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BIOACTIVE COMPOUNDS, PROPERTIES AND TOXICITY OF *BETULA* SP. – A REVIEW

Ioana TOPLICEAN, Adina-Daniela DATCU*, Rebeca IANUȘ
Biology-Chemistry Department, Faculty of Chemistry, Biology, Geography, West University of Timisoara, Romania
Corresponding author's e-mail: dana_datcu19@yahoo.com
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ABSTRACT
The aim of this review was to gather general data about the Betula pendula, but also its properties and toxicity. This is a genus that includes over 140 species distributed on several continents, but is native to Europe and central Siberia. However, birch's ability to colonize empty areas is very strong along with its tolerance to nutrient-poor soils. Furthermore, common birches are rich in resources with important bioactive components, some of which being used even in the pharmaceutical industry. The content of biologically active substances found in birch shows its dependence on the season, weather, and its biological variability. Due to the properties of the substances extracted from the birch, they can modify some proteins. It contains reactive oxygen species, substances which are also mediators of cell damage and play a key role in triggering many diseases by altering the oxidative balance. Birch medicines can also cause side effects such as nausea, diarrhea, allergic reactions such as skin blisters, itching. These medicines are not recommended for people with allergies to pollen or leaves or for people who are hypersensitive. Although, in healthy conditions, it is known that that birch juice along with other components from which teas can be made are very good for certain diseases such as kidneys and heart diseases, rheumatism. Isolated from birch, they are good for treating and caring for the surface, hair loss, cellulite, and scars.
KEY WORDS: *Birch bark, bioactive compounds, antioxidants, pharmaceutical use*

INTRODUCTION

The Betula genus and the family Betulaceae are derived from the latin Beatus (blissful). There are over 140 Betula species known in the world (Mashentseva et al. 2011).

Betula pendula Roth is an intermediate tree that can reach a height of 30 meters, but other species, like *B. pubescens* Ehrh looks to be considerably shorter, seldom, reaching a height of 20 meters and becoming dwarf trees in harsh environments such as northern tundra and mountains (Walters et al. 1993). The bark of the juvenile tree is brown, but as it ages, it turns silvery white with dark gray horizontal lenses that deepen

and break. *B. pendula* bark is brighter white and shinier than *B. pubescens* bark, and its branches droop, whereas *B. pubescens* branches grow upwards or horizontally (Beck et al. 2016).

The taxonomy of the European members of the genus has long been in dispute, but there are generally acknowledged to be two species of tree birch in Britain: *B. pendula* (2n = 28) and the *B. pubescens* complex (2n = 56) (Tuley, 1973).

The European birches form stable climax forests next to the northwestern edge of their range, but towards the center of their range, they are colonists in primary and human-induced secondary successions. Birches are pioneers in two types of habitats in Europe 1. forest or heathland recently cleared by felling or fire, in gaps left by canopy trees, or as primary colonizers of gravel and scree; 2. habitats climatically unsuitable for other tree species, such as northern England and Scotland's upland zones, or edaphically unsuitable habitats such as acidic peat bogs and fens. *Betula pendula* Roth can reach a height of 30m in these habitats (Atkinson, 1992).

Leaf laminae are about 2-5.5 cm in length, glabrous, ovate-deltate. The apex is acuminate and the base is truncate or broadly cuneat. Leaf margins are double serrate, with primary teeth prominent and curved towards the leaf apex. Petioles are 10-18mm long and 1-2mm wide. Male flowers have perianth and two bifid stamens; female flowers are three in the axil of each scale, an ovary with two cells and one anatropous ovule in each cell, and two free styles. Inflorescences of male flowers are 1-2 cm long, 4 mm wide while overwintering, 2-6cm long, 6mm wide at anthesis, 2-4 together on small shoot ends (Moore, 1979).

Inflorescences of females are erect, 1.5-3(-3.5) x 0-7cm, pale green when immature, but turning brown in late autumn. The scales have a short, broad cuneate base, broad lateral lobes, spreading, and curving towards the base, and the middle lobe is deltoid and obtuse. The fruit is a glabrous achene, 1-5-2-4mm long, 0-8-1-3mm wide, with a width of 3-5mm, upper edge of the wings exceeding the stigmas by 0.5-1.5mm (Atkinson, 1992).

Distribution. *B. pendula* is native to most of Europe and central Siberia (Atkinson, 1992). *B. pubescens* has a more northerly and easterly distribution in Europe than for any other tree species, whereas *B. pendula* can reach southern regions such as the Iberian Peninsula, South Italy, and Greece. Since of their widespread distribution, these two birches show a high degree of morphological variability, and several subspecies and varietals have been described (Forbes & Kenworthy, 1973). Furthermore, they are sympatric in most parts of Europe and can naturally hybridize, resulting in plants. The taxonomy and identification of the genus Betula are challenging due to the

capacity of birches to create polyploid forms, as well as variability, hybridization, and the more recent introduction of intentionally grown variants outside their natural habitat (Beck et al. 2016). Both species have a huge spectrum of climatic tolerance, but it is important to bear in mind that *B. pendula* extends further south in Europe and Asia than *B. pubescens*, whereas *B. pubescens'* distribution is more northerly and easterly than *B. pendula*'s. In northwestern Scandinavia's alpine zone. Both species' northern ranges appear to be determined by protection from cold north-easterly winds (Verwijst, 1988). The ability of birches to colonize bare areas quickly, their intolerance of shade, their lack of affinity for any particular soil type, and their ability to grow on nutrient-poor soils are the main characteristics that characterize their attitudes in communities. As a consequence, they have a broad geographical and edaphic range and can grow in marginal habitats (Rackham, 1980; Dimbleby, 1952; Gardiner, 1968).

MAIN BIOACTIVE COMPOUNDS

Common birch is a significant resource of bioactive compounds, of which the most important are terpenes, flavonoids, catechins, lignins and tannins (Table 1). Due to the distribution of this plant species, it is suitable and available for the isolation of bioactive compounds. Recent researches have confirmed a large number of pharmacological activities of birch isolates which can be used in the treatment of a large number of diseases (Vladimirov et al. 2019).

TABLE 1. Chemical composition of the essential oil from the common birch buds obtained by hydrodistillation, and analyzed by GC-MS, (dominant compounds belong to a group of sesquiterpene hydrocarbons, the most abundant being α-copaene, germacrene D and δ-cadinene) and the volatile compounds (BVC) of whole birch buds (Demirci et al. 2004; Isidorov et al. 2014; Demirci et al. 2003)

Compound	Content (%)	BVC (g/mol)
α-Cubebene	0.8	1.16 ± 0.24
α-Copaene	11.8	15.77 ± 2.84
β-Caryophylene	3.4	3.41 ± 0.68
α-Humulene	2.9	3.97 ± 0.72
y-Cadiene	2.4	3.22 ± 0.71
σ-Cadiene	10.8	6.65 ± 1.33

BVC-buds volatile compounds
The chemical composition of diethyl ether extract in these compounds were not detected.

Birch leaves

The chemical composition of flavonoids, the most important phenolic molecules, found mainly in birch leaves, is being studied extensively.

The flavonoids quercetin-3-O-galactoside (hyperoside), quercetin-3-O-glucuronide, myricetin-3-O-galactoside, quercetin-3-O-rhamnoside, and other quercetin glycosides were identified in the birch leaf (Baser et al. 2000, 2007).

Birch bark

Birch bark was valued even during the ancient and historic periods because of its properties and effectiveness, and it is now studied in science and the pharmaceutical business. The pharmaceutical and cosmetic industries are currently conducting substantial research.

The bark contains triterpenes, which represent a new class of putative anti-cancer and anti-HIV bioactive chemicals with a novel mechanism of action (Goun et al. 2002).

Triterpenes of the lupane type are more common than those of the oleane type. The pharmaceutical and cosmetic industries use these bioactive chemicals as dietary supplements, biocides, and bactericides (Krasutsky, 2006).

The average chemical composition of triterpens present in white birch bark extracts are: Betulin (which has a content of approximately 78.1%), Beulinic acid (4.3%), Betulin aldehyde (1.2%), Lupeol (7.9%), Oleanolic acid (2.0%), Betulin-3-caffeate(0.5%), Erythrodiol (2.8%), and others (3.2%). Betulone, betulonic aldehyde, lupenone, betulonic acid, oleanolic aldehyde, and -amyrin are some of the less abundant components (Krasutsky, 2006).

The usage of natural compounds, such as birch bark triterpenes, is, however, very limited. Poor solubility (1 mg L^{-1} in water), a high log P value (>9), and a high molecular weight (>500 Da) are the key reasons for this (Demirci et al. 2004; Demirci, 2000a, b).

Phenolic compounds

Recently, it was shown that the knotwood of some trees, which can be available from the wood processing waste, contain considerable amounts of flavonoid (+)-dihydroquercetin, lignans(–)–secoisolariciresinol (Yashusky et al. 2014) and 7-hydroxymatairesinol, (Holmbom, 2003) stilbenes pinosilvin and its derivatives. This compound has proved to have antioxidant and bactericide properties and affecting cells of the hormonal (antiestrogens) (Zhukova et al. 2010), immune, and nervous systems (Tsvetkov et al. 2015; Westcott & Muir, 2003; Loers et al. 2014).

The interest in nutritional supplements plant based has increased. Plant extracts of the leaves of white birch (*Betula pendula*) have shown the health-promoting properties.

The total phenolic and total flavonoid contents of dry extract of *Betula pendula* leaves were evaluated using the Folin-Ciocalteu methods and aluminum chloride colorimetric assay (Christova et al. 2014).

Extracts of the studied material are required for use to produce medicines and herbal supplements by Bulgarian pharmaceutical industry. The data show that the extracts of the leaves of white birch have some content as a total phenols and flavonoids. The levels of these biologically active substances demonstrated dependence on the season, weather conditions typical for the region and finally - the biological variability. Forthcoming in-depth study of individual flavonoid representatives would provide a more accurate characterization of the biological activity of the product, given their use as food additives and in pharmacy. Nitrate levels are within acceptable limits. The studies reveal the absence of pathogenic microorganisms, mold, and fungi in the preparation of materials for medicinal use. The lack of a tendency to microbiological contamination allows to prepare medicines by these extracts for oral human use.(Christova et al. 2014; Harbone, 1993).

Chemical Composition and Pharmacological Activity

The main components (by hydrodistillation and microdistillation, respectively) found were 12% and 10% alpha-copaene ($C_{15}H_{24}$), 11% and 18% germacrene D($C_{15}H_{24}$) and 11% and 15% delta-cadinene ($C_{15}H_{24}$) in the analyzed essential oils. Diarylheptanoids have been the center of the intensive research efforts for Alzheimer's disease and other neurodegenerative diseases. The *B. pendula* extract showed significant anti-inflammatory activity (Mashentseva et al. 2011).

The major components of the volatile oil from the inner bark of *B. pendula* were trans 31% alpha-bergamotene ($C_{15}H_{24}$) 19%and alpha-santalene ($C_{15}H_{24}$), 18% alpha-bergamotene ($C_{15}H_{24}$), 12% ar-curcumene ($C_{15}H_{22}$), 12% E-beta-farnesene ($C_{15}H_{26}$), 10% Z-beta-farnesene ($C_{15}H_{24}$) and 8% cis-alpha-bergamotene ($C_{15}H_{24}$). Other compounds are 14-hydroxy-beta-caryophyllene ($C_{15}H_{24}O$), beta-betulenal ($C_{15}H_{22}O$), 14-acetoxy-beta-caryophyllene ($C_{17}H_{26}O_2$) (Butnariu et al. 2019).

ANTIOXIDANTS

Because of their action on proteins, DNA, and lipid peroxidation, reactive oxygen species such as superoxide anion, hydroxyl radical, and hydrogen peroxide are extremely reactive chemicals that cause a variety of cell diseases. They are significant mediators of cell damage and play a key role in the onset of many illnesses by altering the oxidative equilibrium (Dimitrova et al. 2010).

Herbal antioxidants have a complicated process of action and a reduced impact on the body, whereas many synthetic antioxidant compounds have been found to be toxic and/or mutagenic. The importance of natural antioxidants has grown as a result of this (Penkov et al. 2018).

For the time being, common birch is seen to be a promising and abundant source of natural antioxidants. Further research aims to determine the antioxidant capacity and preventative activity of extracts obtained from various parts of common birch isolates in the prevention and treatment of diseases caused by UV radiation and other harmful agents, as well as the potential use of extracts obtained from various parts of common birch isolates in the prevention and treatment of diseases caused by UV radiation and other harmful agents (Ju et al. 2004).

Experiments on rats were conducted in vitro and in vivo utilizing a variety of methodologies, including evaluating the extract's ability to eliminate DPPH radicals, ABTS cationic radicals, and hydrogen peroxide, as well as its ability to bond metals as a chelate agent. Acute hypoxia in rats was used to investigate phospholipid oxidation pathways. The effect of birch extract on brain tissue was measured by the change in the interaction between acidic and neutral phospholipids. It was discovered that rats with ischemia had lower levels of acidic phospholipids in their homogenates. The phospholipid ratio was normalized after a preventative injection of birch extract. Due to the largest level of total flavonoids, the extract of young branches had the strongest effectiveness for neutralizing DPPH radicals (Mashentseva et al. 2011). All the materials used in the study, including 2,2-diphenyl-1-picryl hydrazyl (DPPH), Folin-Ciocalteu's reagent, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS), 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH), methanol, potassium persulfate, fluoresce (Penkov et al. 2018).

In vitro and in vivo approaches to test the antioxidant activity of plant extracts and other substances with an antioxidant effect have been reported in the literature.

Several methods were used to completely analyze the extract's antioxidant capability, including the DPPH method, the ABTS method, the HORAC assay, and the FRAP method (Penkov et al. 2018).

Results from the study demonstrate the antioxidant capacity of the dry birch leaves extract. It exhibits a relatively strong antioxidant activity, therefore it can be used as a natural source of antioxidants, presenting the potential opportunity to prepare product with high value, helpful in preventing various oxidative stress related conditions. To summarize, dried birch leaf extract has a strong antioxidant potential and might be employed as a natural antioxidant source (Penkov et al. 2018).

PROPERTIES

Several types of birch isolates are described in the literature as being used as prescription drugs in various parts of the world. The most prevalent uses are in the treatment of urinary tract issues, bones (including arthritis, rheumatism, and gout), and kidney stones (Rastogi et al. 2014).

Birch tree juice and liquid preparations such as teas, infusions, and decocts made from the bark, buds, because of its favorable effects on human health, birch leaves are used to treat arthritis, rheumatism, kidney illness, hypercholesterolemia, colds, heart disease, and liver disease. Birch isolates should only be used to prevent hair loss, cure alopecia, skin problems (cellulite), heal wounds and scars, and as a diuretic (Rastogi et al. 2014).

Rheumatoid arthritis is a chronic, systemic inflammatory illness that affects roughly 1% of the world's population. The most common symptoms are joint pain, stiffness, and edema. The treatment of arthritis and rheumatism is one of the most common uses of birch in traditional medicine in numerous European nations. Several studies were carried out to back up these statements (Vladimirov et al. 2019).

In the research of Peev et al. (2010) among other things, a comparison of diuretic and uricosuric activity (increased excretion of uric acid) of bud extracts and birch sap was evaluated. It has been found that these activities are superior in the birch sap in comparison to the bud extract (Peev et al. 2010)

In the study of Rapp et al., the gastroprotective activity of various concentrations of common birch bark aqueous-ethanolic extracts (20, 30, 35, 40 and 70%) was investigated. The results obtained on the mucous stomach membrane showed that 40% ethanol solution was the best extractant. The birch bark extract thus obtained showed reliable anti-stress and anti-ulcer effects (Rapp et al. 1999).

The in vitro inhibitory effect on xanthine oxidase of herbs historically used to treat gout, arthritis, and rheumatism in the Czech Republic and Central and Eastern Europe was investigated by Havlick et al. Because gout and nephrolithiasis are both caused by high levels of uric acid in the blood, urine monosodium crystals can build up in the joints and kidneys (Grundemann et al. 2011).

The xanthine oxidase enzyme is the target of medications that lower urate levels in hyperuricemia (Grundemann et al. 2011). In the study, *Betula pendula* and *Populus nigra* showed the greatest potential for inhibiting xanthine oxidase. The buds and leaves of these plants were investigated in 80 percent ethanolic and methylene chloride-methanolic extracts. Because it contains salicylates and other phenols, common birch is

the most active. Havlick's research backs up traditional medicine's use of birch as an effective anti-rheumatic and anti-gout treatment (Grundemann et al. 2011).

TOXICITY FOR SOME ORGANISMS

Side effects that have been reported with birch leaf medicines include diarrhea, feeling or being sick, and allergic reactions, such as itching, rash and stuffy and runny nose. Their frequency is unknown. Birch leaf medicines must not be used in patients who are hypersensitive (allergic) to birch leaf or birch pollen. They must also not be used in patient with conditions where a reduced fluid intake is recommended (such as severe heart or kidney disease) (Vladimirov et al. 2019).

Also, Huh et al. investigated the acute oral toxicity of a 50% hydroalcoholic extract and its n-butanol fraction (BFBP) derived from the bark of *Betula platyphylla*. Their single dose toxicity was assessed in both sex fraternal doses of 5.0 g / kg body weight dose, rats were randomly assigned to two experimental groups, vehicle group (distilled water) and treatment group (5 g kg^{-1}), was observed for 14 days following treatment. The 50 percent hydroalcoholic extract and its BFBP had no effect on mortality, changes in human weight, physical results, or clinical symptoms by biochemical analysis at this dose, unbiased of sex. *Betula platyphylla* did not, in theory, induce stomach irritation, erosion, or ulceration. They were supplied at a dose of 5 g/kg, indicating that they are non-toxic at this dosage (Huh et al. 2009, 2011). It has been reported that *Betula platyphylla* bark extract has antioxidant and anticancer activity (Ju et al., 2004).

However, a dry triterpene is produced from the bark of the tree of *Betula pubescens*. White birch usually contains pentacyclictriterpenes, primarily betulin, but moreover betulinic acid, oleanolic acid, lupeol, and erythrodiola has undergone subchronic toxicity studies in rats. Daily doses of triterpene-rich dry extract up to 540 mg / kg for 28 days (Jager et al. 2008).

Betulin, like other pentacyclic triterpenes, has also been demonstrated in studies to be tobenon-toxic (Jager et al. 2008). Betulinic acid was also found to be non-toxic for mice at levels of up to 500 mg kg^{-1} body weight (Pisha et al. 1995).

CONCLUSIONS

Betula pendula has a lot of beneficial properties for the human body. Although, side effects may occur, similarly to other medicines or herbs, they are rare, but not serious and can be easily managed, with the help of a prescription. The sap is very rich in bioactive compounds, and it has many proven health benefits on a variety of diseases.

We have concluded that all components that make up the birch tree: leaves, bark, and sap, can be used in the pharmaceutical field.

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