

## Full Length Research Paper

# Clinical evaluation of green tea polyphenols in treatment of pharyngitis in human subjects

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Tea from *Camellia sinensis* (L.) Kuntze has long been used in herb medicine and recognized to possess anti-inflammatory effects. The aim of the current study was to evaluate the therapeutic effects of green tea polyphenols in treatment of pharyngitis in human subjects. The clinical study was carried out as a randomized, double-blind, parallel-group comparative trial. It was found that the integral scores of all the observed individual clinical signs and symptoms were decreased significantly from pre-treatment to post-treatment ( $P < 0.05$ ) in both green tea polyphenols treatment and the control. Therapeutic effects assessment showed that the decrease in the total integral scores in the green tea polyphenols group was more significant ( $P < 0.05$ ) than in the control medicine group and that green tea polyphenols had a more prominent efficacy ( $P < 0.05$ ) in eliminating pharyngodynia in pharyngitis patients. Green tea polyphenols demonstrated high total effective rate in the pharyngitis treatment ( $n = 60$ , 96.67%). Neither adverse events nor abnormal observation in vital signs were found throughout the study. It can be concluded that green tea polyphenols can be used as a reliable and effective phytochemical in the treatment of pharyngitis.

**Key words:** Green tea polyphenols, clinical evaluation, pharyngitis, human subjects.

## INTRODUCTION

Pharyngitis is one of the most common diseases encountered by physicians and is especially a big problem troubles those who have to use laryngopharynx and vocal holds frequently in their professional activities like teachers, singers and broadcasters (Matthys et al., 2007; Bisno et al., 2002; Huang, 2003). This condition is most often caused by direct infection of the pharynx by various viruses or bacteria (Bisno et al., 2002), among which group A beta-hemolytic *streptococcus* (GABHS) accounts for about 15 to 30% cases in children and 5 to 15% cases in adults (Bisno et al., 2002; Ruppert, 1996; Matthys et al., 2007). There may also be several other causes of pharyngitis, such as gastroesophageal reflux, persistent cough, thyroiditis, allergies, foreign body, alcohol drinking, and smoking (Yazici et al., 2010; Middleton, 1991) and the condition is thus complicated with increased environmental pollution.

Tea was originally used as a medicine in treatment of various illnesses in ancient China and became a worldwide beverage later on, only aside water. In recent years, tea attracted increasing attention for its health benefits by preventing against a variety of disorders ranging from various cancers (Yang et al., 2002; Khan et al., 2008) to cardiovascular (Yang and Koo, 2000; Hodgson et al., 2010) and neurodegenerative (Mandel and Youdim, 2004; Yu et al., 2010) diseases. Tea extract has been included in several nutritional supplements as a featured ingredient. The beneficial effects of tea are mainly attributed to its polyphenolic compounds, particularly catechins (Graham, 1992; Bancirova et al., 2010). Green tea contains catechins in higher quantities than black tea or Oolong tea.

To introduce a medicinal alternative for pharyngitis treatment, in this study, clinical evaluation of green tea polyphenols in the treatment of pharyngitis was conducted in patients with pharyngitis. Caoshanhu tablet is a widely used OTC (over the counter) medicine for pharyngitis treatment with extract of *Sarcandra glabra* (Thunb.) Nakai as the main active components (Shi et al., 2007). In this

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study, the efficacy and therapeutic effects were also assessed with Caoshanhu tablet as a control.

## **MATERIALS AND METHODS**

### **Sample preparation**

Green tea polyphenols were obtained from the Orient Tea Co. Ltd. (Hangzhou, China) which mainly contains catechins (over 85%) as determined by high performance liquid chromatography (HPLC) method with a purity of total polyphenolic compounds of over 98% as determined with the Folin-Ciocalteu colorimetric method (with spectrophotometric detection at 760 nm). Green tea polyphenols combined with other supplement as refined sugar, starch, and citric acid was processed into green tea polyphenols buccal tablet (7% proportion of green tea polyphenols in weight) and was used in human subjects. The green tea polyphenols tablet was manufactured without any detectable difference in weight, size, appearance, shape, color, aroma or taste with the control medicine Caoshanhu tablet.

### **Participants**

Patients with diagnosed pharyngitis were selected to participate in a randomized, double-blind, parallel- group comparative clinical trial based on age and clinical signs and symptoms. The protocol used in the trial and all the related documents were approved by the ethics committee. A written informed consent was obtained from all patients before the experiment.

Adult patients 18 to 65 years of age who had clinical signs and symptoms of acute or chronic pharyngitis, including a sore throat and one or more of the following signs as pharyngodynia, pharynx mucosal hyperemia, dysphagia, thirst, fever, aversion to cold, uvula erythema and edema, posterior pharynx folliculosis were selected for enrollment of the study.

Patients had any suspected infection of deeper tissues of the upper respiratory tract were excluded from enrollment. Those with a history of rheumatic or valvular heart disease, suspected infectious mononucleosis, and measles were also excluded. Patients who had a prior antibacterial or any other medicine for pharyngitis therapy within 7 days of enrollment, or known or suspected hypersensitivity to antibacterials and the products under this clinical evaluation were not selected in the experiment. Patients with concomitant diseases or under treatment with medications that may interfere with the assessment of drug efficacy were also ineligible for enrollment, as were those with cancers, diabetes mellitus, a recent history of alcohol or drug abuse, renal or hepatic impairment, or immunocompromised status. Women patients who were pregnant or possibly pregnant, lactating were also excluded.

### **Study procedures and medication**

All the patients were assessed by investigators in a screening study before the therapy examined as the pre-treatment signs and symptoms and a test-of-cure experiment after the 5 day therapy evaluated as the post-treatment signs and symptoms. In the screening study, patients were assessed for eligibility for inclusion into the study.

After the screening study, patients meeting the study inclusion criteria were subsequently randomized on a balanced 1:1 basis from a computer-generated schedule that linked sequential numbers to treatment codes. Patients were randomized to oral treatment with either green tea polyphenols tablets or Caoshanhu tablets as the control medicine, both given as 2 tablets once and 6 times daily for 5

day. Double blinding was maintained throughout the whole evaluation study in which neither the patients nor the investigators knew whether green tea polyphenols tablet or Caoshanhu tablet was prescribed except the nurses who were required not to mention the medication.

In both the screening study and the test-of-cure experiment, the presence and severity of pharyngitis signs and symptoms were assessed, repeat physical examination was performed, and vital signs were measured. Pharyngitis signs were examined with the aid of laryngendoscope independently by clinicians and symptoms were recorded as the patients reported and confirmed by clinicians throughout the clinical experiment.

### **Efficacy assessment and therapeutic effects**

The efficacy was assessed on the changes in the integral scores of pharyngitis signs and symptoms from the pre- treatment patients and the post-treatment participants of the study. Scores were defined according to the severity of signs and symptoms. For primary pharyngitis signs and symptoms, including sore throat, pharyngodynia, and pharynx mucosal hyperemia, each was assigned with 0 (normal), 2 (mild), 4 (moderate), or 6 (severe) score. Secondary pharyngitis signs and symptoms, namely, dysphagia, thirst, fever, aversion to cold, uvula erythema and edema, and posterior pharynx folliculosis, were given a score as 0 (normal), 1 (mild), 2 (moderate), or 3 (severe) respectively.

The therapeutic effects were assessed according to the difference in integral scores and the improvement in pharyngitis signs and symptoms as clinical cure, markedly effective, effective, and ineffective respectively. Clinical cure was defined as a complete eradication of all pharyngitis signs and symptoms and the integral scores came to zero. Markedly effective therapy was assessed as an absent in most pharyngitis signs and symptoms and the consequent integral scores decreased over 2/3. Effective therapy was measured as a clinical decrease in some of the pharyngitis signs and symptoms and the consequent integral scores decreased between 1/3-2/3. Ineffective therapy means a failure in most pharyngitis signs and symptoms and the decrease in the integral scores was less than 1/3.

### **Safety consideration and evaluation**

All of the patients who received green tea polyphenols or the control medicine were assessed for safety, which was evaluated by collecting all the adverse events reported by the participants. Any suspected treatment related adverse event was one judged by the investigators to be possibly or probably related to the study drug. The severity of an event was rated mild, moderate or severe. In both the screening study and the test-of- cure experiment, repeat physical examination was performed, and vital signs were measured. A medical history was presented and vital signs were measured, including heart rate, body temperature, respiratory rate, and blood pressure. An electrocardiograph (ECG) was recorded. Blood and urine samples were taken for routine laboratory testing in the patients who accepted such tests.

### **Statistical analysis**

Data were analyzed using SPSS software. Quantitative variables were compared using Student's t- test. All the tests were two-sided, with the level of significance set at 0.05. For the comparison of efficacy variables and therapeutic effects, a two sided 95% confidence interval of the difference between the pre-treatment and post-treatment and also between green tea polyphenols and the control medicine.

**Table 1.** Baseline data regarding the patients enrolled in the clinical evaluation.

	Control (n = 60)	GTP (n = 60)
Mean age (years) ± SD	39.81±12.04	38.63±11.71
Mean initial integral scores± SD	16.38±4.12	17.16±4.10
Male/female	15/45	23/37
Acute /chronic pharyngitis	34/26	37/23

GTP, Green tea polyphenols. control, caoshanhu tablet.

**Table 2.** Changes in the scores of pharyngitis signs and symptoms from the pre-treatment patients and the post-treatment participants of the study.

	Control (n = 60)			GTP (n = 60)		
	n	Pre-treatment	Post-treatment	n	Pre-treatment	Post-treatment
Sore throat	60	4.06±1.03	1.43±0.98	60	4.16±0.99	1.36±1.19
Pharyngodynia	58	3.03±1.07	1.20±1.05	59	3.32±1.15	0.93±1.06
Pharynx mucosal hyperemia	60	3.46±1.32	1.73±1.00	59	3.40±1.36	1.40±1.11
Dysphagia	43	1.72±0.59	0.55±0.62	52	1.80±0.59	0.42±0.63
Thirsty	47	1.51±0.54	0.72±0.68	54	1.72±0.56	0.59±0.65
Fever	19	1.47±0.69	0.10±0.31	23	1.47±0.66	0.08±0.28
Aversion to cold	25	1.16±0.47	0.04±0.20	17	1.11±0.33	0.05±0.24
Uvula erythema and edema	54	1.57±0.56	0.81±0.77	58	1.51±0.53	0.51±0.56
Posterior pharynx folliculosis	38	1.68±0.57	0.92±0.78	41	1.39±0.58	0.68±0.60
Total	60	16.38±4.12	6.63±3.84	60	17.16±4.10	5.56±4.06

GTP, Green tea polyphenols. Control, Caoshanhu tablet. \* difference at the significance level of 0.05 as compared with the pre-treatment.

## RESULTS

A total of 120 adult patients with acute or chronic pharyngitis who visited hospitals (38 males and 82 females with an age from 18 to 65 years old) according to the inclusion criteria were enrolled in this clinical evaluation study. The patients were divided into two groups, either receiving green tea polyphenols tablets or Caoshanhu tablets for the 5 day course of pharyngitis therapy. As shown in Table 1, there was no significant difference in age and sex distinction, initial integral scores of pharyngitis signs and symptoms, and the distribution of acute and chronic pharyngitis patients between the green tea polyphenols group and the control medicine group.

Changes in the scores of pharyngitis signs and symptoms from the pre-treatment patients and the post-treatment participants of the study were compared between the green tea polyphenols group and the control medicine group (Table 2). It was found that both green tea polyphenols and the control medicine had an efficient efficacy in the treatment of pharyngitis in human subjects who visited hospital doctors as seen in the changes in integral scores of all the observed individual signs and symptoms between pre-treatment and post-treatment ( $P<0.05$ ). A comparison on the difference in the integral scores of pharyngitis signs and symptoms from the

pre-treatment patients and the post-treatment participants between green tea polyphenols and the control medicine showed that green tea polyphenols had a decrease in the total integral scores more significant ( $P<0.05$ ) than the control medicine (Table 3). The results also demonstrated that green tea polyphenols had a more prominent efficacy ( $P<0.05$ ) in eliminating pharyngodynia in pharyngitis patients than the control medicine.

The assessment of therapeutic effects demonstrated that green tea polyphenols and the control medicine had a similar effective rate in the treatment of pharyngitis (Table 4). However, as for the clinical cure and markedly effective treatment, green tea polyphenols showed a greater proportion than the control medicine. Throughout the whole clinical evaluation study, there were not any adverse events related to either green tea polyphenols or control medicine reported by the participants and the investigators. Also no abnormal event was observed in heart rate, body temperature, respiratory rate, blood pressure and electrocardiograph by the repeat physical examination and vital signs measurement in patients who received green tea polyphenols or control medicine treatment. As shown in Table 5, no visible changes in hemogram, hepatic and renal function of the 30 consecutive subjects who accepted the routine laboratory testing was observed throughout the therapy with

**Table 3.** Comparison on the difference in the scores of pharyngitis signs and symptoms from the pre-treatment patients and the post-treatment participants between green tea polyphenols and the control medicine.

Signs and symptoms	Control		GTP	
	n	Difference in scores	n	Difference in scores
Sore throat	60	2.63±1.24	60	2.80±1.11*
Pharyngodynia	58	1.82±1.01	59	2.38±1.17*
Pharynx mucosal hyperemia	60	1.76±1.56	59	2.00±1.15
Dysphagia	43	1.16±0.61	52	1.38±0.77*
Thirst	47	1.36±0.59	54	1.12±0.58*
Fever	19	1.36±0.59	23	1.39±0.65
Aversion to cold	25	1.16±0.48	17	1.05±0.24
Uvula erythema and edema	54	0.75±0.77	58	1.00±0.67
Posterior pharynx folliculosis	38	0.76±0.78	41	0.70±0.55*
Total	60	9.75±4.64	60	11.60±4.39*

GTP, Green tea polyphenols. Control, caoshanhu tablet. Difference at the significance level of 0.05 between the GTP and the control.

**Table 4.** Therapeutic effects of green tea polyphenols and the control medicine on pharyngitis.

	Clinical cure	Markedly effective	Effective	Ineffective	Total effective rate (%)
GTP (n = 60)	11	19	28	2	96.67
Control (n = 60)	7	13	34	6	90.00

GTP, Green tea polyphenols. Control, Caoshanhu tablet.

**Table 5.** Comparison of hemogram, hepatic function and renal function between the pre-treatment patients and the post-treatment participants of the clinical evaluation of green tea polyphenols.

	n	Pre-treatment	Post-treatment
HGB (g/L)	30	125.67±18.59	129.41±18.13
WBC(10 <sup>9</sup> /L)	30	5.64±1.55	5.91±1.72
PLT(10 <sup>9</sup> /L)	30	153.22±61.78	155.74±51.32
ALT(U/L)	30	22.60±17.14	24.83±16.12
Cr ( M)	30	71.16±21.83	76.35±22.47
BUN(mM)	30	4.44±1.58	4.93±1.34

green tea polyphenols between pre-treatment and post-treatment.

## DISCUSSION

In this randomized, double-blind, parallel-group comparative clinical trial based on age and clinical signs and symptoms, the primary efficacy assessment showed that both green tea polyphenols tablet and the control medicine produced a significant improvement in all the pharyngitis signs and symptoms in human subjects with acute and chronic pharyngitis (P<0.05) based on an analysis of the integral scores against the pre-treatment investigation. Green tea polyphenols had a decrease in

the total integral scores more significant (P<0.05) than the control medicine and had a more prominent efficacy (P<0.05) in eliminating pharyngodynia in pharyngitis patients than the control medicine. In the therapeutic effects assessment, green tea polyphenols demonstrated a similar effective rate (n = 60, 96.67%) to the control medicine Caoshanhu tablet (n = 60, 90.00%). The safety evaluation showed that no adverse events occurred related to the green tea polyphenols and the control medicine treatment and on abnormal changes were observed in heart rate, body temperature, respiratory rate, blood pressure and electrocardiograph by the repeat physical examination and vital signs measurement throughout the study. Caoshanhu tablet is an effective and reliable treatment widely used OTC (over the counter)

medicine for pharyngitis treatment with extract of *S. arcandra glabra* (Thunb.) Nakai as the main active components (Shi et al., 2007). So, the results from systematic efficacy and therapeutic assessment and the safety evaluation with Caoshanhu tablet as the control medicine suggest that tea polyphenols can serve as an effective and safe medicine in the treatment of pharyngitis.

Direct infection of the pharynx by various viruses or bacteria is often diagnosed as the main causative factor in pharyngitis pathogenesis (Bisno et al., 2002). It was found in our study that green tea polyphenols had a strong antibacterial activity against a variety of clinical bacteria and a powerful antiviral potency against influenza virus A3 (H3N2) and Cocksackie virus B4 (Data were not shown). The results are well in agreement with the outcome found earlier by other scientists in bacteria (Bandyopadhyay et al., 2005; Yamada et al., 2003; Bancirova et al., 2010) and virus (Nakayama et al., 1993; Song et al., 2005; Mukoyama et al., 1991). The antibacterial and antiviral activity of green tea polyphenols could be believed to play a role in its therapeutic effects in the treatment of pharyngitis.

Development of resistance to antibiotics of pathogens is a big problem faced with in treating many kinds of disorders including pharyngitis (Mlynarczyk et al., 2001). *Staphylococcus aureus* accounts for a great percentage of the pharyngitis cases both in children and adults (Bisno et al., 2002; Ruppert, 1996; Matthys et al., 2007). It was found that tea exhibited a strong antibacterial activity against methicillin-resistant *S. aureus* in elderly patients (Yamada et al., 2003). Catechins in green tea also showed synergy antibacterial effects against methicillin-resistant *S. aureus* with ampicillin/sulbactam (Hu et al., 2001) and with tetracycline (Roccaro et al., 2004) by inhibiting its efflux from bacterial cells. These effects implied that tea polyphenols could be used together with antibiotics in the treatment of pharyngitis to strengthen the antibiotics effects and thus prevent against antibiotic overuse.

Other causative factors of pharyngitis have also been recognized like alcohol use and smoking in life style than infection cause (Middleton, 1991; Yazici et al., 2010). Tea and its components have been found protective against pharyngeal lesions induced by tobacco (Santhosh et al., 2005; Lee et al., 1997; Tavani et al., 2003) and alcohol (Tavani et al., 2003; Łuczaj and Skrzydlewska, 2004). This capacity is advocated in prevention of pharyngitis of non-infection cause to avoid indiscriminate use of antibiotics. The therapeutic effects of green tea polyphenols in the treatment of pharyngitis could thus be ascribed in its multifunction mechanism.

## Conclusions

Green tea polyphenols decreased the integral scores of all the observed individual signs and symptoms

significantly from pre-treatment to post-treatment. In the therapeutic effects assessment, green tea polyphenols demonstrated a high total effective rate in the treatment of pharyngitis with a greater proportion in clinical cure and markedly effective therapy than the control medicine. The green tea polyphenols treatment did not produce any adverse events. Green tea polyphenols can serve as an effective and safe medicine in the treatment of pharyngitis.

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