

Natural products for treating or preventing influenza

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Abstract

Natural products – including botanicals, minerals, and other substances produced by organisms – not only hold historical significance in various medical traditions, but they also form the basis of many modern-day drugs. On one hand, natural products are considered to be a form of complementary and alternative medicine (CAM); as with many CAM therapies, natural products are often used for primary disease prevention and treatment – or as adjuncts to conventional therapies – despite uncertain effectiveness or safety. On the other hand, natural products have given rise to numerous conventional drugs, which are widely used in mainstream medicine and compose the primary therapeutic strategies for numerous conditions (including influenza). In this review, the available evidence on the use of select natural products for the treatment or prevention of influenza is discussed. Finally, a brief overview of an established influenza drug with botanical origins is provided.

Select natural products used for influenza treatment and prevention

Conventional treatments for influenza include antivirals, antipyretics, and agents that provide temporary symptomatic relief. Similarly, natural influenza therapies are used for purported antiviral, antipyretic, and symptom-relieving effects. The same therapies may also be used in the general population for various related and unrelated indications, such as cardiovascular disease risk reduction, common cold symptoms, or overall well-being. Select natural products that are commonly used in influenza treatment are summarized below. These therapies should not be used in place of vaccination or other FDA-approved therapies, and patients are advised to discuss all therapies used (conventional or alternative) with their primary healthcare providers.

Andrographis (*Andrographis* spp.)

Background and mechanism of action

The leaves of plants from the genus

Andrographis have had a long history of use in Indian folk medicine and Ayurveda to treat a variety of ailments (including influenza).¹ The Chinese and Thai herbal medicine systems have also incorporated this herb, renowned in these traditions mostly for its “bitter” properties as a treatment for digestive problems and for a variety of febrile illnesses. More recently, this herb, in its standardized extract form, has become popular in Scandinavia as a remedy for upper respiratory infections (URI) and influenza. One commonly used preparation is the standardized andrographis extract Kalm Cold[®], which has been shown to have low toxicity *in vitro* and *in vivo*.² Clinical trials using the standardized product Kan Jang[®] (Swedish Herbal Institute) have shown reasonably strong evidence that andrographis may be effective in reducing symptom severity and duration in upper respiratory tract infections (URIs), both in children and adults, if started within 36-48 hours of the onset of symptoms;³ however, fewer studies have examined andrographis specifically for influenza.

Andrographolide, a diterpene lactone compound, is believed to be the principal active agent.⁴ Other purported active constituents include trimethoxy flavone (TMF), a naturally occurring flavone that is isolated from *Andrographis viscosula* and used in the treatment of dyspepsia, influenza, malaria, and respiratory functions and as an astringent and antidote for poisonous stings of some insects. Andrographolide inhibits NF- κ B binding to DNA *in vitro*, reducing expression of a variety of inflammatory proteins, including COX-2.⁵ In rat neutrophils, it also appears to exert anti-inflammatory action via a decrease in gene expression required for neutrophil adhesion and transmigration.⁶ Andrographolide alone and the standardized andrographis combination product Kan Jang[®] were found to increase the formation of TNF- α and β 2MG *in vitro*; the fixed combination was more effective than andrographolide alone.⁷ Andrographis has been shown to inhibit the secretion of pro-inflammatory cytokines by influenza A virus (H1N1)-infected human epithelial cells *in vitro*.⁸

There is reasonably strong evidence from clinical trials to suggest that andrographis is effective in reducing the severity and the duration of URIs when treatment is started within the first 36-48 hours of symptoms. Based on animal and *in vitro* studies, it appears that andrographis may have a number of other potential therapeutic uses, including as an anti-inflammatory agent and as a treatment for chemically induced hepatotoxicity. It has also been studied in human clinical trials for influenza and familial Mediterranean fever; it may be moderately effective in reducing symptoms in both of these conditions, although further research is merited in these areas.

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There are historical data to suggest that andrographis has been effective in the past as part of a regimen to treat influenza in Asian medical systems. The one clinical trial to date of a standardized andrographis preparation does report a significant reduction in the duration and severity of symptoms, as well as a decrease in time off from work, in patients treated for influenza with this herbal. More studies specifically looking at influenza, with clear diagnostic criteria for distinguishing flu from simple URIs, are needed to confirm this finding.

Clinical evidence

Kulichenko *et al.* carried out two randomized parallel-group trials of the SHA-10 extract of andrographis (Kan Jang[®], Swedish Herbal Institute) in adults diagnosed with influenza.⁹ Patients who had been ill for more than 36-48 hours at the time of presentation were excluded. In the pilot study, for which randomization procedures were not described in detail, 71 patients were treated with Kan Jang[®] (two tablets three times daily for 3-5 days) and 469 patients were treated with conventional therapy. In the second trial, which had a clearer randomization procedure, 35 patients were treated with Kan Jang[®] and 31 with conventional treatment. Outcomes assessed were symptoms by patient self-evaluation on days one and five of the study period, and clinical examination by a physician on days one and five. In the pilot study, investigators found that only 30% of treated subjects developed what they described as lingering or “complicated” influenza, while 68% of the control group developed this condition (P<0.01 difference). In the second study, they found both that symptoms disappeared more rapidly in the treatment than in the control group (1-2.5 days sooner, depending on the particular symptom, P<0.01 for all), and that the duration of sick leave in the treated group was significantly shorter than in the con-

tol group (7.2 days vs. 9.8 days, $P < 0.01$). Although the study suffers from its poorly described randomization procedure and a lack of a standardized outcome measures for symptoms, it does seem to provide preliminary evidence that andrographis extract may be effective not only for standard URIs but also for influenza specifically.

Echinacea (*Echinacea* spp.)

Background and mechanism of action

Natural medicine experts frequently recommend oral extracts of echinacea for the treatment of the common cold, influenza, and other conditions requiring immune stimulation. Echinacea has been shown to alter the course of influenza infection in mice.^{10,11} Echinacea may have direct effects on the influenza virus,¹² such as interference with receptor binding and viral entry into cells¹³ or inhibition of viral growth.¹⁴ However, some studies suggest that the anti-influenza effects of echinacea may be through the modulation of cytokines and/or interferons,^{11,14-16} an effect that is retained by echinacea root tinctures for up to two years.^{15,17} Recent studies have shown echinacea alkamides to modulate pro-inflammatory cytokine cannabinoid type-2 (CB2) receptors, presenting a novel and potentially significant immunomodulatory mechanism for echinacea.^{18,19}

Studies have examined the efficacy of echinacea in treating upper respiratory infections in general, but the overall evidence is conflicting and insufficient to either support or rule out potential benefits.^{20,22} Relatively little clinical research has focused specifically on influenza. Despite a paucity of clinical evidence, the German Commission E has approved the oral use of *Echinacea purpurea* for supportive treatment of influenza-like infections and lower urinary tract infections, and for topical treatment of poorly healing wounds/ chronic ulcerations. These indications are also noted in monographs published by the World Health Organization (WHO).

Clinical evidence

Lindenmuth and Lindenmuth conducted a randomized controlled trial of Echinacea Plus® tea (containing echinacea, lemongrass, and spearmint) vs. placebo for upper respiratory tract symptoms.²³ The tea contained the equivalent of 1,275 mg of dried herb and root per tea bag. Participants were instructed to drink 5-6 cups of tea on the first day and titrate down by one cup daily for the next five days. The experimental group rated the effectiveness of echinacea tea as 4.1 on a 5-point scale (SD 0.96), while the control group rated their tea as 2.8 (SD 0.095), with a $P < 0.001$. There was also a statistically significant (although small) difference in the number of days symptoms last-

ed and in the number of days before symptoms diminished in the treatment group vs. control. The statistical analysis may not have been appropriate (t-test for sum scores), but this methodological weakness would not likely explain the results. Therefore, echinacea tea, when taken at the first onset of symptoms, may be effective in relieving symptoms of the common cold and in abbreviating the course of the illness.

Elder (*Sambucus* spp.)

Background and mechanism of action

Sambucus is a genus containing several species of small trees or shrubs, and various parts of the plant (including the bark, leaves, flowers, or berries) have been used for the treatment of influenza. The berries of European elder are recognized by the German Commission E for various medicinal uses.²⁴ The aerial parts of the elder plant contain lectins that have notable carbohydrate-binding properties²⁵ and are therefore often used to study influenza virus agglutination. The antiviral mechanisms of elder lectins are believed to involve rendering viruses nonfunctional by binding influenza virus hemagglutinin, its major viral surface protein that facilitates infection. Preclinical studies suggest that *S. nigra* (flowers and berry) may inhibit influenza virus types A and B by reducing hemagglutination of red blood cells and inhibiting viral replication.^{26,27} Elderberry flavonoids have also been shown to bind influenza virus and prevent infection *in vitro*.²⁸

Sambucol® is a popular influenza remedy that contains 38% standardized black elderberry extract (for adults) or 19% standardized black elderberry juice (for children).²⁷ Many different formulations of this product are available. Sambucol® Active Defense™ contains a 38% standardized black elderberry extract, plus vitamin C, zinc, propolis, and a proprietary blend of *Echinacea angustifolia* and *Echinacea purpurea*. The standardized elderberry product Sinupret® (Quanterra® Sinus Defense) is an herbal mixture containing 18 mg Flos *Sambucus nigra* (elder flower), 18 mg Herba *Verbena off.* (vervain wort), 6 mg Radix *Gentiana lutea* (gentian root), 18 mg Flos *Primulae veris cum calycibus* (cowslip flowers with calyx), and 18 mg Herba *Rumicis acetosae* (sorrel).²⁹ Sambucol® has been shown to increase the production of both pro-inflammatory and anti-inflammatory cytokines.^{30,31}

Clinical evidence

A case report exists of an HIV-positive woman, taking no HIV drugs, who experienced a viral load drop from 17,000 to 4,000 after ingestion of Sambucol® with olive leaf extract.³² The report also included a placebo-controlled, double-blind study of Sambucol®

associated with a rapid recovery from influenza and inhibited replications of nine other strains of the flu virus by elderberry.

Zakay-Rones *et al.* conducted a randomized, double-blind, placebo controlled study of Sambucol® (a syrup containing elderberry juice, raspberry extract, glucose, citric acid, and honey) in the treatment of influenza in otherwise healthy individuals (children and adults) not previously vaccinated against the flu, located in an Israeli agricultural community.²⁷ Patients were included who had at least three symptoms (fever, myalgia, nasal discharge, cough) of less than 24 hours' duration. Children received 2 tbsp. daily and adults received 4 tbsp. daily for three days. Age range and mean age were similar between groups. This was not an intent-to-treat analysis, and out of 40 subjects who were initially enrolled and randomized, 13 were disqualified prior to analysis, due to crossover or protocol violations (five in the treatment group and eight in the placebo group). In subjects who were analyzed, convalescent phase serologies demonstrated higher antibody titers to influenza B in the group treated with Sambucol®, although these results were not statistically significant, and only demonstrated a trend in favor of the treatment group. Follow-up of symptoms was adequately recorded over six days, and significant improvement in symptoms was observed in 93.3% of treated patients within two days, versus the control group, in which it took six days to see improvement in 92.7% of patients ($P < 0.001$). A complete cure was seen within 2-3 days in Sambucol®-treated patients (90%), whereas six days were needed in the placebo group. Although randomization and blinding were adequately described, this study was limited by the small sample size, lack of intent-to-treat analysis, and use of influenza-B rather than influenza-A titer measurement.

Zakay-Rones *et al.* later conducted another randomized, double-blind, placebo-controlled study of oral elderberry syrup in the treatment of influenza A and B virus infections during the influenza season of 1999-2000 in Norway.³³ Patients aged 18-54 years with influenza-like symptoms for 48 hours or less were enrolled. Patients were given 15 mL of elderberry or placebo syrup four times a day for five days and recorded their symptoms using a visual analogue scale. There was no intent-to-treat analysis. Symptoms were relieved on average four days earlier, and use of rescue medication was significantly less in those receiving elderberry extract compared with placebo. The authors concluded that elderberry extract seems to offer an efficient, safe, and cost-effective treatment for influenza. Although the study was randomized and blinded, this study was limited by the small sample size, lack of intent-to-treat analysis, and failure to report any adverse effects or lack of compliance.

Ginseng (*Panax spp.*)

Background and mechanism of action

Panax ginseng has been used in traditional Chinese medicine (TCM) for more than 2,000 years for a wide range of indications. Ginseng is believed to boost immune function and, thus, has been implicated for treatment of respiratory infectious disease.³⁴ In humans and animals, ginseng has been shown to enhance cellular immune function by stimulating natural killer cell activity,³⁵⁻³⁹ macrophages,⁴⁰ tumor necrosis factor (TNF)- α production,⁴¹ cytokine production,^{42,43} antibody-dependent cellular cytotoxicity,^{38,44} intracellular killing in neutrophils, blastogenesis of circulating lymphocytes,⁴⁵ and antibody production.³⁵ Ginseng has also been shown to potentiate the effect of vaccines⁴⁶ and display anticomplement activity.⁴⁷ Preclinical studies have suggested that ginseng has mitogenic activity on lymphocytes,⁴⁸ but preliminary clinical studies did not find significant effects on peripheral blood leukocytes or lymphocyte subsets.⁴⁹ Immunomodulating effects of ginseng may be attributable to its constituents, such as root-derived panaxanes-polysaccharides,⁵⁰ ginsenosides that can differentially modulate lymphocyte proliferation,⁵¹ and ginsenan S-IIA, a potent inducer of IL-8 production by human monocytes and THP-1 cells.⁵² Certain multi-ingredient preparations, such as CKBM (*Panax ginseng*, *Schisandra chinensis*, *Fructus crataegi*, *Ziziphus jujube*, and *Glycine max*), have also been shown to regulate intracellular signaling and the production of cytokines.⁵³ The immuno-regulatory functions of a saccharide-rich proprietary American ginseng extract (*Panax quinquefolius*, CVT-E002) by CV Technologies Inc. may be due to stimulation of a panel of inflammatory cytokines secretion from monocytes and augmentation of IFN- γ secretion upon influenza stimulation. Clinical research has found Cold-fx[®], containing CVT-E002, to be effective in the prevention and treatment of upper respiratory infections.⁵⁴⁻⁵⁶ Cold-fx[®] may increase NK cell and macrophage activity, leading to increased cytolytic and phagocytic killing of pathogens and IFN- γ secretion. Evidence from *in vitro* and *in vivo* studies indicates that Cold-fx[®]-induced antiviral effects could be related to its immunomodulating properties.^{34,57-61}

Ginseng seems to stimulate T-cell and polymorphonuclear (PMN) leukocyte activity, increase clearance of bacterial infections treated with antibiotics, and improve immune response to and efficacy of influenza immunization. Numerous clinical studies have been or are being conducted with Cold-fx[®], involving a total of more than 1,000 study subjects in diverse populations, including healthy adults, nursing home seniors, and athletes. These trials include: two open trials with professional

sport teams for safety, tolerability, severity, duration of cold and flu-like symptoms, general performance, and immune system functions;⁶² one controlled trial with high-performance athletes for doping control urinalysis;⁶³ and three double-blind, placebo-controlled trials in seniors for the prevention of colds and flu.^{55,64} A pivotal large-scale randomized, double-blind, placebo-controlled trial has recently been completed in healthy adults, examining the preventative effect of Cold-fx[®] for upper respiratory tract infections.⁵⁴ Recently, a multicenter trial was launched to investigate the effectiveness of Cold-fx[®] in the prevention of respiratory infections in community-dwelling seniors who had been vaccinated against influenza. Cold-fx[®] appeared safe, well tolerated, and potentially effective for preventing acute respiratory illness due to influenza and respiratory syncytial virus (RSV).^{55,64} These evaluations are based on a few studies, which were all presented by the same lead author. Critical examination of this indication by independent groups is needed for a more definite efficacy evaluation of ginseng for immunostimulation. Future research should also identify the conditions that may benefit most from such immunostimulant properties. Conclusions about safety and efficacy of Cold-fx[®] should not be considered equivalent to other ginseng preparations without further supportive evidence. Ginseng has been associated with an increased risk of bleeding,⁶⁵ so it is contraindicated in acute inflammatory conditions (such as asthma), hypertension, and situations involving blood loss.⁶⁶

Clinical evidence

Scaglione *et al.* found in a randomized, double-blind, placebo-controlled trial that *Panax ginseng* increases efficacy of influenza vaccination.⁶⁷ Two hundred twenty-seven healthy volunteers from three private practices were randomly assigned to either ginseng (G115[®], 200 mg daily) or placebo for 12 weeks. Vaccination was administered after four weeks of treatment. Antibody titers, natural killer cell (NK) activity, intercurrent illnesses, and adverse events were assessed in 2-4-week intervals. Until the end of the study, NK activity almost doubled in the ginseng group, while it remained unchanged in the placebo group ($P < 0.0001$). Antibody titers were one-third higher in the ginseng as compared to the placebo group. The number of common cold/influenza episodes was two-thirds lower in the ginseng vs. the placebo group ($P < 0.001$). Nine patients in the ginseng group complained about adverse events, mainly nausea or insomnia (one control patient complained about insomnia). The results of this well-conducted trial indicate that ginseng may be an effective adjuvant to vaccination against influenza.

McElhane *et al.* conducted a randomized,

double-blind, placebo-controlled trial in community-dwelling seniors to assess the effects of a proprietary extract of American ginseng root (Cold-fx[®]) in the prevention of acute respiratory illness.⁶⁴ Volunteers were included in this study if they were generally healthy and aged 65 and older. Those taking immunosuppressive drugs and corticosteroids and those with a history of allergy or known renal, pulmonary, or hepatic abnormalities were excluded. The participants were asked to take two capsules every morning of either Cold-fx[®] or placebo (200 mg per capsule) for a period of four months. After four weeks on the study drug, the patients received a standard dose of influenza vaccine. Patients self-reported the following symptoms: fever, sore throat, cough, nasal congestion, chills, headache, fatigue, or aches/pains. Patients also were asked to record if the study medication helped in reducing the duration of their symptoms. The effects of Cold-fx[®] or placebo treatment on the frequency and duration of symptoms related to an acute respiratory illness (ARI) prior to the onset of influenza season were analyzed. The Pearson chi-square test was used to compare the proportions of subjects reporting symptoms related to ARI and adverse events. For the subset of subjects who reported ARI-related symptoms, the number of days for which symptoms were reported was calculated, and the two groups were compared using unpaired t-tests. Nausea, heartburn, or diarrhea were reported in six of 22 (27%) of patients; side effects were not significantly different from the placebo group (four of 21, 19%). Dry mouth was also reported in two of 22 patients (9%), but again, this was not significantly different from the placebo group (zero of 21).⁶⁴ Muscle and joint pain were reported in four of 22 (18%) of patients, although side effects were not significantly different from placebo group (three of 21, 14%). During the first eight weeks of the study, in subjects reporting ARI-related symptoms, the average duration of the symptoms per subject was not found to be statistically different between the groups. However, in the last eight weeks, the duration in the Cold-fx[®] group was found to be 55% shorter than in the placebo group (5.6 vs. 12.6 days, $P = 0.04$). The authors concluded that Cold-fx[®] supplementation during an early "cold and flu" season could potentially help in reducing the frequency and duration of symptoms related to ARI in community-dwelling adults aged 65 years or older and immunized against influenza. During the early part of the colds and flu season, regular modest dosing of Cold-fx[®] reduced the relative risk of ARI by 48% and was well tolerated by the study participants.

McElhane *et al.* conducted two phase 2 randomized, double-blind, placebo-controlled, parallel arm investigations in 2000 and 2001 to assess the effects of a proprietary extract of

American ginseng root (CVT-E002) in the prevention of acute respiratory illness.⁵⁵ Volunteers from assisted-living or nursing home facilities were included in this study if they were aged 60 or older. Those taking immunosuppressive drugs and corticosteroids and those with a history of allergy or active renal, pulmonary, or hepatic abnormalities were excluded. Eighty-nine (2000) and 109 (2000-2001) subjects enrolled, with an average age of 81 and 83.5, respectively; 74% were women. Approximately 90% had received influenza vaccines in each of the two years. Subjects received oral administration of a proprietary ginseng extract, CVT-E002, 200 mg or placebo twice daily for either eight or 12 weeks, depending on the study. Cold-fx[®] is standardized to contain 90% poly-furanosyl-saccharides. Acute respiratory illness (ARI) was defined as two new respiratory symptoms or one with a constitutional symptom, which defined the primary outcome of this study. Secondary outcomes included confirmation of viral ARI by culture [influenza or respiratory syncytial virus (RSV)] or serology for influenza. Laboratory safety monitoring was done at zero, four, and eight, or 12 weeks. There were no significant differences in the demographic data between CVT-E002 and placebo groups in either of the studies. The number of side effects was similar between placebo and CVT-E002 groups, with gastrointestinal, nervous, and cardiovascular effects occurring. Combined results in the two studies showed that 11% of the placebo group (8% of whom required hospitalization) and 6% of the CVT-E002 group (4% of whom required hospitalization) experienced a serious adverse effect during the study. All of the serious adverse effects were judged to be unrelated to the study medication. There was no significant difference noted in the primary outcome for the number of ARIs defined by symptoms alone. And there was no significant difference in the severity or duration of symptoms related to ARI between the two groups in either study. For the secondary endpoints, pooled data corrected for drug exposure time showed that the incidence of laboratory-confirmed influenza illness (LCII) was greater in placebo- (seven cases out of 101 subjects) than CVT-E002-treated (one out of 97) groups (odds ratio (OR)=7.73, P=0.033). Combined data for LCII and RSV illness were also greater in placebo- (nine out of 101) than CVT-E002-treated (one out of 97) groups (OR=10.50, P=0.009), for an overall 89% relative risk reduction of ARI in the CVT-E002 group. Although a potentially promising study, the randomization methods and double-blinding methods were unclear in this study. This study did include power calculations for adequate study size and pooled data from two influenza seasons. Based on this study, CVT-E002 does not appear to reduce symptoms of

influenza, but may affect laboratory-confirmed ARI.

McElhane *et al.* conducted a preliminary study on the safety, tolerability, and efficacy of Cold-fx[®] treatment for flu-like or cold symptoms, which was presented at the First International Scientific Congress on Nutrition & Athletic Performance, Edmonton, Alberta, August 8-11, 2001.⁶² Studies of Cold-fx[®] were conducted during the 1997-98 and 1998-99 seasons with the Edmonton Oilers Hockey Club. The first study included subjects on daily or intermittent treatment starting at the first onset of symptoms. In the intermittent treatment group, 71% (five of seven) reported that Cold-fx[®] prevented the cold from developing and that it made them feel better. In the daily treatment group, 57% (eight of 14) reported they felt less run down while traveling, and 50% (seven of 14) reported that Cold-fx[®] allowed them to recover faster from a cold. At season end, 83% (10 of 12) believed that taking Cold-fx[®] helped them to stay healthy during the season, and 67% (eight of 12) reported that if they got a cold, their recovery time was faster. A second study was undertaken, with subjects receiving daily treatment with Cold-fx[®], or no Cold-fx[®] in the control group. Peripheral blood lymphocytes were challenged with influenza virus, and supernatants and cell lysates assayed. Early-season control group results indicated that IL-10 decreased 34.4%, and TNF- α decreased 44.4%, whereas Granzyme B increased 82.5%. End-of-season results differed: TNF- α increased 21.8%, and IL10 and Granzyme B did not change. By comparison, Cold-fx[®]-treated subjects had altered immune responses manifested by stabilizing cytokine or effector levels. These studies suggested that Cold-fx[®] treatment may prevent the onset or reduce the severity of symptoms related to colds and flu and could do so by maintaining the production of inflammatory and immunologic mediators at consistent levels. There was no blinding, randomization, or placebo in these studies, only outcomes.

Tamiflu: an established influenza drug with natural origins

Natural products are often regarded as *alternative* therapies with little or no scientific basis; however, it is important to remember that a significant proportion of the current pharmaceutical market – indeed, even the most commonly used drugs – are derived from naturally occurring plant compounds. In the last decade alone, more than 20 newly approved drugs were derived from natural sources, including plants and microorganisms.⁶⁸ It has been estimated

that 50% of contemporary drugs (those used in the last few decades) are either directly extracted from plants or chemically derived from naturally occurring compounds.⁶⁹ Notable examples include the opiates, which are derived from the latex sap of the opium poppy (*Papaver somniferum*) and compose one of the best-selling classes of prescription medications.⁷⁰ Another example is aspirin (acetylsalicylic acid), the world's first-ever synthetic drug; this commonly used analgesic and anti-inflammatory is derived from salicylic acid, a constituent found in willow (*Salix* spp.) and meadowsweet (*Filipendula ulmaria*, formerly *Spirea ulmaria*). Aspirin has been called “the most popular painkiller in the world” and has shown efficacy in the prevention of colon cancer.⁷¹

Oseltamivir (Tamiflu[®]) is a preeminent example of a conventional drug that is derived from a naturally occurring compound. Oseltamivir inhibits neuraminidase, an influenza enzyme that facilitates viral release from infected cells, thus blocking the virus from spreading in an infected host.⁷² Tamiflu[®] can inhibit both influenza A and B, and is used to prevent and treat influenza in adults and children.⁷³⁻⁷⁷ The Chinese star anise (*Illicium verum*), which has a long history of culinary and medicinal use in China, is the primary industrial source of shikimic acid, the key precursor to oseltamivir (Tamiflu). Limited supplies of star anise and low yields of shikimic acid are limiting factors in oseltamivir production. Additional sources of shikimic acid include sweetgum fruit (*Liquidambar* spp.) and ginkgo (*Ginkgo biloba*); however, *Illicium* species contain the highest concentrations.⁷⁸

Conclusions

Overall, there is insufficient evidence to support the efficacy of many natural products in the treatment of influenza or influenza-like illnesses. Likewise, risk-benefit analyses remain unclear for most natural products. Nonetheless, studies have uncovered antiviral and immunomodulatory mechanisms of action for several phytochemicals, suggesting that they have potential benefits in upper respiratory infections (including influenza). Further studies are needed to determine clinical efficacy, define mechanisms of action, and delineate the safety parameters for natural influenza remedies. Phytochemicals may also form the basis of novel drugs for influenza and influenza-like conditions.

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