American Botanical Council

PROPRIETARY PHYTOMEDICINAL PRODUCT

THERAPEUTIC MONOGRAPH

FOR

CVT-E002 (COLD-fX®)

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Overview

This monograph covers the published and unpublished scientific and clinical research on CVT-E002 (COLD-fX®), a proprietary herbal preparation made from the roots of North American ginseng (*Panax quinquefolius* L., Araliaceae). Because CVT-E002 is a chemically distinct fraction (a group of chemically similar compounds, in this case polysaccharides) made from American ginseng roots (see Description and Chemistry sections below), it has pharmacological properties different from less homogeneous extract preparations made from the root of American ginseng, aka North American ginseng. Accordingly, most of the ethnobotanical, pharmacological, toxicological, and clinical literature on American ginseng root is not applicable to this monograph, and with perhaps a few exceptions, will not be cited herein.

Various species of "ginseng" from the genus *Panax* that have been employed in systems of traditional and folkloric medicine have undergone various levels of modern scientific research—some moderate, some extensive. For example, the famous Asian ginseng (*P. ginseng* C.A. Meyer), aka Chinese ginseng and Korean ginseng, depending on its geographical origin, has been the focus of significant scientific and clinical study for the past 30–40 years in Asia and Europe. Other species in the genus *Panax* (e.g., *P. japonicus* C.A. Meyer and *P. notoginseng* [Burkill] F.H. Chen ex C.Y. Wu & K.M. Feng) have been studied to a lesser extent. From a research perspective, American ginseng has lagged behind these other species, except for a cluster of recent clinical trials conducted in the past 6 years that focused on the blood sugar modulating effects of American ginseng root powder in normal, healthy individuals as well as those with type 2 diabetes.[1,2,3]

To date, the vast majority of chemical, pharmacological (in vitro and in vivo) and toxicological research on American ginseng root has focused on the ginsenosides, a group of saponin glycosides that are characteristic of the ginsengs, being found in no other plant species except *Gynostemma pentaphyllum* [Thunb.] Makino (Curcurbitaceae).[4] In addition to the ginsenosides, chemical analyses have determined the presence of various polysaccharides (see Chemistry section below).[5,6,7]

In vitro and in vivo pharmacological research studies have determined that these polysaccharides exhibit various immunomodulatory effects.[5,6,8,9] In 1992, the late Peter Pang, PhD, and Jacqueline Shan, PhD, DSc, co-founders of CV Technologies, began the development of a phytomedicinal preparation comprised of polysaccharides from American ginseng roots.[10] Their research culminated in the production and patenting of CVT-E002,[11] the proprietary preparation that is the subject of this monograph.

Description

CVT-E002 (marketed under the trade name COLD-fX®) is a special patented aqueous extract of the roots of North American ginseng (*Panax quinquefolius* L., Araliaceae), between 80% and 90% of which consists of the poly-furanosyl-pyranosyl-saccharides, which occur naturally in the ginseng root. Unlike most traditional and conventional preparations made from American ginseng roots, which contain the well-known saponin glycosides called ginsenosides, as well as the naturally-occurring saccharides in undetermined quantities, CVT-E002/COLD-fX does *not* contain ginsenosides, its biological activity presumably being based solely on the saccharide fraction (see Chemistry section below).

Quality control and quality assurance guidelines for CVT-E002 are outlined in a document titled "Quality Systems and Quality Standards of COLD-fX®."[12] Raw material of the appropriate age is obtained from a selected supplier and is tested against established specifications by CV Technologies, including identification of the correct species. In addition to chemical identity, the CVT-E002 extract is tested for physiochemical properties such as appearance, odor, pH, solubility, and bulk density; biological activity; and purity and safety including moisture content, microbiological content, and contaminants such as pesticides and heavy metals.

[Note: In the text below, the term "CVT-E002" is used to denote the patented, proprietary extract, especially when referring to basic research (e.g., chemical analyses, in vitro and in vivo pharmacology, etc.). In most cases, the term "COLD-fX," the product's retail name, has been used when reference is made to human clinical trials, market experience, and other situations that imply the oral dosage form available to the public. In some instances both terms are used.]

Primary Use

Prevention of Acute Respiratory Infections. The primary use of CVT-E002/COLD-fX as documented by published clinical trials is for the prevention of acute respiratory infections (ARI). The claim for the product approved by the Canadian government is "helps reduce the frequency, severity and duration of cold and flu symptoms by boosting the immune system."[13] In studies with adult populations, including the elderly, COLD-fX has been shown to reduce the incidence of ARI when used preventively during the cold and flu season.[14,15,16]

Dosage and Duration of Administration

Each capsule of COLD-fX® contains 200 mg of dried, powdered aqueous extract (CVT-E002), standardized to between 80% and 90% poly-furanosyl-pyranosyl-saccharides.

Daily dose in clinical trials for prevention of respiratory tract infections: In a clinical trial with adults aged 65 and over, the dosage was 400 mg once daily for 4 months.[14] The same dose was used in a prevention trial (also 4 months in duration) with adults aged 18–65 years.[16] A third clinical trial with adults aged 60 years and older employed a dose of 200 mg 2 times daily (total 400 mg/day) for 8 and 12 weeks.[15]

Manufacturer dose recommendations/precautions: For adults and children 12 years and over the recommended dosage is 1 (200 mg) capsule 2 times daily for chronic use. Although specific clinical studies were not performed in children aged 12-17 years, this population is included based on a Drug Identification Number (DIN) that the Therapeutic Products Directorate (drug division) of Health Canada issued to COLD-fX (prior to the new Canadian Natural Health Product regulations in 2004). (See the Regulatory Status section below.) For acute use, the recommended dosage is 3 capsules (600 mg) 3 times on the 1st day, 2 capsules (400 mg) 3 times on the 2nd day, and 1 capsule (200 mg) 3 times on the 3rd day. The recommended dosage for continued use is 1-2 capsules per day until the patient feels better. The product should be taken on an empty stomach. Individuals with serious health conditions (e.g., autoimmune disorders, liver or kidney disease) or taking other medications as well as pregnant or lactating females should consult a health care professional before taking COLD-fX®. (See the Pregnancy and Lactation section below.) As COLD-fX® is a derivative of North American ginseng, it is not recommended for individuals allergic to ginseng.

[Note: "Chronic use" implies use for prevention of ARI, suggested by studies of up to 16 weeks. The acute recommended dose applies to use at the onset of symptoms associated with the common cold or influenza. The previously approved Canadian DIN also included the recommended use of "relief of cough due to cold" with acute daily treatment of 2 capsules 3 times per day.]

Chemistry

CVT-E002 is a proprietary, patented natural compound, consisting mainly of poly-furanosyl-pyranosyl-saccharides isolated from the dried root of North American ginseng. The extraction process used is a proprietary ChemBioPrint™ technology detailed in US Patent # 6,156, 291.[10] (The ChemBioPrint process was developed by CV Technologies and is designed to ensure that each lot is standardized according to precise chemical composition and biological activity through in vitro immunological assays.) Further details on the method of extraction are available in US Patent # 6,432, 454 B1.[11]

According to the manufacturer of this extract (CV Technologies, Edmonton, Alberta, Canada), CVT-E002 is composed of 80% poly-furanosyl-pyranosyl-saccharides, which consist of sugar components, including rhamnose, glucose, galacturonic acid, galctose, and arabinose, indicating that the polysaccharide chain structure consists of mixed furanosyl and pyranosyl ring sugars. According to the manufacturers, the remainder of the extract has been identified as 10% protein with the remaining 10% comprised of residual moisture, with trace amounts of amino acids, vitamins, minerals, and small organic molecules. The extract contains no ginsenosides. A detailed overview of the monsaccharide composition, total carbohydrate, and protein composition of CVT-E002 can be found in US Patent # 6,432, 454 B1.[11]

The published literature on the chemistry of *Panax* spp. is primarily focused on the triterpene saponins known as ginsenosides.[17,18,19] Although less notable in the literature, research on the isolation, characterization, and immunological activity of polysaccharides in both *P. ginseng* and *P. quinquefolius* precedes the isolation and characterization of the polysaccharides comprising CVT-E002.[11]

A series of investigations focused on the isolation, characterization, and biological evaluation of polysaccharides from *P. ginseng* root were carried out by Tomoda and colleagues at the Kyoritsu College of Pharmacy in Tokyo, Japan. In one set of studies, ginseng polysaccharides were fractionated based on their acidity.[5,20] Two polysaccharides with immunological activity were isolated and named ginsenan PA and ginsenan PB. Quantitative analysis showed that ginsenan PA contained 21.3% arabinose, 53.4% galactose, 2.0% rhamnose, 16.0% galacturonic acid, and 2.7% glucuronic acid. The molar ratios of these component sugars were 11:22:1:6:1. Ginsenan PB contained 32.2% galactose, 8.1% rhamnose, 39.9% galacturonic acid, and 5.0% glucuronic acid, with a molar ratio of 3:7:2:8:1. Another study by the same group isolated an additional 2 polysaccharides from *P. ginseng* root that were called ginsenan S-IA and ginsenan S-IIA.[6] Ginsenan S-IA contained 42.3% arabinose, 50.8% galactose, and 6.9% galacturonic acid with a molar ratio of 8:8:1. Ginsenan S-IIA contained 42.0% L-arabinose, 32.6% galactose, 6.2% glucose, and 19.2% galacturonic acid in a molar ratio of 15:10:2:5.

Several polysaccharide fractions have been isolated from *P. ginseng* leaves and roots and their chemical properties and biological activities compared.[21] The roots were found to be higher in polysaccharides and the strongly acidic fractions from the roots were found to have a high content of uronic acid (> 50%). Component sugars detected from all fractions included rhamnose, arabinose, galactose, glucose, galacturonic acid, and glucuronic acid. Galacturonic acid was the main uronic acid component.

In a study completed at the Pharmaceutical Institute, Tohoku University, Sendai, Japan, 3 polysaccharides, designated quinquefolans A, B, and C, were isolated from the roots of *P. quinquefolius*.[7] For

quinquefolan A, the neutral sugar components were mannose and glucose (molar ratio, 1.0:2.3). Mannose and glucose (molar ratio, 1.0:5.5) were the primary neutral sugar components quinquefolan B and xylose for quinquefolan C. The acidic sugar components in quinquefolans A through C were found to be 10.8, 11.7, and 7.1% (by weight), respectively. The peptide moieties in these glycans were 2.7, 2.9, and 2.3%, respectively.

In a study completed at the Department of Biology in the University of Ottawa, a polysaccharide-rich water extract from the roots of *P. quinquefolius* was shown to have significant tumor necrosis factor alpha (TNF-α) stimulating activity in vitro.[8] When subject to acid hydrolysis, the fraction was found to contain glucose, galactose, arabinose, and rhamnose in the approximate ratio of 85:8:6:1, as well as 2 other monosaccharides, fuctose and mannose, in smaller amounts. Further acid hydrolysis also indicated the presence of approximately 9% uronic acid in the extractable polysaccharide fraction.

Pharmacological Actions/Mechanism of Action

In vitro

In 2001, Wang and colleagues at the University of Alberta reported immunological effects following exposure of cultured mouse spleen cells to CVT-E002 extract.[22] Lymphocytes and macrophages were extracted from mouse spleen by standard techniques, then grown in cell culture. CVT-E002 powder was dissolved in Hanks buffered salt solution. Hanks solution without CVT-E002 was used as control. Compared to control, enhanced proliferation of splenocytes, predominantly B lymphocytes, was accompanied by activation of exudate peritoneal macrophages, with enhanced expression of cytokines interleukin 1 (IL-1), IL-6, TNF-α, and nitrous oxide. While not all active-control comparisons reached statistical significance, the pattern of immunostimulation was fairly clear, especially with higher concentration (500 mcg/mL) CVT-E002 exposure.

The same team led by Meiqi Wang continued their investigations, and in 2004 they reported results from exposure of Concanavalin A (Con-A) activated cultured mouse spleen cells to CVT-E002. Compared to control, exposure of immune cells to CVT-E002 at 500 mcg/mL led to increased expression of IL-2 and interferon gamma (IFN-γ), inflammatory cytokines implicated in protection against influenza and other respiratory pathogens.[23] Consistency among three different lots was also investigated, with the authors concluding that biological response is consistent between CVT-E002 preparations, both qualitatively and quantitatively.

A yet-to-be-published study provides further support for CVT-E002's immunomodulatory activities.[24] These investigators incubated human peripheral blood mononuclear cells (PBMC) and natural killer (NK) cells with and without various concentrations of CVT-E002, as well as with and without stimulation of influenza virus. Dose-dependent activation of PBMC was evidenced by increased levels of various cytokines, including IL-1α, IL-1β, IL-6, and IL-8. Other cytokines, including IL-2, IL-7, IL-10, IL-12, IL-13, IL-15, TNF-α, and IL-18 were not significantly increased. In the presence of CVT-E002-activated PBMC and influenza, NK cells were activated, suggesting that CVT-E002 may exert its effects upon NK cells through monocyte activation, with enhanced activity when influenza virus was present.

Together, these in vitro immune cell experiments suggest pharmacological immunomodulating activity of the CVT-E002 extract. In this regard, it is perhaps worth noting that a study by Assinewe et al with an aqueous extract of *P. quinquefolius* provides corroborating information.[8] Those investigators exposed rat alveolar macrophages to a polysaccharide-rich aqueous extract (free of ginsenosides) of American ginseng root, and they reported significantly increased production of the inflammatory cytokine TNF-α. The same researchers reported that a methanol extract of the root containing ginsenosides and free of polysaccharides had no cytokine-stimulating activity.

In vivo—Animals

A 2001 study reported immunological effects of feeding mice different doses of CVT-E002.[22] Groups of 5 BALB/c mice (a transgenic mouse model bred to exhibit immuno-susceptibility) were randomized to 0 mg, 2 mg, 6 mg, or 18 mg daily dose of CVT-E002, with dose regimens continuing for 7 days. Using blood collected from tail veins, standard ELISA techniques were used to quantify total immunoglobulin G (IgG) antibody. Total (nonspecific) IgG can be considered a marker of potential adaptive immunity. Compared to control, the higher doses (8 mg and 16 mg) led to statistically significant increases in IgG production ($p < 0.05$). There were no significant differences between the 0 g (control) and 2 mg groups, or between the 6 mg and 18 mg groups.

In May 2006, a conference lecture titled "The role of phytocompounds in immunoenhancement and cancer abatement" was presented by S.C. Miller in Edmonton, Alberta, Canada, at the North American Research Conference on Complementary and Integrative Medicine.[25] This investigator reported that young male BDA/2 mice injected with erythroleukemia cells were fed 2 mg per day of CVT-E002 extract incorporated into their food. Compared to controls, mice fed CVT-E002 apparently displayed higher levels of mononuclear and NK cells, and fewer erythroleukemia blast cells. However, until the methodology, details, and specific findings are presented in a peer-reviewed article format and repeated in other laboratory settings, these findings should be considered preliminary.

Potential effects on pain receptor/transmission pathways were investigated in a mouse model. Yang and colleagues treated 23 young male ICR mice with 0.3 mL of a standardized CVT-E002 solution by gastrogavage for 4 consecutive days.[26] Twenty control mice received the same volume of water by standard blunt needle gavage technique. A diluted formalin solution was injected into the paws of all mice in both groups in order to elicit pain response. The authors reported that the time spent licking or biting the injured paw at 25 to 30 minutes after injection was significantly less in the CVT-E002-treated group compared to the control group ($p < 0.05$).

Human

Predy et al[27] describe analysis of blood samples from 42 of 323 participants in a randomized, controlled trial testing COLD-fX for the prevention of acute respiratory infection.[16] Blood samples were taken before randomization and again at the end of the study for 21 people from the COLD-fX group and 21 people from the placebo group. Basic white blood cell neutrophil and lymphocyte differentials did not vary between treatment and control groups. However, average concentrations of CD4 helper cells and NK cells increased significantly more in the CVT-E002 group compared to the placebo group ($p < 0.04$ and $p < 0.001$, respectively). Plasma immunoglobulin A (IgA) levels decreased in both groups but were greater in the COLD-fX group compared to placebo ($p < 0.03$).

Contraindications and Precautions

There are no clear contraindications for COLD-fX. However, because of potential harm that could result from stimulation of various immune processes, persons with autoimmune disease are advised to consult their physician before use. Potential areas of theoretical concern include use by persons with inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, although such concerns are speculative and not based on any clinical reports. Persons with more common immune-related diseases, such as allergic rhinitis, asthma, and eczema, might also want to contact their physicians, although there is no clear or even suggestive evidence of harm. To date, there are no known reports of these conditions occurring in association with the use of COLD-fX. Because the immune system is highly complex and only partially predictable, it is possible that COLD-fX or other more conventional ginseng extracts would be beneficial rather than harmful in such conditions. For this reason, and without substantive evidence one way or the other, no blanket warnings can be supported at the time of writing of this monograph.

Although there have been no reports indicating problems in diabetics, persons with diabetes may want to use COLD-fX with caution. While some studies demonstrate the hypoglycemic actions of American ginseng root powder in both diabetic and healthy volunteers, the preparation used in these studies contained ginsenosides.[1,2,3] While earlier studies found that polysaccharides extracted from either *P. ginseng* or *P. quinquefolius* had hypoglycemic actions in mice,[7,28] a study using healthy adults suggests that ginsenoside, rather than polysaccharide, fractions may play a more significant hypoglycemic role, since the American ginseng root product with a depressed ginsenoside profile was found to not affect postprandial hypoglycemia.[29] Hopefully, future safety studies with COLD-fX will address this issue.

Pregnancy and Lactation

There is no available safety data on the use of the proprietary extract CVT-E002/COLD-fX during pregnancy or lactation. The American Botanical Council advises pregnant or lactating women to consult a healthcare practitioner before using any herbal product, dietary supplement, or conventional medication.

Adverse Effects / Safety Data

Pre-Clinical Toxicology

Acute and subchronic toxicity studies (unpublished) have been completed with CVT-E002.[30] Acute oral toxicity of CVT-E002 was tested in healthy adult Sprague Dawley rats at a dose of 2 g per kilogram of body weight. Twenty rats were used (10 female and 10 male; body weight ranged from 130 to 220 g). Rats were either given a single oral dose of CVT-E002 or an equivalent amount of distilled water by oral gavage tube. On day 14, control and test animals were euthanized and necropsied. There were no abnormal clinical observations or mortality associated with CVT-E002. On necropsy, no signs of abnormality were found in any body tissues.

A sub-acute oral toxicity study was conducted in healthy adult Sprague Dawley rats (10 males and 10 pregnant females) at a dose of 50 mg/kg body weight daily for 18 days. Body weight ranged from 183 to 223 g for pregnant female rats and from 214 to 322 g for male rats. Ten of the 20 rats (5 females and 5 males) served as controls and were fed only a normal diet without CVT-E002 added. On day 18, control and test animals were euthanized and necropsied. There were no abnormal clinical observations or mortality associated with CVT-E002. On necropsy, there were no changes that could be attributed to the test medication. The number of feti, stage of development, and viability of feti were within the normally expected values for this strain of rat.

Human Safety Data

There is limited published safety data specific to CVT-E002/COLD-fX. The randomized, controlled clinical trials summarized in the Clinical Review section below provide clinically useful data sets, which, on the whole, suggest reasonable safety for the duration and doses tested.[14,15,16] Reasonable adverse event monitoring was incorporated into trial methods, and no statistically significant differences in the rate of adverse effect occurrence were noted between COLD-fX and control groups. Adverse event monitoring included self-reported symptoms, and, in the case of the two-year McElhaney trial (2004), standard blood laboratory tests (complete blood count, sodium, potassium, phosphorus, calcium, uric acid, liver and kidney function tests, glucose, lipids, and pre-albumin, albumin and total protein).[15] As reassuring as these results are that serious and prevalent adverse effects would likely be uncovered in trials of this size, statistical power considerations do not allow a positive safety assessment for rare but important events. For example, a major adverse event at a frequency of 1 in 100 could easily be missed by a trial of 323 participants, which is the largest and most important of the trials conducted to date.[16] Substantially larger trials, or perhaps large cross-sectional or prospective cohort studies, would be needed to confidently exclude unusual but important adverse effects.

Post-marketing surveillance of COLD-fX in Canada follows standard operating procedure for all government-approved Natural Health Products, including receipt and analysis of spontaneous reports of adverse reactions. The manufacturer provides a toll-free telephone number to consumers and keeps track of all reported information. The data in this paragraph is based on such confidential information shared by the manufacturer and on adverse event reports received since market entry in Canada in 1996.[30] Despite over 200 million doses of COLD-fX sold to consumers in Canada, less than 100 such reports have been filed. Of these, rare allergic reactions, including hives and other skin reactions, may be reasonably considered attributable to ingestion of the product. A potentially confounding factor is that rash is occasionally observed as a symptom of influenza or other infectious diseases that present similarly to cold and flu. One serious adverse event has been reported. A person experienced an anaphylactic-like event characterized by mouth and tongue swelling during both an initial event, and an event 2 weeks later following a second exposure. [Note: Allergy history of this person is not available.] It is important to note that allergic reactions can occur with virtually all foods, dietary supplements, natural health products, and drugs. Given the data available, the apparent rate of allergic reaction does not appear to be higher with COLD-fX than with many other substances in common use such as foods, dietary supplements, or drugs. Other reported reactions or adverse side effects have not formed patterns suggesting causal linkage to COLD-fX. These include headache, insomnia, dizziness, drowsiness, confusion, nausea, vomiting, abdominal pain, diuresis, lowered blood pressure, and joint pain. As these could all easily be due to underlying health conditions, causal linkage is considered possible, but unlikely.

There are no systematic safety reviews of products derived from *P. quinquefolius*, possibly because of the relatively low level use of this type of ginseng in North America, as well as the relatively good safety record of such use. However, in 2002 a systematic safety review of Asian ginseng (*P. ginseng*) was published that may be relevant, as all *Panax* species share some similar phytochemical constituents,[31] even though, as noted throughout this monograph, CVT-E002/COLD-fX does not contain ginsenosides. This comprehensive review included assessment of safety data from 146 clinical trials involving 8,500 individuals, and evaluation of numerous case reports and regulatory data sources across several countries. The review concludes that, while there was some evidence for minor and transient adverse side effects such as abdominal discomfort, lightheadedness, or insomnia, no major risks or dose-dependent adverse effects have been proven for Asian ginseng. Other safety assessments of species of *Panax* exist. For example, a recent but limited safety review highlights potential endocrine effects (estrogenic and adrenergic) as well as both CNS excitation or depression.[32] CVT-E002/COLD-fX has no known estrogenic effects; studies performed on polysaccharide-based aqueous American ginseng extracts similar to CVT-E002 demonstrated no estrogen-like activity.[33]

As noted, safety data on American ginseng products are substantially less extensive. Nevertheless, an assortment of small studies, including those detailed in this report, have failed to find any substantial dose-dependent or serious adverse effects attributable to CVT-E002 or conventional full-spectrum *P. quinquefolius* extracts.[1,2,3,31,32,34,35] It appears reasonable to conclude that serious adverse effects from COLD-fX are unlikely because of the following: (1) CVT-E002/COLD-fX is comprised primarily of oligosaccharides and polysaccharides, complex sugars which are generally recognized as safe; (2) randomized trial and post-marketing surveillance data are reassuring regarding safety; and (3) the overall safety record of ginseng products is good to excellent.

Drug Interactions

There are no known specific drug interactions for CVT-E002/COLD-fX. However, as available evidence is limited, the possibility of significant pharmacological interactions cannot be excluded. Animal model testing for the safety evaluation of CVT-E002 is reassuring, but limited. One experiment in mice evaluated potential effects on cytochrome P450 liver metabolism, an important source of drug-drug and herb-drug interactions.[36] Five C57BL/6J mice were fed 5mg/kg/day of CVT-E002 by gastrogavage for 3 days, while 6 mice were given equal volumes of water. Livers were removed and biological samples analyzed for effects on CYP, UGT, and GST pathways within the P450 cytochrome complex. No statistically significant effects between active and control groups were found. It is unclear whether such small sample sizes provided sufficient statistical power to detect such effects.

A published abstract reported that in vitro studies on 6 cytochrome P450 enzymes (human CYP isoenzymes expressed in cells) indicated no effects of CVT-E002.[37] By comparison a "ginsenoside-rich extract" apparently "inhibited all of the enzymes to some degree." However, methods and results were not detailed, so conclusions are considered preliminary until a peer-reviewed journal article becomes available.

Expanding the scope of safety review to *P. quinquefolius* extracts other than CVT-E002, there are a few potentially relevant reports. For instance, a randomized trial in 20 healthy volunteers, using a preparation derived from *P. quinquefolius* dosed at 1 gram of unrefined dried root per day, was shown to reduce the anticoagulation effect of warfarin.[38] Although this effect may very well be due to phytochemicals that are not present in CVT-E002/COLD-fX (e.g., ginsenosides), it would be helpful to have specific data to evaluate. The manufacturer of CVT-E002/COLD-fX suggests that individuals taking warfarin avoid consumption of the extract as a precaution.

As another example, there have been reports of the effects of ginseng extracts on the measurement of digoxin levels, an effect that seems to occur with extracts from most ginseng species, including *P. quinquefolius*.[39,40] For patients taking digoxin and their clinicians, it might be helpful to know whether these effects occur with COLD-fX, so that clinical decisions made on the basis of potentially false digoxin levels would not be in error.

As noted above in the Contraindications and Precautions section, theoretical concerns may exist for diabetic patients taking oral hypoglycemic drugs or insulin due to a possible hypoglycemic action for the polysaccharides in CVT-E002/COLD-fX. It should be noted that at least one source argues that the ginsenosides in American ginseng root are responsible for this action, thus making this interaction unlikely.[29] No interactions of this kind have been reported to date in clinical studies or post-market surveillance.

Finally, there may be a tendency for some researchers to evaluate the relative safety of CVT-E002/COLD-fX by attempting to expand the scope of review to all *Panax* species. However, as already demonstrated, the CVT-E002/COLD-fX preparation does not contain ginsenosides, universally regarded as the primary active compounds in roots of all *Panax* species. Hence it is problematic whether case reports based on conventional *Panax* preparations will actually be relevant to the potential for COLD-fX to interact with the conventional drugs noted as interacting with *Panax.* The literature contains several case reports, including those cited in safety reviews by Bressler[32] and by Coon and Ernst,[31] which summarized the reports of adverse events and interactions from clinical trials, reports from manufacturers, the World Health Organization drug reporting centers, etc. These include descriptions of decreased effectiveness of several diuretics (bumetanide, furosemide, torsemide, ethacrynic acid), and potential exacerbation of manic-like side effects from a few medications with known CNS/psychiatric effects (isocarboxazid, tranylcypromine, phenelzine).[32] Possible over stimulation with concurrent use of *P. ginseng* and caffeine or amphetamines has also been cited in a recently published safety review.[41] However, as noted in the systematic review of adverse effects and drug interactions on Asian ginseng, "these data suggest that *P. ginseng* monopreparations are rarely associated with adverse events or drug interactions. The ones that are documented are usually mild and transient."[31] The active agents (oligo- and polysaccharides) in CVT-E002/COLD-fX are pharmacologically unlikely to cause any of the side effects or drug interactions noted in reports on *Panax* species.

Drug Testing in Athletes

In a study designed to assess possible interference with tests to detect performance-enhancement drugs (doping), 20 male and 20 female athletes were asked to take 200 mg of COLD-fX 2 times daily for 28 days.[42] Compliance was assessed at 98% by counting returned pills. Urine samples were collected and assessed by an International Olympic Committee certified laboratory. No banned substances (positive doping tests) were detected in any of the samples.

Regulatory Status in Various Countries

Australia: COLD-fX is listed as a medicine with the Therapeutics Goods Administration in Australia (ID # 19884).

Canada: COLD-fX was previously issued a Drug Identification Number (DIN) under the former traditional medicine program of the Therapeutic Products Directorate (drug branch) of Health Canada (DIN 02242024). Like other phytomedicinal products, the DIN status of COLD-fX was changed according to the new Canadian Natural Health Product (NHP) regulations. In accordance with these regulations, the Natural Health Products Directorate (NHPD) evaluates NHPs for quality control, safety, and efficacy. If appropriate standards are met, NHP manufacturers can make drug claims and obtain licenses (Natural Product Number or NPN). In February 2007, the NHPD issued NPN 80002849 for CVT-E002 (COLD-fX) and approved the following claim: "helps reduce the frequency, severity and duration of cold and flu symptoms by boosting the immune system."[13]

United States of America: CVT-E002/COLD-fX meets the legal definition of a dietary supplement pursuant to Section 201 (ff) (1) (C) and (F) of the FDC Act. The Food and Drug Administration (FDA) accepted CVT-E002 as a New Dietary Ingredient (NDI) based on a review of extensive safety and quality manufacturing evidence (FDA Docket # 95S-0316). The FDA has previously approved CVT-E002/COLD-fX for its Phase II clinical trial.

Patents

United States Patent (No. 6,432,454 B1, issued August 13, 2002 with two divisional applications pending: Application No. 20040137087 and 20050196471): Jacqueline J. Shan, Peter P.T. Pang, Buhan Huang, Lei Ling. Process of making North American ginseng fractions, products containing them, and use as immunomodulators.[11] The patent family is directed to chemical processes of preparing fractions from North American ginseng (*P. quinquefolius)* root and pharmaceutical compositions containing these fractions. The patent family covers the use of these fractions to stimulate the production of cytokines and/or antibodies, or as therapeutic products for conditions such as the common cold, influenza, chronic fatigue syndrome, AIDS, and cancer.

United States Patent (No. 6,156,291, issued December 5, 2000): Peter P.T. Pang, Jacqueline J. Shan, Kam Wai Chiu. Chemical and pharmacological standardization of herbal extracts.[10] The patent covers a method for obtaining a reproducible extraction process for use as a standard process for extracting a pharmacologically active mixture of chemical components from a plant and obtaining a biological fingerprint of the pharmacological activity of each extract and a chemical fingerprint of the chosen extract. The patent covers the extraction technique used to identify and manufacture the proprietary, patented natural compound, poly-furanosyl-pyranosyl-saccharides from *P. quinquefolius* that make up the CVT-E002 extract.

Note: All other issued patents listed below are based on the same priority document as United States Patent No. 6,432,454 B1 with minor modifications based on the requirements of the country in which they were issued

Australia (No. 752702)

European (No. 1,037,645)

New Zealand (No. 504975)

Related Patent applications in other countries are pending.

Clinical Review

Three randomized controlled clinical trials have tested CVT-E002/COLD-fX for prevention of acute respiratory infection (ARI). Two of these, which are perhaps best classified as preliminary or phase 2 trials, were in elderly adults.[14,15] The third, which can be classified as a confirmatory or phase 3 trial, tested COLD-fX among 323 adults aged 18 to 65.[16]

Table 1 (see page 11) provides a summary of these trials. All three of these found some evidence of preventive efficacy. Two small, unpublished and preliminary trials tested CVT-E002/COLD-fX for prevention of ARI and immune modulating effects in athletes.[42]

Acute Respiratory Infection Prevention Trials

1. McElhaney et al, 2006. A randomized, double-blind, placebo-controlled trial was conducted with 43 adults aged 65 or older who were in good health.[14] Subjects were randomized to receive either 400 mg of COLD-fX (n = 22) or placebo (n = 21) each morning for 4 months. After 4 weeks of the study, subjects returned for a clinical visit during which they received a standard dose of influenza vaccine containing 15 mcg/mL of hemagglutinin for 3 vaccine strains (A/Johannesberg/82/96, A/Nanchang/933/95, and B/Harbin/07/94). Subsequent visits were at 8 and 16 weeks.

Subjects were asked to record if they experienced any of the following 8 symptoms: fever, sore throat, cough, nasal congestion, chills, headache, fatigue, or aches/pains. On the self assessment, they were asked to record the number of days they experienced each symptom, whether they felt the study medication helped reduce symptoms, and any adverse events. The primary outcome was self-reported incidence and duration of ARI symptoms.

Overall, results from the treatment group were not statistically distinguishable from those in the placebo group on both frequency and duration of ARI symptoms. However, a secondary analysis of the data suggested possible prevention effects during the last 2 months of observation. During these 8 weeks, 62% of the placebo group reported symptoms, compared with 32% in the COLD-fX group ($p < 0.05$). Also, during the last 8 weeks of the study, the duration of ARI-related symptoms was found to be 55% shorter in the COLD-fX group than in the placebo group (5.6 days vs. 12.6 days, $p = 0.04$). Participants did receive influenza immunization after one month of intervention. Although viral identification with either was not completed or reported, antibody response was measured and no significant difference was found between the treatments.

Symptomatic treatment, such as non-steroidal anti-inflammatory drugs (NSAIDs) were used by 5 (22.7%) subjects taking COLD-fX and 7 (33%) in the placebo group. One subject in the COLD-fX group and 3 subjects in the placebo group reported taking antibiotics for the ARIs. Treatment was well tolerated in both groups and rates of perceived side effects were nearly identical. Mild adverse events reported over the 16-week study included gastrointestinal complaints (nausea, heartburn and diarrhea), muscle and joint pain, and dry mouth. The trend towards decrease in ARI symptoms established in this small preliminary study encouraged further investigation.

2. McElhaney et al, 2004. A randomized, double-blind, placebo-controlled study was conducted during the 2000 and 2001 influenza seasons.[15] This was originally planned as a single season study, but when first season infection rates were insufficient to test hypotheses, the trial was extended to a second year. The observation period was for 8 weeks in the first season and 12 weeks in the second season, so it is unclear whether this should be considered a single trial or a meta-analysis of two trials. Either way, the results can be interpreted as preliminary evidence of benefit.

Elderly nursing home and assisted living residents aged 60 years or older were recruited for the study. The average age of the subjects was 81 years for the first observation period (n = 89) and 83.5 years for the second observation period (n = 109) with 74% of the participants being women. Approximately 90% of the participants had received influenza vaccine in each of the 2 years of the study. Subjects were randomized to receive either 200 mg of COLD-fX extract (n = 97) or matched placebo (n = 101) 2 times daily. Seventy-eight subjects completed the first study and 103 subjects completed the second study.

Subjects were monitored twice weekly for signs and symptoms of acute respiratory infection (ARI). ARI was defined by the new onset of 2 symptoms: one respiratory symptom (cough, sore throat, nasal or sinus congestion, or runny nose) and one additional respiratory symptom or one constitutional symptom (feverishness, chills/sweats, myalgia, fatigue, headache, poor endurance, or increased shortness of breath).

When symptoms were identified, a viral throat or nasopharyngeal culture was performed and tested for the presence of influenza, RSV, parainfluenza, and rhinovirus. The primary outcome of the study was the incidence of clinically confirmed ARI. Secondary endpoints included severity of respiratory illness, duration of respiratory illness, laboratory-confirmed respiratory illness, severity of influenza illness, and duration of influenza illness.

Combining data from both seasons revealed 36 episodes meeting ARI case definition in the placebo group and 33 cases in the COLD-fX group. This small positive trend was not statistically significant. However, influenza culture (a secondary endpoint analysis) revealed 7 laboratory and symptom-confirmed cases of influenza in the placebo group versus only 1 case in the COLD-fX group ($p = 0.03$). Laboratory and symptom-confirmed ARI due to RSV was also lower in the COLD-fX group compared to placebo ($p = 0.009$).

Monitoring of adverse effects revealed no significant differences or meaningful trends in self-reporting or laboratory monitoring. While randomization appeared adequate, evidence of blinding was not presented. Adequate interpretation of pooled data analyses is limited by the changes in methods between the 2 seasons (e.g., 8-week vs. 12-week monitoring). Nevertheless, the apparent reduction in confirmed influenza infection is intriguing, and certainly sufficient to justify another larger randomized, double-blind, placebo-controlled trial that tests ability to prevent flu-like respiratory infection.

3. Predy et al, 2005. The most persuasive evidence of the effectiveness of COLD-fX in preventing ARI was reported in 2005. A randomized, double-blind, placebo-controlled (RCT) study recruited 323 subjects aged 18 to 65 who had contracted at least 2 colds in the past year.[16] Subjects were randomized to 400 mg of COLD-fX (n = 153) or placebo (n = 170) daily for 4 months. Of these, 130 in the COLD-fX group and 149 in the placebo group completed the 4-month study. The published report of this Phase 3 clinical trial underwent rigorous peer review, and it was published in the *Canadian Medical Association Journal*. Reported methodology conforms to currently accepted standards for randomized controlled trials, and includes description of *a priori* power calculations, and methods for recruitment, enrollment, randomization, allocation concealment, symptom severity assessment and monitoring, and data management. Statistical methods were rigorous and included an intention-to-treat analysis. Blinding was adequately reported, including blinding of the statistician during most analyses. Success of patient blinding was tested by asking participants whether they thought they were given COLD-fX or placebo.

The primary outcome measure was the number of Jackson-verified colds per subject. Secondary measures included severity of symptoms (total symptom score), number of days symptoms were experienced, and duration of all colds during the 4-month treatment period. Subjects were asked to contact the study investigators at the onset of a cold. Subjects were asked to complete a daily log to document the severity of their cold-related symptoms (sore throat, runny nose, sneeze, nasal congestion, malaise, fever, headache, hoarseness, earaches and cough) on a 4-point scale (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms). The total symptom score was calculated by summing the daily scores for all symptoms. A 2-day total symptom score greater than 14 (modified Jackson criteria) was considered to indicate a Jackson-verified cold (the Jackson criteria are a well-established measure in common cold trials).

Results were positive and relatively consistent across measured outcomes. The mean number of colds per person was 0.68 in the COLD-fX group compared to 0.93 in the placebo group ($p = 0.017$). The number of subjects with 1 cold was 95 (64%) in the placebo group and 71 (55%) in the COLD-fX group—this difference did not reach statistical significance. However, the number of people with ≥ 2 colds was 34 (23%) in the placebo group compared to 13 (10%) in the COLD-fX group. This result was highly statistically significant ($p = 0.004$). For those with Jackson-defined colds, the average duration was 16.5 days in the placebo group and 10.8 days in the COLD-fX group ($p < 0.001$). The average total symptom score was 112.3 in the placebo group and 77.5 in the COLD-fX group ($p = 0.002$). These and other apparent benefits were consistent and statistically significant, hence unlikely to be due to chance.

Rescue medications such as NSAIDs were used by 26.2% and 29.5% of the subjects in the COLD-fX and placebo groups, respectively. Four subjects in the COLD-fX group and 5 in the placebo groups reported taking antibiotics for their colds and flu during the 4-month study period. Adverse effects were monitored in a standard and reasonable fashion and were statistically indistinguishable in the placebo and COLD-fX groups, with no meaningful trends suggestive of underlying risks. Baseline comparisons provided evidence of adequate randomization, as groups were equivalent at baseline. Adequacy of blinding was supported by the fact that 70% of those taking COLD-fX and 77% of those taking placebo indicated that they thought they were given the COLD-fX preparation. Limitations include lack of data on those who could not be reached for follow-up, and lack of generalizability to elderly populations. People over 65 and those who had received a flu shot in the previous 6 months were excluded, and were not represented in this trial.

4. McElhaney et al, 2001. An unpublished abstract from a study was presented at the First International Scientific Congress on Nutrition and Athletic Performance held in Alberta, Canada on August 10, 2001. The abstract described 2 studies: (1) a small, observational

study in 1997 to 1998 in which athletes (professional hockey players) ingesting COLD-fX were questioned regarding perceived efficacy in preventing and relieving cold symptoms, and (2) a study conducted in 1998-99 in which blood samples were taken and lymphocytes challenged with 3 different strains of influenza virus and analyzed for TNF-α and IL-2.[43] According to unpublished manuscripts supplied by CV Technologies, a group of 14 athletes took 400 mg per day of COLD-fX for the season. Eight of 14 respondents at mid-season reported feeling "less run down while on the road." Of 12 respondents at the end of the season, there was a reported decrease in the incidence of ARI compared to the previous year. A second group of 8 athletes reported using the product acutely at the onset of ARI symptoms as follows: 3 capsules [600 mg] 3 times per day on day 1; 2 capsules [400 mg] 3 times per day on day 2; and 1 capsule [200 mg] 3 times per day on day 3. Seven athletes responded to a questionnaire. Five out of 7 reported that COLD-fX prevented their colds from developing and "made them feel better." The only adverse event reported was diarrhea, which may or may not be attributed to the study medication.

The second study cited in the unpublished abstract compared the effect of 400 mg per day of COLD-fX in 18 athletes as compared to 19 athletes who served as controls. Compared to controls, lymphocytes challenged with influenza virus ex vivo were found to have a significantly greater IL-2 ($p < 0.05$) and TNF-α ($p < 0.05$) production.

Discussion

A growing body of literature points toward the ability of various *Panax* spp. extracts to influence several immune pathways, including both specific (adaptive) and nonspecific (innate) mechanisms.[44,45,46,47,48,49,50,51,52,53,54,55,56,57] Enhanced NK cell activity is perhaps best substantiated, having been reported in several different models from several different laboratories.[57,58,59,60,61] In addition to evidence of enhanced innate cellular immunity, there is some indication of adaptive immune activity in the form of vaccine adjuvant effects.[62,63,64,65,66,67,68] While most of this work is based on *P. ginseng* (containing both polysaccharides and ginsenosides), an article by Assinewe et al[8] reported that polysaccharide-rich extracts, but not ginsenoside-rich extracts, of *P. quinquefolius* could stimulate ex vivo rat macrophages to secrete the inflammatory cytokine TNF-α.

Despite these indications of immunological activity from *Panax* extracts, evidence from randomized controlled trials (RCTs) on human subjects is limited, and clinical utility is controversial.[69,70,71,72,73] Prevention of viral respiratory infection (colds and flu) is one potential use of immunomodulation that enjoys some support from controlled trials. The COLD-fX product detailed in this monograph is one good example of a well-defined ginseng extract being subjected to both immunological bioactivity assessment and clinical trials.

CVT-E002/COLD-fX use is supported by both pre-clinical and clinical research. Several laboratory models and methods have indicated immunomodulation. One pilot,[14] one phase II study,[15] and one confirmatory trial[16] have reported evidence suggesting ability to prevent acute respiratory infection. If this is confirmed in future trials, CVT-E002/COLD-fX will become one of the very few—if any—therapies proven to prevent respiratory infection. The benchmark for accepting these results will be high, due to a history of false starts and contradictory evidence with both nutritional and herbal dietary supplements used for both prevention and treatment of ARI. For example, vitamin C, echinacea (*Echinacea* spp.), and zinc are each supported by roughly equivalent data supporting and refuting preventive efficacy with more than a dozen trials and more than 2,000 participants being studied for each intervention.[74,75,76] Also by comparison, 7 trials with at least 896 participants have been published on a proprietary Andrographis and Eleutherococcus extract (containing proprietary extracts of *Andrographis paniculata* [Burm. F.] Nees (Acanthaceae) [SHA-10] and *Eleutherococcus senticosus* [Rupr. & Maxim.] Maxim. (Araliaceae), sold as Kang Jang®, SHA-10, Swedish Herbal Institute, Goteborg, Sweden). These trials demonstrate mostly positive results for treating symptoms of ARI and preliminary evidence for a possible preventive effect.[77,78] There is longstanding controversy regarding modulation of the non-specific innate immune system in a way that can reduce susceptibility to infectious disease. Epidemiological and prospective cohort data suggest that exercise, nutrition, non-smoking, and positive psychological and social health are associated with greater resistance to respiratory infection, but randomized trials supporting specific interventions are lacking.[79,80,81,82] While it is clear that specific adaptive antibody-mediated immunity can be enhanced by immunization, the vast number of antigenic strains of ARI viruses makes immunization impractical.[83,84] Influenza is a special case, with a coordinated global effort aimed at detecting emerging strains and producing vaccinations ("flu shots") in time for each annual epidemic. However, even the highly recommended flu shot is only partially effective, with as many as 30% to 40% of elderly recipients failing to mount a protective antibody response.[85,86] If it turns out that specially formulated extract preparations from ginseng such as CVT-E002/COLD-fX are effective for prevention of influenza illness, the next question will be whether these preventive phytomedicines can enhance the effects of flu shots, prevent infection, and reduce morbidity and mortality.

It should be noted that CVT-E002/COLD-fX is not alone in the literature of ginseng-based extracts employed for immune enhancement and ARI prevention. For example, a ginsenoside-containing extract of *P. ginseng* root marketed as Ginsana® (G115®; Pharmaton, Lugano, Switzerland) has enjoyed a history of both pre-clinical and clinical evaluation. Reported immunomodulatory activities have included lymphocyte proliferation, NK cell stimulation, and enhanced cytokine production in a mouse model.[87,88] Activation of human lymphocytes *in vitro* has also been reported.[47] In contrast to CVT-E002, the G115 formulation is standardized to 4% ginsenosides, not polysaccharides, and is clearly a very different formulation.

At least 2 clinical trials have been reported with varieties of the G115 extract in testing for immunological parameters and ARI. In 1990, Scaglione et al published a study in which 60 human subjects ingested either of 2 extracts at 100 mg 2 times daily for 8 weeks.[67] Blood samples were drawn at intake, then at 4 and at 8 weeks. A battery of immunoassays were conducted, including cell counts and functional assessments of neutrophil, natural killer cells, and T3, T4, and T8 lymphocytes. Increased chemotaxis, phagocytosis, and cellular proliferation were reported for many, but not all, of the measured outcomes.

In 1996, Scaglione and colleagues reported a double-blinded RCT among 227 adults, and reported fewer colds in the G115 group compared to the placebo group during 12 weeks of preventive treatment and observation (42 vs. 15 cases; $p < 0.001$).[89] Flu shots were given in the fourth week. Anti-influenza antibody titers and NK cell activity were assessed at weeks 4, 8, and 12. Increases in antibody titer (272 vs. 171 units; $p < 0.001$) and NK activity (46.0 vs. 26.7; $p < 0.001$) were most prominent at week 8. Limitations include lack of proof of blinding, as well as lack of important detail concerning laboratory procedures and statistical techniques.

Limitations

While impressive and clearly sufficient to warrant further research, the findings for CVT-E002/COLD-fX noted above may be viewed as tentative and incomplete by some medical authorities. This is due not only to a longstanding and perhaps misguided suspicion of herbal therapies, but to several valid scientific concerns regarding these therapies. One concern is the long history of herbal interventions initially supported by positive evidence, and later proved ineffective or minimally effective. Following this rationale, most physicians and health scientists require at least 2 independent high quality RCTs before evidence is deemed sufficient to justify recommending an herbal preparation to patients. The benchmark for accepting natural, chemically-complex therapies appears to be rising as the sophistication of evidence-based medicine increases.

All of the CVT-E002/COLD-fX trials described above are manufacturer-sponsored. Although methodology and outcomes are in general portrayed according to accepted scientific standards, these reports do tend to highlight positive findings rather than limitations. It should also be noted that several of the studies mentioned have not been published, and may be revised when subjected to the peer-review process. Finally, aside from the Predy trial,[16] none of the studies cited here can be considered confirmatory Phase 3 trials. Even the Predy trial is limited by sample size and drop-out rate, as well as by lack of identification of specific viruses involved. Hence, while intriguing and promising, further development and corroboration may be required by some health organizations before the evidence on CVT-E002 could be interpreted as sufficiently robust for incorporation into health policy and practice.

Manufacturer Information

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Conflict of Interest Disclosure

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Table 1: Published Clinical Studies on CVT-E002/COLD-fX®

Placebo-controlled randomized trials testing CVT-E002/COLD-fX for ability to prevent acute respiratory infection (ARI)					
Author/ Year	**Subject**	**Design**	**Duration**	**Dosage**	**Results/Conclusion**
McElhaney et al, 2006[14]	ARI prevention	R, DB, PC n = 43 healthy adults 65 years and older. All subjects received influenza vaccine at week 4 of study.	4 months	400 mg once daily	Secondary analysis of data found that 62% of placebo group reported symptoms, compared with 32% in CVT-E002 group during the last 8 weeks of the study ($p < 0.05$). During the same time period, duration of ARI-related symptoms was 55% shorter in CVT-E002 group than placebo group (5.6 days vs. 12.6 days, $p = 0.04$).
McElhaney et al, 2004[15]	ARI prevention	R, DB, PC Elderly nursing home patients – average age of 81 for the first treatment period (n = 89) and 83.5 years for the second (n = 109). 74% were women and 90% had received influenza vaccine. 78 subjects completed first study & 103 completed second study.	2 study periods: (A) 8 weeks (2000) (B) 12 weeks (2001)	200 mg 2x daily	Overall no statistically significant differences between 2 groups in self-reported ARI symptoms. However, influenza culture (a secondary endpoint analysis) revealed 7 laboratory and symptom confirmed cases of influenza in placebo group vs. only 1 case in CVT-E002 group ($p = 0.03$). Laboratory and symptom confirmed ARI due to RSV was also lower in CVT-E002 group compared to placebo ($p = 0.009$).
Predy et al, 2005[16]	ARI prevention	R, DB, PC n = 323 adults ages 18–65 years (n =279 started included in final analyses)	4 months	400 mg once daily	Mean number of colds per person was 0.68 in the CVT-E002 group and 0.93 in the placebo group ($p = 0.017$). Number of people with ≥ 2 colds was 34 (23%) in the placebo group, and 13 (10%) in the CVT-E002 group ($p = 0.004$). For those with colds, the average duration was 16.5 days in the placebo group and 10.8 days in the CVT-E002 group ($p < 0.001$). The average total symptom score was 112.3 in the placebo group and 77.5 in the CVT-E002 group ($p = 0.002$).

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