Submission of Permitted Ingredients for Draft List
by Artemis Natural Healthcare

NHSP Bill 2015

Prepared by

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1. Additional international Pharmacopoeias to be listed

We confirm the following international pharmacopoeias from our previous submission, should be added to the reference list for permitted ingredients. These pharmacopoeias list common medical plants with an established safety profile:

Deutsches Arzneibuch (German Pharmacopoeia)
Österreichisches Arzneibuch (Austrian Pharmacopoeia)
Pharmacopée Francaise (French Pharmacopoeia)
Pharmacopoeia Helvetica (Swiss Pharmacopoeia)
European Union herbal monograph (comprises the current scientific opinion of the EU Committee on Herbal Medicinal Products)

We further propose that medicinal native plants from New Zealand and Australia are permitted onto the list.

2. Ingredients to add to the draft list

We submit to have the following ingredient added to the list of allowable ingredients:

<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Common name</th>
<th>Pharmacopeia name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentha rotundifolia</td>
<td>Apple mint, Egyptian mint, Round leaved mint</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Our submission:

*Mentha rotundifolia* is a variety of Mentha spp. which is used in a similar way, and with similar actions and constituents to Peppermint (*Mentha piperita*) (Lorenzo, 2002; Grieve & Leyel 1931). It is commonly used for culinary purposes and has no documented contraindications or drug interactions (Seedaholic, 2015).

We recommend you add this species of mint to the list of allowable ingredients without specific requirements, as is the case with other species of mint.
3. Ingredients with requirements to discuss

We submit changes to these ingredients and request some clarifications.

<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Common name</th>
<th>Pharmacopoeia name</th>
<th>Draft list: proposed use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betula pendula</td>
<td>Birch</td>
<td>German Commission E ESCOP Deutsches Arzneibuch Österreiches Arzneibuch Pharmacopée Francaise X Pharmacopoeia Helvetica Health Canada and others.</td>
<td>Topical Use Only</td>
</tr>
<tr>
<td>Citrus limon oleum</td>
<td>Citrus Oil</td>
<td>Lemon oil is freely available for sale in Australia and is allowable for internal use under the Therapeutic Goods Act</td>
<td>Dosage Restrictions: MDD: Must not contain more than 30 mg of oxedrine. Manufacturing Restrictions: Oil: Permitted only when: a) steam distilled or rectified, b) in products for internal use, c) in products containing 0.05% or less of lemon oil, d) in soaps or bath and shower gels that are washed off the skin, or e) packed in appropriately labelled containers.</td>
</tr>
<tr>
<td>Hypericum perforatum</td>
<td>St John’s Wort</td>
<td>American Herbal Pharmacopoeia British Pharmacopoeia European Pharmacopoeia Pharmacopée Francaise X United States Pharmacopoeia- National Formulary German Commission E monograph and others.</td>
<td>Labelling requirements- “May affect the way prescription medicines work, including the oral contraceptive pill. Consult a healthcare practitioner before use”</td>
</tr>
</tbody>
</table>
Our submissions

a) **Betula pendula**

We would like to change the current administration of Birch to include oral use. *Betula pendula* (Birch) has longstanding traditional use taken internally as a diuretic, and has also been used safely as a flavouring in the food industry (Fisher, 2009). We are not using the essential oil (which may contain high levels of methyl salicylate), but the whole plant as either a tincture or a tea.

Many regulatory bodies worldwide have *Betula pendula* listed in their pharmacopoeias for oral use.

- Commission E and ESCOP positively endorse the use of Birch leaf for bacterial and inflammation illnesses of the urinary tract and as an adjuvant therapy for rheumatic complaints (Brendler, Gruenwald, & Jaenicke, 2003; Commission E, 1986)
- Birch leaf is listed in the British Herbal Pharmacopoeia, Deutsches Arzneibuch, Österreiches Arzneibuch, Pharmacopée Française X, and Pharmacopoeia Helvetica (Brendler, Gruenwald, & Jaenicke, 2003)
- Birch leaf is listed in the Health Canada Monographs (2008) for oral use, as a diuretic
b) *Citrus limon oleum*

We would like “cold-pressed” to be added to the permitted methods of manufacturing.

We would also like to know where the burden of proof lies with regards to the amount of the constituent oxedrine, or what documentation you would require to confirm the amounts. The suppliers that we use do not test for oxedrine as it is not a major constituent in *Citrus limon*. It is a constituent usually found in the fruit and peel of *Citrus aurantium* (bitter orange) (Australian Therapeutic Goods Administration, 2014).

In the case of this ingredient, we are using *Citrus limon* mainly as a flavouring agent, and the quantities are so low (0.0015% of the recipe) that it would not be possible for there to be 30mg of oxedrine present. In this case, are we required to have documentation on hand or are we exempt by virtue of the amounts used?

Also, if we are required to show documentation regarding the amount of this constituent, do we need each batch tested, or is the testing one-off?

We believe some further clarification of the requirements surrounding this ingredient is needed.

c) *Hypericum perforatum*

The concern surrounding St John’s Wort’s ability to affect the way prescription medicine works has been a topic of discussion since the late 1990s. The concern has been that certain preparations of St John’s Wort can reduce the efficacy of some pharmaceutical medications via induction of CYP450 liver enzymes, in particular the cytochrome enzyme CYP3A4, thus clearing the medication more rapidly from the body.

In the late 1990s, pharmacological research indicated that the constituent hyperforin may be responsible for the plant’s antidepressant activity. As such, some manufacturers began producing pharmaceutical-type St John’s Wort preparations, which were standardised to contain up to 3% hyperforin.

More recent research now shows that traditional low-hyperforin extracts of St. John’s Wort have little or no effect on CYP3A4 enzymes in humans (Yarnell & Abascal, 2007, p.240), meaning that only St John’s Wort products with artificially elevated and stabilised high levels of hyperforin interact with pharmaceutical medications via CYP450 enzymes.

In its traditionally prepared form (eg: whole herb dried for tea, extracted in alcohol as a tincture, or processed as an oil for topical use), St John’s Wort contains very low levels of hyperforin (<1%), a naturally unstable compound which degrades rapidly in solution and thus has no clinical effect on drug metabolism (Ang et al., 2004; Arold et al., 2005; Bone, 2006; Gurley, Fifer, & Gardner, 2012; Madabushi et al., 2006; Mai et al, 2004; Mueller et al., 2009).

Several regulatory agencies worldwide have acknowledged that preparations with low hyperforin levels do not affect drug metabolism, including the Swiss Ministry of
Health (Swissmedic, 2002), and Medsafe New Zealand (2014). The Swiss Ministry have exempt such products from all safety warnings (Swissmedic, 2002, p. 7).

**St John’s Wort and Contraception**

The proposed labelling requirements states: “May affect the way prescription medicines work, including the oral contraceptive pill. Consult a healthcare practitioner before use”

The most pertinent question that needs to be asked here is whether taking Hypericum perforatum with the oral contraceptive pill will reduce the effectiveness of the drug sufficiently for pregnancy to occur. Breakthrough bleeding is not generally seen as an indication of loss of contraceptive cover and in fact, the clinical evidence is that when breakthrough bleeding occurred (with or without St. John’s Wort in conjunction with the contraceptive pill), it didn’t affect the efficacy of the contraceptive cover.

Two clinical studies have investigated this question. They confirm that St. John’s Wort (capsules made from a whole plant extract which does not contain artificially elevated and stabilised hyperforin), taken concurrently with the contraceptive pill does not change hormonal levels or reduce the effectiveness of the pill (Hall, 2003; Pfrunder, 2003).

The results demonstrate that during concomitant administration of the low-dose oral contraceptive and St. John’s Wort, there was no significant change in follicle maturation, serum oestradiol or progesterone concentrations when compared with oral contraceptive treatment alone. All of the women in these scientific trials maintained full protection when concurrently taking a low-dose pill and St. John’s Wort. This confirms epidemiological data that does not indicate a mass outbreak of unwanted pregnancies in countries such as Germany and Switzerland where a large part of the population, including women on the pill, take St. John’s Wort remedies.

**Recommendations**

Based on our research, we confirm that whole plant extracts of St John’s Wort, prepared traditionally without artificially altering the hyperforin constituents, are safe and effective for use by the general population and do not require special safety warnings. Despite an extensive search we were unable to identify case reports or scientific trials that indicate herb-drug interactions with tea or fresh-plant tincture preparations of St. John’s Wort. We advise against safety warnings that cannot be backed up scientifically, as the public could grow sceptical towards safety regulations. This could cause a safety issue with drugs where a warning is valid.

The labelling requirements above should therefore be mandatory only if St. John’s Wort has been pharmaceutically altered to contain artificially high levels of hyperforin.

People on medication for life-threatening conditions which can interact with other medication, herbs, and food, should be counselled by their doctor to not take anything without prior discussion. For example, broccoli can affect blood clotting in people with Warfarin, but we do not require a warning on broccoli, rather the onus is on the doctor to discuss the seriousness of Warfarin’s effects.
We would, however, endorse that products which are marketed for the treatment of depression should state something to the effect “Depression can be a serious condition. For further support, please consult your healthcare practitioner”.

d) Salvia officinalis

It is unusual for Sage to contain more than 2.5% total essential oil content (including thujone, as well as other constituents such as cineol, camphor, limonene, etc) (Braun & Cohen, 2010). On average, the thujone concentration of an essential oil is 28%, or 0.7% of the whole plant- far below the threshold of 4%.

Also, recent studies suggest that an average of 3-6 cups of Sage tea (of 1.5gm dried herb) could be safely consumed without reaching toxicological thresholds (Walch et al., 2011). As the amount of sage that we use in our Artemis tea blends are at culinary levels and are well below this threshold (approx. 100mg per gram of tea), does this conservative dose require testing and documentation?

If we are required to test Sage for thujone content and provide documentation, what are the requirements?

We believe some further clarification of the requirements surrounding this ingredient is needed.

e) Symphytum officinale

This section examines the proposed restriction of Comfrey for external use only. It argues to permit internal use at a low dosage level based on long-standing traditional use, a deliberation on the issue of adverse effect versus overdose and a summary of toxicity studies.

As illustrated by the section on Hypericum perforatum, plants are, by nature, complex. Symphytum officinale (Comfrey) is another such case.

The concern with Comfrey is that it contains pyrrolizidine alkaloids (PAs). Some of the chemicals in this class may be hepatotoxic.

A thorough investigation of the issues surrounding comfrey reveals that several factors have contributed to the uncertainty of the plants’ safety as reviewed below.

Comfrey in Context: Human Use

The use of Comfrey has been documented in medical literature for over 2000 years, from the antique Greek physicians, throughout the Middle Ages, Renaissance, and into contemporary medical practice (Englert, Mayer & Staiger 2005). Comfrey derives its name from the Latin name confirmare, meaning to heal or unite, and its other names knitbone, boneset, bruisewort, or consormol all reflect its pharmacodynamics properties relating to the recovery from injuries of the musculo-skeletal system. The German name ‘Wallwurz’ which can be translated as ‘knit root’ indicates the traditionally preferred part of the plant.

Comfrey has been consistently listed in international pharmacopoeias up until the present day and has been an important internal and external remedy in traditional
Western medicine (HagerROM, 2009, p.10; Bäumler, 2007, p. 79; Englert, Mayer & Staiger, 2005; Kroeber 1948, p. 58-61; Flamm, Kroeber & Seel, 1942, p. 43-46; Madaus, 1938).

Apart from medicine, many cultures have used Comfrey as a traditional staple food, such as groups in Switzerland, England, Ireland and Russia (Baumler, 2007, p. 79; Weingmann 1999, p. 106).

In some regions of Germany, Comfrey is eaten as a traditional food, and is also fed to animals. These groups of people eat much more than the therapeutic medicinal dose listed in medical textbooks and pharmacopoeias. Nevertheless, there is no epidemiological data or medical reports that suggests any health issues within this cultural group (Weiss & Fintelmann, 1997, p. 338).

There has been a study, which examined 29 people who were longstanding Comfrey users, some for as long as 20 years, in a wide range of preparations and doses from 0.5g to up to 25g per day. None of the participants showed any signs of liver damage as measured by serum concentrations of aspartate aminotransferase (AST), γ-glutamyltransferase (GGT) and bilirubin (elevated with choleostasis), and α-fetoprotein (AFP) (a specific marker for liver cancer) (Anderson & McLean 1989).

Contemporary use

In clinical practice Comfrey is an important remedy for the internal treatment musculoskeletal issues and mucous membrane irritations as illustrated in the 4th edition of “Hagers Handbuch der Pharmazeutischen Praxis”, the pharmaceutical reference textbook for pharmacists and medical doctors in Western Europe (List & Höhammer 1972, p. 708).

In the European market several preparations contain fresh-plant Comfrey tincture (1:10 mother tinctures ø) for internal use, for example ‘Kyttachol’ drops and tablets, ‘Kyttta-Fluid’ and ‘WALLWURZ-Fluid’ (Blascheck & Hager, 2007, pp162-163).

Several randomized controlled studies, comparative effectiveness studies and post-marketing surveillance studies confirm Comfreys therapeutic efficacy in the treatment of ankle sprains and complaints of the skeletal and locomotor system such as osteoarthritis, epicondylitis, tendovaginitis, and periarthritis, including one study that proved equal effects to Diclofenac (ESCOP 2009, p. 249-254; Predel, Giannetti, Koll, Bulitta, & Staiger, 2005). Whilst these clinical studies were undertaken on topical preparations, they relate to the same indications for internal use that herbal clinicians use to accelerate healing in clinical practice (Zimmermann, 1999, p. 387; Yarnell 1999, p.6; Vonarburg 1993, p. 243-246; McIntrye 1995, p.33; Willfort 197514, p. 67-71).

Comfrey safety in the context of long-standing use: Overdose reports and misidentification

Comfrey was never regarded as a poisonous plant. Despite its extensive use over the past 2,000 years, very few incidences have occurred relating to either
misidentification of the plant or overdose. No toxicity study has shown that normal human use of Comfrey can cause death or toxicity.

Overdose is not the same as an appropriate dose. For example, Paracetamol is considered safe enough to be sold widely in pharmacies and supermarkets as long as the label states the recommended dosage and with the assumption that the product should be “taken as directed”. No one would argue that if someone took an inappropriate amount of Paracetamol that this would constitute an overdose, not an adverse reaction.

Medicinal plants are the same - an appropriate dose is a medicine, a very large dose can be poisonous with some plants. Through hundreds of years of clinical observation and careful recording, physicians, being plant medicine experts until very recently, have discovered which medicinal plants are the most potent and have come up with safe and effective doses (Mills & Bone, 2005).

Comparing the relevance, probability, and history of Comfrey with Paracetamol highlights the relative safety of this plant. Poisoning with Paracetamol is common, and the New Zealand National Poisons Centre receives about 1000 calls each year about paracetamol poisoning (NZ National Poisons Centre, 2015).

In July 2015, Health Canada published a safety review on paracetamol (acetaminophen) and liver injury. The paper states, “Acetaminophen has been widely used for over 50 years in Canada to treat pain and fever...Despite its established safety profile, acetaminophen is the leading cause of acute liver failure in Canada” (Health Canada, 2015; my emphasis). This is a perfect example of what has been evaluated as an acceptable risk, and also what is considered an “established safety profile”.

In comparison, there are around 20 cases of poisoning from PAs in humans worldwide within the last 40 years, and 5 believed to be from Comfrey specifically. However, many of these case reports have not validated which plant was consumed and if the plant consumed was indeed Symphytum officinale. Some case reports indicate excessive use (Dharmananda, 2001; Awang, 1994; Yeong, Swinburn, Kennedy, & Nicholson, 1990; Bach, Thung, & Schaffner, 1989; Weston, Cooper, & Davies, 1987; Ridker, Ohkuma, McDermott, Trey, & Huxtable, 1985).

Additional confounding factors in these cases include known underlying illness and poor nutritional status, which could have contributed to reduced liver function, as well as concurrent use of hepatotoxic drugs, which increase the likelihood of veno-occlusive disease (VOD) development when using PA-containing substances (Rode, 2002; Yarnell, 1999; Whitelegg 1996). These confounding factors are well known general risk factors for liver health. In regards to paracetamol use and liver injury, Health Canada states: “There is evidence suggesting that the risk of liver injury with acetaminophen use may be increased in certain situations, such as alcoholism, malnutrition, some liver diseases, or use of acetaminophen for more than the recommended length of time” (Health Canada, 2015).

In some of these cases people have unknowingly eaten the young leaves of Foxglove (Digitalis spp.), a known poisonous plant, and the subsequent poisoning was attributed to Comfrey (Mills & Bone, 2005). An incorrect species needs to be ruled out as well. Case reports in the literature have sometimes interchangeably
discussed common comfrey (*Symphytum officinale*), and Russian comfrey (*Symphytum asperum* or *Symphytum x uplandicum*). Russian comfrey is known to contain echimidine - a toxic PA which is not found in *Symphytum officinale* (Awang, 1994). The potential for adulteration or misidentification with plants is an important avenue to investigate before condemning a plant as toxic.

Proper identification of the herb in question is vital before cases of adverse reactions can be considered causal. Awang (1994) states that “A widespread lack of attention to proper botanical identification of *Symphytum* species by herbal investigators from different disciplines has led to much confusion and perpetuated serious errors in the literature”.

In recent years the internal use of Comfrey has been restricted in some countries, based on reviews by toxicologists that emphasized the health risks associated with oral consumption of PAs found in Comfrey. It is noteworthy that there was no new toxicology research, nor an unacceptable number of adverse events related to the therapeutic or culinary intake of Comfrey that prompted this unexpected change in assessment (Rode 2002, p. 497). This indicates that the restrictions on Comfrey in some countries was not related to an inherent risk associated with the consumption of Comfrey but in the prioritising of theoretical risk on rodent studies over epidemiological data from real human consumption. Governments rely on toxicology reports in good faith. Advisors to the Government need to be aware that an evidence-based approach calls for the inclusion of all available safety data so that hypothetical toxicity reports can be reviewed in the context of real life epidemiology data. Otherwise they are at risk of biased reporting.

The conclusion that Comfrey is absolutely contraindicated for internal use is oversimplified in the context of the paucity of conclusive human toxicity reports and epidemiological data over a prolonged period of time (Yarnell 1999, p.7). Comfrey remains an important and relatively safe remedy for the treatment of musculoskeletal injuries, especially compared with synthetic alternatives that have a proven high risk toxicity profile.

We would welcome more clinical studies that screen liver health status of Comfrey users compared with a comparable population that does not consume Comfrey in order to conclusively define safe use. Currently, the most relevant data we have available is epidemiological data recorded over several centuries. The current scientific data is insufficient to conclude an inherent toxicity danger with Comfrey as explained below.

**Laboratory Studies of PAs & Toxicity**

In this section we review the available toxicity data. Much of the confusion about the toxicity of Comfrey has arisen because of a lack of understanding about the complexity of plant chemicals. PAs are a large and diverse class of chemicals and as such are diverse in terms of their toxicity- some appear to be quite toxic, and some are completely innocuous (Ganora, 2009; Schoental, 1968). Many toxicity studies do not specify which PAs, found in which plants, were used for the tests. This is problematic, as data from human poisonings relating to other plants containing PAs cannot be extrapolated as an accurate reflection of the risk of Comfrey in humans.
Furthermore, toxicology research to date has been undertaken with rodents using abnormally high levels of isolated PAs. To date, there are no systematic toxicity testing or clinical trials available that evaluated human safety with whole herb Comfrey used at a normal therapeutic or culinary levels (Rode 2002, p. 497). It is additionally problematic that these tests used isolated synthetically altered constituents in place of a whole plant preparation, which is phytochemically much more complex. In whole plants - as in foods - various constituents typically cancels out potential toxicity.

Furthermore, data obtained from rodent experiments cannot be extrapolated as an accurate reflection of the risk of a substance in humans. While toxicity studies in animals are a useful guideline, there are inherent flaws with many of the toxicology studies done on animals, if they are repositioned as safety studies for humans.

Here a summary of the issues surrounding current toxicology studies on Comfrey:

- The metabolism and processing of the plant/constituent by other species and between species can alter significantly from humans, eg: rats are sensitive to the PAs in comfrey whereas pigs are not, though pigs are sensitive to PAs in Senecio spp. (Rode, 2002).

- Isolated alkaloids given to laboratory animals is an inappropriate way to measure the effects in humans of taking the whole plant orally. Many common plants, including those used as food, contain small amounts of chemicals that, in isolation and large doses, are poisonous. Potatoes, which contain the constituent solanine, is one such example (Medline Plus, 2015). Tea is another good example- containing several constituents which, in isolation, have been shown to be much more toxic than comfrey (Bone, 1989). These foods are not banned from consumption because a long history of human consumption has proven them to be relatively safe. A plant is not simply a vehicle for the pharmacological effects of a single constituent, and cannot necessarily be judged based on the presence of an individual compound (Hoffmann, 2003, p. 188-191). Absorption, metabolism, and bioavailability of a whole plant in a live organism is not comparable to the effects of an isolated chemical on a cell line in in-vitro or rodent studies.

- The doses used in some of the toxicological experiments are unrealistic when applied to humans. For example, Culvenor et al. (1980) administered PAs by injection (also not the same metabolic route as oral intake), and the equivalent dosage needed to cause death to an average adult would be 66,300 Comfrey leaves (Bone, 1989).

- There has been some concern over the potential carcinogenicity of Comfrey. However, a review of the toxicological studies reveal that there is doubt that PAs cause cancer outside of laboratory experiments; that the incidence of malignant tumours in lab animals, induced by long-term, high-dose comfrey is neither statistically nor biologically significant; and that the relative risk of consuming appropriate amounts of Comfrey is insignificant compared to other known carcinogens such as compounds found in tea or processed meat (Bone, 1989).
As yet, there are no toxicity studies that proves that there has been liver failure at the recommended dose, and no studies or even cases of human carcinogenicity (Bone, 1989).

**Other Constituents**

The reason that this plant has been so vital to Western medicine is because it is invaluable for tissue healing. Modern pharmacological studies have shown that Comfrey contains extremely high quantities of allantoin, as well as many other beneficial phytochemicals.

- Allantoin, a purine derivative, supports granulation and tissue regeneration. It has osmotic properties, which allows the release of fluid from the wound area, and cleanses the injured tissue of bacteria and inflammatory by-products. Subsequently it supports the building of new cells. These wound healing effects are supported by mucilage, which reduce irritation in the tissue.
- Choline supports better circulation in the area, and therefore quicker absorption of haematoma. It also reduces oedema.
- Rosmarinic acid lends anti-inflammatory, analgesic, and antioxidant effects.
- The triterpenoid saponin Symphytoxid A has known antimicrobial properties.
- Tannins further support wound healing.

(Baumler, 2007, p. 77-79; Fisher, 2009; Ganora, 2009; Wenigmann 1999, p. 105-106.)

**Official preparations and dosage regime**

Contemporary official preparations are crude drug, ethanolic extract (1:2), tincture (1:5), fresh-plant tincture (1:10), and fresh plant juice (HagerROM 2009, p.5).

The Comfrey monograph of the British Herbal Pharmacopoeia lists both internal and external applications (British Herbal Medicine Association 1985, pp. 202-203). The listed dose range for internal use is 2g-8g.

The official German Homoeopathic Medical Pharmacopoeia HAB supports the internal use of the fresh-plant tincture ø (1:10) to treat injuries to the bones and periosteum (HAB 34, cited in HagerROM 2009, p.11).

The British Pharmacopoeia BP10 supports both fresh-plant tincture ø (1:10) and fresh-plant decoction for homoeopathic preparations (Sweetman, 2011, p.2505).

**Preparations and dosage regime in clinical practice**

In clinical practice of Traditional European Medicine (TEM), the fresh or dry root is processed into teas, decoctions, fresh-plant tinctures (1:10), dry plant tinctures (1:5) and topical application.

Typical daily doses of the leaf range is from 5 to 30g. The daily doses range of the root is from 0.5g to 10.0g (Hills as cited in Rode 2002, p.497)
Comfrey in Artemis products

Artemis has been selling products in New Zealand containing Comfrey for internal use since 1998. We keep a file of any complaints that we receive from customers and have not had any issues of this nature for our Comfrey product in the last 17 years. A search of the NZ National Poisons Centre for “Comfrey” or “Symphytum” also showed no records of adverse reactions, nor did the Medsafe Suspected Medicine Adverse Reaction Search (Medsafe, 2015; NZ National Poisons Centre, 2015).

Artemis produces one product that contains a Comfrey fresh-plant tincture (at a 1:10 ratio - 1 part herb to 10 parts water/alcohol extract). The maximum suggested dosage provides 2.5mls of the Comfrey extract per day - well within the dosages used in traditional medicine, and far below the toxic dose in experimental studies (Rode, 2002; Bone, 1989).

When weighing up any clinical decision, there is always a risk-benefit analysis that must take place. There is no plant that can substitute Comfrey in terms of its effectiveness for injury recovery. We strongly believe that the benefits outweigh the risks for the internal use of Comfrey.

Recommendations

The scientific evidence does not justify the level of restriction proposed for Comfrey (topical use only), and should continue to be allowed for internal use at an appropriate dose.

Comfrey should be allowed for internal use within the following guidelines:

- A maximum daily dose of 10ml of comfrey extract daily, equivalent to 10ml of a 1:10 Comfrey tincture (root or leaf)
- A maximum daily dose of 10g of crude comfrey
- Symphytum officinale and its subspecies should be only species used.
4. Ingredient with a requirement to discuss dosage

Arnica montana requires a special discussion relating to dose considerations.

<table>
<thead>
<tr>
<th>Botanical name</th>
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<tbody>
<tr>
<td>Arnica montana</td>
<td>Arnica</td>
<td>British Herbal Pharmacopoeia</td>
<td>Preparations not intended for topical use: MDD: 1 mg or less of the equivalent dry material.</td>
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<td></td>
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<td>British Pharmacopoeia</td>
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<td>German Commission E monograph</td>
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<td>French pharmacopoeia (56) Homöopatisches Arzneibuch HAB</td>
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<td>(German homeopathic pharmacopoeia)</td>
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<td>French homoeopathic pharmacopoeia PFX, US homeopathic pharmacopoeia HPUS 78</td>
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<td>and others.</td>
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Our submission

Arnica montana

We welcome the listing of Arnica for internal use. In this section we examine the dose proposition and argue a slightly higher dosage based on long-standing traditional use and a review of regulatory approved levels of Arnica for internal use over the past 150 years. We also deliberate on the issue of adverse effect versus overdose, and provide a brief summary of toxicity studies.

We are of the view that the dose consideration merits a thorough investigation, as without the correct dose, the use of Arnica is compromised. The Artemis product range is rooted in Traditional European Medicine (TEM), so we will mainly evaluate the European literature for this review. It may be important to note that Arnica has been an important remedy in European mainstream medicine and for this reason the reviewed literature includes medical textbooks. In New Zealand however, Arnica comes under the proposed Natural Products and Supplements Bill and we deliver our submission in this context.

Arnica in Context: Human Use

Arnica is an important plant in Traditional European Medicine (TEM) and other regions of the world where it is indigenous. In these countries it has a long history of clinical use for accident recovery and cardiovascular support (Weiss, 2001; Grieve &

From the 1800s onwards, the official Swiss, Bavarian, Prussian and German Pharmacopoeias made it mandatory for pharmacies to stock Arnica tincture for medical care. Its use became so prevalent that towards the end of the 19th century, central European countries placed harvesting restrictions for its collection in the wild.

During World War 1 Arnica was used extensively for the care of soldiers to treat fractures, concussions, haematomas, sprains, phlebitis and thrombosis. It was praised by war physicians as second to none as an internal medicine to reabsorb internal and external bleeding (Spaich, 1978, pp.87-88).

The postgraduate herbal textbook used at the Medical School of the University of Berlin, Germany, authored by the late Professor Rudolf Fritz Weiss - a physician of internal medicine - recommends Arnica internally and externally for a variety of musculoskeletal problems, injury recovery and coronary heart disease (2001, pp. 169-70). Whilst Weiss highlights that “arnica is not without risks” (ditto, p.170), his clinical observations and inter-generational medical expertise let him to the conclusion that these risks can be mitigated by observing the proper dosage regime.

Arnica’s immediate and observable medical effects prompted extensive in vivo, in vitro and animal research from the 19th century onwards to the present day (HagerROM, 2003; Spaich, 1978, p. 87-88; Strumpf, 1855, p. 46-56).

Despite extensive research Arnica has not been able to be synthesised. There is no plant that substitutes Arnica in terms of its unique actions. These actions are described in standard textbooks as anti-inflammatory, anti-echymotic (against bruises), analgesic and antiseptic with additional expectorant, excitant and circulatory stimulant actions when used internally. These evidenced actions have been summarised by the standard pharmaceutical reference book “Hagers Handbuch der Pharmazeutischen Praxis” (Zepernick, Langhammer & Lüdcke, 1984, pp.58; List, Hörhammer, Kern & Hager, 1972, pp.214-220).

Contemporary use

Arnica continues to be used internally in clinical practice (Wurm & Danner 1990, pp.346-355). Several randomized controlled studies confirm Arnica’s therapeutic efficacy in osteoarthritis, bruising, ankle joint distortion and chronic venous insufficiency. An Arnica preparation demonstrated non-inferiority compared with ibuprofen (Bone & Mills, 2013, p.376). Whilst these clinical studies were undertaken on topical preparations, they relate to the same indications where physicians and registered herbal experts in European countries support external applications with internal use to accelerate healing (Bäumler, 2007, p.62-63; Zimmermann, 1999, p. 125; Zizmann, 2011, pp.122,130, 208-209; Vonarburg, 1993, p. 23-27; McIntyre, 1995, p.156; Willfort, 197514, p. 52-54 ).
Active constituents of Arnica

The key active constituent of Arnica is the sesquiterpene lactone helenalin and, to lesser degrees, the sesquiterpene lactones 11alpha,13-dihydrohelenalin and chamissonolid. They are reported to inhibit the activation of the transcription factor NF-kappa B by directly modifying this factor. Activation of NF-kappa B leads to inflammatory activity. This could account, at least in part, for the possible anti-inflammatory and analgesic actions of Arnica preparations. Other constituents are triterpenes, flavonoids, lignans, coumarins, non-toxic (saturated) pyrrolizidine alkaloids, polyacetylenes, essential oils and caffeoylquinic acids with confirmed anti-inflammatory, antimicrobial, antitumor and immune regulating pharmacodynamic properties (Bone & Mills, 2013, p.374).

Toxicity studies

A review of the toxicology studies on animals prepared by the European Medicines Agency suggests the lethal dose (LD₅₀) of oral Arnica is 123mg/kg in mice, which equates to 7.38 grams for a 60kg person. In rats the lethal dose was more than 5g/kg, equating to 300 grams for a 60kg person (EMA 2014, p. 12). Arnica’s active constituents did not show any cytotoxic effect on mouse fibroblast cultures and human lung cells, up to the dose of 500 µg/mL. (Sutovska et al. 2014).

Allergy potential

Several recently published studies report that topical Arnica hypersensitivity and allergy is rare. It accounts for about 1.14% of cases of contact dermatitis (Bone & Mills, 2013, p.378). Allergies to internal use are not quantified, but long-standing clinical observations under physician care point to a low incidence of Arnica allergies (Weiss & Fintelmann, 1997, p.163).

All products containing Arnica are contraindicated for people with hypersensitivity and allergies to Arnica. Cross-sensitivity to other plants of the Asteraceae family (also called Compositae or Daisy family) is known to have occurred.
Official dosage regimes

Arnica preparations made from flowers, whole herb or roots are official in many countries. To illustrate, they are listed in the European, German, Swiss, Austrian and British Herbal Pharmacopoeias.

Listings and strength considerations

We discuss listings and strength considerations related to the crude drug of Arnica flowers and Arnica flower tincture for internal use.

Since the early 20th century the Swiss, German, Belgian, British, Danish, Norwegian, Dutch and Swedish pharmacopoeias stipulate a 1:10 tincture with fresh or dry flowers, whilst the French pharmacopoeia prescribed 1:5 tincture (Frerichs, Arends & Zörnig, 1925, p.549; Hager, 1874, p.789). Changes in processing has contributed to confusion around safe dosing. As an example, from the first to the third edition, the Swiss pharmacopoeias specify that a tincture is to be made with freshly harvested flowers only. From the fourth edition onwards, however, it permits also a 1:10 tincture made with dry flowers due to supply issues (Beuttner, 1909, p.188). In effect this lead to a higher ingestion of equivalent plant material since the official dosage regime remained the same as for the fresh-plant tincture.

Consistently and until the 1980s, official national pharmacopoeial monographs list the internal and external use of Arnica preparations made with various parts of the plant (flowers, whole plant, root); for example the Swiss (Ph. Helv VI.), German (2. AB-DDR; DAB 8), Austrian (ÖAB), French (56) Pharmacopoeias as well as the German Homoeopathic Pharmacopoeia (HAB 1) (Zepernick, Langhammer & Lüdcke, 1984, pp.56-59).

Even though research during the 1980s did not highlight new information regarding Arnica’s constituents and proposed modes of actions, risk assessment by investigators from disciplines outside of clinical herbalism led to much confusion and factual omissions in the literature. This prompted some but not all national regulators to exclude the internal use of Arnica from that time on (Zepernick, Langhammer & Lüdcke, 1984, pp.56-59).

Governments rely on risk assessments in good faith. One key issue national regulators faced during this period was that non-clinical advisors failed to appreciate the importance of different strengths of herbal extracts in medical herbalism, which result in different daily dosages. Arnica belongs to a class commonly described as “low dose herbs” (Khalsa, 2007, p.87). Low dose herbs are a class of herbs that provide beneficial effect at a low dose, which allows them to be used within a clinical framework of safety. Low dose herbs are usually prepared as 1:10 tinctures and are taken at a dosage regime of 10-30 drops (~0.4-1.2ml) per dose. This traditional and officially endorsed type of preparation results in a much lower dose than newer hydro-alcoholic tinctures, which are now commonly 1:1, 1:2 or 1:4 strength tinctures. Any assessment on the risk and benefit of a plant needs to be done on the basis of its actual preparation.

Here are some examples of the official internal dosage regime from the 19th century to present. We include homoeopathic pharmacopoeias, since mother tinctures (Ø)
usually refer to a 1:10 fresh-plant or dry plant tincture. This is the strength used by traditional herbal medicine manufactures.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Arnica flowers (Flores Arnicae) as internal medicinal tea</th>
<th>Arnica tincture (Flores Arnicae) 1:10 for internal use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commentary to the third edition of the German pharmacopoeia (Hager, Fischer, Hartwich 1891, p.664)</td>
<td>0.3g-1g of Arnica flowers per dose</td>
<td>½ teaspoon (~ 2.5ml) in ½ a glass of sugar water per dose</td>
</tr>
<tr>
<td>Editions 1-4 of Swiss pharmacopoeias (Beuttner 1909, XXV)</td>
<td></td>
<td>only maximum tincture doses for strongly acting plants listed. No maximum dose listed for Arnica tincture</td>
</tr>
<tr>
<td>The British Pharmacopoeia (Grieve &amp; Leyel 1931, p.55)</td>
<td></td>
<td>10-20 drops (~0.4ml-0.8ml) per dose</td>
</tr>
<tr>
<td>The United States Pharmacopoeia (Grieve &amp; Leyel 1931, p.55)</td>
<td></td>
<td>10-30 drops (~0.4-1.2ml) per dose</td>
</tr>
<tr>
<td>Commentary to the 8th edition of the German pharmacopoeia DAB 8 (1983, p.167):</td>
<td></td>
<td>20-30 drops (~0.8ml-1.2ml) up to three times a day</td>
</tr>
<tr>
<td>The Austrian Pharmacopoeia OAB 90 (HagerRom 2003):</td>
<td>0.2g per cup and dose</td>
<td>0.5-1.0g</td>
</tr>
<tr>
<td>Homöopatisches Arzneibuch HAB 1 (German Homoeopathic Pharmacopoeia) (Wurm &amp; Danner 1990, p.353)</td>
<td></td>
<td>5-10 drops (~0.2-0.4ml) 1-3 times a day</td>
</tr>
<tr>
<td>French homoeopathic pharmacopoeia PFX (Wurm &amp; Danner 1990, pp.353-355)</td>
<td></td>
<td>mother tinctures ø and dilutions thereof; dose according to patient assessment</td>
</tr>
<tr>
<td>US homeopathic pharmacopoeia HPUS 78 (Wurm &amp; Danner 1990, pp.353-355)</td>
<td></td>
<td>mother tinctures ø and dilutions thereof; dose according to patient assessment</td>
</tr>
</tbody>
</table>

**Arnica tea**

We can see that for the past 100 years the official dosage recommendation for medicinal tea is in the range of 0.2g to 1g of dried flowers per dose up to 3x per day.

**Arnica tincture**

The official dosage range for a 1:10 tincture is in the range of 0.2-1.2ml/g per dose. The upper dosage regime of approximately 2.5ml per dose as listed in the commentary to the third edition of the German pharmacopoeia highlights that a higher dose was officially accepted when medically indicated, for example in shock or paralysis.

It is also important to note that many official pharmacopoeias prescribed the use of Arnica together with other complementing plants (Madaus, 1938, Strumpf, 1855, p.50-56). This synergistic approach meant that only small doses or Arnica were required for a desired therapeutic effect.
Traditional dose regimes in clinical practice

Traditionally, fresh or dry flowerheads, whole plant, or roots are processed into teas, fresh-plant tinctures (1:10), dry plant tinctures (1:5 or 1:10) and topical applications.

Here is a summary of traditional dosage regimes from the 19th century to contemporary use as prescribed by physicians and registered herbal experts:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Arnica flowers (Flores Arnicae) as internal medicinal tea</th>
<th>Arnica tincture (Flores Arnicae) 1:10 for internal use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Bernatzik &amp; Prof. Dr. Vogel (1891, p. 583) based on the official guidelines of the German and Austrian Pharmacopoeias</td>
<td>2g - 10g of flowers per dose</td>
<td>10-30 drops (~0.4ml – 1.2ml) per dose</td>
</tr>
<tr>
<td>Dr Fyfe (1903, n.p.)</td>
<td></td>
<td>10-30 drops (~0.4ml – 1.2ml)</td>
</tr>
<tr>
<td>Dr Gardemin &amp; Dr Weitkamp (1937, p.16)</td>
<td></td>
<td>20-30 drops (~0.8-1.2ml) in ¼ litre of water per day; sip throughout the day</td>
</tr>
<tr>
<td>Pharmacists Flamm, Kroeber and Seel (1942, pp.30-31)</td>
<td></td>
<td>5-10 drops (~0.2-0.4ml) per dose</td>
</tr>
<tr>
<td>Pharmacist Spaich (1978, p. 87-91)</td>
<td></td>
<td>5-20 drops (~0.2-0.8ml) per dose</td>
</tr>
<tr>
<td>Prof. Dr. Weiss, lecturer at the University of Berlin (1974, p. 175):</td>
<td>1-2 teaspoons (1-2g) of Arnica flowers per dose; sip gradually</td>
<td>15-25 drops (~0.6-1ml) of a 1:7 tincture) 3x per day, best with some sugar; several commercial preparations for internal use by Kneipp, Schwabe, Steigerwald and others – as combination preparations with other medicinal plants</td>
</tr>
<tr>
<td>Prof. Dr. Weiss &amp; Dr Fintelmann (1997, p.163)</td>
<td></td>
<td>50 drops (~2ml) to drink within 15 minutes in acute attack of angina pectoris</td>
</tr>
<tr>
<td>Willfort (197514, p.53), medical herbalist</td>
<td></td>
<td>10 to 15 drops (~0.4-0.6ml) per dose</td>
</tr>
<tr>
<td>Dr. Widmaier (1986, pp. 86-87)</td>
<td>1 teaspoonful (1g) per dose; 1-2 doses per day</td>
<td>5-20 drops (~0.2-0.8ml) per dose</td>
</tr>
<tr>
<td>Dr Bäumler (2007, p.62-63)</td>
<td></td>
<td>3-5 drops (~0.12-0.2ml) per dose</td>
</tr>
<tr>
<td>Zizmann (2011, p.208-209), medical herbalist</td>
<td></td>
<td>5-20 drops (0.2ml-0.8ml) per dose</td>
</tr>
</tbody>
</table>

**Arnica tea**

We can see that for the past 100 years expert consensus on the dose of the medicinal tea made with Arnica flowers is between 1g and 2g per dose, recommended up to 3x per day. This is slightly higher than the official recommendation in the pharmacopoeias.
Drs Bernatzik and Vogel’s maximum dose recommendation of 10g highlights that a higher dose was accepted when medically indicated, for example in shock or paralysis. This dosage would only be appropriate under medical supervision.

Arnica tincture
We can see that for the past 100 years the expert consensus on the dosage of a 1:10 tincture is between 0.12ml and 1.2ml per dose, up to 3x per day. This is in line with the official recommendations in the pharmacopoeias.

Prof. Dr Weiss and Dr Fintelmann’s upper dosage regime of 2ml per dose highlights that a higher dose was accepted when medically indicated. The example given by the authors is an acute attack of angina pectoris. This condition requires medical care.

Dosage considerations in the context of overdose reports
As with any medicine, an appropriate dose is paramount to acquiring the desired effect while minimising any possible risk. It is commonly said that with any medicine, the dose makes the poison. Whilst Arnica has been extensively used over several hundred years, adverse effect reports have been comparatively rare. Despite the lack of conclusive causality, these reports tainted Arnica with a reputation as being possibly toxic.

We have extensively reviewed the literature and have found four case reports over the past 150 years discussing an accidental overdose with Arnica.

1) In the first case a man had taken “by mistake about an ounce [30g] of tincture of arnica, which he had bought to make a lotion”. He displayed severe epigastric pain and collapsed. He was admitted to hospital and discharged the next morning when he “walked out of the hospital perfectly recovered, none of the morbid symptoms remaining, except slight dryness of the mouth.” (Bertin, 1864).

2) The second case was reported originally in the French periodical ‘Journal de Pharmacie et de Chimie’ in 1879 and has become a feature case over the past 130 years by some to argue against any internal use of Arnica. It specified that a man accidently ingested approximately 60-80g of Arnica tincture of unknown strength. He developed stomach pain and later died (Hager, 1883, p.115; Lewin, 1992, p.764). A review of this case queried whether the lethal dose – now quoted as an average of 70g - was actually an Arnica preparation, as the very bitter taste and high alcohol content of an Arnica tincture would have made it difficult to swallow (Spaich, 1978, p.90). At the time this case occurred the offending preparation was not analysed and the botanical identification of the starting material is not reported. The original report noted that experimental exposure of concentrated Arnica tincture on a hand can cause irritation and blisters and this was used as the proof that the offending preparation must have been Arnica. However, there are other preparations, which in high concentrations have a caustic effect on skin. Unequivocal causality was not established.
3) The third case occurred in 1938 and describes a man who was admitted to a German hospital with low grade fever and headaches. The attending doctor and author of the case report diagnosed the symptoms as an adverse event due to the inappropriate use of Arnica tea. The patient recovered completely (Schoenemann, 1939). The dosage and possible misidentification of the tea was not conclusively established, although it is likely that in the 1930s German doctors would have been familiar with the botanical characteristics of Arnica.

4) The most recent case report refers to a 19 year old male who took an unknown amount of tea apparently made from the leaves and flowers of Arnica. The preparation referred to in the report is, however, not clear as the account refers to a “bottle” which is a container that holds liquid. According to the instructions on the bottle the content was to be applied as a poultice. The man fell ill and received medical treatment. He recovered and was discharged. Causality, dosage and content of the offending preparation was not established. (Topliff & Grande, 2000).

We also found two case report of deliberate overdose with Arnica to attempt an abortion (Wurm & Danner, 1990; Lenz & Ardens, 1919, p.90).

All four case reports of accidental Arnica poisoning are problematic from an evidence-based point of view, as they do not satisfy current criteria of scientific reporting. In particular they do not provide adequate levels of data to establish clear causality, confirm the dose ingested, and verify botanical identification of the plant used in the preparation. In other words, the poor quality of the information makes it difficult to establish a credible link between cause and effect.

It is therefore surprising that these case reports continue to be quoted in current toxicology textbooks and books of clinical herbalism, without disclosing the issues of uncertain causality, dosage and possible misidentification. For example, Bone & Mills (2013), Roth, Daunnderer & Kormann (2006), HagerRom (2003), and Schulz, Hänsel, Tyler (1998) all quote the case of ‘Arnica’ tincture poisoning from 1879 without apparent awareness that this case actually occurred over 130 years ago. This may not be deliberate as these authors may simply reference other authors who themselves reference a source that did not disclose the lack of unequivocal causality nor the fact that the case is outdated and not evidence-based.

This issue aside, it is unusual that most contemporary authors fail to differentiate between an adverse event and an overdose. Even if Arnica had been the offending plant drug in question, the reported dose ingested by the man was over 70 times more than the recommended therapeutic dose. This case therefore describes an overdose not an adverse event. Misinformed use of a substance cannot be scientifically justified to imply an inherent toxicity issue when that substance is used within the recommended guidelines.

Inadequate or selective reporting leads to bias. Biased reporting in turn can have a grave impact on a plant’s safety appraisal as demonstrated in this following example. Quoting Schulz, Hänsel & Tyler (1998) the WHO monograph (2007, p.83) on Arnica states: “A fatal case of poisoning following the ingestion of 70.0 g of a tincture of Flos Arnicae has been reported. Internal use of Flos Arnicae or extracts of
the flower heads is not recommended." Departing from an evidence-based approach, the WHO monograph on Arnica does not disclose the historic circumstances nor the lack of confirmed causality around this much quoted case as highlighted above. Furthermore, we could not locate in the WHO monograph any discussion regarding the importance of correct dosage and correct preparation nor a clarification that the rare adverse events reported in the literature – apart from allergies – are related to overdoses. No rigorous evaluation process is apparent that would appraise long-standing traditional use alongside toxicology studies and overdose reports.

According to authoritative medical experts, the Commission E monograph on Arnica of the former German Bundesgesundheitsamt suffered a similar overestimation of theoretical toxicity issues compared with the longstanding expert consensus of its safety and effectiveness in real patient care when used within the therapeutic range (Weiss & Fintelmann 1997, p.163).

This is in contrast to regulatory assessments until the 1980s, when plant medicine textbooks highlighted the importance of the right preparation and correct dosage regime when prescribing Arnica for internal use (Bäumler, 2007, pp.62-63; Weiss, 2001, p.200; Zizmann, 1996, pp.218-219; Widmaier, 1986, p.86; Spaich, 1978, pp. 87-91; Flamm, Kroeber, & Seel, 1942, pp. 28-32; Grieve & Leyel, 1931, pp.55; Fyfe, 1903, n.p.; Scudder, 1898, pp.356-357; Husemann, 1892, p.500; Bernatzik & Vogel, 1891, pp. 582-583; Strumpf, 1855, pp.46-56).

In the words of Professor Weiss, medical doctor and respected plant-medicine expert (2001, p.170): "At best, an arnica infusion or tea may be given, with the dosage kept on the low side. If arnica tincture is to be given internally, it will be necessary to start with a very low dose, always diluting with a large volume of water...High doses of it may cause intoxication, with dizziness, tremor, tachycardia and arrhythmia, even collapse...On the other hand, arnica is used as an ingredient in many proprietary preparations [without issues]."

We therefore need to further consider what an appropriate dose of an Arnica preparation means. As already stated, an overdose is not the same as an appropriate dose. For example- Paracetemol is considered safe enough to be sold widely in pharmacies and supermarkets as long as the label states the recommended dosage and with the assumption that the product should be "taken as directed". No one would argue that if someone took an inappropriate amount of Paracetemol that this would constitute an overdose, not an adverse reaction.

Medicinal plants are the same - an appropriate dose is a remedy, a very large dose can be poisonous with some plants.

Risk versus safety

The concern with Arnica is that it contains the active constituent sesquiterpene lactones (SLs). As already illustrated, plants are complex by nature and their risks versus benefits tend to be assessed differently depending on the professional background of the assessor(s). Risk appraisals of researchers trained in theoretical
pharmacology and toxicology have shown to diverge from assessments of clinicians working in actual practice.

Safety of any therapy can never be judged in isolation of its therapeutic merits. Rather, risk must be weighed against the benefit of a therapeutic intervention. In practice, a remedy can only be approved if possible benefits outweigh the potential risks. The difficulty is that analysis of risk versus benefit (the benefit-risk ratio) always involves some subjective judgment as this assessment involves qualitative and not quantitative data. It is therefore imperative that such a decision must include a broad understanding of all facts, including actual clinical use and epidemiological safety data.

Arnica meets the criteria of evidence of long-standing traditional use. As illustrated, this plant has been used in mainstream patient care for several centuries and has been continuously listed in pharmacopoeias since their inception in the 19th century. This points to a positive judgment of its therapeutic benefits by physicians and regulators. The potential risk of Arnica relating to overdose toxicity in inappropriate use has been found acceptable in the context of a positive evaluation of Arnica in first aid, shock and injury recovery.

We too consider the risk-benefit ratio of Arnica as positive since the benefit in injury recovery is noticeable and the relative risk is low when taken at the appropriate dose.

The trend to expect a zero tolerance of risk for herbs as noted since the 1980s (Schilcher, 2013) is problematic, as hardly any pharmaceutical drug meets this threshold. In current evaluations of permitted over-the-counter medicines, misinformed use by some individuals is not seen as an evidence-based criteria to restrict these therapeutic substances. It would therefore be inconsistent to use a different approach for natural products and supplements.

Comparing the relevance, probability, and history of Arnica with the commonly available drug Paracetamol, the data highlights the relative safety of this plant. Poisoning with Paracetamol is common, and the New Zealand National Poisons Centre receives about 1000 calls each year about Paracetamol poisoning compared with no reports for Arnica poisoning (NZ National Poisons Centre, 2015). Post-marketing surveillance is a validated tool for the assessment of the relative safety of a therapeutic product and informs a risk-benefit analysis.

Arnica in Artemis products

Artemis has been selling products in New Zealand containing Arnica for internal use since 1998. Our in-house post-marketing surveillance has not alerted us to any safety issues with these products. In fact, we receive consistently positive responses from people who use our internal Arnica products.

The dosage of Arnica within our products for internal use is well within the recommended and traditional use. Our maximum recommended daily dose is the equivalent of approximately 90mg of fresh herb- well below the 3gm of Arnica herb tea used traditionally in clinical practice.
Recommendations

We believe that we have demonstrated a thorough understanding of the issues relating to the importance of a correct dose to maximise benefit and minimise risk with Arnica preparations. Based on our extensive review of all aspects involved, including traditional expert consensus and official dosage recommendations over a prolonged period of time, as well as toxicity studies and absence of evidence of harm from Artemis remedies containing Arnica in New Zealand over the past 17 years, we respectfully recommend a re-assessment of the proposed requirement of restricting internal use of Arnica. We propose an allowance of a maximum daily dose of 1g per day.

We would like to highlight that a lower dose than this proposed dose, which is at the low end of the dosage scale, would not offer the expected benefits. There is no equivalent plant that could replace Arnica. We consider Arnica an essential plant for remedies based on Traditional European Medicine (TEM).

We also propose that the following parts of Arnica are permitted: flowers, whole plant, roots.

Concluding remarks

We appreciate the time and effort that the Ministry of Health has put into this bill, and are pleased that the opinions of stakeholders and natural medicine experts are being considered.

We would appreciate a response to our proposed changes to the draft list of ingredients, so that we may properly address any questions or concerns that the working group may have.

If possible, we would also like to see our suggestions integrated now into the Draft List, rather than our proposed changes going to the next submission level.

Thank you again and we look forward to working together with the Ministry to ensure the health and wellbeing of New Zealanders.

On behalf of Artemis Natural Healthcare

Sandra Clair
M.A., Post. Grad. Dip. Health Science, PhD Candidate
Founder, R&D Director
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