

MINI REVIEW

Distribution of betulinic acid in plant kingdom

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Abstract

Betulinic acid (3 β -hydroxy-lup-20(29)-en-28-oic acid) is a ubiquitous pentacyclic triterpenoid found in the plants. It is highly valued for its role in wide array of ailments viz. anti-HIV, anti-malarial, anti-cancerous, hepatoprotective, and many more. In lights of tremendous interest in recent years on chemistry and pharmacological properties of betulinic acid (BA), comprehensive data have been collected in this review to present its distribution in plant kingdom.

Keywords: Betulinic acid; Triterpenoids

Introduction

Plants are well known for their medicinal value with the finding of cinchona in 17th century, followed by digitoxin, morphine, introduction of synthetic aspirin, a derivative of a plant-based drug, are wonders of the diverse floristic wealth (Raskin & Ripoll, 2004). Natural products offer large structural diversity and techniques for separation, structure elucidation, screening and combinatorial synthesis have led to revitalization of these secondary metabolites as sources of new drugs (Saklani & Kutty, 2008).

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Betulinic acid (BA) (3 β -hydroxy-lup-20(29)-en-28-oic acid molecular formula: C₃₀H₄₈O₃ and molecular weight: 456.7) is a pentacyclic triterpenoid (Fig. 1). It is moderately soluble in water and relatively nontoxic, found in many plants, especially in tree species. It is a biologically active compound, mainly known for its selective inhibitor of human melanoma (Pisha *et al.*, 1995). The compound gains its name because of its prevalence in the family Betulaceae, which includes *Betula alba*, *B. pubescens*, *B. platyphylla*, *B. maximowicziana*, *B. mandshurica* and others. The family still serves as a major source of betulinic acid. Also its congener betulin, is one of the first natural products isolated in 1788 from the bark of white birch, *Betula alba* (Krasutsky, 2006).

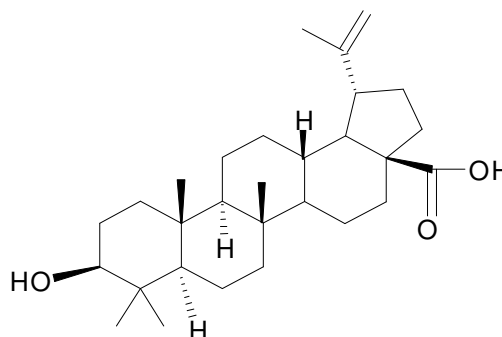


Fig 1. Chemical Structure of betulinic acid

Search tools including, Google Scholar®, PubMed® and Scopus® were used to generate the literature on BA. Over ~800 hits were spotted which are related to betulinic acid. Out of which the reports related to the subject matter of this review were considered.

Distribution of BA in plant species

Betulinic acid is widely distributed in nature and its occurrence across a wide multitude of taxonomically different genera has been reported. Therefore, in this review, attempt has been made to list the plant species in which the compound BA has been accounted (Table 1).

Table 1. Distribution of betulinic acid in various plant species

Plant name	Family	Part	Reference
<i>Achyranthes aspera</i>	Amaranthaceae	Leaf	Pai, Upadhyya, Hegde, Joshi, & Kholkute, 2014
<i>Ampelozizyphus amazonicus</i>	Rhamnaceae	Stem	Rosas <i>et al.</i> , 2007
<i>Ancistrocladus heyneanus</i>	Ancistrocladaceae	Roots	Bringmann <i>et al.</i> , 1997
<i>Ancistrocladus heyneanus</i>	Ancistrocladaceae	Leaf	Pai, Nimbalkar, Pawar, & Dixit, 2011
<i>Arbutus menziesii</i>	Ericaceae	Stem Bark	Yogeeswari & Sriram, 2005
<i>Berlinoa grandiflora</i>	Leguminosae	Stem Bark	Yogeeswari & Sriram, 2005
<i>Betula platyphylla</i>	Betulaceae	Stem Bark	Zhang, Yu, & Wang, 2003
<i>Betula pubescens</i>	Betulaceae	Stem Bark	Abyshev, Zhurkovich, Agaev, Abdulla-zade, & Guseinov, 2006; Abyshev, Agaev, & Guseinov, 2007
<i>Betula pendula</i>	Betulaceae	Stem Bark	Holonec, Ranga, Crainic, Truta, & Socaciu, 2012; Galgon, Hoke, & Drager, 1999
<i>Betula maximowicziana</i>	Betulaceae	Stem Bark	Abyshev <i>et al.</i> , 2007
<i>Betula mandshurica</i>	Betulaceae	Stem Bark	Abyshev <i>et al.</i> , 2007
<i>Caesalpinia paraguariensis</i>	Fabaceae	Arial	Woldemichael, Singh, Maiese, & Timmermann, 2003
<i>Callicarpa macrophylla</i>	Lamiaceae	Herb	Pan, Jia, & Sun, 2008
<i>Cichorium intybus</i>	Asteraceae	Seeds	Atta-ur-Rahman, Zareen, Choudhary, Akhtar, & Khan, 2008
<i>Clerodendrum mandarinorum</i>	Verbenaceae	Root	Zhu, Phillipson, Greengrass, & Bowery, 1996
<i>Coussarea paniculata</i>	Rubiaceae	Stem	Chaturvedula, Schilling, Johnson, & Kingston, 2003
<i>Diospyros leucomelas</i>	Ebenaceae	Stem	Recio <i>et al.</i> , 1995
<i>Diospyros melanoxylon</i>	Ebenaceae	Stem	Kantamreddi & Wright, 2007
<i>Diospyros peregrina</i>	Ebenaceae	Stem	Kantamreddi & Wright, 2007
<i>Diospyros sylvatica</i>	Ebenaceae	Stem	Kantamreddi & Wright, 2007
<i>Diospyros tomentosa</i>	Ebenaceae	Stem	Kantamreddi & Wright, 2007
<i>Dichapetalum gelonioides</i>	Dichapetalaceae	Stem Bark	Fang <i>et al.</i> , 2006
<i>Dillenia papuana</i>	Dilleniaceae	Leaves, Stem	Nick, Wright, Rali, & Sticher, 1995
<i>Doliocarpus schottianus</i>	Dilleniaceae	Arial	De Oliveira, Santos, & Espindola, 2002
<i>Eucalyptus camaldulensis</i>	Myrtaceae	Leaves	Begum, Sultana, Siddiqui, Shaheen, & Gilani, 2002
<i>Henriettella fascicularis</i>	Melastomataceae	Stem	Calderon <i>et al.</i> , 2002
<i>Ipomea pescaprae</i>	Convolvulaceae	Root bark	Yogeeswari & Sriram, 2005
<i>Licania arianeae</i>	Chrysobalanaceae	Stem, Leaves	De Carvalho <i>et al.</i> , 2008
<i>Melaleuca leucadendron</i>	Myrtaceae	Leaves	Lee, 1998
<i>Morus alba</i>	Moraceae	Stem, Root	Nattapong and Omboon, 2008
<i>Morus australis</i>	Moraceae	Roots	Ko, Yu, Ko, Teng, & Lin, 1997
<i>Nepeta nuda</i>	Lamiaceae	Arial	Kokdil, Yalçin, & Topçu, 1999
<i>Nerium oleander</i>	Apocynaceae	Leaves	Fu <i>et al.</i> , 2005
<i>Oenothera biennis</i>	Onagraceae	Arial	Hamburger <i>et al.</i> , 2002
<i>Paeonia suffruticosa</i>	Ranunculaceae	Roots	Lin, Ding, & Wu, 1998
<i>Physocarpus intermedium</i>	Rosaceae	Stem Bark	Yogeeswari & Sriram, 2005
<i>Prunus dulcis</i>	Rosaceae	Hull	Takeoka <i>et al.</i> , 2000
<i>Quercus suber</i>	Fagaceae	Stem Bark	Sousa, Pinto, Silvestre, & Neto, 2006
<i>Rosmarinus officinalis</i>	Lamiaceae	Arial Leaves	R azborek, Voncina, Dolecek, & Voncina, 2007; 2008
<i>Salvia officinalis</i>	Lamiaceae	Leaves	Razborek <i>et al.</i> , 2008
<i>Salvia glutinosa</i>	Lamiaceae	Leaves	Razborek <i>et al.</i> , 2008
<i>Salvia sclarea</i>	Lamiaceae	Leaves	Razborek <i>et al.</i> , 2008
<i>Satureja montana</i>	Lamiaceae	Leaves	Razborek <i>et al.</i> , 2008
<i>Strychnos vanprukii</i>	Loganiaceae	Arial	Chien <i>et al.</i> , 2004
<i>Syncarpa glomulifera</i>	Myrtaceae	Stem Bark	Yogeeswari & Sriram, 2005
<i>Syzygium claviflorum</i>	Myrtaceae	Leaves	Fujioka <i>et al.</i> , 1994
<i>Syzygium formasanum</i>	Myrtaceae	Leaves	Chang, Wu, Hsieh, Kuo, & Lee Chao, 1999
<i>Tabernaemontana cathariensis</i>	Apocynaceae	Root	Pereira <i>et al.</i> , 2008
<i>Tetracentron sinense</i>	Trochodendraceae	Stem bark	How, Wu, Ko, & Chen, 1982
<i>Triphyophyllum peltatum</i>	Dioncophyllaceae	Roots	Bringmann <i>et al.</i> , 1997
<i>Ugni molinae</i>	Myrtaceae	Leaves	Goity <i>et al.</i> , 2013
<i>Vitex negundo</i>	Verbenaceae	Leaves	Yogeeswari & Sriram, 2005
<i>Vitex negundo</i>	Verbenaceae	Leaves	Taralkar & Chattopadhyay, 2012
<i>Viscum album</i>	Viscaceae	Arial	Jäger, Winkler, Pfüller, & Scheffler, 2007
<i>Ziziphus jujuba</i>	Ramnaceae	Fruits	Guo <i>et al.</i> , 2009
<i>Zizyphus xylopyrus</i>	Ramnaceae	Stem	Jagadeesh, David Krupadanam, & Srimannarayana, 1998

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References

- Abyshev, A. Z., Agaev, É. M., & Guseinov, A. B. (2007). Studies of the chemical composition of birch bark Extracts (*Cortex betula*) from the Betulaceae family. *Pharmaceutical Chemistry Journal*, 41(8), 22–26. <http://dx.doi.org/10.1007/s11094-007-0091-5>
- Abyshev, A. Z., Zhurkovich, I. K., Agaev, É. M., Abdulla-zade, A. A., & Guseinov, A. B. (2006). Methods of standardization of the quality of betulenol parent substance and its ready-to-use medicinal forms. *Pharmaceutical Chemistry Journal*, 40(1). <http://dx.doi.org/10.1007/s11094-006-0056-0>
- Atta-ur-Rahman, Zareen S., Choudhary, M. I., Akhtar, M. N., & Khan, S. N. (2008). A-glucosidase inhibitory activity of triterpenoids from *Cichorium intybus*. *Journal of Natural Products*, 71, 910-913, 2008. <http://dx.doi.org/10.1021/np800001v> PMID:18341288
- Begum, S., Sultana, I., Siddiqui, B. S., Shaheen, F., & Gilani, A. H. (2002). Structure and spasmolytic activity of eucalyptanoic acid from *Eucalyptus camaldulensis* var. *obtusata* and synthesis of its active derivative from oleanolic acid. *Journal of Natural Products*, 65, 1939-1941. <http://dx.doi.org/10.1021/np020127x> PMID:12502346
- Bringmann, G., Saeb, W., Aké Assi, L., Francois, G., Sankara Narayanan, A. S., Peters, K., & Peters, E. M. (1997). Betulinic acid: Isolation from *Triphyophyllum peltatum* and *Ancistrocladus heyneanus*, antimalarial activity, and crystal structure of the benzyl ester. *Planta Medica*, 63, 255 – 257. <http://dx.doi.org/10.1055/s-2006-957666> PMID:9225608
- Calderon, A. I., Terreaux, C., Schenk, K., Pattison, P., Burdette, J. E., Pezzuto, J. M., Gupta, M. P., & Hostettmann, K. (2002). Isolation and structure elucidation of an isoflavone and a sesterterpenoid acid from *Henriettella fascicularis*. *Journal of Natural Products*, 65(12), 1749-1753. <http://dx.doi.org/10.1021/np0201164> PMID:12502307
- Chang, C., Wu, T., Hsieh, Y., Kuo, S., & Lee Chao, P. (1999). Terpenoids of *Syzygium formosanum*. *Journal of Natural Products*, 62, 327-328. <http://dx.doi.org/10.1021/np980313w> PMID:10075776
- Chaturvedula, V. S. P., Schilling, J. K., Johnson, R. K., & Kingston, D. G. I. (2003). New cytotoxic lupane triterpenoids from the twigs of *Coussarea paniculata*. *Journal of Natural Products*, 66, 419-422. <http://dx.doi.org/10.1021/np0204848> PMID:12662105
- Chien, N. Q., Hung, N. V., Santarsiero, B. D., Mesecar, A. D., Cuong, N. M., Soejarto, D. D., Pezzuto, J. M., Fong, H. H. S., & Tan, G. T. (2004). New 3-O-acyl betulinic acids from *Strychnos vanprukii* Craib. *Journal of Natural Product*, 67, 994-998. <http://dx.doi.org/10.1021/np030469i> PMID:15217281
- De Carvalho, M. G., de Oliveira Cândido, L. F., da Costa, P. M., do Nascimento, I. A., & Braz-Filho, R. (2008). Triterpenes acids and saponins isolated from *Licania arianae* Prance (Chrysobalanaceae). *Journal of Natural Medicine*, 62, 122–123. <http://dx.doi.org/10.1007/s11418-008-0241-4>
- De Oliveira, B. H., Santos, C. A. M., & Espindola, A. P. D. M. (2002). Determination of the triterpenoid, betulinic acid, in *Doliocarpus schottianus* by HPLC. *Phytochemical Analysis*, 13, 95–98. <http://dx.doi.org/10.1002/pca.628> PMID:12018029
- Fang, L., Ito, A., Chai, H., Mi, Q., Jones, W. P., Madulid, D. R., Oliveros, M. B., Gao, Q., Orjala, J., Farnsworth, N. R., Soejarto, D. D., Cordell, G. A., Swanson, S. M., Pezzuto, J. M., & Kinghorn, A. D. (2006). Cytotoxic constituents from the stem bark of *Dichapetalum gelonioides* collected in the Philippines. *Journal of Natural Product*, 69, 332-337. <http://dx.doi.org/10.1021/np058083q> PMID:16562829
- Fu, L., Zhang, S., Li, N., Wang, J., Zhao, M., Sakai, J., Hasegawa, T., Mitsui, T., Kataoka, T., Oka, S., Kiuchi, M., Hirose, K., & Ando, M. (2005). Three new triterpenes from *Nerium oleander* and biological activity of the isolated compounds. *Journal of Natural Products*, 68, 198-206.
- Fujioka, T., Kashiwada, Y., Kilkuskie, R. E., Cosentino, L. M., Ballas, L. M., Jiang, J. B., Janzen, W. P., Chen, I. S., & Lee, K. H. (1994). Anti-AIDS agents, 11, betulinic acid and platanic acid as anti-HIV principles from *Syzygium claviflorum* and the anti-HIV activity of structurally related triterpenoids. *Journal of Natural Products*, 57(2), 243-247. <http://dx.doi.org/10.1021/np50104a008> PMID:8176401
- Galgon, T., Hoke, D. & Drager, B. (1999). Identification and quantification of betulinic acid. *Phytochemical Analysis*, 10(4), 187 – 190. [http://dx.doi.org/10.1002/\(SICI\)1099-1565\(199907/08\)10:4<187::AID-PCA443>3.0.CO;2-K](http://dx.doi.org/10.1002/(SICI)1099-1565(199907/08)10:4<187::AID-PCA443>3.0.CO;2-K)
- Goity, L.E., Queupil, M. J., Jara, D., Alegría, S. E., Pe-a, M., Barriga, A., Aguirre, M. C., & Delporte, C. (2013). An HPLC-UV and HPLC-ESI-MS based method for identification of anti-inflammatory triterpenoids from the extracts of *Ugni molinae*. *Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas*, 12(1), 108 – 116.
- Guo, S., Duan, J., Tang, Y., Su, S., Shang, E., Ni, S., & Qian, D. (2009). High-performance liquid chromatography-two wavelength detection of triterpenoid acids from the fruits of *Ziziphus jujuba* containing various cultivars in different regions and classification using chemometric analysis. *Journal of Pharmaceutical and Biomedical Analysis*, 49(5), 1296-1302. <http://dx.doi.org/10.1016/j.jpba.2009.03.006> PMID:19359121
- Hamburger, M., Riese, U., Graf, H., Melzig, M. F., Ciesielski, S., Baumann, D., Dittmann, K., & Wegner, C. (2002). Constituents in evening primrose oil with radical scavenging, cyclooxygenase, and neutrophil elastase inhibitory activities. *Journal of Agriculture and Food Chemistry*, 50, 5533-5538.
- Holonec, L., Ranga, F., Crainic, D., Truta, A., & Socaciu, C. (2012). Evaluation of betulin and betulinic acid content in birch bark from different forestry areas of Western Carpathians. *Notulae Botanicae Horti Agrobotanici*, 40(2), 99-105.
- How, F. C., Wu, T. L., Ko, W. C., & Chen, T. C. (1982). In: *A dictionary of the families and genera of Chinese seed*

- plants. Beijing: Science Press. pp 483, <http://dx.doi.org/10.1039/b606816b> PMID:17119640
- Jagadeesh, S. G., David Krupadanam, G. L., & Srimannarayana, G. (1998). Tobacco caterpillar antifeedent from the gotti stem wood triterpene betulinic acid. *Journal of Agriculture and Food Chemistry*, 46, 2797-2799. <http://dx.doi.org/10.1021/jf970768b>
- Jäger, S., Winkler, K., Pfüller, U., & Scheffler, A. (2007). Solubility studies of oleanolic acid and betulinic acid in aqueous solutions and plant extracts of *Viscum album* L. *Planta Medica*, 73, 157-162. <http://dx.doi.org/10.1055/s-2007-967106> PMID:17415876
- Kantamreddi, V. S. S., & Wright, C. W. (2007). Investigation of Indian *Diospyros* species for antiplasmodial properties. *eCAM*, 1- 4.
- Ko, H, Yu, S., Ko, F., Teng, C., & Lin, C. (1997). Bioactive constituents of *Morus australis* and *Broussonetia papyrifera*. *Journal of Natural Product*, 60, 1008-1011. <http://dx.doi.org/10.1021/np970186o> PMID:9358644
- Kokdil, G., Yalçın, S. M., & Topçu, G. (1999). Nepetalactones and other constituents of *Nepeta nuda* ssp. *Albiflora*. *Turkish Journal of Chemistry*, 23, 99-104.
- Krasutsky, P. A. (2006). Birch bark research and development. *Natural Product Reports*, 23(6), 919-942.
- Lee, C. (1998). A new norlupene from the leaves of *Melaleuca leucadendron*. *Journal of Natural Product*, 61, 375-376. <http://dx.doi.org/10.1021/np9606052> PMID:9548878
- Lin, H., Ding, H., & Wu, Y. (1998). Two novel compounds from *Paeonia suffruticosa*. *Journal of Natural Product*, 61(3), 343-346. <http://dx.doi.org/10.1021/np9704258> PMID:9548873
- Nattapong, S., & Omboon, L. (2008). A new source of whitening agent from a Thai Mulberry plant and its betulinic acid quantitation. *Natural Product Research*, 22(9), 727-734. <http://dx.doi.org/10.1080/14786410601130794> PMID:18569714
- Nick, A., Wright, A. D., Rali, T., & Sticher, O. (1995). Antibacterial triterpenoids from *Dillenia papuana* and their structure activity relationship. *Phytochemistry*, 40, 1691-1695. [http://dx.doi.org/10.1016/0031-9422\(95\)00491-0](http://dx.doi.org/10.1016/0031-9422(95)00491-0)
- Pai, S. R. Nimbalkar, M. S., Pawar, N. V., & Dixit, G. B. (2011). Optimization of extraction techniques and quantification of betulinic acid (BA) by RP-HPLC method from *Ancistrocladus heyneanus* Wall. Ex Grah. *Industrial Crops and Products*, 34, 1458-1464. <http://dx.doi.org/10.1016/j.indcrop.2011.05.006>
- Pai, S. R., Upadhya, V., Hegde, H. V., Joshi, R. K., & Kholkute, S. D. (2014). New report of triterpenoid betulinic acid (BA) along with oleanolic acid (OA) from *Achyranthes aspera* by RP-UFLC analysis and confirmation using HPTLC and FTIR techniques. *Journal of Planar Chromatography – Modern TLC*, 27(1), 38-41.
- Pan, P., Jia, L. Y., & Sun, Q. S. (2008). RP-HPLC determination of betulinic acid in *Callicarpa macrophylla*. *Zhongguo Zhong Yao Za Zhi*, 33(7), 753-755. PMID:18589770
- Pereira, P. S., França, S. de C., de Oliveira, P. V. A., de Souza Breves, C. M., e Vaz Pereira, S. I., e Auro Nomizo, S. V. S., & Dias, D. A. (2008). Chemical constituents from *Tabernaemontana catharinensis* root bark: a brief NMR review of indole alkaloids and *in vitro* cytotoxicity. *Quimica Nova*, 31(1), 20-24. <http://dx.doi.org/10.1590/S0100-40422008000100004>
- Pisha, E., Chai, H., Lee, I. S., Chagwedera, T. E., Farnsworth, N. R., Cordell, G. A., Beecher, C. W., Fong, H. H., Kinghorn, A. D., Brown, D. M., Wani, M. C., Wall, M. E., Hieken, T. J., Das Gupta, T. K., & Pezzuto, J. M. (1995). Discovery of betulinic acid as a selective inhibitor of human melanoma that functions by induction of apoptosis. *Nature Medicine*, 1, 1046-1051. <http://dx.doi.org/10.1038/nm1095-1046> PMID:7489361
- Raskin, I., & Ripoll, C. (2004). Can an apple a day keep the doctor away? *Current Pharmaceutical Design*, 10, 3419-3429. <http://dx.doi.org/10.2174/1381612043383070> PMID:15544525
- Razborek, M. I., Voncina, D. B., Dolecek, V., & Voncina, E. (2007). Determination of major phenolic acids, phenolic diterpenes and triterpenes in Rosemary (*Rosmarinus officinalis* L.) by gas chromatography and mass spectrometry. *Acta Chimica Slovenica*, 54, 60-67.
- Razborek, M. I., Voncina, D. B., Dolecek, V., & Voncina, E. (2008). Determination of oleanolic, betulinic and ursolic acid in Lamiaceae and mass spectral fragmentation of their trimethylsilylated derivatives. *Chromatographia*, 67, 433-440. <http://dx.doi.org/10.1365/s10337-008-0533-6>
- Recio, M. C., Giner, R. M., Manez, S., Gueho, J., Julien, H. R., Hostettmann, K., & Rios, J. L. (1995). Investigations on the steroidal anti-inflammatory activity of triterpenoids from *Diospyros leucomelas*. *Planta Medica*, 61, 9-12. <http://dx.doi.org/10.1055/s-2006-957988> PMID:7701004
- Rosas, L. V., Cordeiro, M. S. C., Campos, F. R., Nascimento, S. K. R., Januário, A. H., França, S. C., Nomizo, A., Toldo, M. P. A., Albuquerque, S., & Pereira, P. S. (2007). *In vitro* evaluation of the cytotoxic and trypanocidal activities of *Ampelozizyphus amazonicus* (Rhamnaceae). *Brazilian Journal of Medical and Biological Research*, 40, 663-670. <http://dx.doi.org/10.1590/S0100-879X2007000500009> PMID:17464428
- Saklani, A., & Kutty, S. K. (2008). Plant derived compounds in clinical trials. *Drug Discovery Today*, 13(3-4), 161-171. <http://dx.doi.org/10.1016/j.drudis.2007.10.010> PMID:18275914
- Sousa, A. F., Pinto, P. C. R. O., Silvestre, A. J. D., & Neto, C. P. (2006). Triterpenic and other lipophilic components from industrial cork byproducts. *Journal of Agriculture and Food Chemistry*, 54, 6888-6893. <http://dx.doi.org/10.1021/jf060987> PMID:16939354
- Takeoka, G., Dao, L., Teranishi, R., Wong, R., Flessa, S., Harden, L., & Edwards, R. (2000). Identification of three triterpenoids in *Almond Hulls*. *Journal of Agriculture and Food Chemistry*, 48, 3437-3439. <http://dx.doi.org/10.1021/jf9908289> PMID:10956130
- Taralkar, S. V., & Chattopadhyay, S. (2012). A HPLC Method for determination of ursolic acid and betulinic acids from their methanolic extracts of *Vitex Negundo* Linn. *Journal of Analytical and Bioanalytical Techniques*, 3, 134. <http://dx.doi.org/10.4172/2155-9872.1000134>

- Woldemichael, G. M., Singh, M. P., Maiese, W. M., & Timmermann, B. N. (2003). Constituents of antibacterial extract of *Caesalpinia paraguariensis* Burk. *Zeitschrift für Naturforschung*, 58, 70-75. PMID:12622230
- Yogeeswari, P. & Sriram, D. (2005). Betulinic acid & its derivatives: A review on their biological properties. *Current Medicinal Chemistry*, 12, 657-666. <http://dx.doi.org/10.2174/0929867053202214> PMID:15790304
- Zhang, Y., Yu, T., & Wang, Y. (2003). Extraction of betulin from bark of *Betula platyphylla* by supercritical carbon dioxide extraction. *Journal of Forestry Research*, 14(3), 202-204. <http://dx.doi.org/10.1007/BF02856830>
- Zhu, M., Phillipson, J. D., Greengrass, P. M., & Bowery, N. G. (1996). Chemical and biological investigation of the root bark of *Clerodendrum mandarinorum*. *Planta Medica*, 62(5), 393-396. <http://dx.doi.org/10.1055/s-2006-957923> PMID:9005449.

