Horopito

Pseudowintera colorata

Botanical Family: Winteraceae
Botanical Name: *Pseudowintera colorata*
Common Names: Horopito, New Zealand pepper tree, Red Horopito, Pepperwood, Winter's Bark, Māori painkiller
Plant Part Used: Leaves

Overview

Horopito is an ancient medicinal shrub that only grows in New Zealand. It is member of the primitive Winteraceae family that has features of the earliest evolved flowering plants and appears in the fossil record for more than 65 million years. *P. colorata* is one of only three species within the *Pseudowintera genus*.[1] The leaves have distinguishing red blotches and speckles; leaves with more redness have higher concentrations of active constituents and may protect against harsh ultraviolet radiation[2].

Horopito has been an integral part of traditional Māori medicine and medicinally is used both orally and topically. The key active constituent of the leaves (polygodial) has an intense hot peppery taste.[3] The leaves are so hot to taste that grazing animals learn not to eat them, resulting in Horopito being widespread across New Zealand where other native plants are eaten out.[1, 4]

Key Constituents	Polygodial is the most well researched active constituent, considered to be responsible for the potent anti-fungal and anti-microbial activity of *P. colorata* leaves.[5, 6] Polygodial was first isolated from the leaves of Horopito in 1982 by a team of researchers at New Zealand's University of Canterbury.[3, 7] Other active constituents include: • Volatile oil; containing eugenol and at least 21 terpenes and volatile sesquiterpenes (of which the sesquiterpene polygodial is dominant).[5, 7, 8] • Flavonoids; including Quercetin, Luteolin, Apegenin, and Dihydroquercetin.[5] • Anthocyanins (red coloured leaves contain higher concentrations of anthocyanins and polygodial).[9] • Tannins.[8]
Key Quality Considerations	Research demonstrates that the polygodial content, stability and overall phytochemistry of Horopito leaves and extracts of the plant varies considerably. Quality is contingent on several factors, including harvesting, leaf processing, extraction conditions and formulation excipients. • **Harvesting (Geographical region)** Laboratory testing of 38 leaf samples collected from various geographical regions across New Zealand showed significant variation in polygodial content and effectiveness against *C. albicans*. Anti-fungal activity testing (using the zone of inhibition test) against *C. albicans* showed a twofold difference between the most active and least active samples.[10] • **Leaf processing and extraction** Research comparing the phytochemical profile, stability, and biological activity of different preparations of Horopito leaves found considerable differences in polygodial content and stability. Milling and drying of the crude herb, and choice of extraction solvents resulted in substantial variation. Whilst polygodial was unstable using ethanol as an extraction solvent, a specialised Horopito extract made using supercritical extraction was shown to have superior stability.[10, 11, 12]
Key Actions	Anti-fungal, anti-candida, antibiotic, antimicrobial, analgesic. [3, 7, 13 , 14, 15, 16]
Other Actions	Antibacterial (moderate), anti-inflammatory, gastroprotective, antiviral, anti-Herpes simplex type 1 (HSV-1), astringent, anti-allergic, preservative, insecticidal.[12, 16, 17, 18, 19, 20]
Indications Supported by Clinical Trials	**Oral:** • Vulvovaginal Candidiasis. • Gastrointestinal Candidiasis. • Candiduria (urinary candida infections). **Topical:** • Genital candidiasis. • Relapsing bacterial vaginosis. • Fungal skin complaints.

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Overview Cont.

Indications Based on Laboratory Studies (*in vitro, ex vivo,* and animal)	• Herpes simplex type 1 / cold sores (*in vitro*). • *Tinea pedis* / athlete's foot (*in vitro*). • *Candida albicans* (*in vitro* & animal). • Oral yeast infections (*ex vivo*). • Sugar cravings (reduced perception of sweet taste).
Traditional Therapeutic Uses	The leaves of Horopito have a long history of medicinal use by Indigenous Māori people of New Zealand, both orally and topically. Traditionally, the leaves were bruised, steeped in water and used for paipai (a skin disease), and other skin complaints such as ringworm, rashes, chafing, or to heal wounds. It was also used for venereal disease (sexually transmitted), and occasionally for headaches.[3, 16] A decoction of the leaves was used for stomach pain and was known as 'Māori painkiller', whilst early settlers in New Zealand used it for diarrhoea. The leaves were chewed for toothache and were rubbed on the breasts when weaning infants.[16] More recently, herbal medicine practitioners have used Horopito for digestive and skin conditions,[8] as well as topically for vaginal candidiasis and fungal skin complaints.[21]
Preparations	**Scientific:** Supercritical extraction of leaf, 30-39% polygodial
	Traditional: • Decoction, bruised leaves steeped in water.[3] • Poultice, bruised or chewed leaves applied to the skin.[3]
Dosage	**Oral:** Oral preparation containing *Pseudowintera colorata* (Horopito) leaf extract 10mg once or twice daily.
	Topical: Apply topical preparation (cream, ointment or wash) to affected area 2-3 times daily.
Duration of Use	**Oral:** ***At least 4 weeks.*** A naturopathic case study indicated that some patients may benefit from longer use[36], and clinical studies have administered Horopito extract orally for up to 24 months.[22]
	Topical: ***At least 7 days.*** In clinical trials, topical Horopito cream has been used for up to 2 months.

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Summary of Current Research

Conditions supported by clinical studies

The strongest evidence to support the efficacy of orally ingested Horopito (capsule containing supercritical leaf extract 10mg) is for recurrent vulvovaginal Candidiasis (RVVC). Clinical studies demonstrate that oral Horopito is as effective as conventional anti-fungal drugs in the treatment of RVVC. Whilst Horopito may be slower-acting, it provides better preventative protection, lower relapse rates and reduced growth of drug-resistant species.[22] This is highly encouraging given the recurrent nature of RVVC.

Further evidence from clinical trials supports use of oral Horopito for candida overgrowth in the gastrointestinal and urinary tracts.[23] Polygodial produces anti-fungal effects by damaging the permeability barrier of yeast cells, resulting in cell leakage and cell death.[14]

There is also promising evidence using Horopito topically in relapsing bacterial vaginosis[26], genital candidiasis[21], and fungal skin complaints[21]. Results from clinical trials are reinforced by laboratory studies and the long history of traditional use of topical Horopito in these conditions.

Recurrent vulvovaginal candidiasis (RVVC)

(Oral supplementation)

A prospective randomised controlled trial in 122 women with RVVC compared the clinical efficacy of oral Horopito extract with the anti-fungal drug Itraconazole (positive control) over a 24-month period. Women were randomised to receive either 10 mg of oleoresin from *P. colorata* twice daily for one week per month, or 200mg Itraconazole once weekly. Primary outcomes were RVVC relapse rate, occurrence of non-albicans species growth and susceptibility to anti-fungal drugs. The secondary outcome was rate of mycological cure at the end of the 2-year period.

The Horopito group had a significantly lower number of relapses throughout the two-year study (22 vs 39, $p<0.05$), demonstrating its superior prophylactic effect (refer Figure 1). Growth of non-albicans species was significantly decreased in the Horopito group vs the Itraconazole group (31.8% vs 64.1%, $p< 0.05$). Resistance to anti-fungal drugs was also significantly lower in the Horopito group ($p< 0.05$).

At the end of the trial, the mycological cure rate was similar between the two groups (91% in the Horopito group vs 85% in the Itraconazole group), indicating that Horopito is equally effective as the anti-fungal pharmaceutical drug.

Both treatments were well tolerated with fewer side effects reported in the Horopito group compared to the Itraconazole group (3 vs 19).[22]

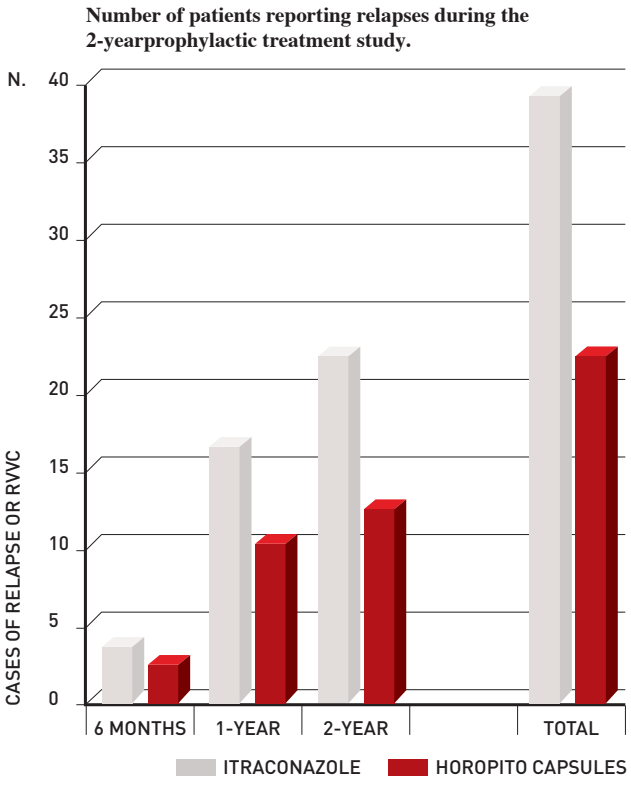

Figure 1: Number of patients reporting relapses during the 2-year prophylactic treatment study. Horopito capsules vs Itraconazole $p<0.05$.

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Summary of Current Research Cont.

Recurrent vulvovaginal candidiasis (RVVC) (Oral supplementation)	A clinical trial in 82 women with RVVC randomised subjects to oral treatment with the anti-fungal pharmaceutical Itraconazole, or Horopito extract standardised to polygodial (10mg extract twice daily for 4-weeks, then 10mg extract twice daily for the first two weeks of each month). The study duration was 12 months, including 6 months treatment followed by 6-months of observation, without treatment. At the end of the 6-month treatment period both groups showed comparable efficacy, despite Itraconazole providing earlier symptomatic relief during the first two weeks. During the observational period, significant benefits of Horopito became apparent, with higher cure rates and less relapses reported. The percentage of women experiencing relapse was significantly lower in the Horopito group compared to the Itraconazole group (34.2% vs 65.7%, $p<0.05$). At the end of the 12-month study, the mycological cure rate was significantly higher in the Horopito group compared to the Itraconazole group (65.8% vs 34.3%, $p<0.05$) - corresponding to almost twice as many Horopito-treated subjects being free from Candida infection. Both treatments were well tolerated. 4 patients in the azole group complained of transient mild symptoms.[24]
Chronic intestinal candidiasis (Oral supplementation)	An unpublished clinical study conducted at the Pavlodar City Centre for Clinical Immunology and Reproduction trialled oral Horopito in patients diagnosed with chronic recurring intestinal candidiasis[25]. 22 patients aged 5-45 years consumed dried, milled Horopito capsules (300 mg per day in two divided doses) for 2-weeks. Results were compared with a group of 10 patients treated with the anti-fungal drug Fluconazole (Diflucan, Pfizer). All patients taking fluconazole and 91% of patients taking Horopito capsules showed a significant improvement after 7 and 14 days respectively. One month after completion of the trial, clinical and bacteriological relapse rates were 80% and 32% in the Fluconazole and Horopito groups respectively; indicating that Horopito offers superior protection against relapse.[25]
Candiduria in patients with gastrointestinal (GIT) malignancies (Oral supplementation)	A 6-month clinical study tested the efficacy and tolerability of an oral formulation containing dried milled Horopito on urinary Candida infections in patients with operated GIT malignancies. Of the 39 patients, 11 had active candiduria at the time of enrolment and were treated with Horopito (combined with Aniseed, L. acidophilus and vitamin C). Within 3-weeks all 11 subjects had negative cultures in the urine. Throughout the study, a further 28 patients developed candiduria and were successfully treated with the Horopito formulation, without any side effects.[23]
Relapsing bacterial vaginosis (gardnerellosis) (Topical)	An uncontrolled clinical trial studied the efficacy of a Horopito cream in relapsing bacterial vaginosis (BV). This vaginal infection is prone to relapses, with more than 30% of treated cases relapsing. Women were treated with a pharmaceutical antibiotic for 7 days, alongside Horopito cream (1 mL) intra-vaginally twice daily for 2 months. All 22 women who completed the treatment had no clinical or laboratory relapses during the 2-month period. The Horopito cream was well tolerated with a minority of cases reporting a tolerable heat sensation during the first days of usage.[26]
Genital candidiasis (Topical)	In a case series Naturopaths across New Zealand prescribed a topical cream containing Horopito to patients with fungal conditions, mostly genital candidiasis. 26 women and one man were prescribed the cream for genital candidiasis and 89% of these subjects reported relief when the cream was applied 2 or 3 times daily for a week. Typically, there was an initial sense of heat for a minute or so followed by a soothing feeling. Itch and irritation usually reduced within hours of the first application while other symptoms reduced throughout the course of therapy.[21]
Fungal skin complaints (Topical)	In the same case series cited above, Naturopaths reported clinical benefits in the majority of cases where Horopito cream was prescribed to patients with uncomplicated cases of fungal skin complaints. Complaints included Tinea (n=2), anal itch (n=3), undiagnosed face rashes (n=3), fungal rashes underneath breasts and in the groin area (n=1), scaly rash on the forehead and scalp (n=1), and itchy genitalia in women, not diagnosed as of fungal origin (n=3). A minority of cases reported no change or worsening of symptoms, notably in cases where the cream was applied to ruptured skin.[21]
Vaginal candidiasis and bacterial vaginosis (Topical)	A single-centre uncontrolled clinical study assessed the efficacy of intravaginal Horopito cream in 17 women with vaginal infections resistant to previous treatment (vaginal candidiasis and BV). The cream was applied to tampons and administered intravaginally 3 times a day as monotherapy for 7 days. At the end of the intervention, all women had clinical improvement. Fishy odour disappeared within days and vaginal inflammation resolved. No yeasts or *Gardnerella vaginalis* was evident in vaginal smears at the end of the 7-day period. A further 7-days after the trial, clinical symptom remained resolved, however vaginal smears found *Gardnerella vaginalis* and yeasts in 33% and 44% of women that presented with BV and candidiasis, respectively. 35% of women reported a sharp heat sensation in the beginning of the treatment but continued use of the cream.[25]

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Summary of Current Research Cont.

Conditions supported by laboratories studies

Herpes simplex type 1 / cold sores (*in vitro*)	Research conducted at The University of Otago demonstrated that a specific Horopito leaf oleoresin extract inhibits Herpes Simplex-1 (HSV-1) virus in vitro. The Horopito extract was shown to have antiviral activity in a dose dependant manner, and results were comparable to the market leading antiviral Acyclovir. A cream containing the same Horopito extract, combined with oils of *Melaleuca alternifolia* and *Leptospermum petersonii* was also shown to be antiviral and effective against HSV-1 *in vitro*.[15]
Tinea pedis / Athlete's foot (*in vitro*)	A specific Horopito-containing cream was found to have higher anti-fungal activity against one of the main Athlete's foot fungi (*T. mentagraphytes*) than any other natural product that was tested *in vitro*.[27]
Candida albicans (*in vitro* & animal)	In vitro and animal studies on a specific Horopito product show strong inhibition of *C. albicans* growth,[28, 29] with stable effects over a two-year shelf life.[7, 30] This specific Horopito product was more effective than other natural products and as effective as the pharmaceutical products tested *in vitro*.[31]
Oral and mucosal candidiasis (*ex vivo*)	A specific Horopito and aniseed mixture was shown to inhibit the growth of Candida species from the oral cavity *ex vivo*. Its anti-fungal effect was reported to be more constant than pharmaceutical antiseptics containing chlorhexidine.[33]
Sugar cravings (reduced perception of sweet taste)	A decoction of the leaves has been reported to desensitise sweet taste sensation.[16]

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Safety Profile

Horopito leaf and its constituents are generally considered safe for both oral and topical administration when appropriately prescribed. There is no documented traditional evidence of toxicity to humans by either oral ingestion or topical application.[33]

Drug Interactions	No known interactions have been identified. Due to the antimicrobial action of the herb, when prescribing a probiotic alongside Horopito formulations the two products should be recommended to be taken at separate times of the day.
Cautions / Contraindications	Avoid large doses of oral Horopito formulations in acute gastritis or peptic ulcers.[8] Avoid topical application to broken skin.[21]
Toxicology	No toxic effects were observed in rats following acute exposure up to 2 grams per kg bodyweight. In contrast to compounds of a similar structure with strong biological activity, polygodial has been shown to be non-mutagenic (Ames and V79/HGPRT assay) and exhibit the least cytotoxicity.[34]
Adverse Events	**Topical:** A case report of contact vulvitis and persistent vulva itch following vaginal application of a Horopito-containing cream in a 16-year-old girl diagnosed with contact dermatitis to *P. colorata* has been published.[35] In clinical studies, a sensation of heat has been reported in a minority of individuals. This was mostly tolerated and dissipated with continued use.
	Oral: Generally, well tolerated. Mild transient digestive side effects have been reported in some clinical trials. Adverse event reports on oral products containing Horopito over the last twenty years show that very few people report mild transient side effects of digestive complaints or skin rashes. Oral Horopito formulations should be taken with food and a glass of water to minimise the risk of digestive upset.
Pregnancy & Lactation	There is insufficient reliable information about the safety of Horopito during pregnancy or breastfeeding. Although there is no evidence of teratogenicity, as a precaution Horopito should be avoided during pregnancy and lactation.
Children (0 - 12 years)	Currently, there is no conclusive evidence on the safety of Horopito in infants and children. As a precaution, Horopito is not recommended for children under the age of 12.

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