A journey into the R&D of Phytomed & How our Latest Extract came to Fruition:

The Development Process for Piper nigrum

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Phil is an experienced phytotherapist with a clinic in Auckland where he has practiced for 25 years. He is also the founder and Technical Director of Phytomed Medicinal Herbs Ltd, a New Zealand-based manufacturer of herbal medicines sold to both practitioners and consumers in NZ and export markets.

Before pursuing herbal medicine, Phil worked for more than 10 years as a pharmacist and undertook research on antidepressant drugs and serotonin. He has lectured to naturopathy, herbal and pharmacy undergraduates, presented at conferences in New Zealand, Australia, and the UK, been on various government expert advisory committees, and written extensively on herbal subjects for both practitioner and consumer publications, for many years.

The selection and creation of new Phytomed extracts can be a long process. This particular journey began when Phil Rasmussen first engaged with the medicinal properties of Kawakawa *(Macropiper excelsum)* - soon after he developed an interest in herbal medicine 30 years ago.

This led him to undertake a comprehensive review of Kawakawa in 2000, in which traditional and modern usage, investigation into the constituents, and analysis of the application of related species around the world, were combined. Phil's first monograph on Kawakawa appeared in "**Phytonews** 7", in 2000, and is still available to practitioners on the Phytomed website.

Phil began to use Kawakawa in clinical practice for a wide range of conditions, developing a deep understanding of its clinical applications. Phytomed subsequently developed several **Kiwiherb**® formulas incorporating Kawakawa.

In the following years, Kawakawa became, and remains, one of the most well-known herbs in NZ, used in a myriad of products, from teas to balms, and of course as a hydroethanolic extract used in practitioner formulas.

Recently, considering the bulk of knowledge gained, a new review was undertaken. One of the interesting developments was a greater understanding of the phytochemical makeup, including the presence of an alkaloid called piperine.

Piperine has an impressive and diverse pharmacology including antioxidant, immunomodulatory, anti-carcinogenic, anti-asthmatic, stimulatory, hepatoprotective, anti-inflammatory (Darshan & Doreswamy, 2004), antimicrobial, anticonvulsant, neuroprotective, anti-arthritic and anti-ulcer activities (Damanhouri & Ahmad, 2014).

This compound is present throughout the *Piper* family (to which plant taxonomists have now decided Kawakawa directly belongs- no more *Macro*, now *Piper excelsum*) – and is particularly prominent, in the fruits of the well-known *Piper nigrum* (Black Pepper).

This finding in particular triggered the decision to start work on developing a *Piper nigrum* liquid extract for use by practitioners in their clinics. Phil will discuss the implications of this alkaloid for Kawakawa applications elsewhere; however, investigating piperine opened new vistas of potential for other herbs.

Black pepper: history and application

In researching piperine and the plants that contain it, it was noted that piperine is found in highest concentrations in *Piper nigrum* (black pepper) and Piper longum (long pepper) seeds, which contain around 4% and 1% piperine respectively, and are amongst the most common spices used in food and folk medicine worldwide (Si, Yang, Lin, & Yang, 2018; Li et al., 2007).

Since herbalism uses the herb, not the constituent, attention turned to black pepper.

Considered 'The King of Spices', *Piper nigrum* has been used and valued for at least 4000 years, as both a spice to add flavour to food, as well as for its many medicinal properties. It is treasured as a health enhancing spice for its antioxidant and antimicrobial potential, and gastro-protective properties. It's rich and complex phytochemistry includes volatile oil, oleoresins and alkaloids (Butt, 2013).

In ancient Indian medicine, black pepper was used to address pain, chills, rheumatism, influenza, muscular pains, and fevers. An infusion was considered to relieve migraine headaches and strep throat, enhance circulation, increase saliva flow, and stimulate appetite and digestion (Gorgani, Mohammadi, Najafpour & Nikzad, 2017).

Originating in India, Egyptian and Arab traders took black pepper to the Greek and Roman Empires, and through Roman and Arab development, to Europe. Arabian and Egyptian traders concealed the origins of black pepper from their Greek customers, inflating the price by weaving stories of fanciful growing conditions. Later, the practical Romans, soon after occupying Egypt, sent large numbers of ships to India from the port of Myos Hormos on the Red Sea. Tamil literature from the time records how Roman traders brought wine and gold to recently conquered Egypt, and returned laden with pepper (Frankopan, 2015). It remained important in the Arabian world more than nine centuries later. Ibn Sīnā (Avicenna) included it as a medicinal spice in his writings (McCormick Science Institute, n.d.).

Black pepper remained highly valuable throughout the Middle Ages (even used as a form of coin), and remains so today. The history of spices perfectly demonstrates the intertwined nature of food and medicine, with pungent spices such as pepper, nutmeg, cloves, frankincense, ginger, sandalwood, cardamom and turmeric valued not only as preservatives and ingredients to make bland foodstuffs more palatable, but also for their medicinal effects (Frankopan, 2015).

The Marco Polo writings (approx. 1298) record 10,000 pounds of pepper brought daily into Hangchow city, and vast plantations on the Malabar Coast (Rosengarten,1969).

Black pepper has been used in India for millennia, and Mehmood & Gilani (2010) noted that the Indian Materia Medica considers black pepper an essential component of gastrointestinal formulas. They compared pepper and piperine extracts in a study which concluded that both exhibited spasmolytic and antispasmodic activities, and when used for diarrhoea and constipation, regulated bowel function.

Pereira, in 1854 noted that *"As a gastric stimulant it is a useful addition to difficultly-digestible foods, as fatty and mucilaginous matters, especially in persons subject to stomach complaints from a torpid or atonic condition of this viscus. Infused in ardent spirit... [it is used for] …intermittent fevers… febrifuge…In the form of ointment…[ringworm]. Mixed with mustard, it is employed to increase the acridity of [warming plasters]."*

Grieve (1931) considered the best pepper to come from Malabar, and recommended its use for paralytic, atonic and arthritic conditions.

A study on the ability of a black pepper extract to inhibit various Gram-positive and Gram-negative bacteria found it to alter membrane permeability resulting in high inhibition of Gram-positive bacteria such as Staphylococcus aureus, Bacillus cereus and Streptococcus faecalis. The Gram-negative bacteria Pseudomonas aeruginosa was also susceptible with smaller yet still significant results against Salmonella typhi and Escherichia coli (Karsha & Lakshmi, 2010).

Black pepper stimulates pancreatic enzymes and decreases food transit time in the gastrointestinal tract, while piperine has been seen to increase saliva production and gastric secretions including the production and activation of salivary amylase (Srinivasan, 2007).

Oral administration stimulated the secretion of bile acids and increased pancreatic amylase activity, protease activity, lipase activity and chymotrypsin activation (Platel & Srinivasan, 2000). Rats administered piperine demonstrated significantly increased activity of intestinal lipase, and sucrase and maltase enzymes, as well as increased brush border uptake and intestinal perfusion (Damanhouri & Ahmad, 2014).

Unpicking the threads of black pepper historical usage centres upon its stimulating, preservative properties, which translate into antioxidant, gastro-protective and bioavailability actions, which are key attributes in the modern phytotherapy world.

As it once enhanced the bland foods of the Romans, and protected traditional and medieval societies from spoilt food, it now becomes an enhancer and facilitator for compromised gastrointestinal tracts and microbiota.

As such, it seemed imperative to add it to the Phytomed repertoire.

Related species

Apart from Kawakawa, other members of the *Piper* family have been used medicinally in traditional cultures for a wide range of conditions. In researching them, it becomes clear that many are underpinned by the same elements of anti-inflammatory, circulatory stimulating and antimicrobial principles with some of these properties potentially present in black pepper.

The leaves of *Piper* species are used by various cultures around the world to relieve toothache and other pains (Duke 1987; Grieve 1981), as well as in bronchial conditions, for anthelmintic activity, and as a circulatory stimulator.

Some have alleged aphrodisiac properties- such as *Piper guineense* and *P umbellatum* found in the Ivory Coast and in East Africa (Bouquet & Debray, 1974; Kokwaro, 1976), and Piper angustifolium used by South American Indians (Lee, 1991).

Phytochemistry

Taking the traditional usage of *Piper nigrum*, such as aiding in gastrointestinal support and as a preservative as a starting point, much of the research into phytochemistry finds potential to translate these into modern applications such as treating stealth pathogens and its bioavailability support by focussing upon piperine and the volatile oils.

Metabolic pathways are dependent on biotransformation enzymes to process the mutagenic and neoplastic effects of carcinogens and toxins. Both phase I and phase II enzymes appear to be positively affected by piperine, which may account for the biotransformation action (Kurian, 2012). Therefore, black pepper may increase absorption of curcumin or resveratrol by slowing the metabolic process, ensuring that these compounds are able to exert an effect rather than being immediately removed. The mechanism of action is believed to include glucuronidation inhibition (Derosa, Maffioli & Sahebkar, 2016). It has also been shown to enhance the effects of the oral hypoglycaemic drug metformin, resulting in lower doses and reduced side effects (Atal et al, 2016). Piperine also inhibits cellular effluxing P-glycoproteins, which may account for the bioavailability enhancement of several other drugs and natural phytochemicals (Derosa, Maffioli & Sahebkar, 2016; Bedada & Boga, 2017).

Piperine exhibits antitumor activities toward various cancer cell lines and has been reported to prevent tumour development in cancers including breast, ovarian, lung, prostate, gastric and rectal (Manayi 2017; Si, Yang, Lin & Yang, 2018; Rather & Bhagat, 2018). It may also assist with reducing chemotherapy drug resistance, though clinical studies are still needed (Li, Krstin, Wang & Wink, 2018).

Another potential adjunct usage, of particular interest considering growing concerns about antibiotic resistance, is the finding that piperine may increase penetration of the antibiotic's ciprofloxacin and azithromycin into *E. coli* CFTO73 biofilms, and may potentially enhance the ability of these antibiotics to disperse pre-established biofilms, reducing the amounts of antibiotic required (Dusane, Hosseinidoust, Asadishad, & Tufenkji, 2014). Extrapolating further, piperine may facilitate herbal formulae directed at stealth pathogens through this anti-biofilm action.

A mixture of Piper longum and Piper nigrum is used traditionally in Chinese herbal medicine for the treatment of stroke, and their administration has been reported to reduce the level of injury in a cerebral ischaemia model in rats (Hua et al., 2018), an activity attributable in large part to piperine.

Reports of piperine attenuating UV radiation-induced damage in human keratinocytes, have also been made; a particularly relevant indication for our local UV situation (Verma et al., 2017).

Piperine also shows strong antioxidant activity (Vijayakumar, Surya, & Nalini, 2004). Water and ethanol extracts of black pepper have demonstrated higher inhibition than standard antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and alpha-tocopherol (Gülçin, 2005).

John - Phytomed Botanist (Phytomed, 2019)

Technical details:

The solvent

Creating a balance between cost, minimum amounts required for efficacy and patient compliance, begins with the ratio of herb to solvent - in this case, water and locally produced ethanol. While we trialled a 1:1 ratio, the 1:2 that we have selected meets more of the above criteria. The alcohol percentage is more than 70%, since the principal constituents include alkaloids and volatile oils.

The dosage

From a starting point of a therapeutic dosage range of piperine, in-house dosing determined the amount of black pepper most likely to have client compliance. Phytomed and Kiwiherb staff bravely fronted up to taste test batches…leading some to be deeply invigorated and rush around solving problems, and others to rush for yoghurt and water, gasping! All herbalists should understand that the amount of herb each client requires is unique to them, and this was clearly demonstrated in the range of reactions to the dosing experiments. The stimulating effect of black pepper came through clearly and suggested potential for use as a pick me up or energy shot.

The Raw Material

Adulteration and identification errors are an ongoing issue for herbal preparations worldwide. At Phytomed, all raw materials are quarantined upon arrival, until John, a botanist who has worked with Phytomed for fifteen years, has analysed a sample both macroscopically and microscopically. It is not sufficient to ensure that it is the correct herb. Many herb growers are small businesses and their quality levels can vary. At times, a shipment has to be rejected because it contains too much foreign matter; for example, too much organic grass in the chamomile. For Piper nigrum, the main issue is quality which means that the supplier is also key. It is also common to test for contaminants such as pesticides or heavy metals.

The Supplier

Where possible, Phytomed supports local New Zealand growers or small local growers in other countries if required. Black pepper does not grow well enough here in New Zealand to become a cost-effective product.

However, finding a supplier is not simply about the cheapest option. Country of origin may affect growing conditions and can contribute to air miles. Cultivation or wild crafting is environmentally sustainable and creating a high-quality product is important - we consider the environment and fair-trade aspects when purchasing product. A supplier's wild crafted herb may be more potent than that of an organic cultivated one and we look at the sustainability of the product. These aspects are discussed and evaluated, and some of John's concerns also come into our relationship with the grower.

This extract uses black pepper from India, produced by a group dedicated to organic spice production as a viable alternative for small and marginal farmers in India whilst helping sustain the environment. Farms are located across Southern India such as Karnataka, Kerala & Tamil Nadu.

Brief Monograph

Piper nigrum (Balcony Garden Web, 2019)

***Piper nigrum* 1:2 fluid extract**

Common Names: Black Pepper, Kali Mirch, Pippali, Milagu.

Botanical family: Piperaceae

Botany:
Black pepper (BP) is a woody perennial vine, up to 4m, often grown in the shade on supporting structures grown in tropical regions including Brazil, Indonesia and India. The small flowers are borne on pendulous spikes at the leaf nodes. Each fruit contains a single seed. The plants bear from the 4th or 5th year and continue to bear for seven years. The unripe green fruits are sun-dried to make black pepper (Damanhouri & Ahmad, 2014).

Part Used: Fruiting body

Dosage: 4-15ml per week

Primary Active Constituents:
Phenolics, flavonoids, alkaloids including piperine, found at levels of around 3-5%, amides and steroids, lignans, neolignans, terpenes, chalcones etc and many other compounds, including cordycepin (3'-deoxyadenosine), which has a structure similar to adenosine, and acts as a nucleoside analogue. Nucleoside analogues are commonly used for patients with cancer, or viral infections. Other constituents include cordyceptic acid, nucleotides and nucleotide derivatives, polysaccharides, sterols and fatty acids.

Piperine, a pungent alkaloid, has an impressive and diverse pharmacology including antioxidant, immunomodulatory, anti-carcinogenic, anti-asthmatic, stimulatory, hepatoprotective, anti-inflammatory (Darshan and Doreswamy, 2004), antimicrobial, anticonvulsant, neuroprotective, anti-arthritic and anti-ulcer activities (Damanhouri & Ahmad, 2014).

Contraindications:

Excessive doses should be avoided by those with a sensitivity to hot spices, acute peptic ulcer or with advanced cardiovascular disease.

Actions:
Bioavailability Enhancer, Anticancer, Antioxidant, Anti-inflammatory, Antimicrobial, Gastrointestinal modulator, Circulatory stimulant, Anti-fatigue, Stimulating Tonic, Hepatoprotective.

Main indications:
Digestive weakness
Prevention of GI infections
Adjunct/bioavailability enhancer
Cancer prevention

Interactions: may potentiate bioavailability of drugs and other herbs.

Summary
Considered 'The king of Spices', *Piper nigrum* has been used and valued for at least 4000 years, as both a spice to add flavour to food, and for its many medicinal properties. It is treasured as a health enhancing spice for its antioxidant, antimicrobial, and gastro-protective properties (Butt, 2013). These properties have been confirmed in recent scientific research, and modern applications extrapolated.

Understanding Black Pepper's past and present, modern herbalists can apply this exciting phytomedicine to enhance bioavailability, support the gastrointestinal tract, address persistent pathogens, and provide a stimulating facilitator in their herbal formulae. ✤

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