Further support for a role of Hypericum in opiate withdrawal has appeared recently through publication of results from various studies using rats[9-12].

A team from Pakistan reported reduced antinociceptive effects of a hydroethanolic extract of Hypericum following administration of the selective opioid receptor antagonist naloxone, suggesting involvement of opioid receptors in the mechanism of Hypericum's analgesic properties[9]. Comparable effects to those of the drug clonidine in reducing acute morphine withdrawal symptoms in rats, have also been reported for an aqueous Hypericum extract[10].

Another study by the same Pakistan researchers compared the effects of an aqueous, 70% hydroethanolic and pure ethanolic extracts of Hypericum on physical signs of heroin withdrawal in rats[11]. Each hypericum extract was given either during the 8 day administration of heroin or as a single dose 90 minutes prior to naloxone-induced withdrawal.

While some withdrawal effects were attenuated by the aqueous extract when administered both acutely and chronically, effects on most of these were only observed for the hydroethanolic and ethanolic extracts after acute treatment.

The most recent study from the Pakistan researchers further explored these effects in opium dependent rats[12]. Rats were given an increasing dosage of opium extract over an 8 day period, and divided into three groups. One group receiving a concurrent daily dose of 20mg/kg twice daily of a hydroethanolic extract of Hypericum, one group opium and a saline control, and the third group opium then a single 20mg/kg dose of Hypericum extract 90 minutes before precipitation of the withdrawal syndrome using the selective opioid receptor antagonist naloxone.

In the group given chronic Hypericum, a significant attenuation in several physical signs of opium withdrawal was observed. In the group given a single Hypericum dose prior to naloxone-precipitated withdrawal, a significant reduction in diarrhoea compared to the saline control group occurred, although other withdrawal signs were unchanged.

While limitations exist in these animal studies, they add to our understanding of Hypericum's possible role during opiate withdrawal, and reinforce the pronounced differences in pharmacological effects through use of chronic versus acute treatment, as well as different types of plant extract with a different phytochemical makeup.

A well-designed study involving humans undergoing a standard methadone withdrawal protocol while taking a Hypericum preparation low in hyperforin is needed. However, the collective information now available, suggests a role for certain types of this phytomedicine to help addicts prior to and during the unpleasant withdrawal period, as well as addressing associated depression and the high rate of relapse in this patient population.

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Ligustrum lucidum and osteoporosis

Osteoporosis is a condition characterised by low bone mass and microarchitectural deterioration of bone tissues which leads to increased bone fragility and imbalance between osteoblasts and osteoclasts in bone homeostasis. It is the leading cause of bone fractures in older adults, and is an increasingly common condition worldwide, with a rising prevalence as populations age. Declining oestrogen levels make osteoporosis particularly common in postmenopausal and Caucasian women, although it is also a condition increasingly seen in aging men[1].

Oestrogen replacement therapy is sometimes used for prevention of postmenopausal bone loss, and drugs such as raloxifene, bisphosphonates, calcium and vitamin D, calcitonin, and parathyroid hormone are also used to prevent and treat osteoporosis. However, the cost and risk of adverse effects from these including hypercalcaemia, increased risk of endometrial and breast cancer, vaginal bleeding, and hot flushes[2], make such treatments undesirable for many patients.

Ligustrum lucidum (Chinese or Glossy Privet), is the most noxious tree in New Zealand, being commonly found in coastal and lowland habitats including roadsides, shrublands and forest margins[3]. It is also a serious invasive species in several other countries including Australia, Argentina, Spain, Italy, South Africa, the midwest and southeast U.S[4,5]. It is a prolific producer of small fruits which are a treasured food for birds who serve to extend its habitat and zones of invasion, making control measures difficult. These are capable of germinating and surviving in a broad range of forest, urban and rural environments, and have higher

survival and faster growth rates than most native plant species.

In China Ligustrum lucidum (*Nu-Zhen-Zi*) fruits are commonly used to strengthen bones, and are a component of many herbal formulae for the treatment of osteoporosis. It is also used to treat conditions such as menopausal problems, blurred vision, tinnitus, rheumatic pains, palpitations, backache, insomnia, liver disorders as well as other age-related complaints[6].

Research into these and other medicinal applications of Ligustrum over recent years, has increased our understanding of how this plant may assist in the prevention and management of osteoporosis and related conditions.

Chinese researchers first reported Ligustrum-induced increased bone calcium content, reduced calcium loss through increased intestinal absorption and reduced urinary excretion, and prevention of increased bone turnover by suppression of both serum osteocalcin and urinary deoxypyridinoline levels, in ovariectomised rats[7].

An ethanolic extract of *Ligustrum* produced significant increases in circulating levels of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) in aged female rats, and expression of vitamin D-dependent calcium binding proteins, effects related to direct stimulation of renal 25-hydroxyvitamin D-1 hydroxylase 1 activity[8,9]. Increased calcium balance was also reported for the water fraction of an ethanolic Ligustrum extract given for 12 weeks to mature female rats whose dietary intake of calcium was low[10]. Inhibition of urinary and faecal calcium excretion, and an associated increase in serum parathyroid hormone levels, were shown as possible mechanisms[10]. Promotion of osteogenesis and upregulation of the expression of several osteoblast differentiation regulators in bone marrow mesenchymal stem cells taken from healthy human donors, has also been reported following a 4 day incubation with Ligustrum extracts[11].

A new study which investigated the effects of chronic Ligustrum administration in male growing rats, has provided evidence of a possible preventative effect against osteoporosis when taken by younger growing adults[12].

Male weaning Sprague-Dawley rats were randomized into four groups and orally administered a formula-based diet supplemented with a 4.3:1 strength Ligustrum ethanolic extract given at three different doses of 0.40, 0.65, and 0.90 % of the diet. A vehicle control group was also included. Following four months treatment, measurements were made of calcium balance, serum levels of calcium, phosphorous, 25(OH)2D3, 1,25(OH)2D3, osteocalcin (OCN), C-terminal telopeptide of type I collagen (CTX-I) and parathyroid hormone. Bone microarchitecture and calcium absorption-related genes expression in duodenum and kidney, were also analyzed.

After Ligustrum treatment, the bone mineral density of the high dose group was significantly higher than in the control group ($P < 0.05$). Trabecular bone volume per unit of total volume was also significantly higher for the high and medium dose group, and a positive effect of Ligustrum was seen on bone microstructure formation.

Increases in the bone formation maker osteocalcin and decreases in the bone resorption maker CTX-1, suggested an alteration in bone turnover. Both calcium absorption and calcium retention rate were increased by Ligustrum treatment, an effect related to up-regulation of calcitropic gene transcription in both the kidney (1a-hydroxylase) and duodenum (vitamin D receptor, calcium transporter calbindin-D9k, and transient receptor potential vanilloid 6). Significant increases in serum 25(OH)D3 and 1,25(OH)2D3 levels were found in the Ligustrum groups, but no changes in serum calcium, phosphorus, and parathyroid hormone[12].

This study extends the evidence of Ligustrum's favourable effects on circulating levels of vitamin D and calcium balance to both male and female growing rats. Several possible mechanisms appear to underly these effects, including up-regulation of calcium absorption-related gene expression in kidney and duodenum, which could then activate 1,25(OH)2D3-dependent calcium transport. It also suggests that in male rats at least, an increased bone mass gain and improved bone properties can be achieved through chronic Ligustrum ingestion during the growing stage. This is of interest as optimising peak bone mass in early life is one of the key preventive measures against osteoporosis.

The antiosteoporotic compounds in Ligustrum are poorly understood, but bioactivity-guided fractionation work indicates contribution from different compounds including the triterpene acids oleanolic and ursolic acid, salidroside and secoiridoids such as nuzhenide[13].

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Ligustrum lucidum (Chinese or Glossy Privet)

Research to date thus suggests a significant opportunity for medical herbalists and other clinicians, researchers, health funding providers and conservation agencies, to collaborate to further investigate the use of this seriously noxious plant, as a safe and cost-effective intervention for both the prevention and management of osteoporosis in humans. By wildcrafting and processing the fruits of this invasive tree into a herbal medicine or dietary supplement with potential benefits for osteoporosis, three key useful outcomes could be achieved. These are a reduction in the rate of spread of our most invasive introduced tree species, improvement in the quality of life of many osteoporosis sufferers, and a reduction in the large and growing budget required for current drug-based treatment options.

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The benefits of Nuts

The benefits of eating nuts have become increasingly apparent in recent years, with various epidemiological studies finding inverse associations between nut consumption, cardiovascular disease, and diabetes.

An association between nut consumption and reduced risk of coronary artery disease (CAD) was first reported in 1992, after a prospective study of 31,208 non-Hispanic white skinned Americans[1]. While results from various cohort studies following this, however, were inconsistent[2-8], in recent years several additional, large cohort studies on nut consumption and CAD risk have been published[4,7,8].

Recent publication of three comprehensive reviews which evaluated a possible association of nut consumption with risk of type 2 diabetes, cardiovascular disease, and all-cause mortality, are therefore of interest[10-12].

The first study, funded by the U.S. National Institutes of Health and the International Tree Nut Council Nutrition Research and Education Foundation, looked into a possible association between nut consumption and subsequent total and cause-specific mortality[9]. This involved 76,464 women in the Nurses' Health Study (1980-2010), and 42,498 men in the Health Professionals Follow-up Study (1986-2010). These are prospective cohort studies involving female nurses enrolled in 1976 and male health professionals enrolled in 1986, who complete questionnaires to update medical and lifestyle information every 2 years. Participants with a history of cancer, heart disease, or stroke, or those who did not provide information on nut intake were excluded. Nut consumption was assessed at baseline and updated every 2 to 4 years.

During 3,038,853 person-years of follow-up, 16,200 women and 11,229 men died. Age-adjusted and multivariate-adjusted analyses showed a significant inverse association between frequency of nut consumption and total mortality among both women and men. Hazard ratios for death for participants who ate nuts, as compared with those who did not, were 0.93 (95% confidence interval [CI], 0.90 to 0.96) for those who ate nuts less than once per week, 0.89 (95% CI, 0.86 to 0.93) for once per week, 0.87 (95% CI< 0.83 to 0.90) for two to four times per week, 0.85 (95% CI, 0.79 to 0.91) for five or six times per week, and 0.80 (95% CI, 0.73 to 0.86) for seven or more times per week (P<0.001 for trend). In addition to showing an inverse association with total mortality among both women and men, after adjustment for other known or suspected risk factors, nut consumption was significantly associated inversely to deaths due to cancer, heart disease and respiratory disease[10].

Data from the Nurse's Health Study has previously been analysed to suggest consumption of nuts as well as peanut butter reduces the risk of type 2 diabetes in women[12].

Evidence of protective properties of nuts against these chronic health conditions and overall mortality, has increased further lately, as a result of two recently published separate meta-analyses of prospective cohort studies, published in May 2014 issues of the *American Journal of Clinical Nutrition*[11, 12].

The first meta-analysis evaluated 31 reports from 18 studies published up to March 2013, including 14 studies conducted in the United States, and one each in China, the Netherlands,