

Complementary and Alternative Medicines: *Artemisia annua*



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There is far less information about the effectiveness, safety and potential for interactions for complementary and alternative medicines (CAMs) compared to conventional medicines. There is no regulation of their quality or contents in New Zealand.

Consider also other risks of CAMs, such as patients choosing them over conventional treatment, and the often substantial cost.

Report any possible adverse effects or interactions to CARM.

What is it?



Artemisia annua is a plant also known as sweet wormwood, sweet annie, sweet sagewort, annual wormwood and qing hao. It was used by Chinese herbalists in ancient times to treat fevers, but fell out of common use until it was rediscovered in 1970, when the Chinese Handbook of Prescriptions for Emergency Treatments (340 AD) was recovered. This publication contained a recipe for a tea from dried qing hao leaves, to be used in case of 'intermittent fevers'. In 1971, scientists demonstrated that the major active constituent of the plant, artemisinin, had antimalarial properties in primate models. Artemisinin derivatives such as artemether and artesunate are used today as prescription medicines to treat some forms of malaria.

What do people use it for?

In New Zealand, *Artemisia annua* is marketed as a dietary supplement to help maintain and support joint health and mobility.

Does it work?

There is only one published clinical study assessing the efficacy of *Artemisia annua* for the above indication. A 12-week randomised, placebo-controlled pilot study using one brand of *Artemisia annua* in a grapeseed oil base (Arthrem®) was published in 2016. The study was funded by the manufacturer (Promisia Ltd.) but headed by a University of Otago rheumatologist. Forty-two patients with hip or knee osteoarthritis took either 300 mg twice daily, 150 mg twice daily, or placebo (n=14 in all groups), in addition to their usual medications. Patients taking the 150 mg dose had statistically significant, modest improvements in stiffness, physical function and pain scores over 12 weeks. No improvement was seen in patients taking placebo, or the 300 mg dose. In an extension phase of the study, 34 patients took 150 mg twice daily, and initial improvements were reported to be maintained over a further six months. No formal statistical analysis was conducted in this phase of the study.

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ORIGINAL ARTICLE

A pilot randomized, placebo-controlled clinical trial to investigate the efficacy and safety of an extract of *Artemisia annua* administered over 12 weeks, for managing pain, stiffness, and functional limitation associated with osteoarthritis of the hip and knee

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Is it safe?

In the pilot study outlined above, three patients in the 300 mg group had gastroesophageal reflux; one of these patients withdrew from the trial. There was also one report each for abdominal pain, vomiting, back pain and hepatitis. The patient who developed hepatitis withdrew from the trial, which was deemed 'possibly' related to treatment by the authors. In the 150 mg group, one patient had vomiting. There was one report each for abdominal pain and back pain in the placebo group. Five patients did not complete the extension phase of the study due to adverse effects: two withdrew due to events considered 'unlikely' to be related to treatment (ovarian cancer and elevated liver enzymes); while three withdrew due to gastrointestinal effects considered 'possibly' related to treatment. These were constipation, stomach pain, flatulence and diarrhoea.

Can it cause liver problems?

In addition to the two cases of liver-related adverse effects reported in the studies summarised above, the Centre for Adverse Reactions Monitoring (CARM) received 14 spontaneous reports of hepatotoxicity possibly associated with *Arthrem*[®] from February 2016 to December 2017. This prompted Medsafe to issue a safety alert in February 2018. Many of the reports included jaundice as a reaction. Where information was provided, the pattern of liver toxicity was either hepatocellular or mixed (hepatocellular and cholestatic). All patients stopped taking the supplement, and at the time of reporting most had recovered or were improving. A US case report describing hepatitis in a patient who had started taking an artemisinin supplement one week prior has also been published. The patient's liver function tests resolved over three weeks following discontinuation of the supplement. Patients who develop signs of hepatotoxicity such as nausea, stomach pain, pale stools, dark urine, itching and jaundice should stop taking it and contact their GP.

Should women who are pregnant or breastfeeding take it?

No. Animal studies show that derivatives of artemisinin can cause foetal resorption and may be teratogenic during the first trimester. Safety in the second and third trimesters is unknown. There is also no reliable information on its safety in breastfeeding.

Does it interact with medicines?

In the studies summarised above, patients remained on all their usual medicines but interactions were not commented on. In vitro research shows that artemisinin induces the drug-metabolising enzymes cytochrome (CYP) 2B6 (increasing its activity 1.6-fold) and 3A (increasing its activity 1.9-fold). This may theoretically lower plasma concentrations, and therefore reduce the effectiveness of any medicines that are metabolised by these enzymes.

Key points

There is a lack of evidence to support the efficacy of Artemisia annua for osteoarthritis. Liver toxicity has been observed in several patients; report any adverse effects to CARM.

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