REVIEW ARTICLE

Comprehensive Pharmacognostic, Phytochemical, and Pharmacological Review of *Anastatica hierochuntica* L. and *Pinus wallichiana* A.B. Jacks

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Abstract

Background: This review will give emphasis on pharmacognostic, phytochemical, and pharmacological studies of *Anastatica hierochuntica* L. and *Pinus wallichiana* A.B. Jacks., two plant species with significant ethnomedicinal importance, with separate extremophytic Ecology. *P. wallichiana*, a Himalayan high alpine conifer, and *A. hierochuntica* is another type of desert plant having different mechanisms through which they are able to synthesize diverse secondary metabolites having various important uses, including anti-cancer properties. **Materials and Methods:** As a comprehensive literature review, available pharmacognostic and pharmacological studies were collated and analyzed. Studies of phytochemicals were specifically evaluated to show the existence of flavonoids, phenolics, terpenoids, sterols, and other bioactive compounds in them, which give them such broad therapeutic properties. **Results:** According to pharmacological studies, both plants show strong antioxidant, antimicrobial, anticancer, antidiabetic, and neuroprotective activities. The reproductive health benefits of *A. hierochuntica* and xanthine oxidase inhibition, hepatoprotective effect, and phytoestrogenic activity of *P. wallichiana* have been noted to be effective in the metabolic regulation of the enzyme inhibition (α-amylase and α-glucosidase) and antiproliferation of various cancer cell lines. It is worthwhile to mention that both of the species exhibit parallel antioxidant mechanisms that confer neuroprotective ability in models of Parkinson's disease. Despite some encouraging preclinical findings, there are concerns over toxicities, mainly the uterine stimulatory effect of *A. hierochuntica* emphasize the need for careful evaluation. **Conclusion:** This review affirms the medicinal resources of these extremophytes, highlighting the need for further molecular, clinical, and pharmacokinetics studies to allow their phasing in modern drug discovery and development.

Key words: *Anastatica hierochuntica*, antidiabetic activity, antimicrobial activity, antioxidant activity, extremophytes, natural product drug discovery, neuroprotection, pharmacognosy, phytochemistry, *Pinus wallichiana,* xanthine oxidase inhibition

INTRODUCTION

In recent years, the paradigm of contemporary pharmacognosy has continuously shifted toward the natural products of extremophytes, which are plants that survive and thrive in extreme environmental conditions. This revelation has compelled researchers to understand that under extreme ecological stress, such as aridity, high-altitude ultraviolet light, and freezing cold, these species have to biosynthesize very complex and resilient secondary metabolites.[1,2] These specialized phytochemicals that constitute the endogenous defense of the plants often have strong drug efficacy in our human system.[3,4] One of the vast botanical reservoirs of such therapeutic compounds is *Anastatica hierochuntica* L, a species which is quite distinct from the other two, and *Pinus wallichiana* A.B. Jacks.[5,6]

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A. hierochuntica refers to an ethnomedicinal plant species from the arid deserts of the Middle East and North Africa region. It is well-known for its reputed uses in promoting reproductive health and metabolic diseases.[7,8] On the contrary, *P. wallichiana* is an alpine conifer native to temperate high-altitude zones of the Himalayan Mountain range. It is used for various purposes, such as inflammatory respiratory and infectious diseases.[9,10] Both plants have obtained much empirical support in recent years, despite being found in opposite ecological niches. Advanced analytical methods have revealed the extract's powerful antioxidant, antimicrobial, antidiabetic, anticancer, and neuroprotective properties.[11,12] This review provides an integrative and critical analysis of fragmented data on morphological, phytochemicals, and bioactivity of *A. hierochuntica* and *P. wallichiana* parasites. By indicating the exact molecular modes of action of their bioactive has been given and showing their evolutionary biochemical divergences, this review provides a background for enabling such traditional systems to be integrated into evidence-based drug discovery.[13,14]

A. HIEROCHUNTICA L.

Botanical overview and ethnobotanical significance

A. hierochuntica L., universally recognized by its vernacular names "Kaff Maryam" (Mary's hand), "Rose of Jericho," and "Blooming Virgin Hand," is a remarkably resilient desert-dwelling plant.[15] It is widely distributed across the hyper-arid plains of Saudi Arabia, Egypt, Jordan, Oman, Libya, Qatar, and adjacent territories in the Middle East and North Africa.[2,5] The ethnobotanical integration of *A. hierochuntica* is profound. The entire plant is traditionally consumed as a hot decoction or steeped herbal tea to treat a wide array of systemic afflictions, including gastrointestinal (GI) disorders, diabetes mellitus, cardiovascular anomalies, and severe fevers.[8,16,17] However, its most renowned ethnomedicinal application lies within the domain of female reproductive health. Herbal preparations of the plant are deeply embedded in regional folklore to enhance female fertility, alleviate menstrual irregularities, and facilitate childbirth.[7,18] In numerous Arab customs, the plant's unique botanical ability to mechanically unfold when exposed to moisture is symbolically associated with the dilation of the human womb during parturition, leading to its widespread use by midwives and traditional healers [depicted in Figure 1].[19]

Taxonomy and systematic position

The identification of *A. hierochuntica* belongs to the complex and historically poorly-studied lineage III of the Brassicaceae/Cruciferae. The plant is the only species in its genus, making it very specialized and a species adapted to survival in desert conditions, as summarized in Table 1.

Figure 1: A depiction of *Anastatica hierochuntica* L[80]

Table 1: Taxonomy of *Anastatica hierochuntica*

Taxonomic rank	Classification
Kingdom	Plantae
Phylum/Division	Tracheophyta/Magnoliophyta
Class	Magnoliopsida
Order	Brassicales
Family	Brassicaceae (Cruciferae)
Genus	*Anastatica*
Species	*Anastatica hierochuntica L.*

A. hierochuntica L., popularly referred to as Kaff Maryam (Mary's hand), the Rose of Jericho, or Blooming Virgin Hand, is a remarkable desert plant.[15] The species has a geographical range that extends across the hyper-arid plains of Saudi Arabia, Egypt, Jordan, Oman, Libya, Qatar, and adjoining areas of the Middle East and North Africa.[2,5] The use of *A. hierochuntica* in ethnobotany is deep. The decoction of the whole plant as a hot drink or steeped tea is traditionally taken for various systemic ailments, which include GI disorders, diabetes mellitus, heart defects, and high fever.[8,16,17] Nonetheless, its most documented ethnomedicinal application is for female reproduction. The plant's herbal preparations are part of the folklore of the region for female fertility, for the regulation of menses, and to assist childbirth.[7,18] In the customs of many Arabs, the ability of the plant to unfold mechanically upon getting wet comes with a suggestion that it is like how the womb expands during childbearing. This makes midwives and traditional healers use it.[19] The distinct genetic markers of the *Anastatica* genus, distinct from other Brassicaceae, such as *Arabidopsis thaliana* or *Eutrema salsugineum*, explain why it is not typically selected to study its biology.[15]

Morphology, anatomy, and ecological adaptations

A. hierochuntica has a morphology and anatomy that are highly specialized to withstand extreme drought. The mature plant's macro-architecture is usually light yellow to grayish,

forming an irregular, dense, umbrella-like structure close to the ground surface. It minimizes wind resistance while maximizing moisture accumulation.[11] The stem, roots, leaves, and fruit of a plant have different structures. Recent micro-anatomical characterizations using light microscopy and scanning electron microscopy reveal important internal adaptations. Powdered samples of the plant have, however, shown well-developed reticulate and spiral vessels and specialized vascular tissues that can transport water relatively rapidly during dry spells.[11] Moreover, within the microscopic architecture are dense non-glandular hairs that hinder cuticular transpiration, highly lignified phloem fibers, thickened epidermal cells, and storage of starch grains.[11]

One of the major ecological adaptations of *A. hierochuntica*, which is a true resurrection plant, as it has a hygrochastic mechanism of seed dispersal.[2,19] In the long dry season of the desert, the dry plant curls its woody branches inward, forming a tight fist-like ball that protects the enclosed seeds from damage caused by the environment, temperature, and animals.[19] When the seasonal rain comes, the dead and very hygroscopic tissues rapidly uncurl mechanically due to the capillary absorption of water, thereby spreading the branches outward to drop the seeds right into the moistening soil.[2] This physical resurrection could happen more than once over the years.

Phytochemistry

The expansive therapeutic effect of *A. hierochuntica* and its secondary angular metabolome is intricately related. The result of the phytochemical screening through spectrometry shows the presence of varieties of steroids, triterpenoids, flavonoids, tannins, saponins, coumarins, alkaloids, and some trace minerals.[5,8]

Flavonoids and phenolic compounds

Flavonoids are the most dominant and bioactive class of secondary metabolites found in the aqueous and methanolic extracts of the plant.[4,11] According to El-Garawani *et al*.,[17] the composition of flavonoids is structurally different, particularly flavonol aglycones, flavonol-3-O-glycosides, glycoflavones, and specific dihydroflavones. The leaves and seeds were definitively characterized by advanced liquid chromatography–quadrupole-time-of-flight-mass-spectrometry and ultra-performance liquid chromatography-mass spectrometry. The key flavonoids are rutin, quercetin, luteolin, isovitexin, kaempferol 7-glucoside, naringenin, aromadendrin, eriodictyol, taxifolin and silybin. Moreover, the species has yielded unique skeleton-flavonones, anastatins A and B, that display powerful hepatoprotective activities.[20] The profile of phenolic acids is a strong one as well on scan with high levels of chlorogenic acid, neochlorogenic acid, and cis-5-caffeoylquinic acid.[11] The Fourier-transform infrared spectroscopy analysis of the extracts shows characteristic absorption peaks at 3337, 2929, and 1659 cm^{-1}, showing the presence of functional hydroxyl and carbonyl groups associated with polyphenols and lignans.[11] The aqueous extracts have a total phenolic content of 52.58 ± 1.24 mg/g and total flavonoid content of 8.32 ± 0.17 mg/g. These figures indicate a strong chemical foundation for the aggressive antioxidant ability of the specific plant.[11]

Neolignans, sterols, and mineral constituents

In addition to the flavonoids, the plant also gave important plant-active neolignans, including hierochin A, B, and C, balaanophonin, and evofolin B, which actively modified nitric oxide production.[20] Using high-performance liquid chromatography and nuclear magnetic resonance methods, campesterol and β-sitosterol were isolated from the phytosterols extract, which are Antioxidant, antimicrobial, and Chemoprotective.[5] The SC plant is an important source of essential trace elements, such as Magnesium, Manganese, Calcium, Cobalt, Chromium, Copper, Iron, and Zinc, which are necessary for enzyme activity.[8,21]

Pharmacological activities

Modern studies, including *in vitro*, *in vivo,* and *in silico,* have systematically validated the ethnomedicinal claims of *A. hierochuntica*. The therapeutic effects of *A. hierochuntica* are studied in terms of the exact pharmacological and molecular mechanisms by which they work.[22-24]

Reproductive health and obstetrical utility

The conventional use of *A. hierochuntica* for female reproductive health is supported by today's pharmacological evaluations. The extracts contain high levels of the specific flavonoids, which possess significant phytoestrogenic capabilities and mimic the action of the endogenous estrogen in the human reproductive system.[7] In obstetrics, evidence shows that plant decoctions stimulate contractions of the myometrium. This refers to enhancing local tissue concentrations of prostaglandin E2 and prostaglandin F2α, which are important labor-inducing mediators.[22] Besides, there have been indications of wider reproductive benefits; oral administration of extracts at doses of 100–300 mg/kg to male mice raised systemic serum testosterone levels, indicating its effect on generalized fertility.[7]

Xanthine oxidase (XO) inhibition and gout management

An innovative finding on *A. hierochuntica* is the powerful inhibitory effect on XO, which is the main metabolic enzyme that catalyzes the oxidation of hypoxanthine to xanthine, and subsequently, xanthine to uric acid.[11] Elevated blood uric acid levels are the primary reason for hyperuricemia and gout. Molecular docking simulations against the bovine XO enzyme found methanolic leaf extract metabolites to possess excellent inhibitory potential.[11] The flavonoid rutin presented a very good docking score of −12.39, as it strongly

forms crucial and highly stable hydrogen bonds with the amino acid residues GLU 802, GLU 879, SER 876, and HIS 875, along with a stabilizing π–π hydrophobic interaction with PHE 1013.[11] The determined IC_{50} of the substance against XO was estimated to be 11.35 μM. The docking score for quercetin and luteolin was −11.15 and −10.43, respectively, and the experimental IC_{50} values were 11.1 μM and 21.58 μM, respectively.[11] Based on the pharmacokinetic modeling analysis data from SwissADME and ProTox-II, the natural metabolites are predicted to have good oral bioavailability and do not pose any serious endocrine disruption risk, thereby indicating that these metabolites are highly effective and safe natural alternatives to synthetic XO inhibitors like allopurinol.[11]

Anticancer and apoptotic mechanisms

The growth-inhibiting and tumor-formation-reducing effects of *A. hierochuntica* have been well-studied against numerous human cancers.[25,26] The hormone-dependent human breast cancer cell line MCF-7 has significant antiproliferative activity on crude extracts from stem, seed, and leaf.[27] The strong induction of cellular apoptosis involves a molecular mechanistic pathway. According to research, the expression of important pro-apoptotic genes, such as Bax, tumor suppressor TP53, and cyclin-dependent kinase inhibitor CDKN1A,[17,27] get greatly upregulated through the aqueous and methanolic extracts. This specific upregulation actively inhibits the cell cycle and induces programmed cell death in tumor tissues. Furthermore, the extracts exhibited potentially cytotoxic activity against HeLa cervical cancer cell lines. The extracts also showed high anti-melanogenic activity, which prevents melanoma progression through the inhibition of vital enzymes in the melanin synthesis pathway.[25,26]

Antimicrobial and antifungal efficacy

A. hierochuntica's extracts suppress the growth of disease-causing microbes that pose a high risk to human health. Agar diffusion techniques showed considerable suppression of pathogenic Gram-positive bacteria, such as *Staphylococcus aureus* and *Bacillus subtilis*, and resistant Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*.[5,28,29] Our research shows good antibacterial efficacy by optical density reduction on pathogenic bacteria to standard strains of *Klebsiella*, *E. coli*, and *B. subtilis*. The presence of membrane-disrupting sterols, β-sitosterol and campesterol, as well as complex flavonoids that intercalate with the nucleic acids of bacteria, prevents replication.[5] The plant is also reported to have systemic microbicidal properties that can potentiate the host's immune resistance against fungi and bacteria through activation of endogenous phagocytes.[30,31]

Antioxidant, hepatoprotective, and metabolic modulations

The extra metabolites contained in *A. hierochuntica* can act as electron donors and act as scavengers of reactive oxygen species. The assessment of the 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and reducing power assay revealed that the aqueous and ethanolic extracts can effectively scavenge free radicals with capability more than 80% at concentrations of as low as 0.5 mg/mL.[11] This action of antioxidant defense is reflected in the organoprotective effects. The skeletal flavanones anastatins A and B have potent hepatoprotective capacity by protecting hepatocytes from toxic degradation.[20] In diabetic mice induced by alloxan, the administration of methanolic extracts reduced liver damage by more than 50% in the level of serum transaminase and alkaline phosphatase activity.[32] In addition, the extracts correct creatinine, urea, and albumin levels in nephrotoxic models and have an ulcer-protective mucosal lining effect for the GI tract.[23,33] Metabolically, the use of *A. hierochuntica* is effective in controlling diabetes mellitus.[24,34,35] The substance lowers blood glucose levels (hypoglycemic effect) and fat levels (hypolipidemic effect).

Neuroprotective potential

Recent studies of neuropharmacology show *A. hierochuntica* can mitigate complex neurodegenerative diseases, including Parkinson's disease (PD). Research by Suman *et al*.[4] indicates this efficacy. Plant extracts at high doses of 200 mg/kg i.p. in the behavioral models using Wistar rats have shown significant and dose-dependent neuroprotective activity.[12,36] The extracts were able to reverse severe motor coordination deficits caused by haloperidol-induced catalepsy (a model of dopamine D2 receptor blockade) and reduce dopaminergic hyperactivity in apomorphine-induced stereotypy models.[37,38] The presence of a high concentration of antioxidant flavonoids scavenges free radicals and modulates dopaminergic pathways within the basal ganglia, significantly decreasing the oxidative stress and neuroinflammation that lead to Parkinsonian pathology.[4,14,39]

Toxicity and clinical contraindications

While the safety of *A. hierochuntica* is proven to be beneficial, improper use can be toxic. Some assays of *Salmonella* mutagenicity (Ames tests) have demonstrated a mutagenic effect of certain secondary metabolites that are obtained from the long-term accumulation of specific secondary metabolites within the plant tissues.[40] Studies show that high doses of ingestion during early or mid-pregnancy can result in gross fetal toxicity mechanisms (modes) and enhancement of the rate of fetal resorption as well as severe fetal malformation, including anencephaly.[7] Thus, it is contraindicated to use it for clinical and traditional use during the present pregnancy until it is biologically useful to induce labor. The plant carries significant risks of dangerous drug interactions; co-use with synthetic labor-inducing drugs can lead to life-threatening uterine hyperstimulation, and co-use with exogenous insulin can worsen life-threatening hypoglycemia.[7,22]

P. WALLICHIANA A.B. JACKS

Botanical overview and ethnobotanical significance

P. wallichiana A.B. Jacks., sometimes called blue pine, Bhutan pine, and Himalayan white pine, is an impressive, ecologically dominant conifer evergreen tree.[6,41] It commands the temperate to sub-alpine ecological zones of the Himalayan, Karakoram, and Hindu Kush mountain ranges. This is a massive being which is found in eastern Afghanistan, Northern Pakistan, Indian Himalaya (Jammu and Kashmir, Himachal Pradesh, Uttarakhand), Tibet, Nepal, Bhutan and eastward to Myanmar and Yunnan Province in South-west China.[9,42] The species occurs at extreme altitudes ranging from 1700 to 4300 m above sea level[43] in severe environmental stresses. In the local Himalayan dialect, the tree is often called Kail, Chil or Kairo.[44]

The local mountain population uses the species for tea, timber, and medicinal purposes. As a non-medicinal resource, it's exploited heavily as timber, second in commercial and structural value only to Deodar cedar (*Cedrus deodara*). The wood is used for important infrastructure construction, furniture, railway sleepers, and as a high-calorific firewood (4995 calorific value).[6,45] In addition, from the live tree, oleoresins are distilled to yield turpentine oil, rosin, needle oil, and camphor (for industrial/commercial uses).[6] From the angle of ethnomedicine, the entire plant is utilized by local healers in some way.[46] According to Joshi *et al*.,[47] indigenous tribes use the raw resin as an effective antiseptic poultice to heal festering wounds, boils, cracked heels, deep abscesses and STDs, such as gonorrhea. The global medical traditions, such as Ayurveda, Unani, and traditional mountain medicine, use decoctions of plants, extracts of bark, and infusions of needles for the treatment of chronic respiratory disorders (influenza, deep coughs and cold), rheumatic pain, and faster physiological healing of fractures, arthritis and dislocation of joints [as depicted in Figure 2].[10,48]

Figure 2: A depiction of *Pinus wallichiana*[81]

Taxonomy and systematic position

Nathaniel Wallich is a 19th-century Danish surgeon and botanist who was the superintendent of Calcutta Botanical Garden. *P. wallichiana* was scientifically named after him.[43] The taxonomy indicates its location among the advanced "soft pines," as detailed in Table 2.

Terms, including *Pinus griffithii* McClelland, *Pinus excelsa* Wall. and *Pinus chylla* Lodd[49] were the species synonyms in old literature. Two botanical varieties of the species are there: var. *wallichiana* (the type species) and var. *parva* (K.C. Sahni), and *parva* taxa are distinguished by distinct vegetative and reproductive cone dimensions.[41]

Morphology, wood anatomy, and dendrochronology

The *P. wallichiana* plants attain a height of more than 50 meters[50] in their natural habitat. The main trunk is very straight and thick, with short branches that curve gracefully downward. When growing as solitary specimens without the competition of other canopies, these branches form a sweeping dome-like crown.[50] The bark in juvenile trees is quite smooth, glaucous and highly resinous. As the tree grows older, the bark changes to a dark-grey corky texture which is shallow and scaly cracked.[50] As a true species of the *Quinquefoliae* section, its characteristic bluish-green foliage (needles) is borne in clusters of five. These needles are sharp-pointed, slender, highly flexible, and range from 12 to 20 cm. The line present on the adaxial surface is with numerous bluish-white stomata that help in gaseous exchange while reducing the loss of water in the frosty alpine air.[41,50]

The species has both male and female reproductive structures on the same plant (monoecious). The male strobili accumulate in large numbers on lower branches and younger twigs, shedding copious amounts of pollen by the beginning of June.[50] The female seed cones appear in clusters of one to six; they are remarkably long and slender (15–32 cm) and

Table 2: Taxonomy of *Pinus wallichiana*

Taxonomic rank	Classification
Kingdom	Plantae
Clade	Gymnospermae
Division	Pinophyta
Class	Pinopsida
Order	Pinales
Family	Pinaceae
Genus	*Pinus*
Subgenus	*Pinus subgenus Strobus* (Soft Pines)
Section/ Subsection	*Pinus subgenus Quinquefoliae/ Strobus*
Species	*Pinus wallichiana* A.B. Jacks.

start erect and bluish green in color. According to Farjon,[41] the heavy, pendant, highly resinous, light brown cones possess grooved, wedge-shaped scales that end in a blunt umbo after a maturation period of 18 months. The seeds have long wings of 15–35 mm to facilitate wind dispersal[41] across mountain valleys. Var. *Parva* is significantly smaller in all respects, with needles of only 6–11 cm and seed cones to about 10 cm long.[41]

The xylem of *P. wallichiana* strictly falls within the *Pinoideae* group of Pinaceae from the micro-anatomical point of view. The presence of axial and radial resin canals and specialized ray tracheids for rapid resin deployment upon wounding and pathogen attack are details of wood anatomy.[51] Dendrochronological investigations carried out in the Himalayan region have confirmed the extremely long life and eco-friendly nature of species. A well-documented live-tree chronology from Astore-Rama, Pakistan, indicated an ancient living specimen with a known age of 689 years. According to PAGES 2k Consortium,[52] Bhattacharyya *et al*.,[53] and Singh and Yadav,[54] snowball earth paleoclimatic temperature estimates and glacier fluctuation studies for the whole region have been made possible from this specific cross-dated record which is of the above plant.

Phytochemistry

The strong resistance of *P. wallichiana* to high levels of ultraviolet radiation, freezing sub-zero temperatures, and strong microbial pathogens at high altitude is due to its highly evolved secondary metabolism.[55,56] The different plant parts (needles, bark, edible cones and xylem resin) are a treasure-trove of biologically active terpenoids, flavonoids, polyphenol acids, and other organic compounds.[6,57]

Essential oils and defensive terpenoids

These essential oils, which are steam distilled from the needles, and the industrial distillation of oleoresin to turpentine, are high in monoterpenes and sesquiterpenes. Sharma *et al*.[58] having conducted a high-resolution gas chromatography-mass spectrometry analysis found that the major constituents are β-Pinene (46.8%), α-Pinene (25.2%), Myrcene (9.5%), α-Terpineol (2.3%) and Caryophyllene Oxide (2.1%). These highly volatile terpenes are the primary defense barrier of the tree, acting as powerful deterrents to phytopathogenic fungi and destructive herbivores.[59] In addition, the mature bark lipophilic fractions provided several diterpenoids, including isopimaric acid (2.78 mg/g) and protective triglycerides.[60]

Flavonoids and polyphenolic fractions

The methanolic and aqueous extracts of both the bark and needles contain extraordinary concentrations of polyphenols and flavonoids, exhibiting a chemical complexity that far surpasses basic timber species.[61,62]

- Needles: Phytochemical research indicates a rich, diverse profile of flavonols, thunbergol, 3-carene, cembrene, and highly specialized xanthones.[10,63]
- Bark (hydrophilic constituents): The bark is characterized by exceedingly high concentrations of sugar alcohols. It also features significant, pharmacologically active quantities of Resveratrol glycoside (9.09 mg/g), Catechin (5.78 mg/g), and Ferulates (4.78 mg/g).[64,65]
- Flavonoid profiling: Precise methanolic extractions identify Quercetin (5.009%), Myricetin (3.0%), Kaempferol (2.30%), and Rhamnetin (2.08%) as the dominant flavonoids within the plant tissues.[6] Comparative analyses reveal that the total phenolic content (TPC) and total flavonoid content (TFC) in the bark significantly eclipse those found in the foliage, establishing the bark as an exceptionally potent antioxidant reservoir.[58]

Cone metabolomics

Recent metabolomics-guided exploration of the edible cones of *P. wallichiana* has unraveled a vast, previously uncharacterized network of 45 distinct chemical compounds.[9,66] Advanced fractionation studies identified that the ethyl acetate fraction of the cones (Pw.EtAc) retained the absolute highest bioactive load. Quantitative assessments of this specific fraction yielded a massive TPC of 258.55 mg gallic acid equivalent/g and a TFC of 63.05 mg quercetin equivalent (QE)/g.[9]

Pharmacological activities

The traditional Himalayan use of *P. wallichiana* is verified by pharmacological investigation yielding very optimistic therapeutic applications of multiple usage.[67,68]

Antioxidant capabilities

P. wallichiana's powerful free-radical scavenging properties come from the numerous polyphenolic and terpenoid molecules it contains. Methanol extracts of leaves, bark, and cones showed high inhibition of reactive oxygen intermediates and high protection against lipid peroxidation on fragile membranes.[69] The cone ethyl acetate fraction (Pw.EtAc) exerted very remarkable and dose-dependent inhibitory activity against DPPH and ABTS radicals in standardized assays. The DPPH assay revealed an IC_{50} value of 13.0 μg/mL for the extract. The ABTS assay yielded an extraordinary 5.3 μg/mL value. This assay is competitive against the pure, synthetic antioxidant standard butylated hydroxytoluene (BHT) and ascorbic acid.[9,70]

Antidiabetic potential and metabolic repair

One of the most important modern findings about *P. wallichiana* is its powerful antidiabetic activity present in the edible cones of the plant, which provides a very novel natural source for diabetes mellitus.[9] The fraction Pw.EtAc is a competitive inhibitor for carbohydrate-digesting enzymes in the GI tract of humans. In precise *in vitro* assays, it significantly inhibited α-amylase with an IC_{50} value of 1.98 μg/mL and α-glucosidase with an IC_{50} value

of 7.2 µg/mL.[9] The direct enzymatic inhibition slows down the breakdown of complex polysaccharides into absorbable glucose, effectively truncating postprandial hyperglycemic spikes. The molecular dynamics simulations and *in silico* docking studies support that the identified phytoconstituents establish highly stable and permanent interactions with the active binding sites of these specific enzymatic targets.[9] Moreover, potent *in vivo* validation in alloxan-induced diabetic mice showed that systemic application of cone extract induced a significant and sustained reduction in fasting blood glucose levels whilst actively ameliorating hyperlipidemia.[9] Significantly, the extract reversed the high degree of weight loss that is characteristic of the metabolic wasting associated with advanced diabetes. Across meticulous histopathological analyses of each treated mouse, solid and compelling microscopic evidence has emerged that structural healing of the tissues is in an active process. The extract is effectively enhancing the repair of alloxan-induced necrotic lesions of the pancreas, specifically repair of the insulin-producing islets of Langerhans, alongside the liver, heart and kidneys.[9]

Antimicrobial, antifungal, and insecticidal efficacy

After traditional usage for septic wounds and systemic infection for centuries, present empirical data show wide-spectrum antimicrobial activity of the plant.[47] The pathogenic Gram-negative bacteria *P. aeruginosa*, *E. coli* and *Agrobacterium tumefaciens* and *Xanthomonas phaseoli* and very virulent Gram-positive bacterium, such as *B. subtilis* are inhibited forcefully by the hydromethanolic and pure essential oil extracts of the needles and bark.[10,44,71] The n-hexane fraction of the needles of *Pinus halepensis* shows very potent anti-fungal activity by inhibiting the mycelial growth of the dermatophyte *Microsporium cannis*. Further, essential oils are directly fungicidal to *Fusarium verticillioides*.[72] Insecticidal toxicity of ethyl acetate fractions is very potent and causes high mortality in agricultural and storage pests *Tribolium castaneum*, *Rhyzopertha dominica* and *Callosobruchus analis*.[73,74]

Anticancer and antiproliferative activity

The essential oils of *P. wallichiana* are highly volatile and exert a remarkable, dose-dependent, targeted antiproliferative action against a diverse panel of aggressive human cancer cell lines.[75,76] Pharmacological tests assessing the cytotoxicity of the oils at 100 µg/mL produced very low IC_{50} values on several malignant lineages:

- THP-1 (Human Leukemia): IC_{50} of 5.6 ± 1.4 µg/mL[6]
- A-549 (Human Lung Carcinoma): IC_{50} of 6.1 ± 0.8 µg/mL[6]
- HEP-2 (Human Liver Carcinoma): IC_{50} of 9.0 ± 1.5 µg/mL[6]
- IGR-OV-1 (Ovarian Cancer) and PC-3 (Prostate Cancer): IC_{50} of 9.9 ± 1.9 and 6.9 ± 1.2 µg/mL, respectively.[6]

Results were sometimes better than the standard positive controls, being highly toxic chemotherapeutics, Paclitaxel and Mitomycin-C. Actions of α-pinene, β-pinene, and selected sesquiterpenes synergistically delay the cell cycle and disrupt malignant cell membrane integrity.

Neuroprotective activity

P. wallichiana shows considerable neuroprotective properties which may be beneficial toward the therapeutic management and reversal of PD pathology, parallel to the findings in *A. hierochuntica*.[4,77] Chauhan and Sharma[12] explored the neuropharmacological activity of high doses of *P. wallichiana* extracts (200 mg/kg i.p.) in the behavior of Wistar rat in standardized assays. In apomorphine-induced stereotypy models (which assess dopaminergic hyperactivity), administration of *P. wallichiana* high-dose extracts substantially curtailed the duration of the hyperactive state, as stereotypy duration on day 7 was recorded as 250.0 ± 10.0 s while on day 14 it was further significantly reduced to 235.0 ± 9.0 s ($P < 0.01$) as compared to untreated toxin controls.[12,36] In addition, the extracts reversed the marked motor rigidity typical of haloperidol-induced catalepsy (a commonly used model of dopamine D2 receptor blockade). The pole-climbing test showed the treated rats had significantly better escape behaviors with improved overall motor coordination.[12,78] Researchers believe that the neuroprotection is due to the ability of the diterpenoids and polyphenols in the plant to cross the blood–brain barrier. Once they enter the central nervous system (CNS), they scavenge reactive radicals produced within the body, furiously downregulate inflammatory cytokines, and actively modulate the dysfunctional dopaminergic pathways in the striatum.[66,79]

COMPARATIVE ANALYSIS AND SYNERGIES: EXTREMOPHYTE BIOCHEMISTRY

Both can survive in the extreme conditions of desert and near being frostbitten, but they thrive. The survival strategies engineered by both have been different and ecological not causing any undesired harm, join in the life mechanisms at the evolutionary convergence point level.[2,58] Both kinds form protective flavonoids and polyphenols in exceptionally high concentrations. For example, Compounds, such as rutin, quercetin, and the unique skeleton flavanones prevent catastrophic cellular degeneration during extreme desiccation and thus allow the hygrochastic resurrection sequence to occur without suffering lethal damage to DNA.[11,20] In contrast, for *P. wallichiana*, a protective biological barrier against high solar radiation and freezing cellular stress was formed by the accumulation of flavonols, catechins, and resveratrol glycosides in the bark and needles.[64,65]

As a result of this overlapping nature, their pharmacological benefits are quite powerful in humans. The deep neuroprotective abilities of both plants are evident from their

common ability to improve haloperidol-induced catalepsy and apomorphine-induced stereotypy. This indicates the ability of polyphenols from both plants to curb oxidative stress and neuroinflammation in the CNS.[4,12] However, there are distinct evolutionary specializations that direct their respective clinical utility. The powerful phytoestrogenic effects of A and the stimulation of myometrial contraction of *A. hierochuntica* are highly specialized to their specific chemical matrix and have no equivalent as is necessary for the alpine pine, and correspond only to their traditional application in parturition.[22] In contrast, the specialized inhibitor (α-amylase and α-glucosidase) demonstrated by the specific diterpenoid-rich cones of *P. wallichiana* indicates a high degree of specificity and localization of this metabolic process for antidiabetic action.[9]

CONCLUSION

A. hierochuntica L., a comprehensive review of *P. wallichiana* A. B. Adolescents! This clearly shows that the plants growing in harsh ecological conditions have high therapeutic value. The desert "Rose of Jericho" or *A. hierochuntica* is a shrub that exhibits remarkable resistance to extreme environmental conditions. This shrub contains a large number of flavonoids and neolignans, which help in offering immense benefits in female reproductive health, gout due to powerful XO inhibition, and liver protection. All these benefits of *A. hierochuntica* have been effective and scientifically proven. At the same time, the *P. wallichiana* of the Himalayas has its traditional trade value as timber, not only looks better as an essential oil-extracting complex of diterpenes and polyphenols of bark for antidiabetic, antiproliferative, and antimicrobial have substantial efficacy.

Most importantly, both extremophyte species have significant neuroprotective abilities through strong antioxidant and dopaminergic regulatory mechanisms, making them highly innovative natural therapies for progressive neurodegenerative diseases, especially PD. Successful migration of these strong plants from proven ethnomedicine to proven scientifically pharmacological agents reinforces an immediate need for further clinical investigation. Future research frameworks must isolate the exact molecules constituting these specific bioactive fractions and conduct typical *in vivo* human clinical trials to establish precise pharmacokinetic and safety profiles, especially for *A. hierochuntica*, which has been shown to cause fetal toxicity. The growth of medicinal plants, a subject of great concern in relation to the matter of over-exploitation, is addressed through cultivation of medicinal plants through sustainable large-scale cultivation to wean the medicinal plants from over-exploitation in the wild.

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