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Commentary

Natural products regulation – Getting the balance right. The case of arbutin

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ABSTRACT

Recently, the TGA published an update stating that herbs which contain arbutin in a concentration exceeding 10 ppm are not eligible to be included in Listed complementary medicines in Australia due to scheduling of hydroquinone in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) (the "Poisons Standard"). This has subsequently had an effect on the availability of medicines and extracts used extemporaneously by practitioners. Of concern is the loss of medicinal herbs with important therapeutic benefits that are commonly used in therapeutic goods or in extemporaneously dispensed preparations, such as Bearberry (*Arctostaphylos uva-ursi*) and Damiana (*Turnera diffusa*). This article briefly discusses the history of arbutin scheduling and the chemistry and metabolism of arbutin. It suggests that the understanding of the metabolism of arbutin and clinical use of the herbs affected should be more closely considered, and amendments to the Poisons Standard is recommended for the oral use of herbal medicines containing arbutin, such that continued use of Bearberry and Damiana can be achieved.

Herbal medicines, particularly those applied by traditional systems of medicine, have been used for thousands of years, drawing on substantial clinical experience as a basis for the safe and effective use of herbal medicines. As the popularity of herbal medicines continues to grow, it is important to consider that they are not necessarily always safe simply because they are natural. Some have given rise to serious adverse reactions, and some contain chemicals which may produce long-term side effects such as carcinogenicity and hepatotoxicity, which highlights the need for regulation of herbal medicine to be based on current pharmacological and traditional understanding of these substances. In the case of a herb such as Bearberry *(Arctostaphylos uva-ursi)*, it is used for short-term, intermittent treatment of acute urinary tract infection, which excludes long-term use in regular clinical practice by default. Concurrently, traditional use of herbs is based upon a broad spectrum extract of medicinal plants. The extracts are a complex mixture of chemicals, not reduced to single chemical compounds. The pharmacology of these mixtures are necessarily different from that of isolated constituents. This phenomenon is known as synergy, and is a fundamental feature of traditional herbal medicine. It has been shown that chemically more complex extracts can be less toxic than extracts of lower complexity from the same plant [1], so decisions on scheduling should take this into account. The current scheduling of bearberry as being equivalent to hydroquinone does not.

In May 2018 the TGA published a website update stating that herbs which contain arbutin in a concentration exceeding 10 ppm will not be eligible to be included in Listed complementary medicines in Australia (medicines with "AUST L" on the label). In response, Complementary Medicines Australia made a submission demonstrating the discrepancy in molecular weight of arbutin and hydroquinone and subsequently achieved an increase in the concentration limit to 25 ppm. However, the concentration of arbutin in Bearberry and Damiana (*Turnera diffusa*) extracts as used extemporaneously by practitioners, the latter of which isn't known or used for its arbutin content, has lead to significant confusion in the herbal medicine practitioner profession. Subsequently . . . , these herbal extracts have been withdrawn from sale by manufacturers, and professional associations have recommended they not be prescribed, in order to avoid the risk of infringing upon

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the requirements of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Normally the Therapeutic Goods Regulations 1990 (Schedule 5) excludes medicines which are extemporaneously compounded by practitioners from the requirement to be included on the Australian Register of Therapeutic Goods (ARTG). But because an extemporaneously dispensed preparation is still considered a medicine for human therapeutic use, in this instance extemporaneously dispensed preparations are not exempt from the restricted supply of arbutin-containing herbs. Any medicine containing more than 25 ppm arbutin would be considered to be Schedule 4 Prescription Only. As such, Bearberry and Damiana are currently considered to be Schedule 4 and restricted.

1. The history of arbutin scheduling

Hydroquinone was included in Schedule 4 as early as 1991 and 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 (a known carcinogen). It appears that the 2010 change has only recently been publicly enforced after the matter was brought to the attention of the TGA by "*someone in industry frustrated that they were the only ones applying the hydroquinone restriction on products containing bearberry extract*" [2] with no evidence of intent by the TGA to single out herbal medicine and no evidence of a conspiracy.

2. The chemistry and metabolism of arbutin

An important question to ask in all this is - does arbutin hydrolyse to free hydroquinone within the gastrointestinal system? Upon oral ingestion, arbutin is transported to the liver, where it is hydrolysed to yield hydroquinone and glucose. However, the free hydroquinone immediately undergoes phase II glucuronidation and sulfation, resulting in hydroquinone glucuronide and hydroquinone sulfate [3]. The hydroquinone conjugates are then eliminated in the urine [4] where they are again converted to hydroquinone, resulting in the known urinary antimicrobial effects [5–11]. However the evidence for this was not available until 2013.

3. Where to from here?

Unless clinical practice is accounted for, valid herbal therapeutic options can be lost. Herbalists and naturopaths across the country are understandably disappointed and frustrated by this recent development and the restriction to herbal medicines which have been used safely for hundreds of years. These cries are not going unheard or unacknowledged. Professional associations and governing bodies are currently working to address this issue with the TGA. The intention is for the industry and profession to collaborate and present a submission to the Medicines Scheduling Secretariat to either alter the classification of arbutin within the SUSMP or have the cross-reference of arbutin to hydroquinone removed in the context of oral usage of herbal medicines containing arbutin.

The re-scheduling of medicinal substances is a lengthy and involved process which realistically may take between 1–2 years. However, members of the profession can be assured that the issue is being represented with one clear and focused voice and are urged not to lose hope. We have seen the power of the profession to protect valued herbal medicines in the past after the removal of Kava from use in the early 2000's. Kava was re-instated after extensive lobbying from leaders in the profession demonstrating its safety and traditional use. Similarly, the profession is keen for Bearberry and Damiana, which have more than a century of safe and effective use, to be allowed back in the hands of qualified herbalists and naturopaths where they can be used for optimal patient outcomes.

Conflict of interest

The Authors declare they have no conflicts of interest.

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