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An overview of betulin: botanical source, derivatives and biological potential: Mini Review

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KEYWORDS

Betulin

Botanical Sources

Derivatives

Biological activities

Triterpenoid

ABSTRACT

This review aims to provide insight into and summarize the potential of betulin and its derivatives as important pharmaceutical molecules, including their underlying mechanisms of action. This investigation compiles comprehensive scientific data regarding betulin as a botanical raw material for industrial and pharmaceutical applications. Betulin, a natural pentacyclic lupane-triterpenoid, exhibits diverse biological activities, addressing metabolic dysfunctions, infectious diseases, cardiovascular disorders, and carcinogenic activity. The extraction of betulin from natural sources, mainly birch bark, is relatively simple and cost-effective, making it an attractive compound for the pharmaceutical and cosmetic industries. This study lists 93 plant sources of betulin and explores its repurposing as an effective therapeutic agent. It highlights its potential as an antiviral, anti-inflammatory, anticancer, and hepatoprotective compound, emphasizing the benefits of derivatizing betulin with various groups or moieties, such as imidazole carboxylic ester, hemisuccinate, hemiphthalate, nicotinate, acetylbetulin-28-o-triphenylphosphonium, succinyl, and 3-substituted glutaryl. The information gathered comes from various sources, including plant databases, Google Scholar, PubMed, ethnobotanical references, and classical texts.

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1 Introduction

Betulin is a natural compound with the systematic name 3β, 28-dihydroxy-20(29)-lupen or lup-20(29)-en-3β, 28-diol. Its molecular formula is $C_{30}H_{50}O_2$, with a molecular weight of 442.728 g/mol (Alakurtti et al. 2006). Betulin is primarily isolated from various species in the families Betulaceae, Platanaceae, Dilleniaceae, Rhamnaceae, Rosaceae, and Fagaceae, particularly from the bark of different species of Betulaceae (Cichewicz and Kouzi 2004; Ghaffari et al. 2012). The structure of betulin is based on a complex polycyclic system characterized by a cyclopentane-perhydrophenanthrene (sterane) core, which comprises four cyclohexane rings and one saturated cyclopentane ring condensed together. The carbon atoms in this structure are designated by the letters A, B, C, D, and E, following the recognized numbering system for carbon skeletons (Takibayeva et al. 2023). Notably, the α-isopropenyl group at the C-19 carbon atom and a five-membered ring E are distinctive features of betulin (Kislitsyn 1994; Krasutsky 2006; Bergelin and Holmbom 2008).

Betulin has a pentacyclic ring structure with hydroxyl groups at positions C_3 and C_{28} (Figure 1). An alkene moiety is also present at carbon 20. The hydroxyl and alkene groups serve as binding sites for simple modifications, while the pentacyclic lupane skeleton contributes to the lipophilicity of betulin, leading to poor water solubility. Betulin is separated from birch bark using sublimation or solvent extraction methods, and its concentration in the extract may vary depending on the birch species and the tree's location. Although betulin can be found in other plant sources, it is abundantly derived from Betula species (Hayek et al. 1989; Tolstikov et al. 2005; Adepoju et al. 2023). The chemical structure and betulin's physical and chemical properties are discussed in detail in several studies (Akihisa et al. 2002; Fulda 2008; Lesellier et al. 2012; Uryash et al. 2014; Amiri et al. 2020). The primary objective of this review is to highlight the potential of betulin and its derivatives as effective therapeutics for various biological activities through the derivatization of groups or moieties at the molecule's C_3 and C_{28} positions.

2 Sources of literature

The information published on Betulin was gathered from various sources, including Google, Web of Science, Elsevier, PubMed, Google Scholar, and Semantic Scholar. The search terms used for this review included "Betulin," "Introduction to Betulin," "structure-activity relationship (SAR) of Betulin," "sources of Betulin," "derivatives of Betulin," and "pharmacological activities of Betulin." The search was conducted in all available languages. The chemical structures of the compounds were drawn using ChemDraw 15.0 software.

3 Botanical sources of betulin

Betulin is extracted from various plant sources. Table 1 lists the different plant sources, their families, the specific plant parts utilized, and their reported percent yields.

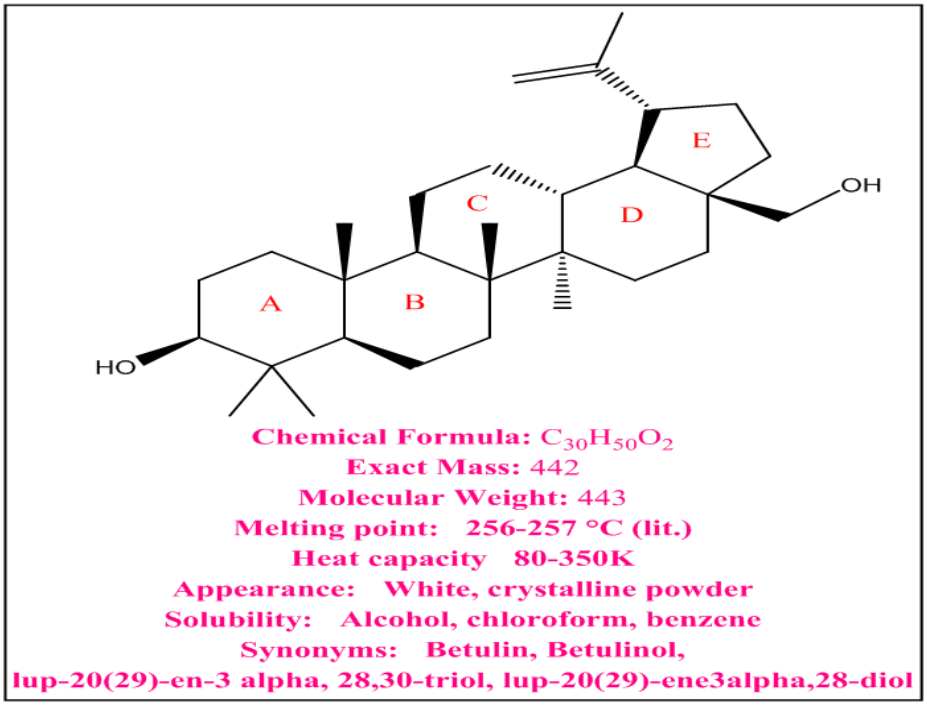


Figure 1 Structure of Betulin with their Chemical and Physical Properties

Table 1 Botanical sources of betulin with its % yield

S.No	Name of Plant	Family	Plant part	% yield	Reference
1	*Betula pumila*	Betulaceae	Bark	18.2% to 22.7%	Rastogi et al. 2015
2	*B. pendula*	Betulaceae	Bark	16-22%	Rastogi et al. 2015
3	*B. jacquemontii*	Betulaceae	Bark	-	Zhang et al. 2023
4	*B. pubescens*	Betulaceae	Bark	95-98%	Abyshev et al. 2007
5	*B. platphylla*	Betulaceae	Bark	51%	Chen et al. 2020
6	*B. papyrifera*	Betulaceae	Bark	28-32%	Blondeau et al. 2020
7	*B. nana*	Betulaceae	Bark	-	Atkinson 1992
8	*B. nigra*	Betulaceae	Bark	20-30%	Alakurtti et al. 2006
9	*B. lente*	Betulaceae	Bark	45%	Holonec et al. 2012
10	*B. alba*	Betulaceae	Bark	95-98%	Abyshev et al. 2007
11	*B. occidentalis*	Betulaceae	Bark	-	White and Bernstein 2003
12	*B. utilis*	Betulaceae	Bark	71%	Siman et al. 2016
13	*Bahuhina recemosa*	Caesalpiniaceae	Root	-	Gupta et al. 2004
14	*Bupleurum flavum*	Apiaceae (Umbelliferae)	Aerial part	-	Tykheev et al. 2020
15	*Buxus microphylla*	Buxaceae	Stem and leaf	-	Fujun et al. 2015
16	*B. papillosa*	Buxaceae	Whole plant	-	Saleem et al. 2020
17	*Byrsonima crassifolia*	Malpighiaceae	Leaf	-	Peraza-Sánchez et al. 2005
18	*B. microphylla*	Malpighiaceae	Wood	0.5% to 2.5%	Aguiar et al. 2005
19	*Cappasis sepiaria*	Capparaceae	Leaf	0.1% - 2%	Mishra et al. 2007
20	*Careya arborea*	Lecythidaceae	Bark	-	Gupta et al. 2012
21	*Carlina corymbosa*	Asteraceae	Bark	-	Oz 2021
22	*Cassia siamea*	Caesalpiniacea	Trunk and Bark	-	Kamagaté et al. 2014
23	*Castanea sativa*	Fagaceae	Leaf	-	Tchatchoua and Aravanopoulos 2015
24	*Celastrus punctalus*	Celastraceae	Stem	2.86%	Huang et al. 2000
25	*Celtis philippinensis*	Capparaceae	Twig	-	Hwang et al. 2003
26	*Ceriops decandra*	Rhizophoraceae	Leaf	-	Hossain et al. 2012
27	*E. divinorum*	Ebenaceae	Root	-	Kaingu et al. 2012
28	*E. kellau*	Ebenaceae	Branch	-	Orzalesi et al. 1970
29	*E. natalensis*	Ebenaceae	Root bark	-	Lall et al. 2006
30	*Euphorbia lathyris*	Euphorbiaceae	Seed oil	-	Ma et al. 2020
31	*Flindersia pimentelliana*	Rutaceae	Bark	0.01 to 0.1 %	Hu et al. 2020
32	*Grevia asiatica*	Malvaceae	Bark and heart wood	-	Zia-Ul-Haq et al. 2013
33	*G. tiliaefolia*	Tiliaceae	Bark	-	Sharma et al 2015
34	*Guazuma tomentosa*	Sterculiaceae	Bark	-	Magid et al. 2008
35	*Guioa villosa*	Sapindaceae	Leaf	-	Magid et al. 2008

S.No	Name of Plant	Family	Plant part	% yield	Reference
36	*Gymnosporia variabilis*	Celastraceae	Aerial part	-	Bhat et al. 2024
37	*Holacantha emoryi*	Simaroubaceae	Seed	-	Stöcklin et al. 1969
38	*Hovenia acerba*	Rhamnaceae	Fruit	-	Zhang et al. 2020
39	*Hypoestes purpurea*	Acanthaceae	Aerial part	45%	Shen et al. 2004
40	*Ilex latifolia*	Aquifoliaceae	Stem bark	-	He et al. 2020
41	*I. macropoela*	Aquifoliaceae	Twig	0.24% to 0.54%	Hu 1949
42	*Ixora chinensis*	Rubiaceae	Leaf	-	Sajini and Chamundeeswari 2023
43	*Jasminum lanceolarium*	Oleaceae	Stem and leaf	-	Ning et al.2013
44	*Juglans regia*	Juglandaceae	Bark	-	Eberle et al. 2023
45	*Lagerstroemia guilinensis*	Lythraceae	Stem	-	Lin et al. 2024
46	*Lasianthus chinensis*	Rubiaceae	Leaf	-	Zhu 2002
47	*Lespedeza bicolor*	Fabaceae	Stem bark	-	Lee et al. 2016
48	*Lithocarpus attenuta*	Fagaceae	Leaf and stem	-	Ye et al. 2024
49	*L. elegans*	Fagaceae	Bark	-	Ye et al. 2024
50	*L. cornea*	Fagaceae	Leaf and stem	-	Ye et al. 2024
51	*L. elizabethae*	Fagaceae	Leaf and stem	-	Ye et al. 2024
52	*L. glabra*	Fagaceae	Leaf and stem	-	Ye et al. 2024
53	*L. haipinii*	Fagaceae	Leaf and stem	-	Ye et al. 2024
54	*L. hancei*	Lauraceae	Leaf and stem	-	Ye et al. 2024
55	*L. harlandii*	Lauraceae	Leaf and stem	-	Ye et al. 2024
56	*L. irwinii*	Lauraceae	Leaf and stem	-	Ye et al. 2024
57	*L. litchioides*	Lauraceae	Leaf and stem	-	Ye et al. 2024
58	*L. polystachyus*	Lauraceae	Leaf and stem	-	Ye et al. 2024
59	*Lonchocarpus laxiflorus*	Lauraceae	Stem	-	Desta et al. 2022
60	*Lophopetalum rigidum*	Celestraceae	Bark	-	Mahajan and Chauhan 2024
61	*L. toxicum*	Celestraceae	Bark	-	Mahajan and Chauhan 2024
62	*Lyonia ovalifolia*	Ericaceae	Shoot	-	Bhandari et al. 2020
63	*Mallotus philippensis*	Euphorbiaceae	Leaf	-	George et al. 2023
64	*Matayba elaeagnoides*	Elaeagnaceae	Bark	-	Rorato et al. 2018
65	*M. chiapensis*	Maytenaceae	Leaf	-	De Figueiredo et al. 2024
66	*M. cuzcoina*	Maytenaceae	Root bark	-	De Figueiredo et al. 2024
67	*M. elacodendroides*	Maytenaceae	Stem bark	-	De Figueiredo et al. 2024
68	*Melaleuca leucadendron*	Myrtaceae	Leaf	-	Melani et al. 2023
69	*Melodinus australis*	Apocynaceae	Aerial part	-	Linde 1965
70	*Valeriana laxiflora*	Valerianaceae	-	88.67	Kaur et al. 2022
71	*Nerium oleander*	Apocynaceae	Leaf	-	Induja et al. 2024

S.No	Name of Plant	Family	Plant part	% yield	Reference
72	*Ocimum basilicum*	Lamiaceae	Root and stem	-	Wirtu et al. 2024
73	*Ormosia emarginata*	Fabaceae	Leaf	-	Tang et al. 2023
74	*Osmanthus cymosus*	Oleaceae	Leaf	-	Kubba et al. 2005
75	*Viscum album*	Loranthaceae	Leaf	27.40	Jäger et al. 2007
76	*Vicia fuba*	Fabaceae	Seed	92.7	Chen et al. 2020
77	*Vaccinium ashei*	Ericaceae	Fruit	27-40	Szakiel et al. 2012
78	*Sophora japonica*	Fabaceae	Flower	0.5-1.5	Guo et al. 2024
79	*Salvia officinalis*	Lamiaceae	Leaf	0.9	Vieira et al. 2020
80	*Phlogacanthus curviflorus*	Acanthaceae	Aerial part	-	Jia et al. 2023
81	*Phyllanthus flexuous*	Phyllanthaceae	Stem bark	-	Guo et al. 2024
82	*Prunus duclis*	Rosaceae	Leaf	-	Vieira et al. 2020
83	*Pterocarpus santalinus*	Fabaceae	Leaf	-	Jia et al. 2023
84	*Pyrostegia venusta*	Apiaceae	Aerial part	-	Pratima et al. 2024
85	*Quercus suber*	Fagaceae	Bark	-	Manzoor et al. 2024
86	*Rhododendron adamsii*	Ericaceae	-	-	Dhadse and Saxena 2024
87	*R. aureum*	Ericaceae	-	-	Dhadse and Saxena 2024
88	*R. dahuricum*	Ericaceae	-	-	Dhadse and Saxena 2024
89	*R. kotschyi*	Ericaceae	-	-	Dhadse and Saxena 2024
90	*R. ledebourii*	Ericaceae	-	-	Dhadse and Saxena 2024
91	*R. luteum*	Ericaceae	-	-	Dhadse and Saxena 2024
92	*R. mucronulatum*	Ericaceae	-	-	Dhadse and Saxena 2024
93	*R. schlippenbachii*	Ericaceae	-	-	Dhadse and Saxena 2024

4 Chemical modifications

Three key locations in betulin allow for simple chemical modification: the primary hydroxyl group at position C-28, the secondary hydroxyl group at position C-3, and the alkene moiety at position C-20. The parent structure of betulin is modified biochemically at positions C-28 to yield betulinic acid (Boryczka et al. 2013; Baratto et al. 2013; Singh et al. 2016; Boparai et al. 2017). The white birch bark can manufacture physiologically active betulin derivatives due to its high betulin concentration (up to 30%)(Boryczka et al. 2013). Chrobak et al. (2021) reported the synthesis of novel, intriguing acetylenic derivatives of betulin by treating a mixture of betulin and pyridine in dry benzene with propargyl chloroformate (a), 2-butyn-1-yl chloroformate (b), 3-butyn-1-yl chloroformate (c), and ethyl chloroformate (d) (Figure 2). The reported betulin derivatives are: Imidazole carboxylic esters, Hemisuccinates, Hemiphthalates, Nicotinates, Acetylbetulin-28-O-hemiphthalate, Monomethacrylate and Dimethacrylate, Acetylenic, Oxime, Olygomeric ester, Phosphate, Triphenylphosphonium, and Succinyl and 3 substituted glutaryl. The biological activities include hepatoprotective, antileishmanial, antiviral, anti-inflammatory, anticancer, and anti-inflammatory (Santos et al. 2010; Veloso et al. 2010; Tang et al. 2014; Bebenek et al. 2015; Wang et al. 2022).

5 Structure-activity relationship of betulin

A therapeutic agent's structure-activity relationship (SAR) is critically determined by its molecular structure and interactions within the body. Betulin, a naturally occurring triterpenoid molecule, exhibits significant interactive potential due to hydroxyl groups at the C_3 and C_{28} positions. Various groups, including nitrile, carbonyl, amino, succinyl, maleic anhydride, oxime, and imidazole, have demonstrated cytotoxic and inhibitory effects against leishmania, inducible nitric oxide synthase (iNOS), tumors, and cancer. Furthermore, the addition of oxime and imidazole moieties enhances the anticancer and antileishmanial activities (Wang et al. 2022; Bebenek et al. 2015). The structure-activity relationship of betulin is illustrated in Figure 3.

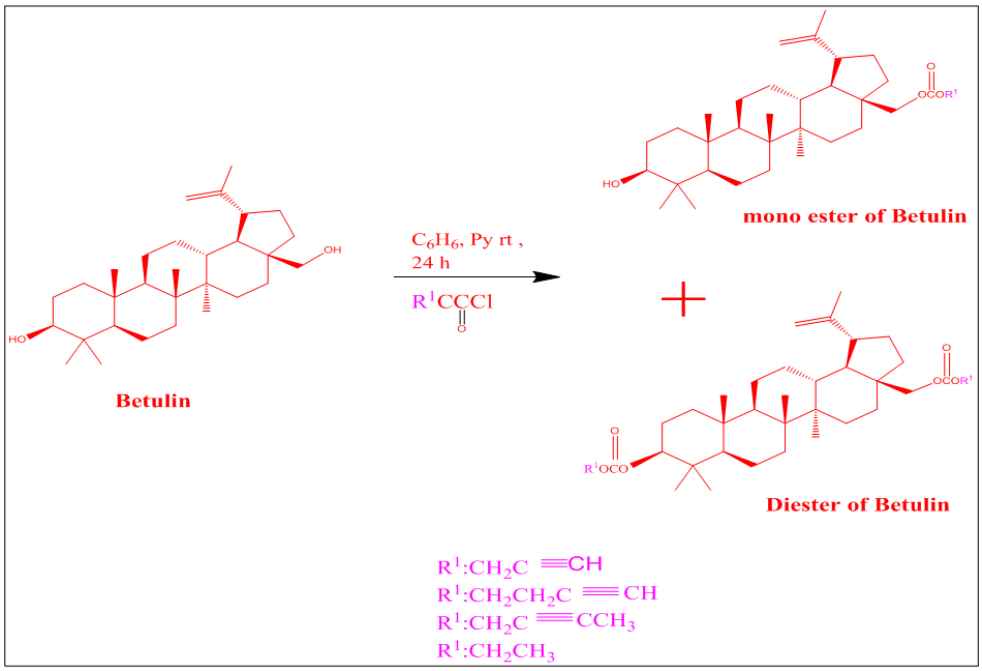


Figure 2 Synthesis of acetylenic derivative of Betulin

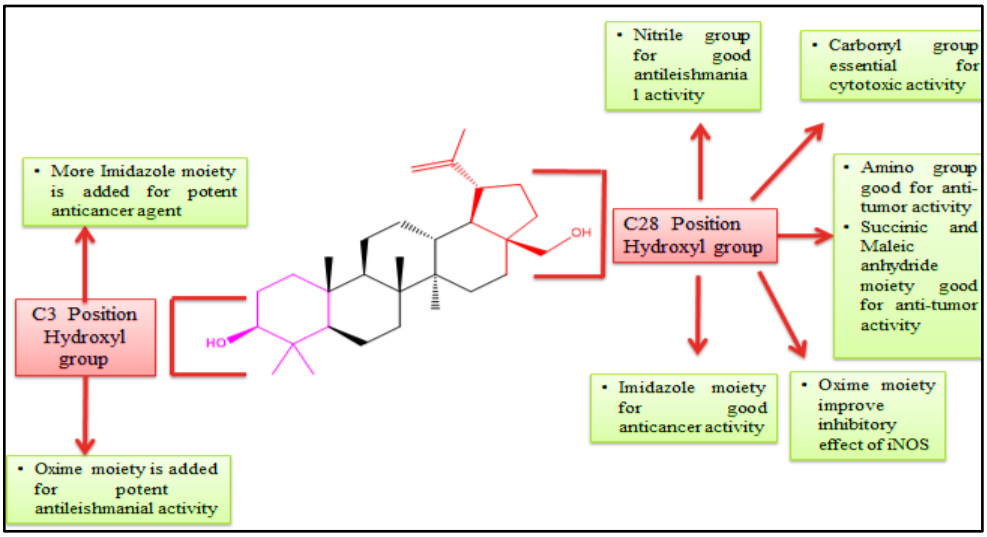


Figure 3 Structure-activity relationship of betulin

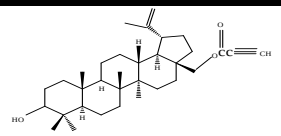
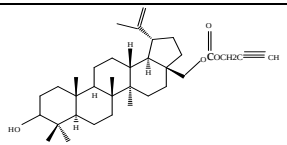
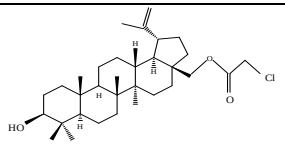
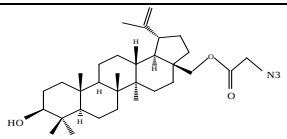
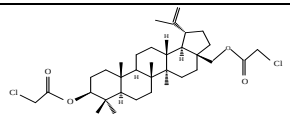
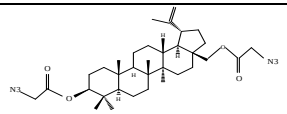
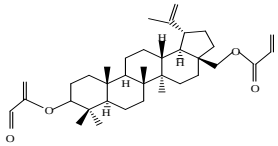
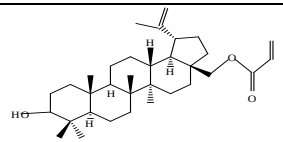
6 Betulin derivatives and its biological activities

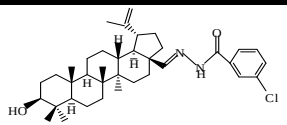
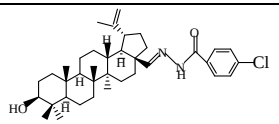
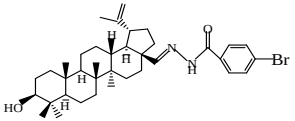
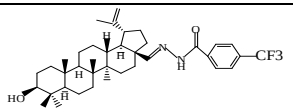
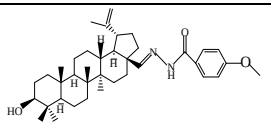
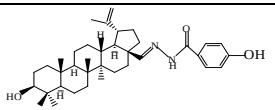
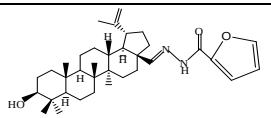
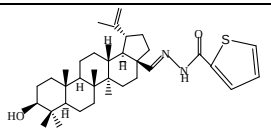
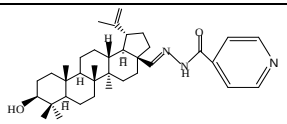
Betulin derivatives exhibit a range of biological activities, including anticancer, antiviral, anti-inflammatory, antioxidant, hepatoprotective, and antidiabetic properties. They present promising opportunities for drug development across various therapeutic areas. Ongoing research aims to create novel compounds demonstrating enhanced potency and selectivity for specific disorders. Tables 2 and 3 detail the biological activities of betulin derivatives, both in vitro and in vivo.

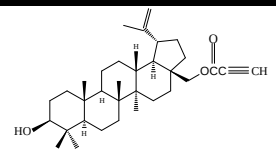
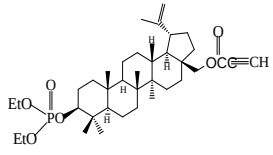
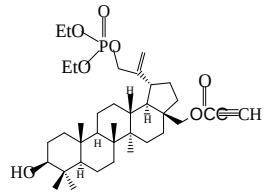
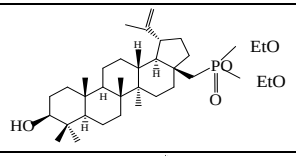
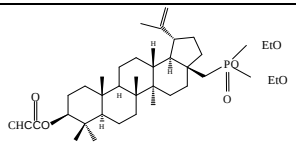
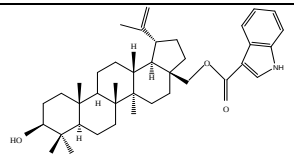
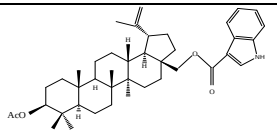
7 Future perspectives

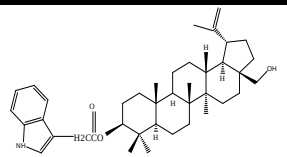
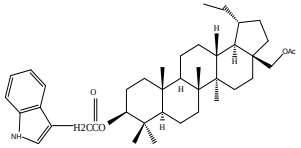
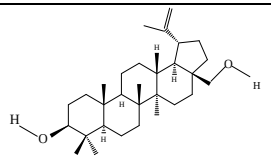
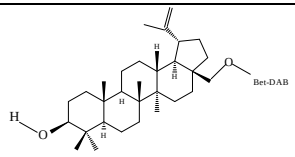
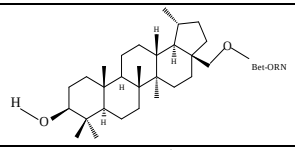
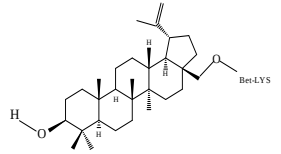
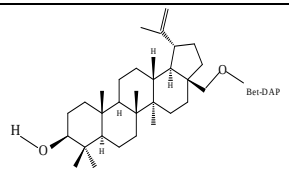
The potential of betulin, particularly in the design and synthesis of derivatives at C_3 and C_{28}, should be explored extensively for therapeutic applications. The study will involve docking studies on the proteins and active sites related to the targeted biological activity. Derivatives such as esters, amino compounds, imidazoles, and chlorinated versions will be commercialized through innovative drug delivery systems. Additionally, preclinical and clinical trials may be conducted to refine these molecules further and develop novel medications to treat various ailments.

Table 2 Betulin derivatives and their biological activities

S. No.	Types of derivatives	Name of the Derivatives	Structure	Biological activities	Mechanism of action	References
1	Acetylenic synthetic derivatives (ASBDs)	28-O-propynoylbetulin		Anticancer	Inhibits tyrosine kinase and C-MET kinase	Mhamdi et al. 2023
		28-O-propargyloxycarbonylbetulin				
2	Glycoconjugation of betulin derivatives	28-O-chloroacetylbetulin		Anticarcinogenic	Caspase cascade activation, modulating signaling pathways (NF-κB and Nrf2), inhibiting angiogenesis, and disrupting mitochondrial membrane	Grymel et al. 2020
		28-O-Azidoacetylbetulin				
		3,28-O,O'-di(chloroacetyl)betulin				
		3,28-O,O'-di(azidoacetyl)betulin				
3	Monomethacrylate- and dimethacrylate-functionalized betulin derivatives	M1Bet		Antibacterial	Disrupting bacterial membrane integrity and causing leakage of intracellular contents	Krol et al. 2020
		M2Bet				

S. No.	Types of derivatives	Name of the Derivatives	Structure	Biological activities	Mechanism of action	References
4	Betulin derivatives containing a hydrazide-hydrazone side-chain	Betulin-28-(3-chloro)benzohydrazide		Anticarcinogenic	Mitochondrial membrane disruption and caspase activation, inhibiting cell proliferation	Zhang et al. 2021
		Betulin-28-(4-chloro) benzohydrazide				
		Betulin-28-(4-bromo) benzohydrazide				
		Betulin-28-(4-trifluoromethyl) benzohydrazide				
		Betulin-28-(4-methoxy) benzohydrazide				
		Betulin-28-(4-hydroxy)benzohydrazide				
		Betulin-28-(2-furan) carbohydrazide				
		Betulin-28-(2-thiophene) carbohydrazide				
		Betulin-28-isonicotinohydrazide				

S. No.	Types of derivatives	Name of the Derivatives	Structure	Biological activities	Mechanism of action	References
5	Acetylenic derivative of betulin phosphate	Betulin derivatives bearing both propynoyloxy and phosphate groups	    	Breast cancer	Mitochondrial dysfunction, disrupting mitochondrial homeostasis, and activating mitochondrial death pathway	Laiolo et al. 2024
6	Indole betulin derivatives	EB355A		Anticarcinogenic	Mitochondrial membrane disruption and DNA fragmentation, arresting the cell cycle at the G1 phase, and inhibiting tubulin polymerization	Wu et al. 2021
		EB365				

S. No.	Types of derivatives	Name of the Derivatives	Structure	Biological activities	Mechanism of action	References
7	*3-indolyl betulin derivatives*	EB366		Anticancer	Mitochondrial membrane disruption and DNA fragmentation, arresting the cell cycle at the G1 phase to prevent progression to the S phase	Orchel et al. 2021
		EB367				
8	Betulin, and its derivatives with amino acids	1,4-diaminebutane (Dab), 1,3-diaminepropane (Dap), ornithine (Orn), and lysine (Lys)		Reduce inflammation and COX-2 activity in macrophages	Reducing IL-6, reorganizing interferon-gamma receptors (IFNγR), and directly inhibiting COX-2 activity	Rzepka et al. 2022
						
						
						
						

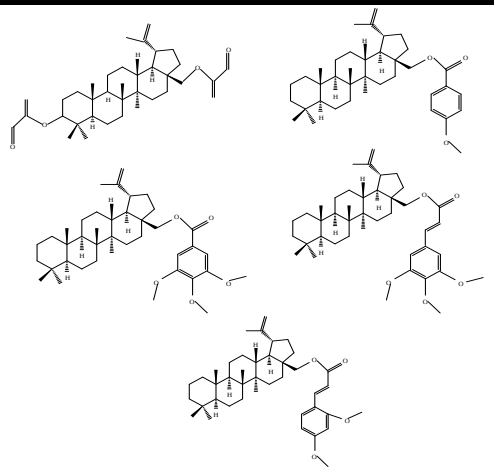
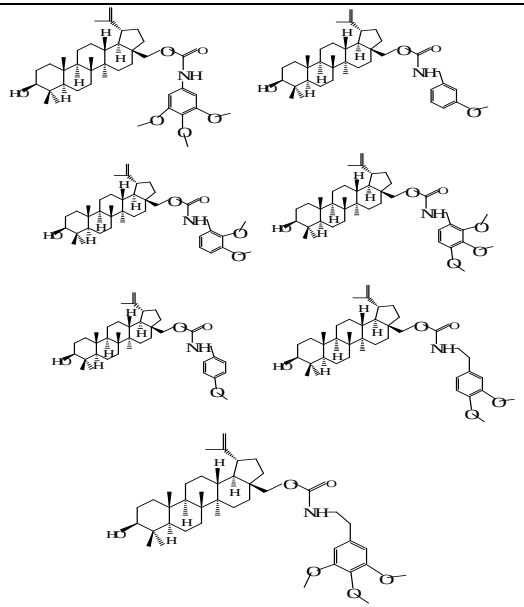
S. No.	Types of derivatives	Name of the Derivatives	Structure	Biological activities	Mechanism of action	References
	Betulin esters					
9	Betulin carbamates	-		Antiproliferative	Reduction of NF-κB, Nrf2, and AMPK, Regulates oxidative stress, inflammation, and energy metabolism	Wu et al. 2021; Bębenek et al. 2022

Table 3 *In-vitro* and *In-vivo* biological effects of betulin and its derivatives

S.No.	Derivatives	*Invitro*	*Invivo*	Activities	Reference
1.	Betulin	HCT116, HT29	-	Anticancer (colon)	Szlasa et al. 2023
2.	Indole	Colo-205, HCT-116	-	Anticancer (colon)	Grymel et al. 2020
3.	Betulin	A549, H1264, Calu-6	Rat	Anticancer (Ling)	Zhou et al. 2018
4.	Triphenylphosphonium	MCF-7, PC-3, MCF-7/Vinb, human skin fibroblast (HSF)	-	Anticancer toward MCF-7/Vinb cells	Khusnutdinova et al. 2018
5.	Ester	Me-45	-	Anticancer (melanoma)	So et al. 2018
6.	Betulin	SGC7901	-	Anticancer (gastric)	Tsepaeva et al. 2017
7.	Azole	A549, Hep-G2, HCT 116, MS, RDTE32	Mice	Anticancer	Drąg-Zalesińska et al. 2017
8.	Hydroxypropargylamines	SW1736, MCF-7, LIPO, DLD-1, A549, A2780, A253, 8505C, 518A2, NiH 3 T3	-	Anticancer	Li et al. 2016
9.	Carbamate and N-acylheterocyclic	Hep-G2, Jurkat, HeLa, HT-29, PC-3	-	Anticancer (carcinoma, leukemia, cervical, colon, prostate)	Grishko et al. 2017
10.	γ-Butyrolactones and butenolides	518A2, A431, A253, FADU, A549, A2780, DLD-1, HCT-8, HCT-116, HT-29, SW480, 8505C, SW1736, MCF-7, Lipo	-	Anticancer	Csuk et al. 2013
11.	α- and β- D-glucopyranose B anomers	8505C, SW1736, A253, FaDu, A431, A2780, DLD-1, HCT-8, HCT-116, HT-29, SW480, MCF-7, 518A2, A549	-	Anticancer (thyroid, head and neck, cervical, ovarian, colon, breast, melanoma, lung)	Santos et al. 2010
12.	Betulin	A431, MCF-7, HeLa	-	Anticancer	Csuk et al. 2010
13.	Betulin	RAW264.7 murine macrophage, Murine J774 macrophages, and RAW 264.7 mouse macrophage	Mice	Antiinflammatory	Kommera et al. 2010; Şoica et al. 2012; Ci et al. 2017
14.	3′-Azido-3′-deoxythy-midine	MT-4	-	AntiHIV-1 maturation	Laavola et al. 2016
15.	Betulin	*Chlamydia pneumoniae*	-	Antimicrobial	Wu et al. 2014
16.	Disuccinyl	*Leishmania donovani*	Mice	Antimicrobial	Xiong et al. 2010
17.	Heterocyclic	*Leishmania donovani*, THP-1	-	Antimicrobial	Salin et al. 2010; Chowdhury et al. 2014
18.	Betulin	CFSC-2G	-	Antifibrotic	Szuster-Ciesielska et al. 2011
19.	Triphenylphosphonium	-	Mice	Antimicrobial (antischistosoma mansoni)	Spivak et al. 2014

Conclusion

Betulin and its derivatives are potent chemotherapeutic agents that warrant further exploration. Betulin can be extracted, purified, and isolated with optimal yield using straightforward methods, such as Soxhlet extraction with green solvents. The C3 and C28 positions are the active sites for derivatization, which can enhance its biological activities.

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Conflicts of interest

The authors declare no conflict of interest.

Ethical Approval

Not Applicable for this study.

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