P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

HerbClip™

File: ■ Sweet Wormwood (*Artemisia annua*, Asteraceae)
■ Sweet Wormwood

HC 082116-685

Date: March 31, 2022

RE: Sweet Wormwood May Prove to be a New Source of Herbal Medicine Based on Recent Clinical Studies

Ekiert H, Świątkowska J, Klin P, Rzepiela A, Szopa A. *Artemisia annua* – Importance in traditional medicine and current state of knowledge on chemistry, biological activity, and possible applications. *Planta Med*. July 2021;87(8):584-599. doi: 10.1055/a-1345-9528.

Sweet wormwood (sweet Annie; *Artemisia annua*, Asteraceae) was used in traditional Asian medicine to treat jaundice, bacterial dysentery, and fever associated with malaria and tuberculosis. In 1972, Dr. Youyou Tu, a professor in pharmaceutical chemistry, discovered the compound artemisinin and proved its effectiveness in treating malaria. In 2015, she was awarded the Nobel Prize in Medicine for her discovery. Since then, research in artemisinin continues to expand. The purpose of this review was to present the current knowledge on the chemistry, biological activity, possible therapeutic actions, and uses of sweet wormwood.

Sweet wormwood is native to the temperate zones of Southeastern Europe and Western Asia. At present, sweet wormwood is found on five continents and is most abundant in Western Europe and the Western United States. Fourteen Latin synonyms and 30 common names are associated with the plant. According to the Chinese Pharmacopeia and the Vietnamese Pharmacopeia, the raw dried leaves are used medicinally; however, the World Health Organization (WHO) and traditional Chinese medicine (TCM) references cite use of the flowers, leaves, stems, and seeds. Sweet wormwood grows on hillsides, forest edges, and wastelands in moderately dry and nutrient-rich sites. Although various varieties have grown successfully in tropical climates, the plant prefers long summer days and a fall bloom. Habitat plays a role in the chemical composition and medicinal value of sweet wormwood.

Sweet wormwood is most known for its antimalarial properties. However, recent research has demonstrated anti-inflammatory, analgesic, antioxidant, antitumor, and nephroprotective properties. Sweet wormwood has been studied as a possible treatment for hepatitis B, bovine viral diarrhea, Epstein-Barr virus, and, most recently, the COVID-19 virus.

The phytochemical composition of sweet wormwood includes sesquiterpene lactones, essential oil with mono- and sesquiterpenes, flavonoids, coumarins, phenolic acids,

tannins, saponins, polyalkenes, phytosterols, fatty acids, and proteins. The most important compound in the sesquiterpene lactones group is artemisinin, which accumulates in the glandular hairs on both sides of the leaves and flowers. Artemisinin is extracted and used to produce synthetic derivatives, including artemether, artesunate, dihydroartemisinin, and arteether. Artesunate is obtained after reducing artemisinin, and is metabolized into the water-soluble, readily bioavailable form of dihydroartemisinin after consumption. The concentration of essential oil varies between 1.4 and 4.0% and is rich in terpenes. The main constituents in the essential oil include artemisia ketone, camphor, β-caryophyllene, β-pinene, germakrene D, borneol, and cuminal.

In TCM, sweet wormwood has been used as an antipyretic and antimalarial drug for more than 2000 years. The first Chinese medical literature on sweet wormwood was written around 200 BCE and describes 224 medicines and methods of their preparation, with sweet wormwood described as a medicine for hemorrhoids. TCM describes its use for "fever caused by summer heat" and "afternoon fever associated with deficiency." It was also used as a remedy for bleeding wounds. In addition to its historical use, sweet wormwood has been used more recently in the cosmetic and food industries.

Artemisinin was shown effective in the early stages of trophozoite malaria. It has also been shown to inhibit the growth of *Plasmodium* schizonts with a gametocytocidal effect. Unfortunately, *Plasmodium* species are becoming resistant to antimalarial drugs, including artemisinin. Artemisinin combined therapy (ACT) uses artemisinin in combination with other antimalarial drugs with different mechanisms of action to combat the parasite; however, its effectiveness is also waning. Medicine based on sweet wormwood must include standardized extractions in the form of tablets and injections. In the case of artemisinin extraction, it was found that pouring boiling water over the leaves was more effective than adding leaves to boiling water. According to Chinese and Vietnamese Pharmacopeias, the leaves should be standardized for an artemisinin content of ≥ 0.7% of dry weight. Artemisinin reacts with iron; thus, the use of metal objects containing iron should be avoided. Uncontrolled use of artemisinin combined therapy (ACT), use of subtherapeutic doses of artemisinin, artemisinin derivatives as prophylactic agents, and substandard or counterfeit drugs may have contributed to resistance against the treatment of malaria.

A randomized, clinical trial of patients diagnosed with uncomplicated malaria caused by *Plasmodium falciparum* confirmed the beneficial use of sweet wormwood infusion after seven days; however, the methods of preparation and doses used were not mentioned. A hydro-ethanolic extract containing 20 mg/kg of artemisinin was more effective than an aqueous extract of the same dose and pure artemisinin at a dose of 140 mg/kg after four days in mice infected with *P. berghei*. This supports a synergistic effect of other components found in sweet wormwood. The suggested mechanism of action included the interference of plant components with protein metabolism and mitochondrial activity of *Plasmodium* spp. In vitro and in vivo models have also confirmed the beneficial use of sweet wormwood extracts against diseases caused by other protozoa, namely *Acanthamoeba castellannii* and *Leishmania donovani*.

Antibacterial activities of sweet wormwood extracts were confirmed in laboratory tests using the disk diffusion method (DDM) against *Escherichia coli*. The study showed that the origin of the plant material had an influence on the strength of bacterial effect in its aqueous extract form. Hexane, chloroform, and methanol extracts were less effective. Another study used the DDM to evaluate antibacterial effects of the essential oil of

blooming sweet wormwood and selected components (1,8-cineol, camphor, and artemisia ketone) against *E. coli*, *Salmonella enteritidis*, *S. typhi*, *Yersinia enterocolitica*, and *Listeria monocytogenes*. All microorganisms tested were sensitive to the essential oil and its components. Additionally, *Y. enterocolitica* was found to be more sensitive to the essential oil over the control (amoxicillin), but the essential oil was less effective than 1,8-cineol against *S. typhi*. In subsequent trials, the antibacterial effects of the essential oil were confirmed against *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii.* That same study confirmed the antifungal properties of the essential oil of sweet wormwood against *Candida famata*, *C. utilis*, and *C. albicans*. Another study used the microdilution method on titration plates method. The following microorganisms demonstrated low to moderate sensitivity to the essential oil: *S. aureus*, *B. cereus*, *Sarina lutea*, *S. enteritidis*, *K. pneumoniae*, *E. coli*, and *Shigella* spp.

Ethanolic extracts of sweet wormwood as an immunosuppressive have been confirmed in vitro and in vivo. An in vitro study evaluated mouse spleen lymphocytes proliferated with concanavalin A and lipopolysaccharide after administration of sweet wormwood (extract type and dose was not disclosed). An in vivo study involved immunizing mice with ovalbumin and, after administration of the plant extract, examining the suppression of specific antibodies and suppression of proliferation of splenic lymphocytes. Both studies support the traditional use of sweet wormwood as treatment for autoimmune diseases. Another study confirmed its use as an immunosuppressant by showing the inhibitory effect of artemisinin on calmodulin in mice.

A randomized, double-blind clinical trial was conducted to assess the safety and anti-inflammatory effects of sweet wormwood extract. A CO_2 extract containing 150 mg of sweet wormwood, (Arthrem®; Promisia Ltd; Wellington, New Zealand) was prepared and administered over a period of 12 weeks to patients with osteoarthritis of the hip or knee joints. Forty-two patients were randomly assigned to the Arthrem 150 mg group, Arthrem 300 mg group, or the placebo. The Western Ontario indicator, McMaster University of Osteoarthritis (WOMAC), and the visual analogue scale (VAS) were used. Significant improvements were observed in patients receiving the lower dose. Additional in vitro studies using sweet wormwood aqueous extracts on inflammation-induced human colon adenoma cells showed that leaf extracts have an anti-inflammatory effect and improve bioavailability of artemisinin by inhibiting cytochrome P450.

Animal studies confirmed a dose-dependent analgesic effect with the essential oil of sweet wormwood and its components, camphor, 1,8-cineol, and α-pinene.

Various extracts including, hexane, chloroform, ethyl acetate, methanol, and water extracts, were tested for their antioxidant potential. Methanol extracts produced the highest antioxidant activity while aqueous extracts were the weakest. The highest concentrations of phenols and flavonoids were also extracted using methanol. In another study, the essential oil and its compounds (1,8-cineol, artemisia ketone, and α-pinene) had an antioxidant effect, but they were less effective than the control compounds (butylated hydroxytoluene and quercetin).

The neuroprotective effects of sweet wormwood essential oil were confirmed by histopathological examination of rodents' kidneys. Concentration and study specifics were not provided.

Several studies evaluated the use of sweet wormwood for its anticancer effects. In vitro experiments using breast cancer cell lines found that the polyphenols isolated from sweet wormwood inhibited adhesion of these cells to endothelial cells, inhibited invasion of tumor cells, and suppressed epithelial-mesenchymal transition; thus, indicating an inhibitory effect against tumor metastasis. Another in vitro study showed that long-term treatment with sweet wormwood extract in combination with short-term use of bicalutamide caused significant regression of advanced stage metastatic prostate cancer. Sweet wormwood was also shown to have a cytotoxic effect on osteosarcoma cells, human breast adenocarcinoma cells, human lung cancer cells, and Chinese hamster ovarian cells. It was noteworthy that one study found that the location where the plant was cultivated made a difference in cytotoxic activity.

Animal studies showed a sweet wormwood leaf 80% ethanol extract reduced insulin resistance and limited liver steatosis. Another study confirmed an anti-obesity action of the essential oil by a reduced accumulation of lipid droplets and the expression of obesity-related proteins.

Numerous in vitro studies have been conducted on parasite egg viability and parasite larval development in goats and sheep. In all tests, the 0.1% sodium bicarbonate extract, produced better results than isolated artemisinin extract. In one study, sheep were orally administered bicarbonate extract from sweet wormwood leaves and pure artemisinin extract. Both extracts were ineffective.

According to the European Coslng (Cosmetics Industry) database, sweet wormwood's use in cosmetic applications is as follows: protection and care of skin and hair, antibacterial agent, antioxidant, masking, fragrant, anti-dandruff, moisturizing, and as a softening substance. Use of both the herbal extract and essential oil was documented. The extract is used in shampoos, essences, serums, hand and eye creams, masks, lotions, and tonics. Products containing sweet wormwood are offered worldwide. In addition to cosmetic use, the green parts of sweet wormwood have been consumed as a vegetable. Sweet wormwood is also used as a source of green dye and an ingredient in vermouth.

Several safety considerations were noted including, inflammatory and allergic reactions, abdominal pain, bradycardia, diarrhea, nausea, vomiting, decreased appetite, flu-like symptoms, reticulocytopenia, and fever. The use of sweet wormwood is contraindicated in patients with known ulcers or gastrointestinal disorders. The European Food Safety Authority lists sweet wormwood leaves as raw material that is not health-neutral due to high concentrations of camphor in the oil.

While there are several safety concerns, the authors conclude that sweet wormwood makes a viable alternative for new discoveries based on its chemical composition and previously supported health benefits. The authors recommend that research should focus on previously unknown areas of its medicinal and paramedicinal applications.

The authors declare no conflict of interest.

—*Samaara Robbins*

Referenced article reprinted with permission from Georg Thieme Verlag.