidant, analgesic, anti-inflammatory, and serotonin-modulating activities. These bioactivities underpin its potential application in neurological, psychological, musculoskeletal, and inflammatory disorders, including epilepsy, melancholy, arthritis, leprosy, and Alzheimer's disease.

Despite these promising findings, several knowledge gaps remain. The precise molecular targets and signaling pathways of its bioactive constituents, including flavonoids, phenolics, catechins, and phytoecdysteroids, are not fully elucidated. Additionally, variability in phytochemical composition due to geographic, environmental, and processing factors complicates standardization, which is essential for reproducible therapeutic outcomes. While preclinical studies provide substantial mechanistic insights, human clinical trials are limited, restricting the direct translation of these findings into clinical practice. Therefore, further research is warranted to isolate and characterize the active compounds, standardize extract formulations, clarify their mechanisms of action, and evaluate safety and efficacy in controlled clinical settings. Comprehensive studies addressing these areas could unlock the full therapeutic potential of *P. vulgare*, bridging traditional knowledge with modern evidence-based medicine and ultimately contributing to human health and well-being

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Ethics Statement

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