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Friday, 10 May 2019

Therapeutic Goods Administration
Department of Health

By email: medicines.scheduling@health.gov.au
'Proposed Amendments to the Poisons Standard (Medicines/Chemicals)'

**Submission – Un-scheduling Arbutin in Herbal Medicines**

The Australian Traditional-Medicine Society (ATMS) is Australia's largest national professional association of natural medicine practitioners. ATMS is a multi-disciplinary association representing around 10,000 accredited practitioners throughout Australia, including practitioners of western herbal medicine.

ATMS promotes and represents professional practitioners of natural medicine, who are encouraged to pursue the highest ideals of professionalism in their natural medicine practice and education.

Arbutin is a constituent of a number of herbs, however the scheduling has particularly affected the supply of herbal preparations of Bearberry (*Arctostaphylus uva ursi*) and Damiana (*Turnera diffusa*).

These herbal preparations that contain Arbutin have a long history of use by western herbal medicine practitioners in Australia without adverse effects (see Appendices 1 and 2); they are important herbal preparations to the professional community of western herbal medicine practitioners in Australia (see Appendices 3 and 4); and they lack the potential for abuse by ATMS prescribers, as these prescribers meet the minimum education standards set by ATMS for practitioners of western herbal medicine.

ATMS supports the following proposed scheduling amendment changes:-

1. To delete the cross-reference in the index of Arbutin to hydroquinone;

2. Include Arbutin as a specific entry in the Poisons Standard in Schedule 2 and Schedule 4;

3. In Schedule 4 for herbal preparations, Arbutin is to be noted as an exception in oral herbal preparations containing **500**mg or less of Arbutin per recommended daily dose.

The un-scheduling of naturally occurring Arbutin in Herbal Medicines does not present an unacceptable risk to human health. This will benefit the members of the Australian general public who choose to see a safe and competent ATMS accredited western herbal medicine practitioner, by making more herbs available to potentially be individualised for their selection in extemporaneously prepared herbal preparations for their intended therapeutic internal/oral use.

Please keep me informed about further opportunities to comment in the following phases of considerations, consultations and interim decisions made by the scheduling committees.

Kind regards,

[redacted]

Peter Berryman
ATMS President
Inc. TGA Consultation submission coversheet

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## Appendix 1

"Damiana is the name given to a drug *(Turnera di'Qusa* var. *aphrodisiaca)* long used by the Mexicans as a powerful stimulant to the, reproductive centres. The leaves and flowers are the parts used in medicine as an aphrodisiac. It has been used in America with success in melancholia and many forms of brain exhaustion, and want of tone in various regions of the nervous system especially about the genito-urinary centres. It is a mild laxative, and has been given in paraplegia with apparent benefit, and in sick headaches. The writer has obtained good results from it in cases of sexual debility and hypochondriasis. It is a tonic in its action upon the appetite it resembles quinine and calumba, and it acts also as a stimulating diuretic and in full doses as a purgative. Dose-I dr. of the fluid extract (I in I), or 2 to 8 grs. of the extract."

William W, Elements of Pharmacy, Materia Medica, and Therapeutics, Henry Renshaw, UK, 1892, p435

## Appendix 2

**Bearberry**
From Wikipedia, the free encyclopedia

**Bearberries** are three species of dwarf shrubs in the genus *Arctostaphylos*. Unlike the other species of *Arctostaphylos* (see manzanita), they are adapted to Arctic and Subarctic climates, and have a circumpolar distribution in northern North America, Asia and Europe, one with a small highly disjunctive population in Central America.

**Species**
The name "bearberry" for the plant derives from the edible fruit which is a favorite food of bears.[1] The fruit, also called bearberries, are edible and are sometimes gathered as food for humans. The leaves of the plant are used in herbal medicine.[2]

- **Alpine bearberry**: *Arctostaphylos alpina* (L.) Spreng (syn. *Arctous alpinus* (L.) Niedenzu). This is a procumbent shrub 10–30 cm high (3.9–11.8 in). Leaves not winter green, but dead leaves persist on stems for several years. Berries dark purple to black. Distribution: circumpolar, at high latitudes, from Scotland east across Scandinavia, Russia, Alaska, Canada and Greenland; southern limits in Europe in the Pyrenees and the Alps, in Asia to the Altay Mountains, and in North America to British Columbia in the west, and Maine and New Hampshire in the United States in the east.
- **Red bearberry**: *Arctostaphylos rubra* (Rehd. & Wilson) Fernald (syn. *Arctous rubra* (Rehder and E.H. Wilson) Nakai; *Arctous alpinus* var. *ruber* Rehd. and Wilson). This is a procumbent shrub 10–30 cm high (3.9–11.8 in). Leaves deciduous, falling in autumn to leave bare stems. Berries red. Distribution: in the mountains of Sichuan, southwestern China north and east to eastern Siberia, Alaska and northern Canada east to northern Quebec.
- **Common bearberry**: *Arctostaphylos uva-ursi* (L.) Spreng.

**Phytochemicals and folk medicine**
The plant contains diverse phytochemicals, including ursolic acid, tannic acid, gallic acid, some essential oils and resin, hydroquinones (mainly arbutin, up to 17%), tannins (up to 15%), phenolic glycosides and flavonoids.[2]
The leaves are picked any time during the summer and dried for use in teas, liquid extracts, medicinal tea bags and tablets for traditional medicine uses.[3]
Bearberry appears to be relatively safe, although large doses may cause nausea, vomiting, fever, chills, back pain and tinnitus.[4] Cautions for use apply during pregnancy, breast feeding, or in people with kidney disease.[3][5]

**History and folklore**
Bearberry was first documented in *The Physicians of Myddfai*, a 13th-century Welsh herbal. It was also described by Clusius in 1601, and recommended for medicinal use in 1763 by Gerhard and others. Often called uva-ursi, from the Latin uva, "grape, berry of the vine", ursi, "bear", i.e. "bear's grape". It first appeared in the London Pharmacopoeia in 1788.

Folk tales suggest Marco Polo thought the Chinese were using it as a diuretic. Bearberry leaves are used in traditional medicine in parts of Europe, and are officially classified as a phytomedicine.[2] Native Americans use bearberry leaves with tobacco and other herbs in religious ceremonies, both as a smudge (type of incense) or smoked in a sacred pipe carrying the smoker's prayers to the Great Spirit. When mixed with tobacco or other herbs, it is referred to as kinnikinnick, from an Algonquian (probably Delaware) word for "mixture". Among the ingredients in kinnikinnick were non-poisonous sumac leaves,[6] and the inner bark of certain bushes such as red osier dogwood (silky cornell),[6] chokecherry, and alder, to improve the taste of the bearberry leaf.[7]

**References**


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## Appendix 3

**Damiana**

**Species (Family)**
*Turnera diffusa* Willd. ex Schult. (Turneraceae)

**Synonym(s)**
*Turnera aphrodisiaca* Ward, *T. diffusa* var. *aphrodisiaca* (Ward) Urb.

**Part(s) Used**
Leaf, stem

**Pharmacopoeial and Other Monographs**
In ***BHC 1992*** (Damiana); ***BHP 1996*** (Damiana).

**Constituents**
The following is compiled from several sources.[G6]
**Carbohydrates**
Gum 13.5%, starch 6%, sugars.
**Cyanogenic glycosides**
Tetraphyllin B.[1]
**Phenolic glycoside**
Arbutin (up to 0.7%).[2]
**Tannins**
3.5%. Type unspecified.
**Volatile oils**

0.5–1.0%. At least 20 components including 1,8-cineole (11%), *p*-cymene (2%), α- and β-pinene (2%), thymol, α-copaene, δ-cadinene and calamene. The presence of 1,8-cineole and *p*-cymene has been disputed.[2]

**Other constituents**

Acids (fatty, plant), alkanes (e.g. hexacosanol-1 and triacontane), damianin (7%) (a bitter principle), flavone (gonzalitosin-1), β-sitosterol, resin (6.5%).[3]

## Food Use

Damiana is used in foods and is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that damiana can be added to foodstuffs in small quantities with a possible limitation of an active principle (as yet unspecified) in the final product.[G16] Previously in the USA, damiana has been approved for food use.[G41]

## Herbal Use

Damiana is stated to possess antidepressant, thymoleptic, mild purgative, stomachic and reputedly aphrodisiac properties.[4] It has been used for depression, nervous dyspepsia, atonic constipation, coital inadequacy, and specifically for anxiety neurosis with a predominant sexual factor.[G6G7G8G64]

**Dosage**

Dosages for oral administration (adults) for traditional uses recommended in older and contemporary standard reference texts are given below.

**Dried leaf**

2–4 g as an infusion three times daily.[G6G7]

**Liquid Extract of Damiana**

(BPC 1934) 2–4 mL.

## Pharmacological Actions

### *In vitro* and animal studies

Hypoglycaemic activity has been reported in mice following both oral and intraperitoneal administration of damiana.[5] An ethanolic extract was stated to exhibit CNS-depressant activity although no other experimental details were available.[6]

Antibacterial activity against *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* has been documented for a mixed herbal preparation, with some of the activity attributed to damiana.[7] The same herbal preparation was also reported to inhibit acetylcholine-induced spasm of the isolated guinea-pig ileum, although none of the antispasmodic activity was attributed to damiana.[7]

Arbutin is stated to be responsible for the urinary antiseptic properties (*see* Uva-Ursi). However, the arbutin content of damiana is much less than that quoted for uva-ursi (0.7% and 5 to 18%, respectively).

### Clinical studies

There is a lack of clinical research assessing the effects of damiana and rigorous randomised controlled clinical trials are required. A herbal preparation containing damiana as one of the ingredients was reported to have a favourable effect on the symptoms of irritable bladder associated with functional and neurohormonal disorders, and on bacterial bladder infections.[7] However, because of the methodological limitations of this study, these effects cannot be attributed to damiana.

## Side-effects, Toxicity

There is a lack of clinical safety and toxicity data for damiana and further investigation of these aspects is required.

Tetanus-like convulsions and paroxysms resulting in symptoms similar to those of rabies or strychnine poisoning have been described in one individual following the ingestion of approximately 200 g damiana extract; cyanide poisoning was considered to be a possible cause. No other reported side-effects for damiana were located.

High doses of arbutin (e.g. 1 g) are considered to be toxic, although the concentration of arbutin documented for damiana (1 g arbutin is equivalent to more than 100 g plant material) is probably too low to warrant concerns over safety.

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**Contra-indications, Warnings**
Excessive use should be avoided because of the presence of cyanogenetic glycosides and arbutin.

**Drug interactions**
None found. However, the potential for preparations of damiana to interact with other medicines administered concurrently, particularly those with similar or opposing effects, should be considered. There is limited evidence from preclinical studies that damiana has hypoglycaemic activity.

**Pregnancy and lactation**
The safety of damiana has not been established. In view of the lack of toxicity data and possible cyanogenetic constituents, doses greatly exceeding amounts used in foods should not be taken during pregnancy or lactation.

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## Appendix 4

**Uva-Ursi**

**Species (Family)**
*Arctostaphylos uva-ursi* (L.) Spreng. (Ericaceae)

**Synonym(s)**
Bearberry

**Part(s) Used**
Leaf

**Pharmacopoeial and Other Monographs**

[redacted]

In ***BHC 1992*** (Uva Ursi); ***BHP 1996*** (Bearberry Leaf); ***BP 2019*** (Bearberry leaf).
**PhEur 9.7**
**Bearberry Leaf**: The whole or fragmented, dried leaf of *Arctostaphylos uva-ursi* (L.) Spreng.
Uva-Ursi is also included in the American Herbal Pharmacopoeia, HMPC monographs and WHO monographs on selected medicinal plants volume 2 2004.

## Constituents

### Flavonoids

Flavonols (e.g. myricetin, quercetin, kaempferol)[1] and their glycosides[2–4] including hyperoside.[2,3]

### Iridoids

Asperuloside (disputed), monotropein.[5]

### Quinones

Total content at least 6%, mainly arbutin[1–4] (5–15%)[4] and methyl-arbutin (glycosides),[1–4] with lesser amounts of piceoside (a phenolic glycoside)[1–3,6], free hydroquinone[2,4] and free *p*-methoxyphenol.[7]

### Tannins

6–7% (range 6–40%). Hydrolysable-type (e.g. corilagin); ellagic and gallic acids[2] (usually associated with hydrolysable tannins).[1]

### Terpenoids

α-Amyrin, α-amyrin acetate, β-amyrin, lupeol, uvaol, ursolic acid, and a mixture of mono- and di-ketonic α-amyrin derivatives.[2,8,9]

### Other plant parts

The root is reported to contain unedoside (iridoid glucoside).[10]
Figure 1. Selected constituents of uva-ursi.

## Food Use

Uva-ursi is not used in foods.

## Herbal Use

Uva-ursi is stated to possess urinary antiseptic[2–4,11], and astringent[2] properties. Traditionally, it has been used for inflammatory disorders of the urinary tract,[3,4,12] including cystitis[4,13], urethritis, and pyelitis, for acute catarrhal cystitis with dysuria, and also for lithuria, and highly acidic urine.[13]

## Dosage

Dosages for oral administration (adults) for traditional uses recommended in older and contemporary standard herbal and pharmaceutical reference texts are given below.
Uva-ursi should not be taken for longer than seven days, and acidic foods should be avoided for the duration of treatment.[2]

### Dried leaves

1.5–2.5 g as an infusion or cold-water maceration three to four times daily;[2] total arbutin content 400–840 mg.[4,12]

### Liquid extract

1.5–2.5 mL (1 : 1 in 25% alcohol) three to four times daily.[2]

### Tincture

2–4 mL (1:5 in 25% ethanol) three to four times daily.[2]

### Concentrated Infusion of Bearberry

(BPC 1934) 2–4 mL.

### Fresh Infusion of Bearberry

(BPC 1934) 15–30 mL.

## Pharmacological Actions

### *In vitro* and animal studies

Uva-ursi has exhibited antimicrobial activity towards a variety of organisms including *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Mycobacterium smegmatis*, *Shigella sonnei* and *Shigella flexneri*.[14] The antimicrobial activity of arbutin towards bacteria implicated in producing urinary tract infections, has been found to be directly dependent on the β-glucosidase activity of the infective organism.[15] Highest enzymatic activity was

shown by *Enterobacter*, *Klebsiella* and *Streptococcus* genera, and lowest by *Escherichia coli*.[15] The minimum inhibitory concentration for arbutin is reported to be 0.4–0.8% depending on the micro-organism.[15] Aqueous and methanolic extracts have demonstrated molluscicidal activity against *Biomphalaria glabrata*, at a concentration of 50 ppm.[16] The activity was attributed to the tannin constituents (condensed and hydrolysable).
Anti-inflammatory activity (rat paw oedema tests) has been documented for uva-ursi against a variety of chemical inducers such as carrageenan, histamine and prostaglandins.[17]
Uva-ursi failed to exhibit any *in vitro* uterotonic action when tested on rabbit and guinea-pig uteri.[18]
Hydroquinone has been reported to show a concentration-dependent cytotoxic activity on cultured rat hepatoma cells (HTC line); arbutin was not found to inhibit growth of the HTC cells.[19] It was stated that hydroquinone appeared to have greater cytotoxic activity towards rat hepatoma cells than agents like azauridin or colchicine, but less than valtrate from valerian (*Valeriana officinalis*). The cytoxicity of hydroquinone has also been tested on L1210, CA-755 and S-180 tumour systems.[19]

**Clinical studies**
Clinical research assessing the effects of uva-ursi is limited and rigorous randomised clinical trials are required.
A herbal preparation, whose ingredients included uva-ursi, hops and peppermint, has been used to treat patients suffering from compulsive strangury, enuresis and painful micturition.[20] Of 915 patients treated for six weeks, success was reported in about 70%. The design of this study, however, does not allow the observed effects to be attributed to uva-ursi.
The antiseptic and diuretic properties claimed for uva-ursi can be attributed to the hydroquinone derivatives, especially arbutin. The latter is absorbed from the gastrointestinal tract virtually unchanged and during renal excretion is hydrolysed to yield the active principle, hydroquinone, which exerts an antiseptic and astringent action on the urinary mucous membranes.[21,22] The crude extract is reported to be more effective than isolated arbutin as an astringent and antiseptic;[23] this may be due to the other hydroquinone derivatives, in addition to arbutin, that are present in the crude extract and which will also yield hydroquinone.

**Side-effects, Toxicity**
**Clinical data**
There is a lack of clinical safety and toxicity data for uva-ursi and further investigation of these aspects is required.
Hydroquinone is present in uva-ursi in low concentrations and is a metabolite of the major constituent arbutin. Hydroquinone is toxic at high concentrations in mice (LD50 0.39–0.68 g/kg, oral),[24] which had led to safety concerns about the use of uva-ursi. Clinical studies reported in a review[24] indicated that arbutin is predominantly metabolised in the liver to hydroquinone and then rapidly detoxified to glucuronide and sulfate conjugates for excretion in the urine. A small portion is excreted as free hydroquinone; however, it has since been concluded that the exposure to free hydroquinone from uva-ursi use is small enough not to pose a safety concern.[24–26]
Hydroquinone is reported to be toxic if ingested in large quantities: 1 g (equivalent to 6–20 g plant material) has caused tinnitus, nausea and vomiting, headache, dizziness, delirium, cyanosis, muscular twitching, shortness of breath, convulsions, and collapse.[26,27] Doses of 5–15 g have proven fatal, although other toxic chemicals could not be ruled out as contributing factors in these cases: a full recovery after 13 days of hospitalisation upon consumption of 12 g of hydroquinone alone has been reported.[27]

**Non-clinical data**
Cytotoxic activity has been documented for hydroquinone (*see* Pharmacological Actions, *In vitro* and animal studies).
Uva-ursi herb can sometimes be adulterated with box leaves (*Buxus sempervirens*), which contain toxic steroidal alkaloids. However, this is reportedly rare.[3]

**Contra-indications, Warnings**
Uva-ursi requires an alkaline urine for it to be effective as a urinary antiseptic; an alkaline reaction is needed to yield hydroquinone from the inactive esters such as arbutin.[21] Patients have been advised to avoid eating highly acidic foods, such as acidic fruits and their juices.[21] The presence of hydroquinone may impart a greenish-brown colour to the urine, which darkens following exposure to air due to oxidation of hydroquinone.
Excessive use of uva-ursi should be avoided in view of the high tannin content and potential toxicity of hydroquinone.

Prolonged use of uva-ursi to treat a urinary tract infection is not advisable. Patients in whom symptoms persist for longer than 48 hours should consult their doctor.

**Drug interactions**

None found. However, the potential for preparations of uva-ursi to interact with other medicines administered concurrently, particularly those with similar or opposing effects, should be considered.

**Pregnancy and lactation**

Large doses of uva-ursi are reported to be oxytocic,[28] although *in vitro* studies have reported a lack of utero-activity. In view of the potential toxicity of hydroquinone, the use of uva-ursi during pregnancy and lactation should be avoided.

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