

## Betulin – A Future Key-Player in the Treatment of Neoplastic Diseases

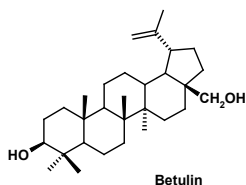
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Natural compounds have been used for hundreds of years to treat various diseases that the body is exposed to; giving the remarkable progresses achieved by organic synthesis chemistry, natural products went temporarily into obscurity, synthetic derivatives occupying an increasingly important place in drug therapy. However, the use of totally synthetic products is not entirely risk free, especially regarding side effects or even lack of therapeutical response. That is why a growing interest has arisen in the last years for the discovery of alternative therapies, heading for the re-discovery of natural therapies, together with the use of semisynthetic derivatives of phytocompounds, thus reuniting the classical drug chemistry with the advantages of biosynthesis, especially in the field of the 21<sup>st</sup> severe pathologies such as AIDS, cancer or autoimmune diseases.

Pentacyclic triterpenes research began with the publication by Pisha et al. [1] of the anticancer activity of betulinic acid, tested on melanoma cell lines; antitumor activity of betulinic acid is currently known to be manifested on numerous tumor cell lines (breast, colon, lung, neuroblastoma) [2,3] mainly by inducing apoptosis.

Betulin, (lup-20(29)-ene-3 $\beta$ ,28-diol), is a natural compound which can be relatively easily produced from plant sources (birch tree, plane tree, etc.), by sublimation or extraction in different solvents such as methanol, dichloromethane or chloroform [4,5].



Data concerning biological activity of betulin are rather poor, betulin being much less studied compared to its relative, betulinic acid. Still, in the last years, many researchers focused on the potential use of betulin in the pharmacological field, probably due to an increasing and continuous need for new cancer fighting agents. Together with other pentacyclic triterpenes, betulin was the object of an excellent review published in 2009 by Laszczyk M [3], which corroborated scientific data available so far on pentacyclic triterpenes.

Betulin's activity is rather weak on several tumor cell lines: melanoma [6], leukemia and neuroblastoma [7]; still, a proapoptotic activity can be noted together with an inhibitory effect on tumor cell line A549 (lung cancer) [8,9]. Also, an important effect was noticed on other tumor cell lines such as: colorectal (DLD-1), breast (MCF7) and prostate (PC-3). [8], another paper [10] revealed an important increase of antitumor properties by association with cholesterol. Betulin exhibits an antioxidant (especially in association with other triterpenes) and cytoprotective effect [3]. In addition, betulin shows an antibacterial, antifungal and antiviral activity [3].

Giving its lower activity compared to betulinic acid, why bother to study betulin any further?

The main advantage betulin has to offer is that the substance may serve as starting point for a high number of semisynthetic derivatives, with improved biological activity, especially in cancer and HIV infection

[11]. Chemical synthesis of such derivatives has led to the establishment of structure-activity relationships [12]. An overall conclusion of the mentioned study was that, an increase in the amphiphilic character of betulin's derivatives is generally accompanied by a better biological activity. The biologically active triterpenes generally show a relatively polar fragment bonded to a non-polar center, the presence of the polar moiety being essential [12].

Betulin and birch bark extract have been the subject of patents, as interferon inducers; antihypoxo agents; hepatitis C, influenza and tuberculosis prophylactic agents; additives in cosmetology and food products (Russ. Pat., 2.240.799, 2004., Russ. Pat., 2.252.775, 2005., Russ. Pat., 2.252.773, 2005., Russ. Pat., 2.244.554, 2005., Russ. Pat., 2.252.774, 2005., Russ. Pat., 2.262.349, 2005., Jpn. Pat., 10265328, 1998.) [12].

Recent studies [13] have revealed that, although betulin's water solubility does not overcome 0.10  $\mu\text{g/ml}$ , its intraperitoneally administration in rats for 28 days leads to a concentration of 0.13-0.14  $\mu\text{g/ml}$  in blood flow, independent of the dose. The administration was accomplished by suspending total birch extract (main component: betulin) in sesame oil. Subcutaneous administration in dogs, as a fine suspension in PEG 400 and saline solution, 300 mg/kg, led to a plasmatic concentration of 0.33  $\mu\text{g/ml}$  and a relation between the dose and plasmatic level. The same study could not reveal any toxic effects, regardless of the administration route or the animal species, concluding though that topical administration is the most appropriate; further studies are necessary.

Betulin's poor water solubility may be the reason for the lack of detailed data on its biological activity; that is why some recent studies reported attempts to increase triterpene water solubility by preparing nanoformulations [14] or cyclodextrin complexes [15].

Unlike its relative, betulinic acid, which is currently undergoing clinical trials [2], betulin has yet to wait for more scientific evidence regarding its use in cancer therapy; however, it is becoming more and more obvious that betulin will join the therapeutical arsenal against neoplastic diseases in the near future.

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Received November 11, 2012; Accepted November 13, 2012; Published November 20, 2012

Citation: Șoica C (2012) Betulin – A Future Key-Player in the Treatment of Neoplastic Diseases. *Med Aromat Plants* 1:e135. doi:10.4172/2167-0412.1000e135

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