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Betula utilis (Bhojpatra): A potent herb with its traditional uses, phytochemistry, clinical application, pharmacology, and toxicology

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ABSTRACT

Betula utilis D. Don, (*B.utilis*) commonly known as the Himalayan silver birch or Bhojpatra, is a long-lived member of the Betulaceae family and grows in the subalpine zones of the Himalayan region at elevations ranging from 2,700 to 4,500 m. This species of *Betula* genus holds significant value in traditional and folk medicine, particularly in Ayurvedic medicine, where its bark has been used to cure various illnesses, such as blood and ear infections, pneumonia, convulsions, skin ailments, and many more. Phytochemical investigations reveal that *B. utilis* is abundant in triterpenoids, flavonoids, phenols, vitamins, and essential oils, among other compounds. Pharmacologically, the species exhibits a wide range of activities, including anti-inflammatory, antimicrobial, anticancer, hepatoprotective, anti-psoriatic, anti-obesity, anti-urolithiasis, anticonvulsant, anti-HIV, and antioxidant properties. This study summarizes research on the botanical taxonomy, phytochemistry, pharmacological properties, and ethnomedicinal uses, of *B. utilis* that was published between 1968 and 2024. Furthermore, toxicological studies are also discussed to provide insights into the safety profile of this species, an essential consideration for its therapeutic applications. To retrieve literature, search engines, including PubMed, Scopus, and Google Scholar, were used. This comprehensive review provides detailed information on the traditional uses, phytochemical composition, pharmacological activity, and toxicological aspects of *B. utilis* by integrating traditional knowledge with current findings. These reviews aim to serve as a valuable resource for researchers to guide future investigations.

INTRODUCTION

The World Health Organization estimates that more than 80% of the world's population uses traditional medicine to prevent illness and that more than 70,000 plant species are utilized medicinally [1]. The Ayurvedic system of medicine in India plays an important role because of its therapeutic activities for the development of herbal plants [2]. Apart from Ayurveda, conventional medicine is also used as a home remedy [3]. Herbal remedies have achieved interest among people in the COVID-19 pandemic era due to their proven efficacy as preventatives and immunomodulatory. It is necessary to do extensive, evidence-based research on the therapeutic properties of Ayurvedic medicines and medicinal plants. In the Ayurvedic literature, it is suggested that dhupana karma and yagya karma should be carried out in janpadodhwamsa to defend against infection and clean up the contaminated atmosphere caused by the COVID-19 epidemic, which may be associated with janpadodhwamsa [4].

Native to the Himalayan region, *Betula utilis* D. Don is found in the subalpine zone and grows between 2,700 and 4,500 m above sea level [4] is also called Himalayan silver birch and Bhojpatra belongs to the Betulaceae family and is broadleaved deciduous angiosperm [5]. *Betula utilis* survives more than 400 years (long-lived species) [6]. Hindus used it in various religious rituals, and the outer bark is a most valuable part used for writing scriptures, mantras, and texts, especially in Sanskrit. It is a tie around the arm or worn around the neck to protect the kids from all the misfortunes and receive

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blessings. According to Hindu astrology, people collect the outer bark in a specific nakshatra (lunar mansion, specific day, and time are considered) and make yantras for a prosperous life. In addition, *B. utilis* wood is aromatic, and hence, it is used in havan for marriage, birth, and religious prayers [7]. The striking Himalayan birch, *B. utilis*, is known by a variety of local names in the Himalayan region, each of which reflects the distinctive cultural and regional ties that run through this varied atmosphere (Table 1) [8] and taxonomy positions of *B. utilis* mentioned in (Table 2) [9].

A medium-sized tree, *B.utilis*, can grow to a height of 20 m. The bole of this multibranched tree is typically asymmetrical (Fig. 1A). Short, silky hairs cover its stalk, juvenile leaves, and bracts. It has alternately oriented, deciduous leaves that are oval and irregularly serrated. Its bracts continue to be wider than the nut's wings. It blooms in May and June and produces lenticular winged nuts on a spike as fruit [10]. Its bark is smooth, shiny, and reddish-white or white. Its outer bark is composed of several smooth layers that can be peeled off in flakes and its inner cortex is reddish and moist. The soil should be well-drained, as the plant selects a variety of soil types, including light sandy, medium loamy, and heavy clay soils. The plant can thrive in soils that are acidic, neutral, or alkaline. It can grow well in semi-shade (light woods) or in the absence of shade [11].

According to Ayurvedic Pharmacopoeia, therapeutic uses of *B. utilis* bark are karnaroga, raktapitta, kustharoga, raksoghnadhupana, vrana, aparapatana, garbhasanga, granthivisarpa, and balagraha [12]. The bark of plants is frequently used in various Ayurvedic medicines to cure several illnesses, such as ear and blood disorders, pneumonia, convulsions, leprosy, and skin infections [13]. Numerous biochemical components of the tree are also utilized for a range of therapeutic purposes. The main phytoconstituents of *B. utilis* are betulin, lupeol, acetyloleanolic acid, betulitc acid, lupenone, sitosterol, methyl betulonate, and methyl betulate. Various phytochemicals, such as betulinic aldehyde, ursolic acid (UA), and oleanolic acid, are also reported minorly [14].

SOURCES OF LITERATURE

The published information on *B. utilis* was collected from scientific datasets such as Google, Web of Science, Elsevier, PubMed, Google Scholar, and Semantic Scholar. Search terms were used in this review, "*Betula utilis*" or "bark of *B. utilis*," or "Betulaceae," "Bhojpatra" or "Birch," or the genus of *Betula* along with phrases like "Botanical description," or "Taxonomy or distribution" or "Phytochemistry," or "Traditional uses," "Pharmacology," or "Toxicology" or "applications." The search was conducted in any available language. Compound chemical structures were drawn using ChemDraw 15.0 software.

Table 1. Vernacular name of *B. utilis.*

English: Silver birch
Sanskrit: Bhurja
Gujarati: Bhojpatra
Malayalam: Bhujapatram
Tamil: Bhurjjamaram
Telugu: Bhujipatri
Hindi: Bhojpatra and Bujpatri
Marathi: Bhojjapatravain
Kannad: Bhurjapatra
Bengali: Bhujjipater

BOTANICAL AND GEOGRAPHICAL DESCRIPTION

Botanical description

The oval, 5–10 cm (2.0–3.9 in) long leaves with serrated margins and a light covering of hairs. Only a few male catkins and short, solitary (sometimes paired) female catkins are present throughout flowering, which lasts from May to July. In male flowers, the perianth has four components; it is missing in female flowers. From September to October, fruits ripen. The thin, paper-like bark has horizontal lenticels and is reddish brown, reddish-white, or white (Fig. 1B). It is extremely glossy. The timber is exceedingly heavy, brittle, and hard. The heartwood is pale reddish brown or pink [15].

Geographical description

Since *B. utilis* is well suited to cold climates, it can be found in the Himalayas (subalpine region) and is distributed up to high altitudes between 2,700 m and 4,500 m [4]. In the Nanda Devi Biosphere Reserve (Uttarakhand), *B. utilis* was discovered to be the predominant tree species, with the highest density (739 Ind/ha and 1525 Ind/ha), basal cover (between 22.13 and 28.61 m2/ha), and maximum IVI (between IVI: 217.31 and IVI: 266.56) [16]. Afghanistan, Kazakhstan, Bhutan, China, Nepal, India, Pakistan, Kyrgyzstan, Tajikistan, and Uzbekistan are among their native countries. Its growth ranges from 2,500 m to 4,300 m, and it can be found from the Afghan province of Nuristan to Hebei in northern China [17].

SPECIES OF *BETULA*

According to the literature and data that are currently available, the twelve most popular species of *Betula* have been traditionally utilized as medicines in various world regions given in Table 3.

TRADITIONAL USES

Betula utilis is one of the most valuable tree species in Indian traditional medicine. It is used in the Tridosha, which includes "Vata" (air), "Pitta" (phlegm), and "Kapha" (cough). It prepares its herbal medicine as an infusion, powder, paste, and decoction for the treatment of ailments. In addition, plants

Table 2. Taxonomy position of *B. utilis.*

Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Order: Corylales
Family: Betulaceae
Genus: *Betula*
Species: *utilis*

Table 3. Species of *Betula* with their medicinal uses.

S. No	Species	Common name	Distribution	Medicinal Uses	References
1	*B. alnoides*	Paiyun	China, Nepal, Bhutan, and Myanmar,	decoction mass of bark to heal micro-fracture or dislocated bone	[18]
2	*B. pumila*	Wamp birch and glandular birch	North America	Using smoke inhalation to treat respiratory illnesses	[19]
3	*B.cylindrostachya*	-------	China, India, Bhutan, Myanmar, and Pakistan.	Bladder contaminations, neuralgia, rubefacient, tonic, analgesic, rheumatism, and skin illnesses	[20]
4	*B. nigra*	Black, water, and red birch	Eastern USA	Boiled sap (sweetener comparable to maple syrup), and the inner bark to use as nutrition for survival	[21]
5	*B. lenta*	Cherry, black, sweet, and Virginia birch	Eastern US from Maine to northern Georgia	Treatment of rheumatism, bladder infections, and neuralgia	[22]
6	*B. nana*	Bog birch and arctic birch.	Greenland, Iceland, northern Europe, Asia, and North America	antirheumatic, astringent, lithontripic, salve, and sedative	[23]
7	*B. pendula*	Sliver birch and white birch	Europe and Asia	Tea for rheumatism, kidney illness, and blood cleansing	[24]
8	*B. utilis*	Himalayan birch	India and Nepal	Powder (consumed orally) treat leprosy and convulsion	[25]
9	*B. platyphylla*	Japanese White Birch	Manchuria, Korea, and Japan	Decoction (consumed orally) bone conditions	[18]
10	*B. papyrifera*	Paper bark birch	Northern North America	Used as a preservative	[26]
11	*B. occidentalis or B. fontinalis*	Water birch	Western North America, mountainous regions	The bark has sedative, salve, lithontripic, abortifacient, and anti-rheumatic actions.	[24]
12	*B. alleghaniensis*	Yellow birch	Northeastern North America	Blood cleanser with emetic and cathartic properties that help the body get clean	[26]

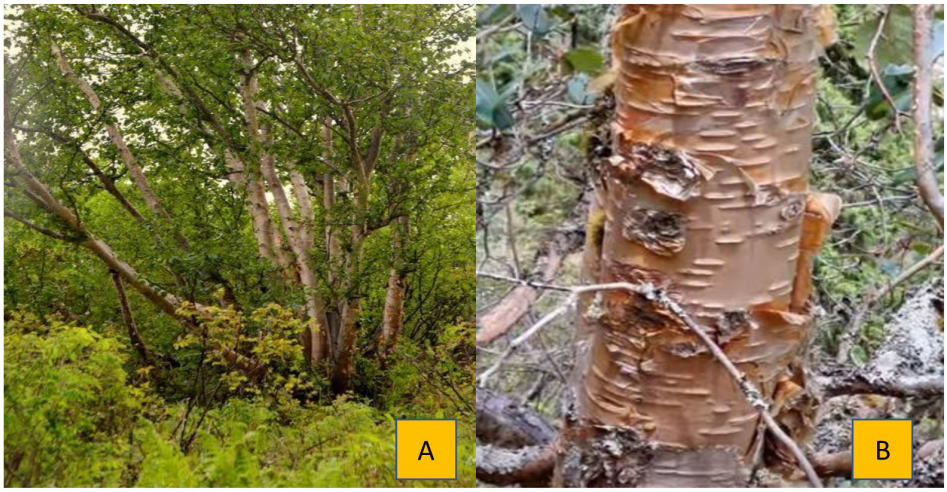

Figure 1. (A) Plant of *Betula utilis*. (B) Bark of *Betula utilis*.

produce food, gums, and resins. The bark, leaves, and resin are used to cure rheumatism, broken bones, joint stiffness, swellings, asthma, and blood purification [27,28]. The stem bark's astringent properties make it effective for treating wounds, leprosy, and styptic [29,13]. Its resin is used to treat burns and external wounds as well as for contraception.

The bark is used to cure earaches, kidney, and bladder issues. It is used to treat insanity, epilepsy, and hysteria because it is thought to be a good therapeutic agent for treating psychological diseases. Jaundice, constipation, and cough are also treated with bark [30]. Bark infusion is used to treat flatulence [31]. The bark is also used to heal domesticated animals. The bark is reduced to ashes and its paste is used for the deep wounds and cuts of animals [28].

The leaves are used to treat kidney and bladder stones, and urinary tract infections, as diuretics, and a leaf decoction of *B. utilis* is frequently utilized. Fever can be treated and fear released with bark paper. To promote family peace, a part of

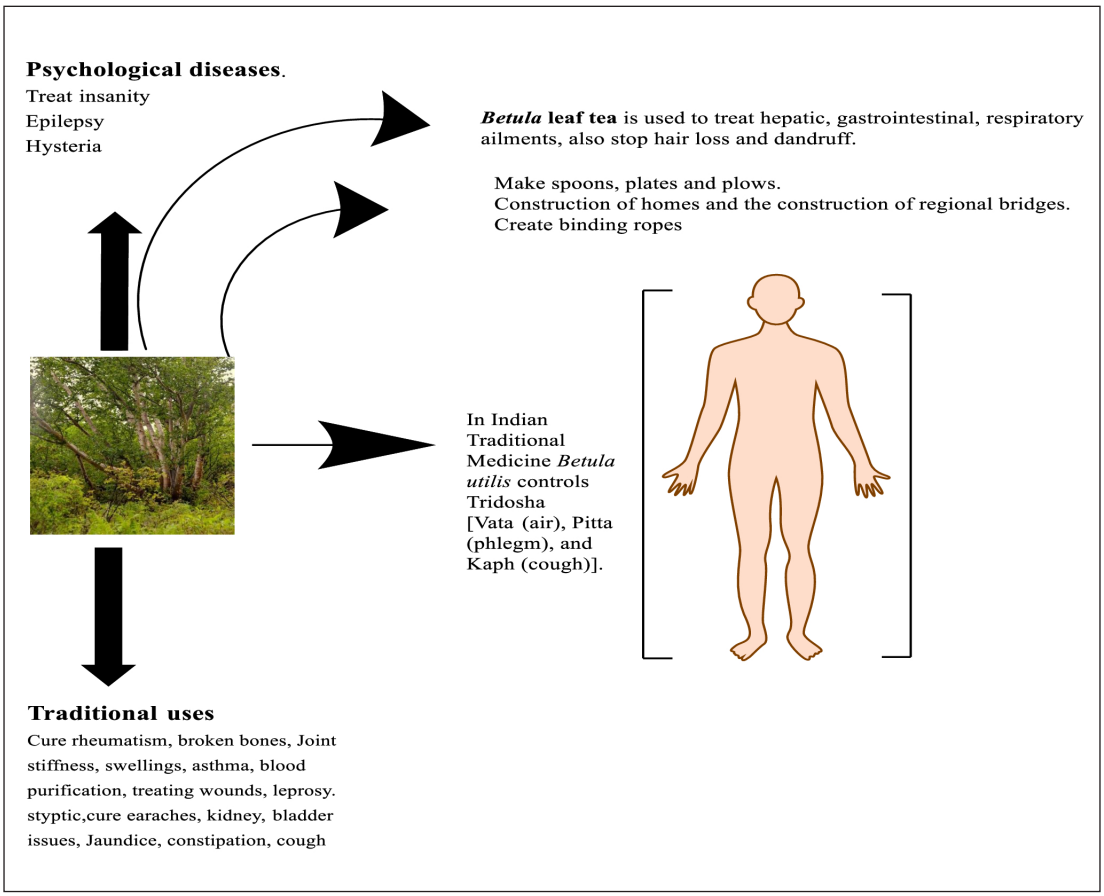

Figure 2. Traditional uses of *Betula utilis*.

papery bark is kept in households [32]. The bark paper is used to compress ghee, create binding ropes, shield wood from the elements, and relieve ear-related problems. Wood is a fuel source and is used to make spoons and plows [33].

The bark and roots of *Betula* provide a home for numerous insects and beetles, giving them a niche [34]. *Betula* leaf tea is used to treat hepatic, gastrointestinal, and respiratory ailments, and also stop hair loss and dandruff [35,36]. Other uses of *B. utilis* include the making of wrapping material, roof construction, home construction, and the construction of regional bridges by the locals of its distribution range (Fig. 2). The wood is tough and substantial. While living at high altitudes in the Himalayas, pastoral people utilize this wood to build shelters and firewood. These communities also make umbrella covers and rooftops out of the papery bark of *B. utilis* [8].

Perybark is used to make plates, while the leaves are used as fodder. *Betula utilis* trees are also used for landscape beautification and decorative purposes. Numerous wild animals, including musk deer, black bears, and monal, are frequently seen in the *B. utilis* forest. Additionally, it provides high-altitude wild herbivores food [37]. Ethnomedicinal uses of *B. utilis* are reported in (Table 4) and traditional uses of different dosage forms are reported in (Table 5).

CONVENTIONAL AND MODERN APPLICATION

Asanadi kashaya and Ayaskrithi are two significant herbal remedies used as prescriptions in Ayurveda. Asanadi kashaya is a liquid Ayurvedic medicine that treats various ailments such as diabetes, skin diseases, and obesity and also relieves intestinal worms. Ayaskrithi is also liquid Ayurvedic medicine and is used for the treatment of anemia, skin diseases, chronic urinary disorders, diabetes, hemorrhoids, leucoderma, anorexia, intestinal worm, malabsorption disorder, and obesity [12].

Bharat bhojpatra tablet (a herbal product) manufactured by Bharat and the product number is GHTYR76594. Intimate vaginal tablets (Veeon) manufactured by Veeon are a natural solution for leucorrhoea and vaginal contraction and help in contracting, toning up lax, and sagging vaginal muscles, HOO-IMM PLUS 750 mg for Functiono immune restorative, Jiva Ayurveda (SCIM detox tea) 75 mg for Functiono immune restorative, and aswagandharishtam (Ayurvedic medicine) effective for treating fainting, epilepsy, insanity, swelling, piles emaciation, and arthritis conditions.

PHYTOCHEMISTRY

A wide array of chemicals, including betulin, betulinic acid, acetyloleanolic acid, lupenone, methyl betulonate, sitosterol, and methyl betultriterpenoid, are found in the bark of *B. utilis*, along with tannins, flavonoids, phenolics, triterpenoids, and essential oils [55,56,57]. Numerous vitamins, minerals, sugars, and carbohydrates are also found in the sap of Himalayan birch trees. Additionally, monoterpenes, phenylpropenes, terpene alcohol, sesquiterpenes, alkenals, esters, acid, and sesquiterpenoid alcohols are found

Table 4. Ethnomedicinal uses of various parts of *B. utilis*.

Part used	Geographical location	Common name	Ethnomedicinal uses	References
Bark	(Dolpa, Nepal)	Bhuj	Bark paste is used to heal cuts, wounds, and burns. Bark decoction for sores. Use of a poultice for injuries, swellings, etc.	[41–43]
Bark and leaves	(Manang, Nepal), Buspath		Fever is treated by combining bark and leaves with other herbs.	[43,44]
Resin			Used in bile and phlegm disorders.	[43,44]
Bark and resin.			Antiseptic, carminative. Bark decoction treats a sore throat. The bark cures bacterial infections, skin diseases, and bronchitis cough.	[18]
Flower	(USA)	Bog birch	Treat respiratory tract diseases	[45]
Bark	(Bulashbar Nullah, Astore; Northern Pakistan)	Joonsh, Zhoonsh	Locals wrap desi ghee in its bark and bury it in the ground; after 10–20 years, the ghee's flavor improves. The value of this ghee exceeds that of regular desi ghee.	[46]
			Because the paper is waterproof, they cover the potatoes and wheat that are kept in shallow pits dug in the ground as well as put it like sheets on the roofs of their homes during building.	
Bark, Root	(Western Ladakh, India)	Towa	Burns, leprosy, bronchitis, and jaundice.	[47]
Bark	(Leepa Valley; Azad Jammu and Kashmir, Pakistan)	Birch	The powder is consumed orally to treat seizures and leprosy.	[25]
	(India)	Bhohpattra	Abortifacient	[48]
	(Johari tribals; Uttarakhand, India)	Bhojpattra	Antiseptic, for ear complaints, hysteria, and jaundice	[49,50]

abundantly in the whole plant of *B. utilis* [51]. The stem bark of *B. utilis* contains essential oils such as geranic acid (11.38%), seleneol (10.98%), linalool (10.91%), terragon (10.61%), sesquiphellendrene (8.02%), champacol (6.33%), and 1,8-cineol (5.49%), which were also identified by GCMS [52]. The bark of *B. utilis* contains phenolic compounds such as ferulic acid, caffeic acid, and chlorogenic acid and estimated by UHPLC-ESI-MS/MS [53]. The stem bark of *B. utilis* contains flavonoids such as quercetin, kaempferol, apigenin, catechin, and luteolin identified by UHPLC-ESI-MS/MS [54,55]. The linoleic (17.66%), myristic (15.9%), palmitic (9.09%), and oleic (11.30%) fatty acid components are also found in *B. utilis* bark [56,55]. Various minerals, such as calcium, manganese, potassium, magnesium, iron, zinc, sodium, phosphorus, and copper [53], and apart from these minerals, various vitamins, such as B complex and Vitamin C, are also reported in plant [57]. The bark of *B. utilis* contains triterpenoids such as betulin, betulinic acid, lupeol, karachic acid and oleanolic acid-3-acetate (Fig. 3) [12,58]. Apart from that various modification in botulin and betulinic acid shows their potential as promising agents in various medical treatments [52,59].

The two most prevalent active compounds in *B. utilis* are betulin and betulinic acid [60]. Betulin is a pentacyclic triterpene (lupane series) natural compound with systematic name 3β, 28-dihydroxy-20(29)-lupen or lup-20(29)-en-3β, 28-diol, molecular formula $C_{30}H_{50}O_2$, molecular weight 442.728 $g.mol^{-1}$ (Fig. 3) [61,62]. Betulin is isolated from the various species of Betulaceae, Platanaceae, Dilleniaceae, Rhamnaceae, Rosaceae, and Fagaceae, mainly from the bark of different species of Betulaceae. Betulin was first observed by Lowitz in 1788, from the sublimation products of birch bark. Betulinic acid, the oxidation product of Betulin, was first discovered by Retzlaff in 1902 and was described as an unknown compound extracted from *Gratiola officinalis* (Plantaginaceae), which was further named as betulinic acid and identified as the oxidation product of betulin by Robertson and colleagues in 1939. This compound was first isolated as a pure chemical substance in 1788, being one of the first natural products identified from plants [63]. Birch bark's white color is caused by the crystal clustering in the thick-walled, massive cells and betulin occurs in spring [64]. This wide range of betulin content in the dry weight, which ranges from 10% to even 45%, is the result of several elements, including tree type and age, climate patterns, and geographic locality [65,66]. The content of betulin in the root skin and leaves is also present; however, it is considerably lower than that in the outer bark [67]. Betulin exhibits various pharmacological activities, such as antitumor, anti-HIV, antiviral, antibacterial, anti-inflammatory, antileishmanial, antimalarial properties, and anticonvulsant [68–70].

Betulinic acid well-known triterpene, with the chemical formula $C_{30}H_{48}O_3$, chemical name (3-beta-hydroxy-lup20(29)-en-28-oic acid (Fig. 3) is found in the bark of some trees, including the *Betula pubescens*, *Ziziphus mauritiana*, *sycamore*, and other members of the Platanus family (*Platanus occidentalis*, *Platanus orientalis*, and *Platanus acerfolia*). The pharmacological effects of betulinic acid are quite diverse, including the suppression of the human immunodeficiency virus (HIV), as well as antibacterial, antimalarial, anti-inflammatory, anthelmintic, antinociceptive, anti-HSV-1, and anti-cancer properties. Due to its specific cytotoxicity against tumor cells and good therapeutic index, even at doses up to 500-mg/kg body weight, betulinic acid is a very promising innovative chemotherapeutic agent for the treatment of HIV infection and cancer [71]. Betulinic acid is a new anticancer medication that promotes apoptosis, distinguishing it from "classical" anticancer medicines such as doxorubicin. Betulinic acid is a prototypical cytotoxic substance that causes apoptosis through a direct action on mitochondria. In isolated mitochondria, betulinic acid causes a decrease of transmembrane potential that is independent of a benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone inhibitable caspase. This is suppressed by

Table 5. Traditional uses of different dosage forms reported in India.

S.no	Dosage form	Therapeutic potential	Ancient resources	References
	Lepa (Pradeha) (ointment)	Kilas (whitish discoloration of the skin), Indralupta (alopecia), Kitibha (rough dry skin), Dadru (skin disease having circular patches), Bhagandar (fistula in ano), Arsha (piles) Apachi, and Pama	Charaka Samhita	[72,73]
	Kustha (various skin diseases)	Kustha (various skin diseases)		
	Dhupana (fumigation)	Anagata Prasav		
	Yoni Dhupana (fumigation)	Prasav ki Tritiya avastha		
	Vesthyeta sarpiguda	Kshatkshina		
	Baladi Lepa (ointment)	Visarpa (Erysipelas)		
	Lepa (ointment)	Vrana (wound)		
	Kshar Tail (oil)	Karna Rog (Otalgia)		
	Patradan (covering the wound with medicinal leaves)	Vataja Vrana (wound)	Sushruta Samhita	[74]
	Ksharagad	Sarpa visha (anti-toxic)		
	Dhupana Karm (fumigation)	Dhupana Karm (fumigation)	Astanga Hridya	[75]
	Dhupana (fumigation)	Shravagrahanirbarhana		
	Kshar Tail (oil)	Karna rog (Otalgia)		
	Dhupana Karma (fumigation)	Vrana (wound)		
	Chandrodya Agad	Sarpavisha (anti-toxic)		
	Patradan (covering the wound with medicinal leaves)	Vrana (wound)		
	Dhupana (fumigation)	Garbhadhomukhsampadan	Astang Sangraha	[76]
	Yoni Dhupana (fumigation)	Aprasangh		
	Lepa (ointment)	Visarpa (Erysipelas)		
	Vesthyeta Baladisarpiguda	Kshatshina		
	Dhupana (fumigation)	Shravagrahanirbarhana		
	Vesthyeta sarpiguda	Rajyakshama	Chakradatta	[77]
	Dhupana (fumigation)	Vrana (wound)		
	Lepa (ointment)	Kusth (various skin diseases)		
	Tail (oil)	Karnashula (Otalgia)		
	Yoni Dhupana (fumigation)	Garbhaniroga chikitsa	Bhaisajyaratnawali	[78]

bongkrekic acid, which stabilizes the permeability transition pore complex (PTPC). In a cell-free system, mitochondria are subjected to betulinic acid-induced PT-mediated cleavage of caspase-8 and caspase-3. Significant factors, such as cytochrome C or AIF (apoptosis-inducing factor) generated by betulinic acid-treated mitochondria, are sufficient for caspase cleavage and nuclear fragmentation. The addition of cytochrome C to cytosolic samples causes caspase-3 to be cleaved, but not caspase-8. However, supernatants of PT-treated mitochondria, as well as partly purified AIF, activate both caspase-8 and caspase-3 in cytosolic extracts and are sufficient to activate recombinant caspase-8. These findings suggest that the development of mitochondrial PT alone is inadequate to initiate the whole apoptotic mechanism and that betulinic acid may induce apoptosis by a direct action on mitochondria [79].

Pharmacological activities

This botanical treasure trove is noteworthy because it exhibits a wide range of pharmacological actions, including anti-inflammatory, anti-microbial, anti-cancer, hepatoprotective, anti-psoriatic, anti-obesity, anti-urolithiatic capabilities, anticonvulsant potential, anti-HIV, as well as antioxidant (Fig. 4).

Anti-inflammatory activity

Methanolic and water extracts were used to evaluate antioxidant and anti-inflammatory activity of *B. utilis*. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical assay and the 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay were used to assess the extracts' antioxidant properties. The lipoxygenase inhibition assay was used to measure the anti-inflammatory activity. While indomethacin was utilized as the standard for the lipoxygenase inhibition experiment, ascorbic acid and gallic acid served as reference standards for the DPPH and ABTS assays. With IC_{50} values of 8.4 µg/ml and 35.08 µg/ml for the DPPH assay and 83.18 µg/ml and 37.14 µg/ml for the ABTS assay, the methanol and water extracts of *B. utilis* demonstrated strong antioxidant activity. The extracts also displayed anti-inflammatory activity, with 18.74% and 28.78% lipoxygenase

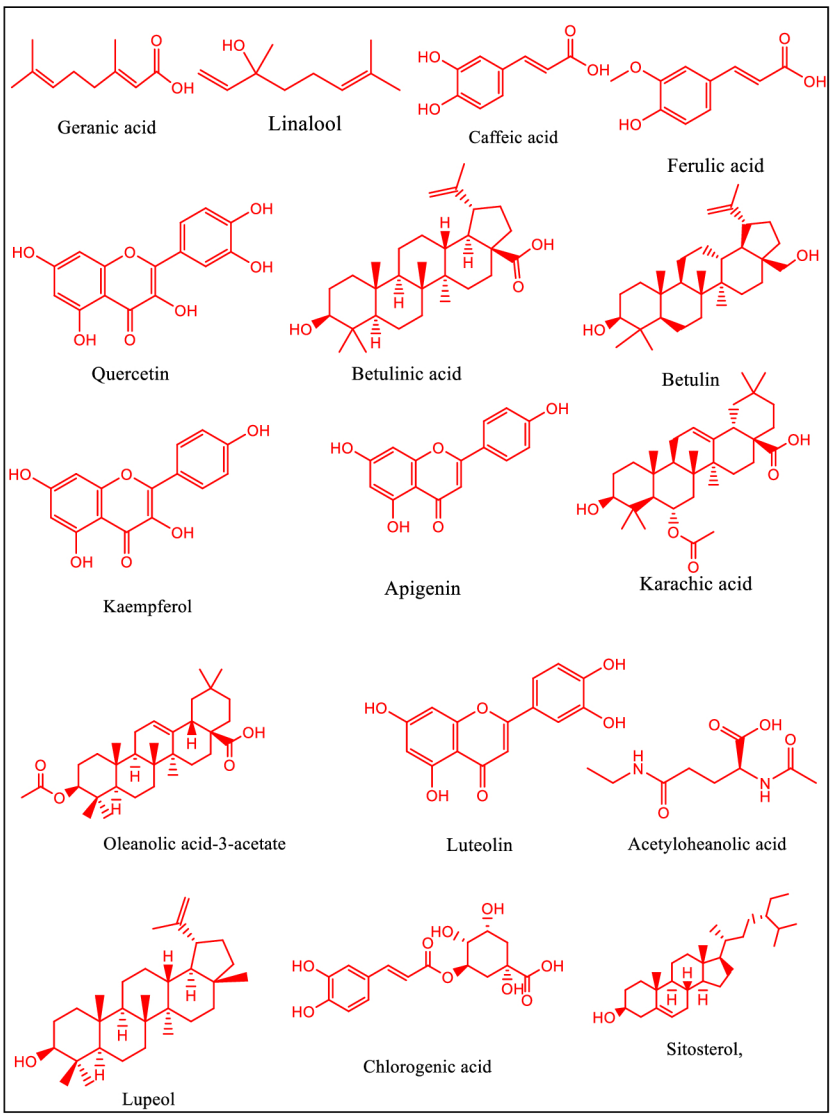

Figure 3. Structures of chemical constituents present in *B utilis.*

inhibition at a dosage of 1.0 mg/ml for the methanol and water extracts, respectively [80,81].

Anti-microbial activity

Plant-based compounds having antibacterial properties are useful as new tools in the fight against antibiotic resistance. The current work determines the chemical components that give *B. utilis*, a plant grown at high altitudes in the Himalayas of India, its antibacterial properties, and evaluates the antimicrobial activity of the essential oil isolated from the fresh bark [40,82]. Bark of *B. utilis* has antimicrobial activity in contradiction of many significant human pathogenic bacteria. The chemical composition of the essential oil was analyzed using gas chromatography–mass spectrometry, which revealed the major constituents as geranic acid (11.38%), β-seleneol (10.98%), β-linalool (10.91%), terragon (10.61%), β-sesquiphellandrene (8.02%), champacol (6.33%), and 1,8-cineole (5.49%). The antimicrobial activity of the essential oil was assessed using a micro-dilution assay against human pathogenic bacteria and fungi. The results demonstrated that the essential oil exhibited strong antimicrobial activity, particularly against *Candida albicans* Gram-positive and Gram-negative human pathogenic bacteria, with minimum inhibitory concentrations ranging from 60.5 to 240 µg/ml [40].

Anti-cancer activity

The *in vitro* anticancer activity of different *B. utilis* fractions in nine different cancer cell lines and the ethyl acetate fraction proved to be one of the most effective fractions in terms of inducing cytotoxic activity against various cancer cell lines. Six triterpenes, including betulin, betulinic acid, lupeol, UA, oleanolic acid, and amyrin, have also been isolated from ethyl acetate extract. The *in vitro* cytotoxic activity of isolated triterpenes against six distinct cancer cell lines was then examined, and it was discovered that UA was selective for breast cancer cells over nontumorigenic breast epithelial cells

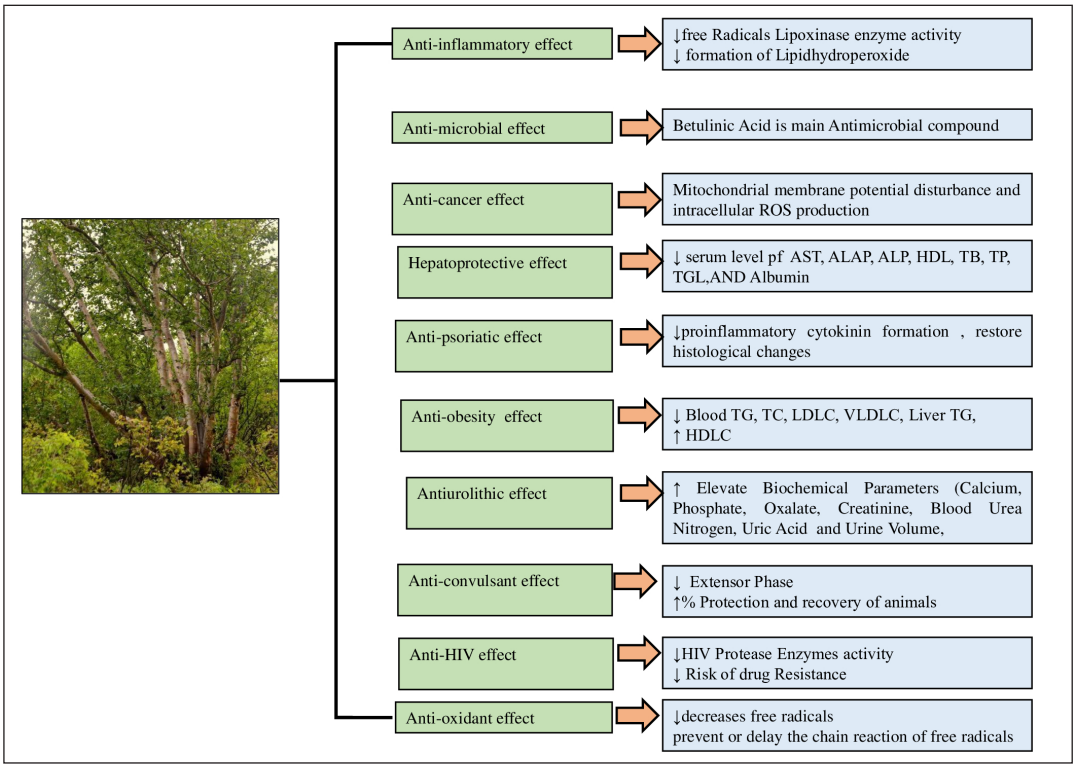

Figure 4. Pharmacological effect of *B. utilis.*

(MCF 10A). The main cause of UA tumor cell-specific apoptotic effect was related to the upregulation of DR4, DR5, and PARP cleavage in MCF-7 cells over nontumorigenic MCF-10A cells, which activated the extrinsic apoptosis pathway. Additionally, the anti-cancer effects of UA are significantly influenced by mitochondrial membrane potential disturbance and intracellular ROS production caused by UA and also prevent the spread of breast cancer [78].

Hepatoprotective activity

The hepatoprotective potential of *B. utilis* ethanolic and aqueous extracts against D-galactosamine-induced liver damage was assessed *in vitro* and *in vivo*. The hepatoprotective efficacy of ethanolic and aqueous *B. utilis* extracts against D-galactosamine (D-galN) at various concentrations was evaluated *in vitro* on isolated rat hepatocytes. Then, against D-galN, which when administered intravenously at a dose of 400-mg/kg body weight caused liver damage in rats, *in vivo* hepatoprotective studies of BUE and BUA at doses of 100- and 200-mg/kg body weight were performed. The hepatocytes were tested with 50 µl of a 10-mM D-galN solution. When contrast to the control group, the group to which the toxicant was introduced displayed a significantly higher level of the ASAT, ALAT, and ALP enzymes. Significantly, more of all the biochemical indicators were restored to normal. The plant extract's minimum restoration level was 62.5 g/ml in both cases. Additionally, *in vivo* administration of the BUE and BUA extract resulted in dose-dependent significant reductions in the serum levels of ASAT, ALAT, ALP, LDH, and TB and significant increases in the serum levels of TP, TGL, and albumin. However, the liver of the DgalN-treated group showed severe centrilobular necrosis, localized necrosis, and bile duct growth, entirely losing its normal architecture [83].

Anti-psoriatic activity

Evaluation of anti-psoriatic efficacy was done by imiquimod (IMQ 5%)-induced psoriasis-like skin inflammation model. The experimental groups assessed psoriasis area and severity index (PASI) scores, macroscopically and behavioral evaluation, splenomegaly, cytokine levels, and histological alterations in the *in vivo* screening models [52]**.** The outcome is consistent with the PASI score (57.14% and 61.9%), with rehabilitation rates of test BE solution (180 mg/kg) and standard Betamethasone dipropionate ointment (BD-oint.0.5 mg/g), respectively. By focusing on other factors, BE demonstrates related outcomes, including improved macroscopically with behavioral circumstances, decreased proinflammatory cytokine affirmation, and restored histological changes with those of BD. Phytoconstituents from *B. utilis* BE-isolated *Betula* are a promising agent and a first step in the treatment of psoriasis, according to results [84].

Anti-obesity activity

The bark of *B. utilis* has anti-obesity properties against cafeteria diet-induced obesity in mice. The cafeteria diet experimental model was used to evaluate body weight, glucose level, liver weight, and TG level in the serum. According to reported activity for the experimental models, in rats with cafeteria diet-induced obesity models, *B. utilis* bark extract showed dose-dependent significant anti-obesity action by

reducing blood TG, TC, LDL-C, VLDL-C, and liver TG and rising serum HDL-C as well as by boosting locomotor activity. Body weight, liver weight, and food intake all decreased as well. According to the findings, animals with EBEB at 200 mg/kg are more significant than those at 100 mg/kg [84]. The anti-obesity activity of *Betula utilis* was observed to exhibit a dose-dependent effect. After 4 weeks of HFD treatment, BU (100–400 mg/kg/day p.o) was given along with a high-fat diet for further 6 weeks, which significantly reduced HFD-induced body weight gain and an increase in adipose tissue mass in a dose-dependent manner. Moreover, BU attenuated HFD-induced augmented serum glucose, TG, and TC. The anti-obesity potential of BU was comparable to a marketed drug orlistat. These results reflect that BU supplementation decreases body weight and improves obesity serum biomarkers (TG, TC, and LDL), and the weight-reducing activity of BU may be mediated by decreased fat absorption from the GIT [85].

Anti-urolithic activity

Alcoholic *B. utilis* extract has anti-urolithiatic activity in rats using an ethylene glycol model. *Betula utilis* alcohol extract (250 and 500 mg/kg) and common medications (750-mg/kg cystone) were utilized. Numerous criteria were examined, such as urinary volume, urine pH, urine analysis, serum analysis, kidney homogenate, and histology of the kidney. In comparison to the model control, the results showed that giving rats with ethylene glycol-induced lithiasis an alcoholic extract of *B. utilis* significantly decreased all of the elevated biochemical parameters (calcium, phosphate, oxalate, creatinine, blood urea nitrogen, and uric acid), returned the urine pH to normal, and increased the urine volume. According to this study, alcoholic *B. utilis* extract can treat urolithiasis [86].

Anticonvulsant activity

The hydroalcoholic extract of *B. utilis* was used for the anticonvulsant and anxiolytic activity. According to OECD 425 Guidelines, an acute oral toxicity study revealed that at a dose of 2,000 mg/kg, 63% of the animals perished. Therefore, 100 mg/kg and 200 mg/kg orally were chosen for their convulsant and anxiolytic activities. At doses of 100 and 200 mg/kg, the extract demonstrated a reduction in the duration of the extensor phase and an increase in the percentage of protection. All animals were entirely protected by phenytoin, which completely decreased the duration of the tonic extensor phase [87].

Anti-HIV activity

Betulinic acid prevents HIV-1 replication at several points throughout the viral life cycle [88]. The capacity including its capacity to interfere with viral entry into host cells and suppress the activity of the HIV protease enzyme, both of which are necessary for the virus to mature. Researchers have created betulinic acid compounds with improved anti-HIV efficacy [89].

Bioassay-guided fractionation of the ethanol extract of *Betula* species stems using chromatographic techniques yielded five pentacyclic triterpenoids: betulinic acid, betulin, lupeol, oleanolic acid, and UA. Among these, betulin demonstrated the most potent inhibitory activity against HIV-1 integrase (IN) with an IC50 value of 17.7 μM. Computational docking studies revealed interactions of the active compounds with key residues of the IN active site, including Asp64, involved in 3′-processing, and Thr66, His67, and Lys159, which participate in strand-transfer reactions during the integration process. Furthermore, all compounds exhibited significant anti-inflammatory effects by inhibiting LPS-induced nitric oxide production (IC50 < 68.7 μM). These findings provide additional scientific evidence supporting the traditional medicinal use of Betula species in the treatment of HIV and related inflammatory conditions [90,91].

Anti-oxidant activity

The antioxidant activity by using the DPPH, 2, 2'-Azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and lipoxygenase inhibition assays, and the antioxidant properties of the *B. utilis* extracts were assessed. The *B. utilis* methanolic and water extract demonstrated DPPH and ABS scavenging activities (8.4, 35.08 g/ml IC_{50} for DPPH and 83.18, 37.14 g/ml IC_{50} for ABS test), but very little activity against ABS and lipoxygenase inhibition (18.74% and 28.78% inhibition at 1.0 mg/ml). The findings of this investigation suggest that *B. utilis* may be a source of antioxidants. Although *B. utilis* possesses free radical scavenging activity, it decreases free radicals, which could prevent or delay the chain reaction of free radicals that slows the spread of the oxidation mechanism [79]. Antioxidant activity by using various *in vitro* techniques includes the DPPH free radical scavenging assay, SOS activity, hydroxyl radical scavenging, and ferric thiocyanate activity of *B. utilis* extracts. The ethyl acetate and methanolic extracts had a percent inhibition of 72% and an IC_{50} value of 30.16 g/ml and 83.86% and 27.62 g/ml for their ability to scavenge DPPH radicals. The reference substance utilized was ascorbic acid, which had an IC_{50} value of 25.82 g/ml and a percent inhibition of 91.81%. The SOS activity of the ethyl acetate extract indicated a percent inhibition of 72.49% and an IC_{50} value of 44.47 g/ml. Similar results were seen for the SOS scavenger activity of methanol extract, which showed a percent inhibition of 81.49% and an IC_{50} value of 20 g/ml. Ascorbic acid was utilized as a reference substance for SOS activity; it displayed a percent inhibition of 86.72% and an IC_{50} value of 12.01 g/ml. The extracts of ethyl acetate and methanol showed a percent inhibition of 76.93% and 81.62%, and their respective IC_{50} values were reported to be 48.003 and 27.14 g/ml. Similar to this, ethyl acetate and methanol extract's ferric thiocyanate activity showed percent inhibition values of 74.68% and 81.27%, and their respective IC_{50} values were reported to be 40.112 and 23.79 g/ml. The *B. utilis* may be a valuable source of antioxidants that can be used to create effective therapeutic products in the future [92].

TOXICITY AND SIDE EFFECTS

Himalayan birch may be safe at therapeutic doses for the majority of humans, even for brief periods. Regarding the usage of Himalayan birch, while breastfeeding or during pregnancy, there is not enough trustworthy information available. Birch pollen is a major cause of airborne allergies, with many patients also hypersensitive to apples. This study investigated the role of HLA class II genes in birch pollen

allergy with or without food allergies. Blood samples from 42 atopic patients and 42 healthy controls were analyzed. The antibody responses were assessed, and DNA was genotyped using PCR-RFLP. While no differences were found in DPB1 alleles, HLA-DR4 and/or DR7 alleles were present in 42.6% of patients but only 2.4% of controls. The study concludes that HLA-DR7 is linked to allergen presentation and atopy, rather than specific allergen responses [93].

The utilization of birch leaf extract by those with high blood pressure raises some questions because it may raise the quantity of Na (salt) that the body preserves, which can exacerbate the condition [28].

CONCLUSION

In conclusion, *B. utilis*, also known as Himalayan birch or Bhojpatra, is a medicinal plant with a rich phytochemical composition. This plant has been used traditionally in various cultures and has drawn attention in modern research for its potential pharmacological properties. *Betula utilis* is abundant in triterpenoids (betulin and betulinic acid), flavonoids, and essential oils, which are associated with their medicinal properties. Research has indicated that *B. utilis* and its constituents exhibit a wide range of pharmacological actions, including anticancer, antiviral (against influenza and HIV), anti-inflammatory, antibacterial, hepatoprotective, antioxidant, anti-psoriatic, anti-convulsant, and anti-urolithiatic effects. *Betula* species, including *B. utilis*, have a historical tradition of use in various cultures for conditions such as arthritis, pain relief, and bone-related disorders. *Betula utilis* is incorporated into Ayurvedic formulations, such as Asanadi kashaya and Ayaskrithi, for the management of various ailments. It is also utilized as an active ingredient in modern herbal products, including tablets and vaginal tablets, reflecting its potential in contemporary herbal medicine. While promising, further research is needed to uncover additional properties, conduct toxicity studies, and better understand the full scope of benefits and potential side effects associated with *B. utilis*.

FUTURE PERSPECTIVE

Future applications for *B. utilis* include medicine, pharmaceuticals, natural products, and conservation. Realizing its full potential and guaranteeing its sustainability in the wild will depend on continued research and ethical use. The nutraceutical and functional food sectors might use extracts from *B. utilis*. They might be used in food goods intended to improve health and well-being. Conservation efforts to safeguard the plant and its environment in the Himalayan region may become more urgent as interest in *B. utilis* develops. To guarantee a steady supply of this priceless resource, it could be possible to investigate sustainable harvesting methods and agricultural practices. The *B. utilis* tree might be important to the natural products sector. Making use of their potential health and aesthetic benefits, their extracts and derivatives could be added to skin care products, herbal treatments, and dietary supplements. In laboratory experiments, compounds produced from *B. utilis*, particularly betulinic acid and its derivatives, have demonstrated potential as therapeutic development prospects. Preclinical and clinical trials may be conducted in the future to further refine these molecules and produce novel medications to treat various ailments.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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