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Mini review

The significance of arbutin and its derivatives in therapy and cosmetics

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ABSTRACT

The ongoing studies on biological activity of arbutin and its derivatives show a wide range of their possible applications. Arbutin containing plant substances are used mostly in the treatment of urinary tract infections (UTI). However, several *in vitro* and *in vivo* studies revealed anti-melanogenic activity of arbutin, which can be useful in hyperpigmentation therapy. Moreover, it was found that the modifications in arbutin structure lead to an increase of the above-mentioned activity. The lack of significant adverse effects of arbutin and its derivatives makes them a valuable alternative to hydroquinone. Therefore, an increasing interest in arbutin and its derivatives is observed especially in the cosmetics industry.

The scope of biological activity covered by the findings of *in vivo* and *in vitro* studies on arbutin and its derivatives are discussed.

Contents

1. Introduction

Based on SCOPUS data, arbutin and its derivatives were a subject of at least 120 scientific papers over the last ten years. According to EMEA (2012) monographs, arbutin-containing plant materials are used in the treatment of urinary tract infections. Thanks to the studies on the biological activities of arbutin, its derivatives and arbutin-containing extracts the spectrum of their uses is broadening. The need for new sources and methods of arbutin derivatives synthesis is justifiable. Until now, plant substances, especially *Uvae ursi* folium, have been the basic sources of arbutin. Nowadays, plant extracts are replaced by chemically and biotechnologically synthesized arbutin and its derivatives.

New sources, structure, biological activities and application of arbutin and its derivatives are described in the presented work.

2. Chemical structure and occurrence in the plant kingdom

Arbutin as hydroquinone derivative is 4-hydroxyphenyl-β-glucopyranoside named also β-arbutin (Fig. 1).

This simple phenol glucoside is biosynthesized mainly by Ericaceae and Saxifragaceae species. Arbutin-containing extracts from the leaves of *Arctostaphyllos uva ursi* (Ericaceae) have been used in phytotherapy for centuries. Nowadays, it is recognized as a

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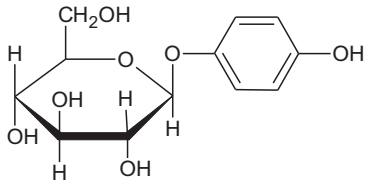

Fig. 1. Structure of arbutin.

medicinal plant herbal (EMEA, 2012). Arbutin is also encountered in the species of Asteraceae, Rosaceae, Lamiaceae and Apiaceae families. It occurs in species of the genus *Origanum* (especially *O. majorana*), pears, wheat products, coffee and tea (Cádiz-Gurrea et al., 2013; Chauhan et al., 2013; Deisinger et al., 1996; Lukas et al., 2010; Rychlińska and Nowak, 2012; Tomosaka et al., 2012; Venditti et al., 2013). In plants arbutin exists in a free, ether or esterified form (Fig. 2).

The leaves of *Arctostaphylos uva ursi* contain arbutin, methyl arbutin together with arbutin galloyl derivatives (O-galloyl arbutin, 2-O-galloyl arbutin, 6-O-galloyl arbutin) (EMEA, 2012). 6′-O-(3,4-dihydroxycinnamoyl arbutin) (robustasid B) was isolated from the leaves of *Cenestis ferruginea* (Capparaceae) (Adisa et al., 2011). 6′-E-(2-methyl-2-buteonyl)-arbutin and 6′-(2,5-dihydroxycinnamoyl)-arbutin were identified in the leaves of *Heliciopsis lobata* (Liu et al., 2008, 2010). 6′-O-[(2R)-methyl-3-propanoyl-veratroyloxy]-arbutin and 4′-O-[(2R)-methyl-3-veratroyloxy-propanoyl]-arbutin were recognized in the leaves of *Gentiana pyreneica* (Garcia et al., 1989) while the leaves of Ilex theezans contained 2′-sulfonyl arbutin (Andrade et al., 2004). Two other derivatives, 6′-O-(3-(2-(hexamethyl) acryloyloxy)-2-methylpropanoyl)-arbutin and 6′-O-(2-methylacryloyl)-arbutin, were recognized in the stems of *Grevillea banksii* (Wang et al., 2008). Moreover, a number of esterified arbutin derivatives—grevillosides J-Q, were found in *Grevillea robusta* (Yamashita-Higuchi et al., 2014).

The amount of arbutin in the plant material is variable. The drying method and vegetation period of the plant have a great influence on arbutin content. For example, the largest quantity of arbutin was determined in the young, completely developed, green leaves of *Bergenia crassifolia* (Saxifragaceae) dried at 80–100 °C (Lubsandorzhieva et al., 1999).

Due to the increasing use of arbutin in cosmetics and pharmaceuticals new sources of arbutin are being sought out. It was found out that both plants and bacteria in *in vitro* cultures can biosynthesize arbutin and its derivatives. However, supplementation of the culture media with hydroquinone is needed for biotransformation reaction to take place.

Piekoszewska et al. (2010) obtained 7.2–7.8% of arbutin in the dried shoots of *Ruta graveolens* and *Hypericum perforatum* cultivated *in vitro*. Both plant cultures synthesized arbutin from hydroquinone added to the culture medium (Piekoszewska et al., 2010). Kwiecień et al. (2013) showed that hydroquinone can be biotransformed into arbutin by agitating tissue cultures of *Aronia melanocarpa*, too. The quantitative HPLC analysis showed that the biomass synthesized arbutin in higher amounts (up to 8.27 g/100 g dry weight) than required by European Pharmacopoeia for Uva ursi leaves (7.0 g/100 g dry weight) (Kwiecień et al., 2013). These results confirm that active metabolic pathways of arbutin biosynthesis are present not only in species of Eriaceae family.

α-Arbutin (Fig. 3) and other arbutin derivatives are obtained mainly by enzymatic or chemical synthesis from hydroquinone or arbutin (Liu et al., 2013; Seo et al., 2012a,b; Wang et al., 2006).

α-Arbutin was synthesized by glucosidation of hydroquinone in the presence of enzymes from different bacterial strains: amylase of *Bacillus subtilis* and sucrose phosphorylase of *Leuconostoc mesenteroides* (Liu et al., 2013; Nishimura et al., 1994). Wu et al. (2008) used a recombinant *Escherichia coli* with surface anchored transglucosidase as a biocatalyst for glucosidation of hydroquinone to α-arbutin. Moreover, the use of lyophilized cells of *Xanthomonas campestris* WU-9701 made the biosynthesis of α-arbutin more effective and less expensive (Kurosu et al., 2002). In turn, glycosides of α-arbutin, 4-hydroxyphenyl β-maltoside, 4-hydroxyphenyl β-maltotrioside, 4-hydroxyphenyl α-maltoside and 4-hydroxyphenyl α-maltotrioside, were obtained by glucosidation of α-arbutin in the presence of cyclodextrin glucanotransferase, *Bacillus macerans* and soluble starch mixture (Sugimoto et al., 2003, 2005). A wide variety of arbutin derivatives were synthesized with the method described by Ishihara et al. (2010). The reaction mixture contained arbutin, aromatic or aliphatic acids as an acyl donor and β-lipase from *Candida antarctica*. The method was used in the synthesis of arbutin ferulate and arbutin lipoate (Ishihara et al., 2005). Acyl arbutin derivatives were products of arbutin condensation with saturated fatty acids (C6–18) by lipase in a bath reaction (Nagai et al., 2009). Tokiwa et al. (2007) synthesized 6-O-undecylenoyl-p-hydroxyphenyl-β-D-glucopyranoside in transesterification reaction of arbutin and undecylenic acid vinyl ester in the presence of alkaline protease.

3. Stability of arbutin in preparations

Arbutin is relatively stable in ethanol extracts. It is resistant to light and pH 2. Therefore, it is stable in cosmetics within 4–8 pH range (SCCP, 2008). In the aqueous extracts, arbutin may undergo partial hydrolysis to hydroquinone that can be oxidized to benzoquinone. In some cases, the formation of benzoquinone, which has a wider spectrum of antibacterial activity, may be desirable in external use of the plant extracts (Himejima et al., 2004; Jin and Sato, 2003).

4. The biological activity and the use of arbutin and its derivatives

4.1. The use in the treatment of urinary tract infection (UTI)

Aqueous and ethanol–water extracts of arbutin-containing plant materials, are used only in the treatment of UTI mostly as components of complex herbal drugs.

Hydroquinone as an aglycone of arbutin is responsible for antibacterial activity of plant extracts. It exhibits astringent, disinfectant and antioxidant properties. (Garcia de Arriba et al., 2010; Garcia de Arriba et al., 2013; Geetha et al., 2011; Halberstein,

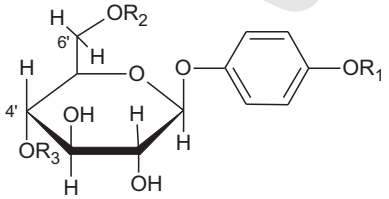

Fig. 2. Positions of substituents in the arbutin structure.

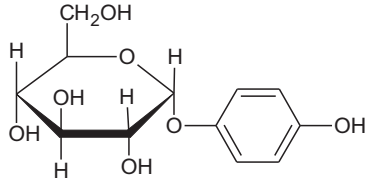

Fig. 3. Structure of α-arbutin.