

# INTEGRATED HEALTHCARE PRACTITIONERS

Integrated Healthcare Practitioners' Dietary and Nutritional  
Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING  
EDUCATION BY THE BDDT-N; 1.0 CREDIT BOTANICAL MEDICINE AND BY THE CNPBC; ONE CE HOUR.

## Green tea

Antiviral effects

### Abstract

*Green tea (Camellia sinensis) and its extracts are well-recognized for their antioxidant content and associated human health benefits. In recent years, evidence from in vitro and human clinical trials has accumulated to indicate that green tea-derived antioxidants, including its chief catechin, epigallocatechin gallate (EGCG), may have potentially beneficial antimicrobial activity against various strains of pathogenic yeast, bacteria and viruses. This article aims to synthesize the available evidence concerning the use of green tea extracts in the prevention or treatment of human viral illnesses. The human viral illnesses on which the majority of the research is focused with respect to the use of green tea include viral upper respiratory tract infections (oral or buccal use), and human papilloma virus (HPV)-induced anogenital warts (topical use). Five human observational and randomized controlled trials support the use of green tea in the prophylaxis or treatment of influenza and/or the common cold. A recent systematic review and meta-analysis involving 1247 men and women found a proprietary green tea catechin formula to be effective in the topical treatment and prevention of recurrences of condylomata acuminata due to HPV.*

### Introduction

Besides water, tea is the most commonly consumed beverage worldwide (Mazzanti 2009). Prepared from fresh *Camellia sinensis* leaves, green tea is dry-heated or steamed, then rolled, dried and roasted (Mazzanti 2009). Constituents of unfermented *Camellia sinensis* leaves include polyphenols (20%-45% of dry weight), caffeine (2%-5%), amino acids (4%), lignin (6.5%), organic acids (1.5%), protein (15%) and chlorophyll (0.5%) (Mazzanti 2009, Meltzer 2009, Sarma 2008, Schneider 2009). EGCG ((-)-epigallocatechin gallate) is the most potent green tea antioxidant (Mazzanti 2009) and comprises 60%-80% of its catechin content (Schneider 2009).

### Green Tea as an Antiviral Agent

In vitro and human evidence supports the potential antiviral prophylactic and treatment uses of green tea (Meltzer 2009, Rowe 2007, Schutz 2010). Green tea polyphenols, chiefly the catechins, are antioxidants to which a majority of the anti-microbial, anti-inflammatory, anti-tumor and immunostimulatory properties of green tea have been ascribed (Mazzanti 2009, Meltzer 2009,

Schneider 2009). EGCG has direct in vitro viricidal, inhibitory and anti-infective properties against several viruses, including HIV (Hauber 2009, Nance 2009), herpes simplex virus (HSV-1) (Isaacs 2008), hepatitis A (Kuzuhara 2009) and B viruses (Xu 2008). Green tea catechin derivatives have been shown to have in vitro inhibitory effects on six influenza virus subtypes (Song 2007). EGCG is also highly anti-inflammatory and inhibits pro-inflammatory chemokines, prostaglandins and tumor necrosis factor (TNF), which contribute to symptom production during human viral infections (Rowe 2007).

### Viral Upper Respiratory Tract Infections

A prospective cohort study reported influenza prophylaxis in nursing home residents who gargled with a green tea catechin solution. Seventy-six elderly nursing home residents in Japan gargled with a 200 µg/mL green tea catechin or control solution, three times daily for three months, while 48 age- and sex-matched

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control participants gargled with a placebo solution. The catechin solution (60% EGCG) was approximately half the concentration of commercially available green tea beverages (Yamada 2006). All participants had received the World Health Organization (WHO)-recommended seasonal influenza vaccine prior to enrollment. Influenza A and B rapid assay was performed on nasal secretions of any resident who presented with influenza-like illness. Significantly fewer residents developed influenza B with treatment (1.3%) than control (10%), ( $p=0.028$ ). None of the residents developed influenza A infection. This relatively small study was limited by the lack of dose-response determination for the treatment and non-randomization, which allowed residents to choose whether they would receive catechin or control solutions at the outset of the study (Yamada 2006).

Green tea constituents were identified to reduce incidence of influenza in health care workers in a recent, randomized, double-blind trial (Matsumoto 2011). Participants ( $n=197$ ) were randomized to receive six capsules daily containing either a total of 378 mg catechin and 210 mg theanine, or placebo throughout influenza season (five months). The incidences of clinically-defined and laboratory-confirmed influenza infection and each individual's symptom-free period were recorded. Treatment significantly decreased clinically-defined influenza ( $n=4$ , 4.1%) compared to placebo ( $n=13$ , 13%), ( $p=0.022$ ). The incidence of laboratory-confirmed influenza was lower with treatment but did not significantly differ from control ( $p=0.112$ ) (Matsumoto 2011). The high rate of influenza vaccination (92.9%) among all participants may have caused an underestimation of the prophylactic efficacy of catechin/theanine treatment and the need was suggested for further, large-scale randomized trials to confirm effects (Matsumoto 2011).

A large observational study reported an inverse relationship between green tea consumption and influenza infection in

children (Park 2011). Elementary school students ( $n=2050$ ) completed a series of two questionnaires during Japan's endemic influenza A season. The consumption of 1-5 cups (200 mL/cup) of green tea daily compared with <1 cup per day was associated with a significantly lower risk of developing influenza. The incidence of clinically- and laboratory-confirmed influenza infection was also inversely related to consumption of green tea almost daily (i.e.  $\geq 6$  days per week) compared with <3 days per week. In contrast, no associations were observed between influenza incidence and conventional preventive measures such as hand hygiene, use of facemasks, or seasonal influenza vaccination in these children (Park 2011).

Rowe et al. (2007) conducted a randomized, double-blind, placebo-controlled study investigating whether a standardized green tea extract containing L-theanine and EGCG would prevent the development of influenza and common cold symptoms in healthy adults. Participants were randomized to receive either one treatment capsule containing a proprietary preparation of L-theanine and EGCG (ImmuneGuard; standardization not reported) ( $n=53$ ), or placebo ( $n=55$ ) capsule twice daily with food. Participants were asked to log daily cold and flu symptoms, including fever, runny nose, sore throat, cough, headache, diarrhea and nausea during the 12-week study. During the 12-week study period, there was a 32.1% lower rate of symptom development in the treatment group (43.2%) versus control (63.6%), ( $p=0.035$ ). There were 33.3% fewer symptomatic days in the treatment group versus placebo ( $p<0.022$ ). There was a 22.9% lower incidence of illness ( $p=0.092$ ) in the treatment group during the study period, but no significant differences in illness incidence from month to month (February to May). In the same study, peripheral blood mononuclear cells (PBMC) obtained from all subjects at baseline and on study day 21 were cultured for 24 hours in either media containing ethylamine (a catabolic product of L-theanine and a  $\gamma\delta$  T cell antigen) or control media.

PBMC obtained from participants after 21 days of treatment secreted 26% more IFN- $\gamma$  in response to ethylamine than those from the placebo group ( $p=0.046$ ), supporting the hypothesis that L-theanine could prime human  $\gamma\delta$  T cells to secrete more antimicrobial IFN- $\gamma$  *ex vivo* (Rowe 2007). Adverse effects were mild and transient, with similar rates between treatment and control groups. A limitation of this study was the self-reporting of symptoms, which precluded both objective clinical diagnosis and the ability to rule out causation of symptoms by other illnesses such as asthma, bronchitis or allergy (Rowe 2007). Results of this study were consistent with previous work cited by the same authors, wherein PBMC obtained from subjects who had begun drinking five to six cups of green tea daily for one week secreted significantly more IFN- $\gamma$  in response to  $\gamma\delta$  T cell antigens compared to baseline (Rowe 2007).

A multi-ingredient formulation containing green tea has been demonstrated to provide symptomatic benefits in the common cold (Schutz 2010). In a randomized, double-blind, placebo-controlled, multi-centre trial, participants with symptoms of a general feeling of sickness, headache and/or joint aches, sore throat and/or difficulty swallowing, hoarseness and/or cough, and stuffy nose/sniffle were randomly assigned to receive either a polyphenol-rich beverage containing green tea extract (3g/L), grape skin extract (12 g/L), grape seed extract (0.5 g/L), shiitake mushroom extract (0.05 g/L) and vitamin C (0.3 g/L) or placebo beverage containing water, sugar, citric acid and flavour, twice daily for 10 days. Participants underwent a total of three clinical examinations during the study period and logged their symptoms daily. By the third scheduled clinical examination, 19 of 49 treatment patients (38.8%) and 4 of 47 placebo patients (8.3%) who completed the study were asymptomatic ( $p<0.001$ ). By their own evaluations, 41.9% of treatment patients and 5.0% of placebo patients were complaint-free by day seven of the study ( $p<0.001$ ). Significant differences in sleep disorders, disturbances of daily activities and tissue use were also reported with treatment beverage (Schutz 2010). Blinded patient and physician ratings of the efficacy of the beverages received supported the superiority

of the polyphenol treatment (Schutz 2010). Interestingly, the incidence of herpes labialis, a common concomitant symptom of the common cold, was significantly lower in the treatment group at the end of the study than that in the placebo group (Schutz 2010). The observed improvements in all common cold symptoms assessed suggested a general increase in defense and immunity rather than symptom-specific effects of the polyphenol beverage (Schutz 2010). This study supports the use of green tea extract in a multi-agent immunomodulatory approach to treatment of the common cold, although the presence of several antioxidant and immunomodulatory substances precludes the conclusion that the observed benefits could be solely attributed to green tea.

#### Human Papilloma Virus (HPV)

A recent meta-analysis demonstrated the efficacy of a *Camellia sinensis* leaf extract known as Polyphenon E (MediGene AG, Germany) in the topical treatment of anogenital warts (condylomata acuminata, HPV-6 and -11) (Tzellos 2011). Polyphenon E contains > 80% green tea catechins (Stockfleth 2008), which appear to inhibit HPV viral transcription and binding to cell receptors; have antiproliferative effects; and promote apoptosis when applied topically (Tzellos 2011 citing others). Three randomized, double-blind, placebo-controlled, multicentre studies enrolling a total of 660 men and 587 women met inclusion criteria for the meta-analysis; all three studies used Polyphenon E 15% or 10% (green tea catechins) ointment for HPV-induced anogenital warts. Both Polyphenon E formulations were found to be efficacious for clearance of lesions in both men and women, and compared to conventional therapies showed a low recurrence rate (Tzellos 2011). The treatment was generally well tolerated in all trials, with mild local skin reactions peaking at weeks two to four of treatment being considered essential to achieving a clinical response (Tzellos 2011).



Viral Disease	Authors	Study Design	Participants	Treatment	Results
Influenza	Yamada 2006	3-month, prospective cohort study	Nursing home residents (N=124) ≥ 65 yoa	Gargling with tea catechin solution (n=76) residents; 48 matched controls gargled without tea catechins	Significantly lower influenza incidence with treatment (1.3%, n=1) vs. control (10%, n=5).
Influenza	Matsumoto 2011	5-month, randomized, double-blind, 2-group parallel study	Healthcare workers ≥ 20 yoa	6 capsules daily: 378 mg catechins + 210 mg L-theanine (n=98) or placebo (n=99)	Incidence of clinically-defined influenza was significantly lower with treatment (4.1%, n=4) vs. placebo (13.1%, n=13).
Influenza	Park 2011	4-month observational study	2050 elementary school students 6-13 yoa	Ad libitum consumption of green tea recorded in 2 questionnaires	1-5 cups (200-1000 mL) green tea daily was inversely associated with influenza incidence
Influenza & Common cold	Rowe 2007	Randomized, double-blind, placebo-controlled, 12-week parallel study	Healthy women (n=72) and men (n=52), 21-70 yoa	ImmuneGuard (decaffeinated Camellia sinensis extract) or placebo, 1 capsule bid for 12 weeks	Treatment resulted in a 33.3% reduction in symptomatic days (p<0.002) and a 32.1% reduction in the experience of any cold or flu symptom compared to placebo (p=0.035)
Common cold symptoms	Schutz 2010	Randomized, double-blind, placebo-controlled, multi-centre study	98 patients reporting common cold symptoms ≤24 hrs before beginning study intervention	Green tea polyphenol-rich (n=49) or placebo beverage (n=49) bid for 10 days	Symptoms declined faster with polyphenol-rich beverage than placebo (p<0.001)
HPV (Condylomata acuminata)	Tzellos 2011	Systematic review & meta-analysis	Three studies involving 660 men, 587 women included in meta-analysis	Polyphenon 15% or 10% (catechins) applied by patients 3 times daily to anogenital warts for 12 weeks	Polyphenon 15% and 10% are effective in treatment and prevention of anogenital warts

### Safety

Green tea infusion has been widely consumed throughout the world, at typical intake levels of one to three cups per day in the U.S. and up to nine cups per day in Japan, with a low incidence of adverse effects in adults (Sarma 2008 citing Imai 1997) and children (Park 2011). The most common adverse effects of green tea are gastrointestinal upset and central nervous stimulation from caffeine (Schneider 2009). As of 2009, two systematic reviews had identified 34 cases of possible or probable hepatotoxicity following intake of green tea products (Mazzanti 2009, Sarma 2008). Some of the case reports were confounded by the concomitant

use, or non-reporting of other potentially hepatotoxic substances (Mazzanti 2009). The mechanism of liver damage is theoretically ascribed to paradoxical pro-oxidant activities of EGCG when present in high concentrations (Mazzanti 2009). Oral bioavailability of catechins is generally low but increases with fasting and repeated administration (Mazzanti 2009). Therefore, green tea extracts should be consumed with food (Sarma 2008). Extracts providing up to 690 mg total catechins and up to 150 mg caffeine per day are considered safe for adult use for up to 12 weeks; green tea extracts are contraindicated in individuals with liver disorders (Health Canada 2008).





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# Questions

- Green tea catechins exhibit antiviral activity through which of the following mechanisms?
  - Direct viricidal activity
  - Inhibition of the ability of a virus to infect a host cell
  - Stimulate antibody production, with memory, protecting the host from future infection for up to a decade
  - All of the above are correct
  - A and B above are correct.
- While demonstrating preclinical promise against herpes simplex virus, hepatitis A and hepatitis B viruses, green tea catechins have failed to demonstrate antiviral activity towards influenza viruses.
  - True
  - False
- Why do trials evaluating safety and efficacy of natural medicines in flu prevention and treatment recruit patients who have received the seasonal influenza vaccine?
  - It makes it harder to show efficacy of the natural medicine, thereby making it easier to continue with the status quo.
  - It controls for variation in participants previous exposures, or lack there of, to the influenza virus.
  - The vaccine is the current standard of care for flu prevention, and therefore a medicine needs to show benefit above and beyond the current standard to be considered useful.
  - There is no basis to recruit participants who have received the flu vaccine. It would be more appropriate to recruit patients who have not received the flu vaccine.
- Human intervention trials have demonstrated efficacy of green tea administration for prevention and/ or treatment of flu among which of the following populations?
  - Elderly
  - Health care workers
  - Healthy adults
  - Children
- Human intervention trials have demonstrated administration of green tea preparations to be effective against which of the following viral infections?
  - Herpes simplex virus
  - Influenza
  - Human papilloma virus
  - Hepatitis B
- A and B are correct
- B and C are correct
- C and D are correct
- Green tea as reviewed in this article has been shown to act as an antimicrobial agent when given via which routes of administration?
  - oral
  - topical
  - gargle
  - intravenous
  - A and B are correct
  - B and D are correct
  - A, B, and C, are correct
- Intake of one to five cups of green tea per day (200-1000 mL) has been associated with lower incidence of influenza.
  - True
  - False
- Topical preparations with anti-HPV properties are of the following concentrations:
  - 5% green tea catechins
  - 15% green tea catechins
  - 25% green tea catechins
  - all of the above
- Green tea is generally well tolerated, however there have been 34 reports of liver damage associated with use of green tea products. Which of the following is true?
  - Use of other potentially hepatotoxic substances was ruled out as a potential contributing cause.
  - These patients had pre-existing liver diseases, increasing their risk for a negative reaction.
  - This is thought to be mediated by paradoxical pro-oxidant effects of green tea when it is present in high concentrations
  - all of the above.
- Products providing up to 690 mg total catechins and 150 mg caffeine per day are considered safe for adult use for up to 12 weeks, but green tea extracts should not be used in patients with liver disorders.
  - True
  - False

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