Evaluation of a new Class 1 substance

Macropiper excelsum (Kawakawa) leaf

Sponsors: XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Permitted Ingredients List Project

Office of Complementary Medicines (TGA) and Medsafe

Evaluator:

XXXXXXXXXXXXXXXXXXXX

Abbreviations:

CG	Compositional Guideline
GMP	Good Manufacturing Practice
QC	Quality Control
TDLo	Lowest published toxic dose

SUMMARY & ASSESSMENT

The purpose of this evaluation is to determine whether or not *Macropiper excelsum* leaf is suitable for use as an ingredient in Class 1 (currently Listed) medicines, and to consider whether any restrictions should be imposed to assure its safety-in-use.

Characterisation of the substance

M. excelsum is a small evergreen shrub-like tree with large heart-shaped leaves, usually known as 'kawakawa' or 'pepper tree'. It grows to a hight of six metres, and is reasonably well known and common throughout NZ, particularly in shady gullies and on shady outcrops in coastal regions. The taxonomy of *M. excelsum* and its subspecies has been studied extensively and described in detail in the literature; confusion between subspecies is unlikely.

There is no uniformly accepted standard for phytochemical characterisation of *M. excelsum* leaf, and none of the constituents listed in section 2.4 has been proposed as a unique phytochemical marker of the herbal material in order to distinguish it from a lesser quality or contaminated plant material.

An essential oil may be distilled from *M. excelsum* leaf; this principally contains myristicin, which is thought to contribute to the peppery taste of the leaf and also to be the major psychoactive constituent in nutmeg. The amount of myristicin in *M. excelsum* leaf is comparatively small, and the maximum recommended dose of the sponsored product would contain less than 100 mg of myristicin, compared with the reported human oral TDLo of 342 mg for a 60 kg person (at which dose 'wakefulness' is the only behavioural effect reported).

History and pattern of use

The literature surveyed indicates that *M. excelsum* leaf has been used in traditional Maori medicine in NZ for more than 160 years. The main uses have included treatment of urinary complaints, stomach pains and indigestion, skin conditions such as eczema and boils, circulatory insufficiency including chilblains, and colds, coughs and bronchitis. No adverse effects have been recorded.

Despite a popular concept of a connection of 'kawakawa' with the mildly psychotropic beverage kava (from *Piper methysticum* root), there is no evidence of the use of *M. excelsum* for psychotropic purposes in NZ, at least after 1848.

The form in which *M. excelsum* was used traditionally (and is still currently used) includes consumption of the fresh leaf and fruit (chewed), infusions and decoctions, and steam baths, and the dried leaf. Modern use is essentially similar, with the addition of a fluid extract prepared with aqueous alcohol. The latter would not be expected to introduce any additional substances that were not present in the original herb, although the phytochemical profile may be different. There is no reason to anticipate that the use of a fluid extract would introduce any additional risk of toxicity or adverse effects. The fruit is not covered in this evaluation.

M. excelsum leaf or any other plant part is not permitted for use as an ingredient in Listed or Registered therapeutic goods in Australia; there are no entries on the ARTG for products containing the substance. There is no reference to *M. excelsum* leaf or any other plant part in the Standard for the Uniform Scheduling of Drugs and Poisons.

Biological activity

The putative biological actions listed in section 4 appear to be suggestions arising from the historical patterns of use of *M. excelsum* leaf. No scientific studies have been found to substantiate these.

The only constituent of *M. excelsum* leaf to have been studied extensively is myristicin, but this substance accounts for only 2.8% or less of the dried herb. Nevertheless, it may contribute to antiinflammatory, anthelmintic and analgesic activity of *M. excelsum*.

Toxicology

No toxicological studies were found on *M. excelsum* leaf.

The only quantified individual constituent to have been studied in detail is myristicin, but this substance, which is a major component of the essential oil of *M. excelsum* leaf, constitutes only 2.8% or less of the whole dried herb. Myristicin is reported to be of low toxicity; the oral LD_{50} (rat) is 4.26 g/kg. This amount of myristicin would be equivalent to a quantity of more than 170 g/kg of *M. excelsum* leaf, or 10.2 kg for a 60 kg person, or 2500 times the maximum recommended daily dose of *M. excelsum* leaf (4 g/day). Thus, *M. excelsum* leaf would not be expected to exhibit acute oral toxicity due to its myristicin content.

Myristicin was reported to have anti-tumour activity in mice when administered orally (10 mg given three times a week for a total of 15 doses) for a period of five weeks. Although this is suggestive of a lack of carcinogenic activity under the *in vivo* conditions studied, the relevance of this finding is limited as the dose given to mice would be equivalent to about 1 kg every second day of *M. excelsum* leaf for a 60 kg person, or about 267 times the maximum recommended daily dose of *M. excelsum* leaf.

Clinical data

There have been no clinical trials of *M. excelsum* leaf.

Adverse reactions

Neither the Australian Adverse Drug Reactions Advisory Committee nor the New Zealand Centre for Adverse Reactions Monitoring have received any reports of adverse reactions to preparations or products containing *M. excelsum* leaf. No data were retrieved from the WHO on adverse reactions relating to *M. excelsum* leaf.

Conclusions

The traditional use of *M. excelsum* leaf in the form proposed by sponsors has been recorded since 1842, without evidence suggestive of unacceptable safety risks.

However, there is an almost complete lack of information on the toxicological and pharmacokinetic properties of the herb. It is therefore important to consider if, in the virtual absence of pre-clinical and clinical safety data, the history of apparently safe traditional therapeutic use could be considered as the evidence of safety-in-use of the herb, thus justifying its use as ingredients in Class 1 medicines.

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1 INTRODUCTION

This safety evaluation has been undertaken under the Permitted Ingredients List (PIL) project within the Joint Agency Establishment Group, which has been set up to assist in the transition of New Zealand's nutritional supplement sector into a joint regulatory agency environment. The objective of the PIL project is to determine whether or not substances that have been notified by New Zealand sponsors as being low-risk ingredients of nutritional supplements marketed in New Zealand prior to 2004 do meet the safety and quality standards for the inclusion as permitted ingredients in Listed (Class 1) medicines under the Australian Therapeutic Goods Act (1989) and the Therapeutic Goods Regulations (1990), and therefore, under the forthcoming joint regulatory agency scheme.

The purpose of this evaluation is to determine whether or not *Macropiper excelsum* leaf is suitable for use as ingredients in Class 1 medicines, and to consider whether any restrictions should be imposed to assure its safety-in-use.

Interest in the inclusion of *M. excelsum* leaf was notified to Medsafe in May 2004 by the following four companies (sponsors): XXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

2 CHARACTERISATION OF THE SUBSTANCE

2.1 General Information

There are three subspecies of *M. excelsum*. The subspecies *M. excelsum* ssp *excelsum* is the one found on the two main islands of New Zealand and on the Chatham Islands; this is the subspecies used in traditional Maori medicine and in modern medicine, and is the subject of this evaluation.

The other two subspecies are *M. excelsum* ssp *psittascorum*, found on Lord Howe Island, Norfolk Island and Kermadec Island, and *M. excelsum* ssp *peltatum*, found on the islands offshore from the north coast of the NZ North Island. The taxonomy of these subspecies has been studied extensively and described in detail by Gardner (1997).

2.1.1 Names and synonyms

Macropiper excelsum was formerly known as *Piper excelsum* (Forst.f.)

Common names: 'Kawakawa', 'pepper tree'.

2.1.2 Approved names

The approved name for this substance is expected to be:

'*Macropiper excelsum* leaf'

This name is comprised of the Latin binomial name for kawakawa with the plant part defined. This name will need to be considered by the appropriate joint Agency naming committee in due course.

2.2 Descriptions

2.2.1 Botanical description

Botanical binomial: *Macropiper excelsum* (Forst.f.) Miq.

Family: *Piperaceae*.

M. excelsum is a small evergreen shrub-like tree with large heart-shaped leaves. It grows to a hight of six metres, and is reasonably common throughout NZ, particularly in shady gullies and on shady outcrops in coastal regions. The zigzag branches are swollen and jointed at the nodes, and the shiny leaves are usually 5-10 cm long, 6-12 cm wide, and are often holed by chewing insects. The fruits, which develop on the female spike, are small drupes 2-3 mm in diameter, each of which contains a single seed enclosed by a fleshy covering that does not spontaneously open to release the seed. When in season, the fruits may be harvested with the leaves, but may subsequently be separated from the leaves by screening. The plant is aromatic, and derives the common name 'pepper tree' from the taste of the leaves (XXXXXXXXXXXXXXXXXXXXXXXX).

2.2.2 Plant parts used

The leaves are most often used and are the subject of this evaluation, although the fruit, root and bark are also used in traditional medicine (Phytomed 2000, Rasmussen 2001).

2.3 Manufacture

2.3.1 Manufacturer(s)

Two companies (XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX) manufacture the dried leaf product, and one (XXXXXXXXXXXXXXXXXX) manufactures the alcoholic fluid extract.

No information has been supplied on the GMP status of any NZ growers or suppliers, but this information is not critical for a Class 1 substance.

2.3.2 Description of manufacturing process and process controls

The leaves of *M. excelsum* are harvested from the growing shrub or tree, dried and shredded. The dried leaf may be used as such, or extracted with a solvent (XXXXXXXXXXXXXX XXXXXXXXXXX) to produce a liquid extract. No further information was supplied by sponsors on the process of extraction (XXXXXXXXXXXXXXXXXXXX).

One sponsor, XXXXXXXXXXXXXXXXX, provided Medsafe with a flowchart describing the harvesting, inspection, drying (at <45°C), separation of leaf from small twigs and seeds, and packaging of the dried leaf. Samples were taken at three stages, for initial quality assessment, for determination of moisture content (in-house), and for microbiological standard compliance (independent laboratory) as follows:

XXXXXXXXXXXXXXXX dried leaf processing method

In the field

Kawakawa brush harvested from natural plantations by hand, packed in bales and delivered to factory.

In the factory — XXXXXXXXXXXXXXXXX

1. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX for impurities (foreign materials).
2. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXX.
3. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
4. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.

5. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXX.
6. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXX
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9. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
10. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXX

2.3.2.1 Control of materials

As specified above, the 'in the factory' process flow provided by the sponsor, XXXXXXXXXX XXXXXXXXXXXXXXX includes material control steps at three manufacturing stages.

The sponsor has also provided Medsafe with a product specification indicating the microbiological assay of the dried leaf. The possibility of contamination with *Bacillus cereus*, *Clostridium perfringens*, coagulase-producing *Staphylococcus*, faecal Coliform and *Salmonella* is controlled (see subsection 2.5.1 below).

2.3.2.2 Control of critical steps and intermediates

Not specified, but refer to the subsection 2.3.2.1 above. This information is not critical for manufacturing of a raw ingredient of Listable/Class 1 medicines.

2.3.2.3 Process validation and/or evaluation

No information provided (not critical for a raw ingredient of Listable/Class 1 medicines).

2.3.2.4 Manufacturing process development

No information provided (not critical for a raw ingredient of Listable/Class 1 medicines).

2.4 Characterisation

2.4.1 Monographs

No monographs for M. excelsum leaf were found in international pharmacopoeias.

2.4.2 Phytochemical characterization

The phytochemical profile of *M. excelsum* leaf has not been well characterised. Some information is available on the leaves, which are variously reported to contain essential oil at yields from 0.095% (Briggs 1941) to 3.5% (Phytomed 2000) expressed as a percent of the dry herb. The major constituent of the essential oil is myristicin, reported as 45-70% of the oil (Briggs et al 1975, Phytomed 2000).

Constituents of the essential oil that have been quantified are listed in Table 2.1, with an indication of the maximum amounts likely present in the dry herb based on an assumed 3.5% yield of essential oil from dry herb (data adapted from Mohi 2000).

Table 2.1 Constituents of essential oil of *M. excelsum* leaves

Constituent	% in essential oil	% in dry herb
Myristicin	45-70	1.6-2.5
Mixed cadinenes	12.2	0.43
Elemicin	4.0	0.14
Aromadendrene	2.0	0.07
Mixed esters	2.0	0.07
Mixed terpenes	1.9	0.07

Other minor constituents of the essential oil have been identified in smaller amounts, but not usually quantified, including camphene, β-phellandrine and palmitic acid. No information has been found on non-volatile constituents of the leaf; the presence of polyphenols, flavonoids and tannins would be anticipated.

There is no uniformly accepted standard for phytochemical characterisation of *M. excelsum* leaf, and none of the constituents listed above has been proposed as a unique phytochemical marker for the herbal material, in order to distinguish it from a lesser quality or contaminated plant material.

2.4.2.1 Individual constituents - myristicin

The individual constituents of *M. excelsum* leaf have not been identified, other than the major constituents of the essential oil (up to 3.5% of the dry herb). Of these, only myristicin appears to be present in a pharmacologically significant amount (up to 2.5% of the dry herb). Data on myristicin are therefore included in this evaluation.

Myristicin is a naturally-occurring alkylbenzine compound found in nutmeg, mace, parsley, carrot, black pepper, and many natural oils and flavouring agents with which humans have contact. Non-alcoholic drinks including cola, and baked goods, seem to be the largest sources of human myristicin intake, estimated at a few mg per person per day (Hallström & Thuvander 1998).

Name of substance entered in ChemIDplus: Myristicin

CAS Registry Number: 607-91-0

Synonyms: Methoxysafrole; 1,3-Benzodioxole, 4-methoxy-6-(2-propenyl)-, plus 10 other synonyms depending on the nomenclature system used.

Systematic names: 1,3-Benzodioxole, 4-methoxy-6-(2-propenyl)- (9CI), plus 10 other synonyms depending on the nomenclature system used.

Molecular formula of myristicin: $C_{11}H_{12}O_3$

2.4.3 Impurities, contaminants and substitution

There have been no reports of impurities, contaminants or substitution in the use of *M. excelsum*. The plant is plentiful and well known in NZ. *M. excelsum* is easily identified and distinguished from other species; substitution, either accidental or deliberate, is therefore unlikely.

2.5 Control of the Active Substance

2.5.1 Specifications

Specification for *M. excelsum* dried leaf was provided by XXXXXXXXXXXXXXXXXXX but it may not comply with all the requirements of the *ARGCM* Part III and/or joint agency guidelines.

Product name:	Tairawhiti 'KawaKawa' - Dried Leaf
Description:	
Genus	*Macropiper excelsum*
Plant Part	Leaf
Appearance	Ovate, heart shaped, shiny - leathery
Leaf Size	5-8 cm long and 5-8 cm wide
Colour	Green
Aroma	Very little
Taste	Spicy
Analysis:	
Loss on Drying:	Not more than 8% at 105°C
Microbiology:	
Standard Plate count	n = 5,c = 2, m = $5x10^5$/g , M = $5x10^6$/g
Bascillus cereus	n = 5,c = 2, m = 10^3/g, M = 10^4/g
Clostridium perfringens	n = 5,c = 2, m = 10^2/g, M = 10^3/g
Coagulase producing *Staphylococcus*	n = 5, c = 2, m = 10^2/g, M = 10^3/g
Faecal Coliform	n = 5, c = 2, m = 10/g, M = 10^2/g
Salmonella	n = 5, c = 0, m = 0 (Absent in 25g)

2.5.1.1 Draft compositional guideline

Compositional Guidelines (CG) for *M. excelsum* leaf have not been developed by any of the sponsors, but a draft CG is suggested below.

Macropiper excelsum leaf	
Definition	Dried leaves of *Macropiper excelsum* ssp *excelsum* (Forst.f.) Miq.
Characters	The leaves of *M. excelsum* are green in colour, with very little odour and a spicy taste. Macroscopic characteristics are described below under *Identification*.
Identification	The shiny leaves are heart-shaped, 5-10 cm long and 5-12 cm wide, and are often holed by chewing insects.
Tests	
Foreign Matter	Complies with limits as per Appendix XI D of the *BP*: maximum of 2%.
Loss on drying	Complies with limits as per Appendix IX D of the *BP*: maximum 12%, determined by drying at 100-105°C for 2 h.
Total Ash	Complies with limits as per Appendix XI J of the BP: need to conduct tests to determine typical values.
Heavy Metals	Complies with limits as dictated in the *ARGCM* Part III and/or joint agency guidelines - 20 ppm total.
Pesticide Residues	Complies with limits as per Appendix XI L of the *BP*.
Microbiological	Complies with limits for specific microbes as dictated in the *ARGCM* Part III and/or joint agency guidelines.
Assay	HPLC/MS or another validated analytical method.

2.5.2 Analytical procedures

2.5.2.1 Validation of analytical procedures

No information available.

2.5.2.2 Batch analyses

No information available.

2.5.2.3 Justification of specification

No justification has been provided for the specification.

2.5.3 Reference standards or materials

None specified.

2.5.4 Container closure system

No information provided (not critical for a raw ingredient of Listable/Class 1 medicines).

2.5.5 Stability

No evidence regarding the herbal substance *M. excelsum* leaf was supplied by the sponsors nor was any retrieved during literature searches. However, this alone is not considered grounds for rejection of an application for a Class 1 product lience as stability data are not currently required for raw ingredients of Listable goods.

3 HISTORY AND PATTERN OF USE

3.1 Traditional Uses

Riley (1994) states: "The kawakawa tree has always played a significant role in the Maori spiritual and physical world, tracing the life cycle from birth to death. It begins with conception itself, in a custom where a woman may sleep with a sprig of kawakawa under her before intercourse takes place, as a sort of good luck charm; through birth and naming ceremonies; the removal of tapu at the opening of a new meeting house; the launching of a new canoe; the blessing of food or of war enterprises; and finally kawakawa leaves are a symbol of mourning, being carried at funerals. Like other sacred trees with great powers, it is to be treated with respect, for despite the many uses to which its leaves, fruit and root are put, not the least of which are those medicinal, many Maori today would still refuse to sleep under its branches if the need arose on a summer's night.

"Kawakawa is botanically related to plants in the South Pacific with similar names: to the 'kava', 'kawa', 'ava 'ava', or 'awa', the *Piper methysticum* of Fiji, Hawaii and elsewhere, and to the 'ava'ava aitu', *P. tutuilae,* and the 'ava atua', *P. puberulum,* of Samoa. Its leaves however are not quite as large as those of its Pacific Island cousins, nor is a drink made from its root like that from the kawa root."

Several authors have attempted to make a connection between kawakawa (*M. excelsum*) and kava (from *P. methysticum*), the mildly psychotropic drug. Any similarity appears to be superficial; the evidence of use does not support a connection, although kawakawa used to be classified in the *Piper* genus.

Riley (1994) reports 78 references to the traditional uses of kawakawa. Of these, 42 refer to external or topical use, ranging in date from 1834 to 1992, and 36 refer to internal (oral) use, ranging from 1842 to 1991.

[Note: Most of the original source documents cited in Riley's textbook have not been checked for the purposes of this evaluation report although they are fully referenced in the textbook. Riley's textbook and references are generally regarded as reliable. They would be unlikely to materially affect this evaluation and in any case some of the historical documents are difficult to access.]

Examples of internal use, selected from Riley's text, are (Riley 1994):

Year 1842 – (Kawakawa is) "... used in the place of tea; the taste is pleasant and very aromatic . . . medically is estimed (sic) as a purgative. These two plants (manuka and kawakawa), together with the fernroot, which is a mild astringent, are of much dietary service in the 'bush' and one soon becomes reconciled to their taste." (Heaphy)

Year 1843 – "Some of the Europeans mix it (harakeke root) with the leaves of kawakawa, which are spicy and aromatic; or with those of the manuka, which contain a more fixed balsamic principle, and which themselves are in very common use as well-flavoured and highly diuretic substitutes for tea." (Dieffenbach).

Not Dated (but before 1848) – "The New Zealanders chew the root as a remedy for toothache but do not now use it as a beverage." (Taylor Notebook 30).

Year 1861 – "For dysentery the kawakawa root was chewed." (White).

Year 1883 – "The leaves and fruit are chewed for the toothache, the patient fills the mouth with the leaves or fruit and whilst chewing them, swallows the saliva, leaving the mouth filled with the leaves or fruit for a considerable time. A decoction of the leaves and young

twigs is made by putting hot stones into a calabash with water, which liquid is taken warm for pains of the stomach. Also this liquid is taken freely and for many days for gonorrhoea." (White)

Year 1887 – "Its effects are stimulating; it excites the salivary glands, the kidneys, and the bowels slightly; it is aphrodisiac. The fruit and seeds, ripe or unripe, are more powerful than the leaves, although the latter are generally used. Mr. Fitzgerald (a Wellington chemist) has also prepared an extract of this plant." (Baber).

Year 1889 – "Very aromatic, diuretic (increases the flow of urine)." (Neil)

Not Dated – (Mother Aubert classified its leaves under 'Bitters', as used in the medical sense. Kawakawa was an ingredient of her Paramo, Marupa and Wanena medicines for asthma, worms, influenza, etc.) (Aubert)

Year 1905-07 – "Whewhe (boils): This appears to have been a fairly common complaint in former times. When ripe they are squeezed, so as to force the core (whatu) out, and in former times human milk was then applied. A sort of decoction made from the leaves of the kawakawa shrub is now used; it is drunk as a blood purifier. It is probably a modern item." (Best)

Year 1905 – "As a 'tonic' they (the Maori) took internally an infusion of the leaves of the kawakawa shrub." (Goldie).

Year 1929 – "Urine flow relief. Boil equal quantities of karamu and kawakawa for one hour and drink the liquid. This is said to be a very effective remedy." (Ahuriri)

Not Dated – "Leaves (green) might be left overnight clenched between the teeth (for toothache). Overeating was an accomplishment with the Maori guest and was relieved through chewing the leaves. . . Ill-effects from eating the fatty titi – preserved mutton-bird – often caused eruptions on the arms and thighs. Some of these ill-effects could be staved off if kawakawa leaves were eaten between mouthfuls." (Cranwell)

Year 1941 – "Blood purifier. Cures boils. Also effective in bladder complaints. I know of a fairly serious case of this cured by kawakawa, a decoction of the leaves being used." (Pickmere)

Year 1946 – "An infusion of the kawakawa (pepper tree) leaves for colds." (MacMillan).

Year 1948 – (Ex Tama Mokau Te Rangihaeata). "The kawakawa was highly valued by the Maoris of pre-Pakeha days because from the leaves a medicine bitter to the taste was brewed which was esteemed as being highly efficacious in the treatment of digestive tract complaints. The action of the medicine was purgative only. The curative properties of the leaves of the kawakawa led to the tree itself being regarded as possessing sacred qualities so that the sprigs of kawakawa were universally used by tribal tohungas in the performance of many religious ceremonies." (Mitchell)

Year 1956-62 – "Infusions of the leaves were taken for asthma and other chest complaints." (Glenn June 1st 1956).

Year 1959 – "Taken for chest troubles, has a pleasant taste and is light green after infusion." (Collier)

Year 1982 – (A man from Chatham Islands - Rekohu or Wharekauri - gave Rev. Tioke this treatment for influenza, using water in which kawakawa leaves had been boiled). "He took a coloured ice cube from the fridge and let it melt in a cup of boiling water. Tioke was made to

drink it. “Well, in four or five minutes I broke into a deep sweat. I felt open you know, cleared.” Also for tea they use the leaf in the Chathams.” (Interview with Tioke)

Year 1984 – (At New Plymouth). “I, and a number of others, pick the kawakawa leaves from near the top of the bush on the sunny side, and away from high tension power lines, as these make the whole tree bitter. A handful of young leaves are put in a small saucepan – preferably enamel or stainless steel – with one and a half to two cups of water. Boil for 15 to 20 minutes. I then drink about a quarter of a cup of this ‘tea’ hot. Some drink it cold with sugar added to sweeten it, but I find it more effective hot. I am a fireman with a not very good chest – too much smoke – and when I get bronchitis, once every two or three years, normal antibiotics fail to shift it – I've had it over six months at a time. Unbelievably, a quarter of a cup, taken twelve hours apart for three times, clears the bronchitis for another two to three years.” (Watemburg).

Year 1991 – “Chew the leaf for abdominal pains. Boil the leaves and twigs. Strain and drink. Increases the urine flow in kidney problems. Also useful as a blood purifier, for blood disorders and as a drink for painful and rheumatic joints.” (Martin)

3.2 Existing Availability and Regulatory Status

3.2.1 Products manufactured and/or sold in NZ in 2003

M. excelsum leaf has been certified as having been sold in NZ in 2003.

M. excelsum leaf has not been classified in NZ as a therapeutic substance and is available as an ingredient in dietary supplements products.

3.2.2 Products available in Australia

M. excelsum leaf or any other plant part is not permitted for use as an ingredient in Listed or Registered therapeutic goods in Australia; there are no entries on the ARTG for products containing the substance. There is no reference to M. excelsum leaf or any other plant part in the Standard for the Uniform Scheduling of Drugs and Poisons.

3.2.3 Products available internationally

No information available.

3.3 Posology

3.3.1 Route(s) of administration

M. excelsum leaf is taken orally or topically.

3.3.2 Dose form(s)

M. excelsum leaf is available in two dose forms: as the dried powdered leaf, and as a 1:2 alcoholic extract (1 part by weight of dried leaf extracted into 2 parts by volume of aqueous alcohol). An infusion or decoction may be made with the dried leaf.

3.3.3 Dosing range, frequency and duration

The recommended oral dose is 1.5-4g per day of the dried leaf or 3-8 mL per day of 1:2 alcoholic extract (in each case divided into 2-3 doses). No limits on duration are recommended.

3.3.4 Indications and contraindications

The following therapeutic indications were proposed by a sponsor for internal and topical use (Rasmussen 2001):

Orally:

Urinary complaints - sometimes combined with Karamu.

Stomach pains and indigestion, particularly where due to overeating.

Digestive aid - appetite stimulant and carminative effect.

Skin conditions such as eczema and boils - popular drink as a depurative.

Circulatory insufficiency, including chilblains, arterial and venous insufficiency and Raynauds.

Colds, coughs and bronchitis - probably as an expectorant and antimicrobial.

Worm infestations.

Gonorrhoea and syphilis - was used both internally and topically.

Debility and general fatigue - tonic properties reported.

Topically:

Cuts, boils, abscesses and wounds - a popular treatment for numerous skin conditions.

Eczema - anti-inflammatory activity likely.

Neuralgia, rheumatic pains and bruises.

Toothache (chewed)

Insect repellent.

M. excelsum leaf has not been evaluated for efficacy against any of the above indications as part of this report.

A number of above-listed indication refer to the high-level claims which would not be allowed for Listed (Class 1) medicines. Indications for treatment of serious conditions, such as venereal disease, cardiovascular disorders, or chronic skin conditions (eg eczema) require the support of the clinical efficacy data, and as such, can only be made for Class 2 medicines, subject to the issue of a product licence.

Contraindications:

No precautions or contraindications were noted by Rasmussen (2001).

4 BIOLOGICAL ACTIVITY

4.1 Primary Pharmacodynamics

4.1.1 *In vitro*

Bloor (1995) tested an aqueous ethanolic extract of *M. excelsum* leaves for biological activity against a number of pathogenic organisms, using standardised screening protocols that were considered to be sensitive enough to detect the activity of low levels of active compounds. The bioassays used involved cancer cells (P338 murine leukaemia), viruses (five types including *Herpes*, *Polio* and *Influenza*), fungi (five types), one yeast (*Candida*

albicans) and four multi-resistant bacteria. The extract of *M. excelsum* leaves exhibited no anti-pathogen activity under the experimental conditions employed.

4.1.2 *In vivo*

Rasmussen (2001) lists the following possible pharmacological actions for *M. excelsum* leaf:

- anti-inflammatory (elemicin is an inhibitor of 5-lipoxygenase; myristicin is probably contributory);
- analgesic (myristicin is related to eugenol, a local anaesthetic found in clove oil);
- carminative;
- spasmolytic;
- antimicrobial;
- anthelmintic (myristicin);
- insecticide;
- diaphoretic;
- circulatory stimulant and counter-irritant/rubefacient;
- depurative/alterative; and
- diuretic (effects reported by settlers drinking tea; used for urinary retention).

No studies were found on the pharmacodynamics of *M. excelsum* leaf.

Zhang et al. (1992) found that myristicin inhibited tumorigenesis in mice at a dose of 10 mg given three times a week for a total of 15 doses. The number of tumours induced by benzo[α]pyrene (1 mg twice a week for four weeks) was reduced by 65%. The mechanism was thought to be by the induction of glutathione S-transferase, a major carcinogen-detoxifying enzyme system, which was increased 3.4-fold.

4.2 Secondary Pharmacodynamics

No data available.

4.3 Safety Pharmacology

No data available.

4.3.1 Pharmacodynamic drug interactions

No data available.

4.4 Pharmacokinetics

No pharmacokinetic studies were found on the absorption, systemic distribution, metabolism and excretion of pharmacologically active constituents of *M. excelsum* leaf. However, the constituent profile of *M. excelsum* is complex and largely unknown, and this makes it impractical to undertake pharmacokinetic investigations of the herb. Furthermore, it is unclear which of the currently identified constituents of the substance are responsible for its various activities, although it is likely that myristicin may be partly responsible for some of the effects mentioned above.

Myristicin is metabolised to 3-methoxy-4,5-methlene-dioxyamphetamine (MMDA), which is said to have a hallucinogenic effect greater than that of mescaline. It is also a weak

monoamine oxidase inhibitor (Stein et al 2001). However, the small amount of myristicin ingested in the recommended dose of *M. excelsum* leaf is unlikely to be enough to cause neurological effects.

4.4.1 Pharmacokinetic drug interactions

No data available.

5 TOXICOLOGY

5.1 Single-Dose Toxicity

5.1.1 *M. excelsum* leaf

No toxicity studies of *M. excelsum* leaf were found.

5.1.2 Myristicin

5.1.2.1 Rat

The oral LD_{50} (rat) of myristicin is 4260 mg/kg (Journal of Agricultural Food Chemistry 1982).

5.1.2.2 Human

The human oral TDLo of myristicin is 5.7 mg/kg, resulting in wakefulness (American Journal of Pharmacy 1909).

5.2 Repeat-Dose Toxicity

5.2.1 *M. excelsum* leaf

No repeat-dose toxicity studies of *M. excelsum* leaf have been found.

The only reference to repeated doses is a quote from a fireman who took a quarter-cup of a decoction of *M. excelsum* leaves three time at 12-hour intervals and presumably repeated this dose 2-3 years later. No toxic effects were reported (Riley 1994).

5.2.2 Myristicin

No toxic effects were observed after oral administration of 10 mg/kg of myristicin daily to 12 white rats for 26 days. Histological studies of livers and kidneys showed no abnormalities attributable to myristicin (result cited by Hallström & Thuvander 1998; original article not seen).

5.3 Genotoxicity

5.3.1 *M. excelsum* leaf

No studies designed to assess the genotoxic potential of *M. excelsum* leaf were found.

5.3.2 Myristicin

Myristicin was not found to be genotoxic in an 'Unscheduled DNA Synthesis' (UDS) assay (result cited by Hallström & Thuvander 1998; original article not seen).

5.4 Carcinogenicity

5.4.1 *M. excelsum* leaf

No studies designed to assess the carcinogenic potential of *M. excelsum* leaf were found.

5.4.2 Myristicin

As mentioned in section 4.1 above, myristicin was found to inhibit (by 65%) benzo[α]pyrene-induced tumorigenesis in mice at an oral dose of 10 mg/dose of myristicin three times a week for a total of 15 doses (Zhang et al 1992).

According to Hallström & Thuvander (1998), myristicin showed no detectable activity for the initiation of hepatic tumours on administration to male mice prior to weaning (result cited by Hallström & Thuvander 1998; original article not seen).

5.5 Reproductive and Developmental Toxicity

No studies designed to assess the reproductive and developmental toxicity potential of *M. excelsum* leaf, or myristicin, were found.

5.6 Local Tolerance

5.6.1 *M. excelsum* leaf

No local tolerance studies of *M. excelsum* leaf have been found, although the traditional use included topical applications without adverse effects being recorded (Riley 1994).

5.6.2 Myristicin

The subcutaneous LDLo of myristicin is 2000 mg/kg for guinea pig and 900 mg/kg for rabbit (ChemIDplus 2005).

6 CLINICAL DATA

There are no clinical studies of *M. excelsum* leaf.

7 ADVERSE REACTIONS

7.1 Australian Adverse Reactions Database

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received no reports of adverse reactions to *M. exclesum*, kawakawa, or myristicin.

7.2 New Zealand Adverse Reactions Database

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received no reports of adverse reactions to *M. excelsum*, kawakawa, or myristicin.

7.3 International Adverse Reaction Databases

No data were retrieved from WHO on adverse reactions relating to *M. excelsum* leaf.

7.4 Literature-reported Events

7.4.1 *M. excelsum* leaf

There were no literature reports of adverse reactions relating to *M. excelsum* leaf.

7.4.2 Myristicin

There has been one fatal case of nutmeg poisoning that has been attributed to myristicin in nutmeg (Stein et al 2001). However, the case report of the autopsy revealed the presence of flunitrazepam, a benzodiazepine-derivative hypnotic, at a toxic concentration in the serum of the 55-year-old female deceased. The case report suggested that the toxic dose of flunitrazepamin in combination with a high dose of nutmeg (estimated as 39-59 g per 70 kg body weight) led to the fatal outcome. The case report also named two other components, elemicin and safrole, as being toxicologically relevant components of nutmeg. The role of myristicin in, or its possible contribution to, in the fatal outcome was therefore unclear.

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ATTACHMENT

TGA Library Literature search report

TGA Library was asked to conduct literature searches covering the medicinal use, safety and potential toxicity of Macropiper Excelsum, or Kawakawa, both in traditional medicine and in current use. Search terms were identified from relevant literature already available, pharmacopoeias and materia medica.

The search was conducted in several parts:

1. A search of Medline (1966 to date) on the Ovid system.

The Medline search strategy was:

1. macropiper excelsium.mp. [mp=title, original title, abstract, name of substance word, subject heading word]0

2. kawakawa.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 4

3. kawa.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 33 4. maori kava.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 0

3 and 4 =33

33 results were retrieved from Medline. The four results from kawakawa came from the fish of the same name, and were disregarded.

2. A search of Embase (1988 to date) on the Ovid system.

The Embase search strategy was:

1. macropiper excelsum.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 0

2. kawakawa.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 0

3. kawa.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 21

4. maori kava.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]0

21 results were retrieved from Embase, all from the keyword kawa.

3. A search of BIOSIS and CABI for all available years. The search terms were as follows:

BIOSIS

1. KAWAKAWA OR KAWA OR MACROPIPER ADJ EXCELSUM OR MAORI ADJ KAVA NOT (FISH OR FISHES OR FISHERIES OR SEA OR OCEAN) unrestricted 909

2. 1 AND new ADJ zealand unrestricted 33

CABI

1. KAWAKAWA OR KAWA OR MACROPIPER ADJ EXCELSUM OR MAORI ADJ KAVA NOT (FISH OR FISHES OR FISHERIES OR SEA OR OCEAN) unrestricted 66 show titles2. 1 AND new ADJ zealand unrestricted 28 show titles

4. A multifile search of DIALOG databases (all years available for each file).

Dialindex was searched in the medicine, toxicology, pharmacology, alternative medicine and food science database clusters to identify relevant further files for searching. The following were selected:

File 5:Biosis Previews(R) 1969-2005/May W1

(c) 2005 BIOSIS

File 34:SciSearch(R) Cited Ref Sci 1990-2005/May W1

(c) 2005 Inst for Sci Info

File 65:Inside Conferences 1993-2005/May W2

(c) 2005 BLDSC all rts. reserv.

File 71:ELSEVIER BIOBASE 1994-2005/May W1

(c) 2005 Elsevier Science B.V.

File 144:Pascal 1973-2005/May W1

(c) 2005 INIST/CNRS

File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec

(c) 1998 Inst for Sci Info

File 399:CA SEARCH(R) 1967-2005/UD=14220

(c) 2005 American Chemical Society

The search strategy was as follows:

S MACROPIPER(W)EXCELSUM

54 citations were retrieved

During the search it was noted that one of the active ingredients was myristicin, so an additional search was conducted.

5. A search of Medline (1966 to date) and on the Ovid system.

The Medline search strategy was:

1 myristicin.mp. (51)

2 from 1 keep 1-51 (51)

51 citations were retrieved.

6. A search of Embase (1988 to date) on the Ovid system.

The Embase search strategy was:

1 MYRISTICIN/an, to, pd, it [Drug Analysis, Drug Toxicity, Pharmacology, Drug Interaction] (32)

2 from 1 keep 1-32 (32)

32 citations were retrieved.

7. A search of BIOSIS and CABI for all available years. The search terms were as follows:

BIOSIS and CABI

1. myristicine and (toxic or toxicity or medicine or medicinal or adverse or poison)

8. A multifile search of DIALOG databases (all years available for each file).

Dialindex was searched in the medicine, toxicology, pharmacology, alternative medicine and food science database clusters to identify relevant further files for searching. The following were selected:

File 149:TGG Health&Wellness DB(SM) 1976-2005/May W1

(c) 2005 The Gale Group

File 399:CA SEARCH(R) 1967-2005/UD=14220

(c) 2005 American Chemical Society

The search strategy was as follows:

S (MACROPIPER(W)EXCELSUM OR KAWAKAWA OR KAWA(W)KAWA OR KAWA OR MAORI(W)KAVA) AND (MYRISTICIN OR RN=607-91-0)

9. The ChemID record was also searched, and the monograph sent to the client.

10. In addition, the book Maori Healing and Herbal by Murdoch Riley was consulted and the monograph on Macropiper Excelsum sent to the client.

A complete list of databases searched and titles retrieved was supplied to the evaluator for scrutiny.

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Therapeutic Goods Administration

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