naturopaths & herbalists association of australia

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NHAA MEMBER ALERT

Poisons Standard Scheduling of Herbs that contain Arbutin

Has there been a recent change to the Scheduling of arbutin and arbutin-containing herbs?

No. The change occurred in 2010. There is a TGA administrative follow-through on previous Scheduling decisions about the chemical substance hydroquinone and related substances found in certain herbs. Arbutin is included as a cross-reference to hydroquinone in the Appendices to the *Poisons Standard* and is affected by this follow-up. Therefore, the TGA is correct in communicating there is 'no change' in the Scheduling of arbutin-containing herbs per se. What has changed, is the TGA's follow through and further analysis on arbutin-containing herbs, such as *Arctostaphylos uva-ursi folium* (bearberry leaf) and *Turnera diffusa folium* (damiana leaf), and how they are to be captured by this rescheduling.

Hydroquinone (in oral medicines) is included in Schedule 4 (Prescription Only Medicines) of the *Poisons Standard* (also known as the SUSMP: Standard for the Uniform Scheduling of Medicines and Poisons). It is believed that hydroquinone was included in Schedule 4 as early as 1991. Arbutin first appeared as a cross-reference to hydroquinone in the August 2010 version of the *Poisons Standard*. The 2010 change arose due to safety concerns about possible carcinogenicity of hydroquinone and arbutin, a glycoside of hydroquinone, likely because some literature sources suggest that it is a theoretical possibility that arbutin might hydrolyse into free hydroquinone.

As such, both hydroquinone and preparations containing above 10 parts per million (10ppm) of the component arbutin were included as Schedule 4 Prescription Only in 2009.[1] This means that arbutin, when present in herbal preparations at a level above 10ppm, is effectively captured by Schedule 4 and therefore are restricted for general sale and supply. Herbs containing less than 10ppm arbutin are not affected and can still be included in herbal preparations.[2]

It appears that the incongruence between the 2010 change and what is happening now appears to have come to light after "*someone in industry frustrated that they were the only ones applying the hydroquinone restriction on products containing bearberry extract"*[3] brought the matter to the attention of the TGA. We believe that there is no intent by the TGA to single out herbal medicine and there is no evidence of a conspiracy.

In the coming days and weeks, we intend to work with other interested industry and professional bodies affected by this Scheduling and administrative follow-up by the TGA, to contribute to an application to the TGA's Advisory Committee on Medicines Scheduling try to rectify this Scheduling of arbutin, and/or to protect the availability and safe use of herbs containing arbutin.

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Understanding Arbutin and Hydroquinone

Hydroquinone is used as a photographic developer, antioxidant, stabilizer (in paints, fuels, oils and polymers), as a chemical intermediate and in pharmaceuticals. Hydroquinone is also used as a skin depigmenting agent and in hair preparations.[4]

Arbutin and Bearberry leaf are also used as skin lightening agents in cosmetics.[5]

The National Drugs and Poisons Schedule Committee 2009 reported that "*although the general toxicological assessment of arbutin suggests that the substance may be safe, the bioavailability of hydroquinone under conditions of intended use of the substance is of concern."*[3]

Pharmacology of arbutin

Arbutin, a glycoside of hydroquinone, is a major constituent of Bearberry leaf.[6] It is stable in gastric acid,[7] and can be absorbed by the human intestinal sodium/glucose co-transporter (SGLT2).[8] After being absorbed from the small intestine, arbutin is transported to the liver, where it is deglycosylated to yield hydroquinone (HQ) and glucose. The HQ immediately undergoes phase II glucuronidation and sulfation, resulting in HQ-glucuronide and HQ-sulfate, respectively. Arbutin itself has not been detected in urine, suggesting complete metabolism.[9] The HQ metabolites are then eliminated via the urine.[10] See Illustration 1 below for a graphical representation of this process.

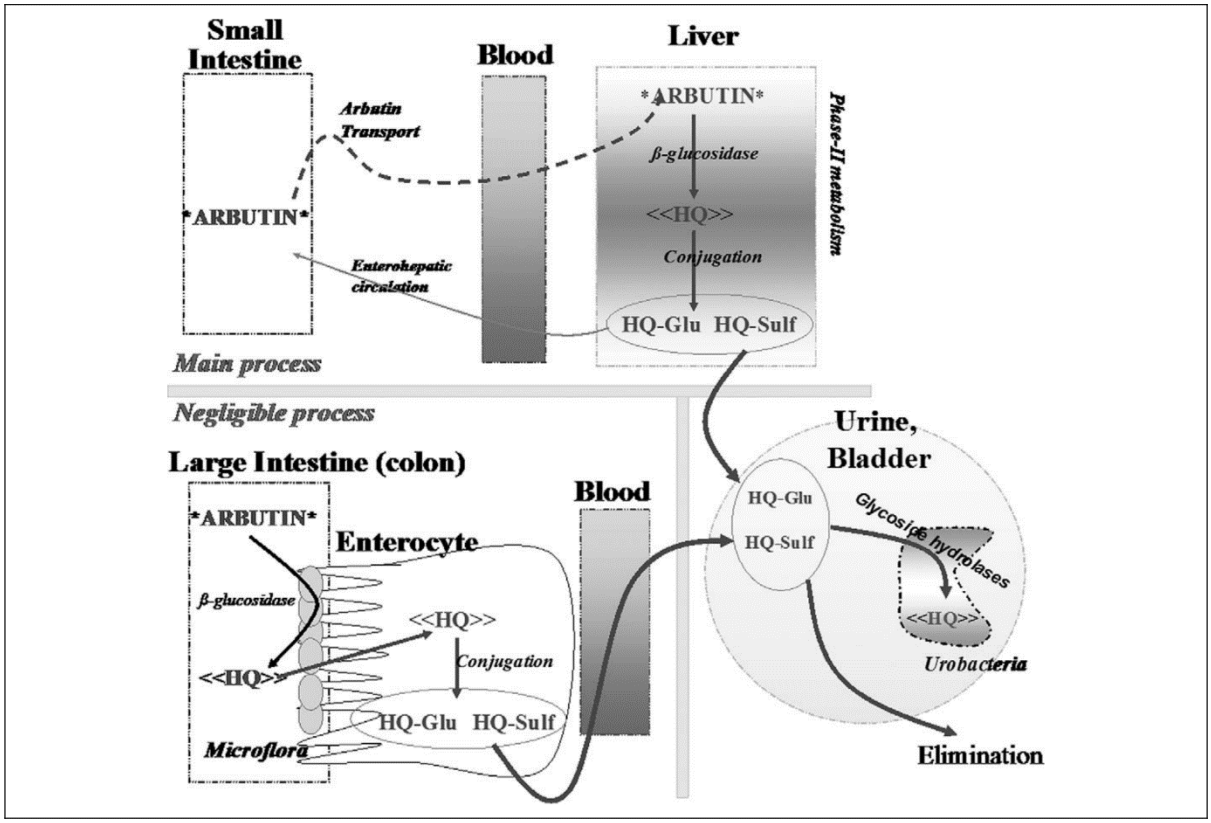
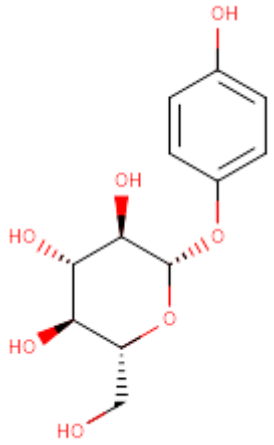
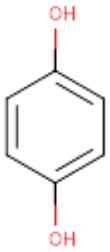
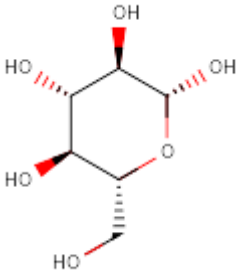


Illustration 1: Pharmacokinetics of arbutin in vivo, from Garcia de Arriba et al. (2013).

Various bacterial strains are known to have beta-glucuronidase activity,[11] including strains that may be pathogenic in the urinary tract.[12] These strains are therefore capable of deconjugating HQ-glucuronide, which leads to the release of free hydroquinone. HQ-sulfates also have the potential to be deconjugated into free hydroquinone.[13] In alkaline solution, hydroquinone may auto-oxidise to benzoquinone,[14] which may also have bacteriostatic effects,[15] perhaps being part of the basis for recommending that urine be more alkaline during treatment of urinary tract infection,[16] however it has been shown that urinary pH does not affect the efficacy of Bearberry leaf.[17] Simple phenolics, like hydroquinone, exert their antimicrobial effects by causing leakage of bacterial cellular constituents through the disruption of their cell membranes.[18]

The SUSMP considers arbutin and hydroquinone to be equivalent. With respect to dosage, these substances cannot be considered as equivalent due to significant differences in molecular weight, with arbutin being approximately 147% larger than hydroquinone. See Table 1 for a comparison.

Chemical	Arbutin	Hydroquinone	beta-D-glucose
Structural formula			
Molecular formula	$C_{12}H_{16}O_7$	$C_6H_6O_2$	$C_6H_{12}O_6$
Molar mass (g/mol)	272.253	110.112	180.156
CAS number	497-76-7	57534-13-1	108942-17-2

Marvin was used for drawing, displaying and characterising chemical structures. Marvin 18.12, 2018. ChemAxon (http://www.chemaxon.com).

Which herbs are affected?

The TGA published a website update in May 2018 that herbs which contain arbutin as a herbal component in a concentration exceeding 10ppm will not be eligible to be included in Listed complementary medicines in Australia (medicines with “AUST L” on the label). If any herb contains less than 10ppm arbutin, it can still be included in complementary medicines. The TGA page can be viewed here: https://www.tga.gov.au/upcoming-changes-permissible-ingredients-june-2018

Arbutin naturally occurs as a component in some herbs and foods, but due to the levels of arbutin in Bearberry leaf and in Damiana leaf, they have not met the TGA requirements for an AUST L listing since 2009 and as such will no longer be available in any AUST L medicines (including medicines labelled as Practitioner Only).

At this stage it is the NHAA’s understanding that whilst *Achillea millefolium* (yarrow) does contain arbutin, the level in extracts is below the threshold, and thus as of publication of this notice it remains available for medicinal usage.

What about teas and liquid extracts/tinctures?

At this time, both Bearberry leaf and Damiana leaf are Schedule 4 substances, and thus unable to be dispensed in any form by herbalists and naturopaths. This includes tablets, capsules, teas, liquid extracts or tinctures, or any other form.

Whilst normally the Therapeutic Goods Regulations 1990 excludes medicines that are extemporaneously compounded by practitioners from the requirement to be included on the Australian Register of Therapeutic Goods (ARTG) and to be subject to GMP manufacturing requirements (see our member guidance on Extemporaneous Dispensing https://www.nhaa.org.au/docs/Member_docs/Extemporaneous_Dispensing_Guide.pdf), any medicine containing more than 10ppm arbutin would be considered to be Schedule 4 Prescription Only.

What has been done so far?

As the main concern is with free hydroquinone, not directly with arbutin, Complementary Medicines Australia (CMA)[19] has written to the TGA requesting that the level of arbutin in permissible herbs within listed complementary medicines be increased to a level of 25ppm (according to the molecular weight of arbutin, 25ppm is equivalent to 10ppm of hydroquinone). We have been informed that this new level has been accepted, and will be reflected in the upcoming TGA documentation changes.

CMA will also be coordinating an industry-wide application to the TGA's Advisory Committee on Medicines Scheduling to either remove or down-schedule arbutin from the Schedules, or to exempt herbs that contain arbutin from the Schedules. CMA advise that de-scheduling applications and TGA processes are involved, lengthy and protracted: in almost all cases the time period involved is extended (such as 1 to 2 years).

The NHAA plans to work with CMA and ARONAH (and all other interested associations) to represent this issue with one clear and focused voice.

And what should members do?

While a letter writing campaign might seem advantageous and the logical next step, NHAA respectfully requests members not to write until requested. Should the need arise, members will be supplied with an example letter and asked to support the de-scheduling of arbutin-containing herbs in writing. The NHAA is investigating the best option to move this forward and will keep members informed.

References

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[3] https://www.tga.gov.au/sites/default/files/submissions-received-the-scheduling-policy-framework-and-advertising-of-pharmacist-only-medicines-schedule-3-substances-acc.pdf

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[19] Complementary Medicines Australia (CMA) is the industry body for the complementary medicines industry. See: http://www.cmaustralia.org.au/