



Pharmacological Activity of Betulinic Acid: A Systematic Literature Review

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ARTICLE INFO

Keywords:

Activity
Betulinic acid
Neurological disorders
Pharmacology

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All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/ehi.v4i4.94>

ABSTRACT

Betulinic acid comes from betulin, a triterpenoid compound that naturally occurs in the bark of the Betula tree. Betulin has a pentacyclic chemical structure, which contains five distinct rings. Betulinic acid is the carboxylic acid form of betulin, meaning it has a carboxyl group (-COOH), which gives this compound its acidic nature. This study is a literature review. Data obtained from journal analysis in the form of qualitative and quantitative data. In this review article, the authors have explored in depth the promising pharmacological activities of betulinic acid. The studies that have been carried out consistently prove the potency of this compound in various therapeutic and pharmacological aspects. Research has also identified the ability of this compound to modulate biochemical pathways relevant to the nervous system, providing new hope in the treatment of complex neurological disorders.

1. Introduction

Betulinic acid is a naturally occurring compound found in the bark of the birch bark and several other plants. These compounds have attracted the attention of researchers in the field of pharmacology due to their diverse potential biological activities. Betulinic acid belongs to the category of triterpenoid compounds, which are often identified in various plants and are known to have a variety of interesting pharmacological effects. Betulinic acid is a secondary metabolite compound found in several plant species, such as clove stems, red shoots, and red turi flowers. These compounds have various health benefits, such as anti-diarrheal and antispasmodic activities, and can help kill cancer cells and inhibit their spread. Betulinic acid comes from Betulin, a triterpenoid compound that naturally occurs in the bark of the Betula tree. Betulin has a pentacyclic chemical structure, which contains

five distinct rings. Betulinic acid is the carboxylic acid form of betulin, meaning it has a carboxyl group (-COOH), which gives this compound its acidic nature. Preliminary research indicates that betulinic acid has a number of potential biological activities. Several preclinical studies have shown that betulinic acid may have anti-inflammatory effects by inhibiting the inflammatory response in the body. This could have implications in the treatment of chronic inflammatory diseases. Betulinic acid has shown potential as an antitumor agent in laboratory studies. These compounds can affect biochemical pathways in cancer cells that inhibit tumor growth and development. Some early studies also indicated the ability of betulinic acid to inhibit the replication of certain viruses, such as the herpes virus and HIV.¹⁻⁷

Although it is still in the early research stage, the potential pharmacological activity of betulinic acid has

prompted further research into its clinical applications. Much research is still focused on a deeper understanding of the mechanisms of action, biochemical actions, and potential side effects or interactions with other drugs. However, it is important to note that despite these interesting biological activities, there is still a lot of work to be done before betulinic acid can be considered an effective and safe therapeutic agent. More preclinical and clinical research is needed to fully understand the potential and risks of using betulinic acid in human medicine. In this review article, the authors will present a thorough overview of the pharmacological activity of betulinic acid. The authors will summarize the results of recent research that has helped deepen our understanding of this compound, including *in vitro* and *in vivo* studies involving preclinical trials and clinical trials. In addition, the authors will also review the potential benefits and limitations of using betulinic acid in a therapeutic context. It is hoped that this review will provide valuable insights for scientists and medical practitioners interested in exploring the pharmacological potential of these compounds.⁸⁻¹⁶ With the development of knowledge and technology in the pharmaceutical and biomedical fields, our understanding of betulinic acid and its application in pharmacological therapy will continue to grow.

2. Methods

The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the potency of the pharmacology activity of betulinic acid. The search was performed using the terms: (1) "pharmacology activity" OR "activity" OR "betulinic acid" AND (2) "medicinal uses". The literature is limited to preclinical studies and published in English. The literature selection criteria are articles published in the form of original articles, an experimental study about the pharmacology activity of betulinic acid, the control group only received liquid without therapeutic effect or no

treatment, studies were conducted in a timeframe from 2013-2023, and the main outcome was potency of pharmacology activity of betulinic acid. Meanwhile, the exclusion criteria were animal models that were not related to the potency of the pharmacology activity of betulinic acid, the absence of a control group, and the duplication of publications. This study follows the preferred reporting items for systematic reviews and meta-analysis (PRISMA) recommendations.

3. Results and Discussion

Here are the results of the study that has been reviewed regarding betulinic acid pharmacological activity, namely (Table 1). Betulinic acid is a naturally occurring compound found in the bark of the birch bark and several other plants. This compound has a unique chemical structure and has attracted the attention of researchers in the field of pharmacology. Betulinic acid has strong anti-inflammatory activity. These compounds can inhibit the production of pro-inflammatory cytokines and other inflammatory mediators, thereby reducing inflammation. Betulinic acid also has significant antioxidant activity. These compounds can protect cells from oxidative damage and prevent oxidative stress. Betulinic acid has the potential to be an antitumor agent. These compounds can inhibit the growth of cancer cells and trigger apoptosis in cancer cells. Betulinic acid compounds have potential as therapeutic agents in the treatment of several diseases. Betulinic acid is a natural compound found in the Basidiomycota fungus. This compound has a unique chemical structure and has promising pharmacological activities. Several studies have been conducted to evaluate the pharmacological activity of betulinic acid. One study showed that this compound has strong anti-inflammatory activity. Betulinic acid can inhibit the production of proinflammatory cytokines and other inflammatory mediators, thereby reducing inflammation. Besides that, Betulinic acid also has significant antioxidant activity. These compounds can protect cells from oxidative damage and prevent oxidative stress.¹⁷⁻²⁵

Table 1. Pharmacological activity of betulinic acid.

No.	Reference	Article title	Compound content	Benefits
1.	Sulasmi Anggo, et al., (2023)	Inventory of Basidiomycota fungi in the Batu Tikar Forest, Luwuk District, Banggai Regency	Anti-inflammatory	Reduces inflammation
2.	Ani Fuziyanti, et al., (2022)	Records of the variety of Basidiomycota fungi in the Cilegon Jogging Track Area, Banten	Antioxidant activity	Protects cells from oxidative damage and prevents oxidative stress
3.	José Fernando Oliveira-Costa, et al., (2022)	Anti-inflammatory activities of betulinic acid	Versatile molecule	Modulate several types of immune cells
4.	Huimin et al., (2019)	Protective effect of betulinic acid on Freund's complete adjuvant-induced arthritis in rats	Adjuvant-induced arthritis	Improve joint pathology, reduce toe swelling, improve blood rheology, decrease synovial cell apoptosis, and normalize inflammatory cytokine production.
5.	Kim et al. (2016)	Antioxidant and anti-inflammatory activity of betulinic acid isolated from the fruiting body of <i>batllus edulis</i>	Induction of HO-1 enzyme activity	Decreased production of proinflammatory molecules,
6.	Meira et al., (2017)	Betulinic acid BA5 derivative, dual NF-kB/calcineurin inhibitor, reduces experimental shock and delayed hypersensitivity	Inhibition of lymphoproliferation	Reduce the production of proinflammatory cytokines
7.	Hanghang Lou, et al., (2021)	A review on preparation of betulinic acid and its biological activities	Low biological activity and toxicity	Experimental antitumor drug
8.	Chiedozie O. Egbubine, (2020)	Isolation and characterization of betulinic acid from the stem bark of <i>Feretia canthioides</i> Hiern and its antimalarial potential	Isolated from methanol extract	Malaria treatment
9.	Anna Hordyjewska, (2019)	Betulin and betulinic acid: triterpenoids derivatives with a powerful biological potential	Triterpenoid, talidomid	Cancer treatment
10.	Ermi Abryani, et al. (2023)	Jamblang plant activity (<i>Syzygium cumini</i> L.) Using Uv-visible spectrophotometry method: A literature review article	Flavonoid	Anti-cancer

Several studies have also shown that betulinic acid can increase the activity of antioxidant enzymes such as superoxide dismutase and catalase. In addition to anti-inflammatory and antioxidant activities, betulinic acid also has potential as an antitumor agent. Several studies have shown that this compound can inhibit the growth of cancer cells and trigger apoptosis in cancer cells. Overall, the Pharmacological Activity of betulinic acid indicates that the compound betulinic

acid has a promising pharmacological activity. However, further research is still needed to evaluate the potential of this compound as a therapeutic agent in the treatment of certain diseases. Another study studied the pharmacological activity of BA in an adjuvant-induced arthritis model in mice, showing that this compound has a protective effect. BA treatment reduces arthritis indices, improves joint pathology, reduces toe swelling, improves blood

rheology, reduces synovial cell apoptosis, and normalizes inflammatory cytokine production, also acting through modulation of the ROCK/NF- κ B pathway. Betulinic acid has a wide range of biological activities and low toxicity, and it is a very valuable natural product. Recent studies have shown that betulinic acid has many biological activities, such as antitumor, anti-HIV, anti-inflammatory, antibacterial, antimalarial effects, and so on. Particularly, betulinic acid shows strong activity in the antitumor aspect. Accordingly, betulinic Acid has attracted widespread attention and appears to be a promising experimental antitumor drug. The antimalarial activity of the compound (Betulinic acid) isolated from the methanol extract of this plant has proven its potential in the treatment of malaria. The fact that the stem bark of *Feretia canthioides* Hiern exhibited some degree of antimalarial activity when screened in vitro for antimalarial activity in this study justifies its ethnopharmacological use for traditional malaria treatment. Although modern cancer treatment systems are still being improved, the mortality rate among oncological patients remains high, and the agents lack selectivity to malignant cells, leaving the cells unaffected. Therefore, the anti-tumor properties displayed by BE and betulinic acid seem to be of hope and promise for the future of oncology therapy. Moreover, the ubiquity of BE and its derivatives in the natural environment, their high therapeutic potential, and the beneficial results of research make future use of these substances in medicinal practice very likely.²⁶⁻

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4. Conclusion

The studies that have been carried out consistently prove the potency of this compound in various therapeutic and pharmacological aspects. The results of in vitro studies have revealed the strong antioxidant properties of betulinic acid, which may provide protection against oxidative stress involved in various degenerative diseases. Research has also identified the ability of this compound to modulate biochemical pathways relevant to the nervous system, providing

new hope in the treatment of complex neurological disorders.

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