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REVIEW ARTICLE

Betula utilis: A Potential Herbal Medicine

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ABSTRACT

Betula utilis common name bhojpatra used in traditional medicine and is known for its beneficial and medicinal value. This review highlights with different pharmacological activities of plant with different extracts and solvents. The active constituents of *Betula utilis* obtained from the plant shows anticancer, anti-inflammatory, anti HIV, antioxidant and antibacterial activity. The present review reveals the scope and application of *Betula utilis* as a potential herbal drug.

Key words: *Betula utilis*, betulinic acid, anticancer, anti-inflammatory, anti HIV, antioxidant, antimicrobial.

INTRODUCTION

Herbal medicines represent one of the most important fields of traditional medicine all over the world. Since medieval times, plants have been the source of medicines for the treatment of diseases. Regardless of the availability of a wealth of synthetic drugs, plants remain even in the 21st century, an integral part of the health care in different countries, especially the developing ones. In the late 90's, WHO stated that a big percentage of the world population depend on herbal medicinal therapy to cover the needs of the primary health care [4]. The herbal medicines have enormous therapeutic potential to heal many infectious diseases [18]. There are at least 250,000 species of plants out of which more than one thousand plants have been found to possess significant pharmacological properties among these a traditional medicinal plant *Betula utilis* (Himalayan birch, *bhojpatra*, Sanskrit: Bhurja) is a birch tree native to the Himalayas, growing at elevations up to 4,500 m (14,800 ft). *Betula utilis* possess various pharmacological activities like antimicrobial, anti-inflammatory, anticancer, antioxidant and anti HIV activities. The plant possesses various alkaloids which have various therapeutic effects. *Betula utilis* bark is antiseptic and carminative. The specific epithet, *utilis*, refers to the many uses of the different parts of the tree [13].

The present review has been undertaken to explore the possible anti-cancer, anti-oxidative, anti-HIV and antimicrobial potential of herbal plant *Betula utilis*.

Taxonomical description

Kingdom: Plantae
Division: Magnoliophyta
Class: Mangoliopsida
Order: Falages
Family: Betulaceae
Genus: *Betula*
Subgenus: *Betula*
Species: *utilis*

Botanical description and distribution

The plant belongs to the family Betulaceae. In uttarakhand *Betula utilis* grows along moraines around Bhojbasa, close to the snout of the Gangotri glacier in India [3]. *Betula utilis* D. Don (Betulaceae) is a moderate-sized tree that grows up to 20 m in height (**Fig 1**). The bark is shining, reddish-white or white, with white horizontals smooth, lenticels. The outer bark consists of layers, exfoliating in broad horizontal rolls (**Fig 2**). The leaves are ovate-acuminate, elliptic, and irregularly serrate. The flowers bloom in May June, in pendulous spikes. The flowers are monoecious (individual flowers are either male or female, but both sexes can be found on the same plant) and are pollinated by wind. Seeds are thin and winged. The plant prefers light (sandy), medium (loamy) and heavy (clay) soils, requires well-drained soil and can grow in heavy clay soil. The plant prefers acid, neutral and basic (alkaline) soils. It can grow in semi-shade (light woodland)

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or no shade. It requires moist soil [2]. Its therapeutic constitute antiseptic, aromatic, carminative and contraceptive effects. The bark contains betulin, lupeol, oleanolic acid, acetyloheanolic acid, betulitc acid, lupenone sitosterol, methyle betulonate, methyl betultriterpenoid, karachic acid. *Betula utilis* contains betulin up to 12% of its weight. It has aromatic and has antiseptic properties [21,1].

Fig 1:.*Betula utilis* plant- The plant belongs to the family Betulaceae. *Betula utilis* D. Don (Betulaceae) is a moderate-sized tree that grows up to 20 m in height.

Fig 2: Bark of *Betula utilis*- The bark of Himalayan birch was used centuries ago in India as paper for writing lengthy scriptures and texts in Sanskrit and other scripts. The bark of *Betula utilis* contains betulin that can be easily converted into betulinic acid.

Traditional use of *Betula Utilis.*

The bark of Himalayan birch was used centuries ago in India as paper for writing lengthy scriptures and texts in Sanskrit and other scripts**.** The Sanskrit word for the tree is *bhûrja*—sharing a similarity with other Indo European words that provide the origin for the common name "birch". The bark is widely used for packaging material, roof construction etc. The leaves of the plant show efficacy in treatment of urinary tract infections and in kidney and bladder stones. The wood is used for construction, and the foliage for fodder. The most widespread use is for firewood, which has caused large areas of habitat to be eliminated or reduced. Parts of the plant, including the fungal growth (*bhurja-granthi*) have also long been used in local traditional medicine.

Anticancer activity

Betula utilis contains betulin that can be easily converted into betulinic acid (3â-hydroxy-lup-20(29)-en-28-oic acid) (**Fig 3**). Studies revealed that betulinic acid inhibits growth of malignant melanoma and cancers of the liver and the lung [23].

Betulinic acid was identified as a highly selective growth inhibitor of human melanoma, neuroectodermal and malignant tumor cells and was reported to induce apoptosis in these cells. Anticancer agents with different modes of action have been reported to trigger apoptosis in chemoselective cells [6]. Alterations of mitochondrial functions such as permeability transition (PT) have been found to play a major role in the apoptosis process including cell death induced by chemotherapeutic agents [13]. The antitumor cytotoxicity of betulinic acid has been extensively studied in a panel of cancer cell lines, primary tumor samples and xenograft mouse models (**Table 1**). Some reports suggested that betulinic acid is selectively cytotoxic against melanoma cell lines [19].

Selzer *et al* studied the effect of betulinic acid alone and in combination with irradiation in human melanoma cells. Betulinic acid strongly and consistently suppressed the growth and colony forming ability of all human melanoma cell lines. In combination with ionizing radiation, the effect of betulinic acid on growth inhibition was additive in colony-forming assays. Betulinic acid also induced apoptosis in human melanoma cell [22].

Zuco *et al* studied the *in vitro* cytotoxicity of betulinic acid in melanoma and non-melanoma tumor cell lines and compared with that of doxorubicin (also an anticancer drug). It was also tested on cell lines expressing a different p53 status. Betulinic acid proved active *in vitro* against a panel of neoplastic cell lines, including melanomas, small and non small cell lung carcinomas, ovarian and cervical carcinomas. It exerted its antiproliferative activity on all the tested lines in a very narrow range of doses (1.5-4.5 mg/ml) [27].

Fulda *et al* identified betulinic acid as a new cytotoxic agent against neuroectodermal tumor cell including neuroblastoma, medulloblastoma, glioblastoma and Ewing's sarcoma cells, which represent the most common solid tumors of childhood. Neuroblastoma cells resistant to CD95

or doxorubicin-triggered apoptosis remained sensitive to treatment with betulinic acid, and betulinic acid exhibited potent antitumor activity on primary tumor cell cultures from all neuroblastoma, all medulloblastoma with an ED50 of 3-15 mg/ml and most glioblastoma patients with an ED50 of 5-16 µg/ml *ex vivo*. These findings suggest that betulinic acid may be a promising new lead in the treatment of neuroectodermal tumors *in vivo*. [8, 9, 10, 11]

Kim *et al* modified the C-20 alkene functional group of betulinic acid **(Fig 4(a))**. The chemical modification at this position was initiated by converting the double bond to a ketone (15a) using a OsO4/NaIO4 system. The ketone functionality was readily transformed to oximes (15b and 15c). The compounds were evaluated for their cytotoxicity against the human colon carcinoma cell line HCY-116, and human melanoma cell lines M14-MEL, SK-MEL-2, and UACC-257. The results showed that when the double bond was oxidized to a ketone (15a), loss of cytotoxicity was observed, suggesting that the presence of highly electronegative oxygen atom may change the electrostatic property of betulinic acid, rendering it less toxic. Converting to oximes (15b and 15c) also appeared to result in the loss of cytotoxicity, probably due to the same reason described above. These results suggest that the cytotoxicity profile of betulinic acid derivatives may be sensitive to both the size of substituent at the C-20 position and its electrostatic properties [12].

Fig 3: Structure of Betulinic acid-Active constituent of betula utilis.

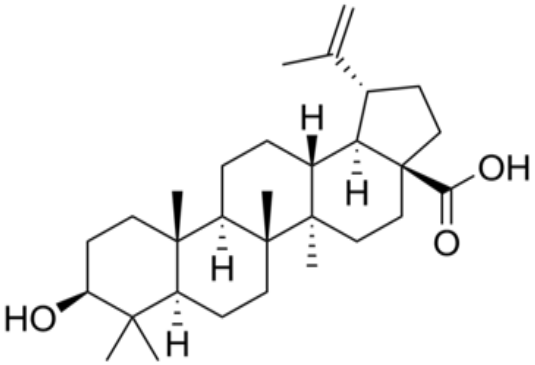


Table 1: ***In vitro*** **cytotoxic effect of betulinic acid on human cancer cell lines.**

Cancer type	ED*50 (µg/ml)	References
Melanoma	1.1–4.8	[19]
Neuroblastoma	2–10	[8]
Medulloblastoma	3–15	[9]
Glioblastoma	5–16	[9]
Head & Neck cancer	8	[24]
Ovarian carcinoma	1.8–4.5	[27]
Cervix carcinoma	1.8	[27]
Lung carcinoma	1.5–4.2	[27]
Leukemia	2–15	[5]

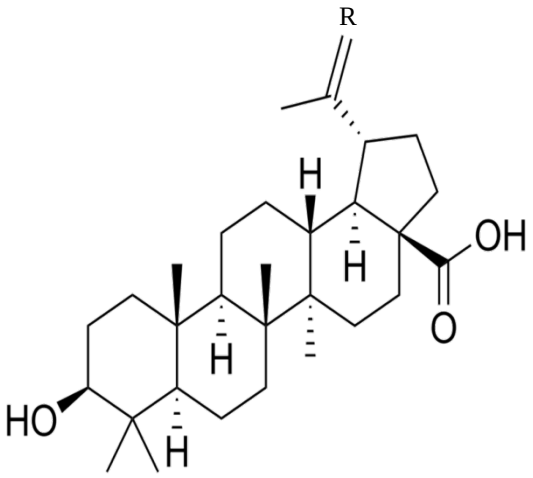
**Effective Dose*

Mode of action

Betulinic acid is a novel anticancer drug and induces apoptosis and hence differs from "classical" anticancer agents such as doxorubicin [8]. Betulinic acid is a prototype cytotoxic agent that triggers apoptosis by a direct effect on mitochondria [10].

In isolated mitochondria betulinic acid directly induces a loss of transmembrane potential independent of a benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone inhibitable caspase. This is inhibited by bongkrekic acid, an agent that stabilizes the PTPC (Permeability transition pore complex). Mitochondria undergo betulinic acid induced PT mediated cleavage of caspase-8 and caspase-3 in a cell-free system. Soluble factors such as cytochrome C or AIF (apoptosis-inducing factor) released from betulinic acid treated mitochondria are sufficient for cleavage of caspases and nuclear fragmentation. Addition of cytochrome C to cytosolic extracts results in the cleavage of caspase-3, but not of caspase-8. However, supernatants of mitochondria, which have undergone PT, as well as partially purified AIF, activate both caspase-8 and caspase-3 in cytosolic extracts and suffice to activate recombinant caspase-8. These finding show that the induction of mitochondrial PT alone insufficient to trigger the full apoptosis program and that betulinic acid may induce apoptosis via a direct effect on mitochondria [26] (**Fig 4(b)**).

Fig 4(a): C 20 modified Betulinic acid derivatives- Modified the C-20 alkene functional group of betulinic acid. The chemical modification at this position was initiated by converting the double bond to a ketone (15a) using a OsO4/NaIO4 system



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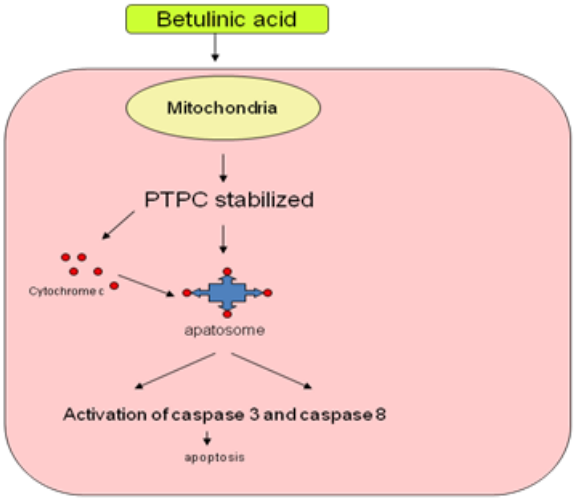
15a = O; 15b = NAO; 15c = NAOCH3

Fig 4(b): The mechanism of action of Betulinic acid in apoptosis of a tumor cell - Betulinic acid binds mitochondria and it induce the loss of transmembrane potential and permeability increases which results in release of cytochrome c, which binds to apatosomes and induces apoptosis.



Anti HIV activity

Betulinic acid has been shown to inhibit HIV (Human Immunodeficiency Virus)-1replication [7]. Based on its chemical structure, betulinic acid derivatives have been reported as inhibitors of HIV-1entry [16], HIV-protease [25]. Since a number of betulinic acid derivatives have been shown to inhibit HIV-1 at a very early stage of the viral life cycle, these compounds have the potential to become useful additions to current anti-HIV therapy, which relies primarily on combination of reverse transcriptase and protease inhibitors.

Antimicrobial Activity

Betulinic acid extracted from the bark of *Betula utilis* has antibacterial activity against some important human pathogenic bacteria like *Citrobacter* sp., *Escherichia coli* , *Klebsiella pneumoniae* ,*Pseudomonas aeruginosa, Proteus mirabilis, Salmonella typhi, Salmonella paratyphi, Salmonella paratyphi* B-*Salmonella typhimurium, Shigella boydii -Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Streptococcus faecalis and* it mostly affect the gram positive bacteria [14]. A dried stored sample of bark of Betula utilis (Bhojpatra) has been found to be active against *Aspergillus niger and Aspergillus flavus* [20].

Antioxidant activity

Betulinic acid extracted from the bark of *Betula utilis* is found to possess potent antioxidant activity [15]. Though *B. utilis* has free radical scavenging activity, it reduces free radicals which may stop the free radical initiation or retard free radical chain reaction in the propagation of the oxidation mechanism. It has to be evaluated for other pharmacological properties.

Anti-inflammatory Activity

It has been reported the ability of methanolic and water extract of *Betula utilis* reduce free radicals which may stop the free radical initiation or retard free radical chain reaction in the propagation of the oxidation mechanism. This indicates that the plants are more useful in the treatment of inflammation. During inhibition the activity of *Betula utilis* was found to be less in lipoxygenase enzyme. It may act on free radical to reduce the inflammation.

Lipoxygenases (LOX's) are sensitive to antioxidants, and the most of their action may consist in inhibition of lipid hydroperoxide formation due to scavenging of lipidoxy or lipidperoxy-radicals formed in course of enzymic peroxidation. This can limit the availability of lipid hydroperoxide substrate necessary for the catalytic cycle of LOX. [15].

CONCLUSION

Betula utilis is versatile medicinal plant which is a unique source of phytochemical compounds. The phytochemical constituent of *Betula utilis* is betulinic acid, shows many biological activities. Now it has been proved that it has tremendous anticancer properties. Thus this plant play a significant role in the prevention and treatment of cancer and various other diseases by having various pharmacological activities like antibacterial, anti-inflammatory, antioxidant and anti HIV activities and there is a need of further studies on this plant in order to reveal its other characteristic features hidden in it.

The review indicates the therapeutic potency of *B. utilis* used in traditional medicine. In addition it forms a good basis for selection of the plant for further phytochemical and pharmacological investigation.

REFERENCES

1. Batty, AK, and Rangswami S., Angiosperm dicotyledonae: Crystalline chemical components of some vegetable drugs, Photochemistry. 1973; 12, 214.
2. Bean, W**.** Trees and Shrubs Hardy in Great Britain. Vol 1 – 4, 1981.
3. Bhattacharyya, A., Shah, S.K., Chaudhary, V. Would tree ring data of *Betula utilis* is potential for the analysis of Himalayan glacial fluctuations? Current Science 2006; 91: 754–761.

4. Dikshit. A., Shahi, S.K., Pandey, K.P., Patra, M., Shukla, A.C. Aromatic plants a source of natural chemotherapeutants. National Academy Sciences Letters 2004; 27 (5, 6), 145-164.
5. Ehrhardt, H., Fulda, S., Fuhrer, M., Debatin, K.M., Jeremias, I. Betulinic acid-induced apoptosis in leukemia cells. Leukemia 2004; 18, 1406–1412.
6. Fisher, D.E. Apoptosis in cancer therapy: crossing the threshold. Cell 78, 539–542.*fruticosa* kurz. flower (lythraceae). Brazilian Journal of Microbiology 1994; 38: 204-207.
7. Fujoka, T.; Kashiwada, Y.; Kilkushi, R.E.; Consentino, L.M.; Ballas, L.M.; Jiang, J.B.; Janzen, W.P.; Chen, I.S.; Lee, K.H. Current Developments in the Discovery and Design of New Drug Candidates from Plant Natural Product Leads Prod. Journal of Natural Products 1994; 57, 243.
8. Fulda, S., Friesen, C., Los, M., Scaffidi, C., Mier, W., Benedict, M., Nunez, G., Krammer, P.H., Peter, M.E., Debatin, K.M. Betulinic acid triggers CD95 (APO-1/Fas)-and p53-independent apoptosis via activation of caspases in neuroectodermal tumors. Cancer Research 1997; 57, 4956–4964.
9. Fulda, S., Jeremias, I., Steiner, H.H., Pietsch, T., Debatin, K.M. Betulinic acid a new cytotoxic agent against malignant brain-tumor cells. International Journal of Cancer 1999; 82, 435–441.
10. Fulda, S., Scaffidi, C., Susin, S.A., Krammer, P.H., Kroemer, G., Peter, M.E., and Debatin, K.M. Activation of mitochondria and release of mitochondrial apoptogenic factors by betulinic acid. Journal of Biological Chemistry 1998; 273, 33942-33948.
11. Fulda, S.; Jeremias, I.; Pietsh, T.; Debatin, K.M. Klin. Sensitization for Anticancer Drug-Induced Apoptosis by Betulinic Acid. Padiatr 2009; 211, 319.
12. Kim, J.Y.; Koo, H.M.; Kim, D.S.H.L. Advances in the study of structural modifications and biological activities of betulinic acids. Bioorganic & Medicinal Chemistry Letters 2001; 11, 2405.
13. Kroemer, G., Zamzami, N., Susin, S.A. Mitochondrial control of apoptosis. Immunology Today 1997; 18, 44- 51.
14. Kumaraswamy, M., Kavitha, H., Satish, S. Antibacterial evalution and phytochemical analysis of B.utilis against some Human Pathogenic Bacteria.Advance in Biological Research 2008; 2:21-25.
15. Kumaraswamy, M. V., and Satish S.,. Free radical scavenging activity and lipoxygenase inhibition of *Woodfordia fructicosa* Kurz and *Betula utilis* Wall. African Journal of Biotechnology 2008; 7 (12), 2013-2016.
16. Mayaux, J.F.; Bousseau, A.; Pauwels, R.; Huet, T.; Henin, Y.;Dereu, N.; Evers, M.; Soler, F.; Poujado, C.; De Clercq, E.; Le Pecq, J.B. *Proc.* Activation and inhibition of proteasomes by betulinic acid and its derivatives. National Academy Sciences 1994, 91, 3564.
17. Mukherjee A.K., Basu S., Sarkar N., Ghosh A.C. Advances in Cancer Therapy with Plant Based Natural Products. Current Medicinal Chemistry 2001; 8 (20), 1467-1486.
18. Parekh, J. and Chanda S. *In vitro* antibacterial activity of the crude methanol extract of Woodfordia. Pharmacognosy Magazine. 2007, 2(3), 61-94.
19. Pisha, E., Chai, H., Lee, IS., Chagwedera, TE., Farnsworth, NR., Cordell, GA., Beecher, CW., Fong, HH., Kinghorn, AD., Brown, DM. Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis. Natural Medicine 1995; 1, 1046–1051.
20. Sareen, an Ahirwar, R Gautam, a Bhadauria R, Fungal Contamination of Some Common Medicinal Plant Samples of Himachal Pradesh. Sci. & Cult. 2010; 76 (3–4) 118-120.
21. Selvam, A.B.D. Inventory of Vegetable Crude Drug samples housed in Botanical Survey of India Howrah. Pharmacognosy magazine 2008; 2 (3), 61-94.
22. Setzer, E., Pimental, E., Wacheck, V., Schlegal, W.,Pehamberger, H., Jansen, B., Kodym R., Effects of betulinic acid alone and in combination with irradiation in human melanoma cells, , Journal of investigative dermatology 2000; 114, 935.
23. The wealth of India. A dictionary of Indian raw material and industrial product. Cancer Research 1985; 1(AB), 185.
24. Thurnher, D., Turhani, D., Pelzmann, M., Wannemacher, B., Knerer, B., Formanek, M., Wacheck, V., Selzer, E. Betulinic acid a new cytotoxic compound against

malignant head and neck cancer cells. Head Neck 2003; 25, 732–740.
25. Xu, H.X.; Zeng, F.Q.; Wan, M.; Sim, K.Y. Anti-HIV triterpene acids from Geum japonicum. Journal of Natural Products, 1996, 59, 643.
26. Yogeeswari, P., Sriram, D. Betulinic acid and its derivative. A review on their biological properties. Current medicinal chemistry 2005; 12, 657-666.
27. Zuco, V., Supino. R., Righetti, C., Cleris, L., Marchesi, E., Gambacorti C., Formelli, F. Selective cytotoxicity of betulinic acid on tumor cell lines, but not on normal cells. Cancer Letters 2002; 175, 17–25.