

Betulin a pentacyclic tri-terpenoid: an hour to rethink the compound

Abstract

Betulin a pentacyclic triterpenoid member of lupane family occurs widely in numerous plants. Betulin, unlike most other constituents is easily isolated that it can be utilized for various pharmacological actions. It is interesting to know that betulin can be easily extracted from bark, stem, leaves, flower, roots etc. of plant. This review summarizes plethora of reliable pharmacological activities like anti-inflammatory, anti-ulcer, anti-diabetic, anti-bacterial, anti-microbial, anti-malarial, anti-viral, anti hyperlipidaemic, anti-cancer and anti HIV exhibited by betulin and its derivatives. For this it can be utilized in herbal as well as synthetic pharmaceutical industries because of its promising efficacy and low levels of toxicity. Although betulin possess a wide range of pharmacological activities, there is still lack of awareness of its proper utilization in the field of medicine. So, need of the hour is to refocus on naturally occurring betulin and its derivatives to avoid side effects caused by synthetic compounds utilized in treating various ailments. Therefore, the aim of the present review is to re-explore the potential of betulin, as an alternative to the compounds possessing higher side effects.

Keywords: betulin, pentacyclic triterpenoid, betulinic acid, lupine, pharmacological activities

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Introduction

Mother earth, a bionetwork enriched with plethora of remarkable plants holding numerous beneficial chemical compounds, which play an integral role in maintaining the lives stealth and safe. Betulin lup20 (29)-ene-3 β , 28-diol, a pentacyclitriterpene alcohol with a lupane skeleton is one of such chemical compounds contributing towards the advancement in field of medicine.¹⁻³ It is obtained from outer bark of Birch trees.⁴⁻⁶ As described in Figure 1: Betulin has a pentacyclic ring structure and hydroxyl groups in positions C₃ and C₂₈.⁷⁻⁹ Betulin in presence of acid agents undergoes rearrangement to form allobetulin.¹⁰ It is acknowledged that plants with lupine series are helpful in curing various diseases for this one relies on betulin which on conversion to betulinic acid, the alcohol group replaced by a carboxylic acid group has more biological activity.^{2,7,10,11} The alcohol group cannot join with stationary phase because two groups are located on opposite sides of compound.¹ Betulinic acid, the more bioactive compound exhibits choleric, antihelminthic, powerful prophylactic, anti-HIV, antimutagenic, antiviral, anti-fungal, anti-leukemia, anti-leishmanial, anti-inflammatory, immunomodulator.^{7,12-15}

Adding on it acts as anti-parasitic against *Plasmodium falciparum* and *Trypanosoma brucei rhodesiense*, anti-microbial, anti-obesity by improving the lipid profile, also stabilizes atherosclerotic plaques.^{15,16-20} Betulin is also used as plaster for sterilization of wounds, acts as liver protectant in chronic hepatitis therapy, antirachitic, antitrypanosomal also supports apoptosis i.e. self-destruction of tumor cells.^{2,7,21,22} As betulin is found in various other plants so people of vernacular regions take numerous benefits depending on the necessity. Infusion of red alder is used in lymphatic disorders and tuberculosis. Native Americans use it to mediate insect bites, poison oak, digestive tract infections and skin inflammation.²³⁻²⁶ Rather than possessing pharmacological activities, due to elegant bark of Birch trees they are considered

choice of trees for landscape too. The substantial Birch trees grows well in all soils due to which they are used as screen or window break. Moreover, due to hard bark they are also used in carpentry and aquatic industry. It is also used in cosmetic products. The birch bark extract may be used in hair conditioners and shampoos.²⁷⁻²⁹

Physical properties of betulin

Standard betulin has weak water solubility, thus it requires modification for better cellular uptake and desired activity however its derivatives like betulin diacetate (BDA) and betulin dipropionate (BDP) possess greater water solubility as compared to betulin.^{32,33} Therefore, betulin still remains relevant in synthesizing compounds with higher solubility pattern that are considered more biologically active (Table 1) (Figure 1).³⁴

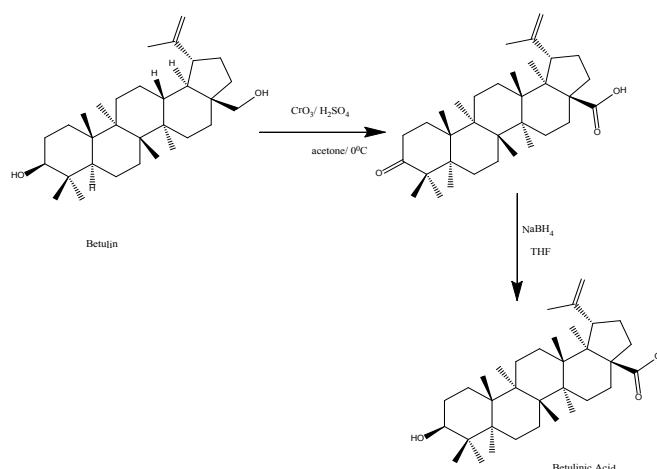


Figure 1 Represents the preparation of betulinic acid from betulin.⁷⁻¹¹

Table 1 Represents the physical properties of betulin.^{1,30,31}

1	Chemical formula	C ₃₀ H ₅₀ O ₂
2	Synonyms	Betulin, Betulinol, lup-20(29)-en-3 alpha, 28,30-triol, lup-20(29)-ene3alpha,28-diol
3	Appearance	White, crystalline powder
4	Molar mass	442.7 g/mol
5	Melting point	256–257°C (lit.)
6	Solubility	Alcohol, chloroform, benzene
7	Heat capacity	80–350K

Occurrence of betulin in nature

Betulin has long been explored by research scientist because of

Table 2 List of plants possessing betulin

S. no	Name of plant	Family of plant	Part of plant	Reference
1	<i>Betula pumila</i>	Betulaceae	Bark	47
2	<i>Betula pendula</i> (silver birch)	Betulaceae	Bark	35,47–51
3	<i>Betula jacquemontii</i>	Betulaceae	Bark	47
4	<i>Betula pubescens</i>	Betulaceae	Bark	29,47
5	<i>Betula platphylla</i>	Betulaceae	Bark	29,47
6	<i>Betula papyrifera</i> (paper birch)	Betulaceae	Bark	12,30,47,52
7	<i>Betula nana</i>	Betulaceae	Bark	47,53
8	<i>Betula nigra</i>	Betulaceae	Bark	47
9	<i>Betula lente</i>	Betulaceae	Bark	47,54
10	<i>Betula alba</i>	Betulaceae	Bark	29,49
11	<i>Betula occidentalis</i>	Betulaceae	Bark	55
12	<i>Platanus acerifolia</i>	Platanaceae	Bark	56
13	<i>Sambucus nigra</i>	Adoxaceae	Bark	57
14	<i>Olea europeae</i>	Oleaceae	Bark	58
15	<i>Aldus subcordata</i>	Betulaceae	Bark	59,60
16	<i>Ziziphus jujube</i>	Rhamnaceae	Bark	59,61
15	<i>Atractylis liscarduus</i>	Asteraceae	Aerial parts of plant	59,62
16	<i>Platanus hypbrida</i>	Platanaceae	Bark	59,63,64
17	<i>Platanus hyspanica</i>	Platanaceae	Bark	48
18	<i>Nerium oleander</i>	Apocynaceae	Leaves	8
19	<i>Dillenia indica</i>	Dilleniaceae	Stem bark	2,12
20	<i>Tectona grandis</i>	Verbenaceae	Stem bark	2
21	<i>Alangium salvifolium</i>	Cornaceae	Seeds	65–67
22	<i>Alstonia scholaris</i>	Apocynaceae	Stem bark	68
23	<i>Cornus macrophylla</i>	Cornaceae	Stem bark	66–69
24	<i>Plumeria obtusa</i>	Apocynaceae	Leaves	70–72

the fact that it has anticancer properties^{35,36} and its derivative Betulinic acid is favored due to its anti-HIV activity.^{12,6,37} As mentioned in Figure 1: betulin has three most prominent positions where chemical modifications can be easily accomplished, namely primary hydroxyl group at position C–28, secondary hydroxyl group at position C–3, and alkene moiety at position C–20. The bio-chemical modifications at positions C–28 of the parent structure of betulin produces betulinic acid.^{12,27,38–41} The chief source of Betulin is bark of Birch trees, belonging to family Betulaceae the family of flowering plants. Mostly placed in order Fagales, it can also be placed in order Betulales. The sub-families include Betuloideae genera *Betula* (birch), *Alnus* (alder) and Coryloideae genera *Carpinus* (hornbeam), *Corylus* (hazel), *Ostrya* and *Ostryopsis*.^{42–44} Betulin, a pentacyclitriterpenoid is derived from linear hydrocarbon squalene.³¹ Triterpenes have three main classes oleane, ursane and lupane triterpenes. Lupane family comprises betulin, betulinic acid, lupeol.^{6,45} Triterpenes are used as traditional herbal medicine and the esters of betulin and fatty acids are used in the production of cosmetics and as plasticizers for PVC (Table 2).^{31,46}

Table Continued...

S. no	Name of plant	Family of plant	Part of plant	Reference
25	<i>Astercantha longifolia</i>	Acanthaceae	Aerial parts of plant	73
26	<i>Aerva lanata</i>	Amaranthaceae	Flower, leaf	74
27	<i>Quercus suber</i>	Fagaceae	Bark	75,76
28	<i>Acacia mellifera</i>	Fabaceae	Bark	77
29	<i>Celtis philippinensis</i>	Cannabaceae	Twigs	78,79
30	<i>Coccoloba acrostichoides</i>	Polygonaceae	Aerial parts	80,81
31	<i>Anemone raddeana</i>	Ranunculaceae	Roots	82,83
32	<i>Diospyros leucomelas</i>	Ebenaceae	Leaves	29,84
33	<i>Ziziphus vulgaris</i>	Rhamnaceae	Seeds	29,84
34	<i>Trochodendron aralioides</i>	Trochodendraceae	Bark	29,84
35	<i>Torenia concolor</i>	Scrophulariaceae	Flower	85–87
36	<i>Belamcanda chinensis</i>	Iridaceae	Root	88
37	<i>Chaenomeles sinensis</i>	Rosaceae	Fruit	89,90
38	<i>Cyrtomium fortunei</i>	Dryopteridaceae	Rhizomes	91

Pharmacological studies

Betulin, as we all known till now possess vast pharmacological properties including choleric, antihelminthic, powerful prophylactic, anti-HIV, antimutagenic agent, antiviral, anti-fungal, anti-leukemia, anti-leishmanial, anti-inflammatory, immunomodulator activities. The latest research suggests some of the major pharmacological properties as discussed below.

Anti-inflammatory and Anti-ulcer activity

Inflammation is a physiological process which involves pain as a secondary process and its hallmarks include swelling, redness, pain and fever.⁹² Bernard et al.⁹³ determined that Betulin and betulonic acid were found to inhibit phospholipase A2 activity at 5M concentrations by 30% and 40% respectively.⁹³ It has also been demonstrated to exhibit inhibitory effects on nitric oxide (NO) and prostaglandin E2 production in mouse macrophages.⁹⁴ According to the latest research done by Singh et al.² stem bark extract of *Dillenia indica* f. *elongata* (Miq.) Miq. showed significant (P<0.01) anti-inflammatory activity in formalin and carrageenan induced inflammation models.¹² Moreover, Betulonic acid exhibited antiulcer action exceeding that of Venter preparation for the models of affection of mucous coat of stomach in rats caused by indomethacin and aspirin with the dose of 50mg/kg.⁹⁵

Anti-diabetic

Diabetes is a metabolic disorder associated with abnormalities in insulin production or secretion along with modifications in carbohydrate, fat and protein metabolism.^{96,97} In accordance to, Riya et al.,⁷⁴ determined the presence of betulin, alpha amyryl and beta sitosterol in flower, leaf and roots of *Aerva lanata*.^{7,98} However, there are reports that betulin is useful in treatment of diabetes.^{99,100} As 70% ethanolic extract (ALE) for 21 days in STZ-induced diabetic rat demonstrated that ALE was successful in refining postprandial hyperglycemia in sucrose-loaded normal and STZ diabetic rats, through its promising alpha glucosidase inhibitory potential.^{101,102} Agarwal et al.¹⁰¹ reported that the alkaloid-enriched fraction of root of *Aervalanata* possesses anti-hyperglycemic potential in streptozotocin-nicotinamide-induced type II diabetic rats.¹⁰³

Anti-bacterial and anti-microbial activity

Bacterial infections alone are the cause of around two million deaths globally and it is found that bacterial pathogens probably infect more than one-third of the population around the world.¹⁰⁴

In accordance to Valterová et al.,¹⁰³ the antibacterial activity of C-3 substituted derivatives of betulin with respect to a number of bacteria (*Staphylococcus aureus*, *Staphylococcus faecalis* and *Staphylococcus beta haemolyticus*) was depicted.¹⁰⁵ Furthermore, Hess et al.,¹⁰⁴ concluded that Betulinic acid has been found to be inactive against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Micrococcus luteus*.¹⁰⁶

Antimicrobial activity of betulin and its derivatives have been reported against *Streptococcus pyogenes* with a minimum inhibitory concentration (MIC) of 85µg/mL, and considerable activity has also been observed against other bacteria, i.e. *Escherichia coli*, *Staphylococcus aureus* and *Enterococcus faecalis*.^{107,108}

Anti-malarial activity

Betulin, betulonic acid, ursolic acid and oleanolic acid have also been tested for monitoring antimalarial activity against chloroquine sensitive (T9-96 strain) and resistant (K1 strain) *Plasmodium falciparum*. It was concluded that betulin was inactive, whereas the others showed moderate activity, betulonic acid being most active in vitro against both strains of *P. falciparum* at IC50 values 19.6g/mL (K1) and 25.9g/mL (T9-96) respectively.¹⁰⁹ But, in vivo experiments with the NK65 (*P. Berghei*) model of malaria revealed that betulonic acid turned out to be inactive and even toxic at the dose of 250mg/kg per day.¹¹⁰

Anti-viral activity

According to Karachurina et al.,¹⁰⁹ Betulinbismethylphthalate and betulin dinicotinate stimulate the production of antibody-forming cells in mouse spleen 1.3 and 1.8 times more actively in comparison with the reference.¹¹¹ Adding on, the indicated compounds prevent death of animals from acute radiation sickness. However, Kanamoto et al.¹¹⁰ and Baltina et al.¹¹¹ studied anti-viral activity of betulin, betulonic acid

and its derivatives against influenza A, herpes simplex type 1 (HSV-1), influenza FPV/Rostock and ECHO-6 enterovirus. Betulin and betulinic acid were inactive against influenza FPV/Rostock virus on the other hand betulonic acid 3 showed a weak antiviral activity.^{112,113}

Anti-hyperlipidaemic activity

Tang et al.¹⁶ identified a small-molecule inhibitor of SREBP, betulin, by compound screening. Where SREBP is a major transcription factor that controls the biosynthesis of cholesterol, fatty acid, and triglyceride.¹¹⁴ Betulin inhibits SREBP by binding SCAP and making the interaction between SCAP and Insig easier, which leads to the ER-retention of SREBP. Betulin down regulates the genes in cholesterol and fatty acid biosynthesis and decreases the content of cellular lipids, enhances insulin sensitivity, and reduces the development of atherosclerotic plaques.¹⁶

Anti-cancer activities

According to the latest research done by Bębenek et al.¹¹⁴ Betulin and its semisynthetic derivatives possesses cytotoxic activity toward various cancer cell lines. Experimentation for the antiproliferative activity in vitro against T47D breast cancer, CCRF/CEM leukemia, HL-60 promyelocytic leukemia, SW707 colorectal, murine P388 leukemia, as well as BALB3T3 normal fibroblasts cell lines was done by using betulin and its derivatives. It was discovered that that the derivative of betulin with a propynoyl group at C-28 position, has strong cytotoxic effects against human leukemia (CCRF/CEM) and murine leukemia (P388) cancer cells.¹¹⁵

Anti-HIV activities

Hashimoto et al.¹¹⁵ researched that betulin and 3, 28-diacetylbetulin are inactive as anti-HIV agents which confirm the importance of the presence of carboxylic group at C-28.¹¹⁶ However, betulinic acid and its derivatives have been discovered as a new class of compounds that seem to act as immunomodulator and protect the cells *in vitro* from attack by the HIV virus.¹¹⁷ Furthermore, synthetic betulinic acid derivatives, especially 3-alkylamido-3-deoxy-betulinic acid derivatives, inhibit the life cycle of the virus in the infected cells in its early phase hence; defend the surrounding cells from HIV proliferation.¹¹⁸ Also, one must take into consideration that anti-HIV activity increases in amides and peptides of betulinic and betulonic acids.^{119,120}

Conclusion

It is commendable that betulin is found in 200 different types of plants indefinitely distributed across the plantae kingdom and owes to diverse pharmacological activities. But despite of its easy and free availability in nature, betulin and its derivatives are still not empathized in pharmaceutical industries. The good side of picture is that the isolation of betulin is not a tough job and need not require complex analytical techniques. The tool of biotechnology can further be applied to gain maximum pharmaceutical advantages of betulin. Due to the fact that it is a compound obtained from plant source and possess vast significant pharmacological properties it can be utilized in herbal pharmaceutical industries with a new concept of nano-medicine. Having minimal side effects gives betulin an edge over other compounds and plant extracts containing betulin are also of equal importance for possessing signified efficacy resulting in decreased level of toxicity. At last, it seems that betulin requires our

re-attention so that with the help of growing analytical techniques we can produce its new derivatives which could be a boon to society for treating various ailments.

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Conflict of interest

The author declares no conflict of interest.

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