Evaluating the therapeutic efficacy, tolerability, and safety of an aqueous extract of *Costus speciosus* rhizome in acute pharyngitis and acute tonsillitis. *A pilot study*

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ABSTRACT

Objectives: To determine the efficacy, tolerability, and safety of an aqueous extract of *Costus speciosus* (*C. speciosus*) rhizome in pediatric and adult patients suffering from acute pharyngitis and tonsillitis as an alternative to antibiotics use.

Methods: This pilot cohort trial was conducted at King Abdulaziz University in Saudi Arabia between May and December 2014, among 15 patients with acute pharyngitis and tonsillitis who were administered nasal drops of aqueous extract of *C. speciosus* rhizome at a dose of 15-30 drops every 8 hours for 3 days. The primary outcome measure was the clinical improvement and remission rate within the first 5 days.

Results: The administration of *C. speciosus* resulted in an improvement in acute symptoms in 60% of the patients treated within the first 24 hours, and remission rate of 93% by day 5, without any recorded adverse effects.

Conclusion: This study revealed a significant efficacy of the aqueous extract of *C. speciosus* rhizome in acute pharyngitis and tonsillitis.

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The overuse of antibiotics in respiratory tract infections is considered to be a significant cause of antibiotic resistance in the community.[1] However, acute pharyngitis is a self-limiting disease, and antibiotics are indicated only if the patient has not improved over a period of time. This strategy to delay prescription is likely to provide similar benefits to an immediate antibiotic prescription, with the benefit of decreasing the overuse of antibiotics.[2] Furthermore, the antibiotics may cause a range of adverse effects including gastrointestinal manifestations, skin allergy, hepatic toxicity, anaphylactic reaction, and neuro-psychiatric problems.[3] Phytomedicine will only become incorporated into orthodox medicine, which is defined as the practice of medicine where the disease is viewed as a physical disorder with little relationship to the person's psychological and spiritual affiliation,[4] if the safety and efficacy of phytomedicine are proven with credible evidence-based clinical data to be comparable or superior to conventional drugs.[5] The current study used the *C. speciosus* rhizome that is classified under the genus of *Costus Linn*, which belongs to the *Costaceae* family and the *Zingiberales* order. Turshar et al[6] conducted a survey of the use of *Zingiberaceous* plants and found that the rhizomes were the primary plant material used as a source of medication. They also indicated that *C. speciosus* and *Zinggiber purpureum* are 2 of the important species for future work. In traditional medicine, *C. speciosus* has many uses in medical treatment as in fever, asthma, tonsillitis, bronchitis, skin disease, constipation, and snake and insect bites.[6] In Prophetic medicine, the use of *C. speciosus* was specifically recommended for the treatment of inflammation of the pharynx/tonsils in children, pleurisy, and as a snake venom antidote.[7] As documented by Anas Ibn Malek: "Cupping (Hijama) and Qust al-Bahri (*Sea Incense Costus*) are the best of your remedies, and don't harm your children by treating tonsillitis by pressing their tonsils" [Saheeh Muslim 1577]. Currently in the literature, numerous studies have reported various bioactivities of *C. speciosus* to support its medical use as anti-fungal, anti-microbial, and anti-inflammatory. Duraipandiyan et al[8] conducted an *in vitro* study of *C. speciosus* in which it was found that it exhibited a moderate activity against *Staphylococcus aureus*, *Staphylococcus epidermis,* and *Bacilus subtilis*, and it had a significant anti-fungal effect in hexane extract, which has the active compound of costunolide and eremanthin. Srivastava et al[9] confirmed that a methanol extract of *C. speciosus* has significant anti-inflammatory, analgesic, and antipyretic activities in an animal study at a dose of 400 and 800 mg/kg. Therefore, we conducted the current pilot study to determine the objective and subjective effects, tolerability, and safety of the alternative treatment of aqueous *Costus speciosus* (*C. speciosus*) rhizome in pediatric and adult patients suffering from acute pharyngitis and tonsillitis.

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Methods. The current pilot cohort non-blinded non-controlled trial was conducted at the Otolaryngology-Head and Neck Clinic and Prophet Medicine Clinic, King Abdulaziz University (KAU), Jeddah, Kingdom of Saudi Arabia between May and December 2014. Ethical approval was granted according to the Declaration of Helsinki from the ethical committee of KAU. The primary outcome measure was the remission rate, which was defined as complete absence of all symptoms on day 5. Improvement was defined as any decrease in symptom severity from day one to day 5, excluding remission. The *C. speciosus* rhizomes used in this study were purchased from a local market in Jeddah, Kingdom of Saudi Arabia. The plant rhizomes were finely ground, and the resultant powder was macerated with deionized water (10% w/v) for 16 hours at room temperature with continuous shaking at 150 rpm in an orbital shaker (Model VS-8480SFN, Vision Scientific, Daejeon, South Korea). The extract was filtered, and the filtrate obtained was lyophilized using a freeze dryer (model FD5512 from ilShin BioBase Co., Ltd, South Korea). Then, a vacuum was used under 5 mm Torr. After the extraction of water from 100 g of the plant rhizome, this yielded 28 g of lyophilized powder. Nasal drops were prepared by suspending the lyophilized extracted powder in distilled water at a concentration of 280 mg/ml. Regarding the selection of concentration, there has been no published study on the use of *C. speciosus* as a nasal drop. The preparation of the concentration dose was suggested after collecting data from the users of these plants (50 patients).

Patients who fulfilled the following inclusion criteria were included in the study: Male and female patients aged between 3-65 years, with acute pharyngitis or tonsillitis, who agreed to written informed consent; the age of 3 years was selected as members of this age group are at high-risk of group B *haemolytic streptococcus*, according to the Centor criteria.[10] The exclusion criteria were the use of the following agents during the period preceding the study: analgesics <12 hours; antibiotics <24 hours; topical throat pain medication such as echinacea spray or chlorohexidine/lidocaine treatment <4 hours; or systemic corticosteroids within the last month. Serious illness, such as tumors, was also specified as an exclusion criterion. Participation in another clinical trial[11] within the previous 30 days was not permitted, and patients who did not present at the follow-up were excluded from the study. One otolaryngologist evaluated the patients clinically. The examination included a detailed history of sore throat, headache, abdominal pain, rhinitis, and cough that were assessed by a Visual Analogue Scale (VAS), and examination for fever, pharyngeal redness and exudate, cervical lymphadenopathy, otitis media, and conjunctivitis. The patients were evaluated by using the Centor score to determine the likelihood of group A *beta streptococcus*.[10] Centor criteria include: fever more than 38°C, absence of cough, tender cervical adenopathy, tonsillar swelling, and age of 3-14 years.

The aqueous solution of *C. speciosus* was administered as nasal drops at a dose of 0.75 ml (15 drops containing 210 mg extract) for patients aged 2-6 years, and 1.5 ml (30 drops containing 420 mg of the extract) for patients older than 6 years, every 8 hours for 3 days. In the current study, the *Costus* nasal drop was used at this low dose, as it was mentioned in the literature that the specific dose of nasal administration of other species such as *Pelargonium sidoides* was 30 drops/3 times per day/7 days in the treatment of acute bronchitis.[5] The patients were supplied with 2 degradation bottles of 15 ml, and with daily diaries that contained 6 variables (fever, throat pain, difficulty swallowing, headache, myalgia, and the inability to work) to be scored on a 4-point scale (0: none, 1: mild, 2: moderate, 3: severe). We used the nasal mode of administration as confirmed by Djupesland et al[12] that the nasal method has the advantage to overcome the poor bioavailability and slow absorption of systemic drug administration in local rhinosinsitis disease. However, when considering the nasal root, it is important to ensure the protection of the lungs from hazardous exposures of substances through the nose. For this reason, the *Costus* nasal drops were administered at low doses for shorter durations. Subsequently, the follow-up visit was conducted after one week, during which the patients were evaluated with a full history and examination and for persistent symptoms of acute tonsillitis and pharyngitis by the otolaryngologist. At these follow-up visits, the diaries were collected.

Data were analysed using the Statistical Package for Social Sciences version 16.00 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for all variables. Gender was expressed as a female-to-male ratio. Age was calculated as mean ± standard deviation (SD). Frequency (percent) was calculated on the type of diagnosis and on the improvement and remission rates. The sum of the 6 variants that were scored on 4-point scales was calculated for each of the 15 patients for each of the 5 days. The *p*-value was set at a value of less than 0.05 with a confidence interval of 95% to determine whether there was a significant difference in the score between each of 2 consecutive days during the duration of the recorded period.

Results. The current pilot study enrolled 19 patients with acute pharyngitis and tonsillitis at the

beginning of the study. However, the follow-up rate was 78%. Consequently, the study ultimately included 15 patients. The remission rate on day 5 was 93.3%, as just one patient had continued to complain of mild headache (scale 1 out of 3) on day 5. As indicated in **Table 1**, the first 11 patients revealed an improvement in the score during the first 24 hours (60%), and 2 patients (number 12 and 13) had improved after 48 hours. The last 2 patients demonstrated an improvement after 72 hours. The p-value had a significant difference between days one and 2, and between day 2 and 3 (**Table 2**).

Discussion. The use of an aqueous extract prepared from *C. speciosus* in patients with acute pharyngitis and tonsillitis resulted in a remission rate of 93.3% on day 5, which showed a slight benefit compared with the placebo group in the literature, as it has been shown that sore throat and fever disappeared in approximately 40-85% of patients on day 3, and 82% of patients were symptom-free by the end of one week.[13] The remission rate in the current study was similar to that associated with the use of antibiotics as reported by Regoli et al.[10] They reported that patients who use antibiotics in the treatment of acute bacterial pharyngitis will demonstrate improvement by day 5. However, the course of antibiotics should be continued until day 10 to eradicate the bacteria. Del Mar et al[13] conducted a review of 27 randomized controlled trials using antibiotics versus placebo on 12,835 cases of sore throat. It was demonstrated that antibiotics shorten the duration of symptoms by 16 hours, and it was concluded that antibiotics will lead to relative benefit in the treatment of sore throat. However, the absolute benefit is trivial. The patients were evaluated by using the Centor score. However, this score is useful in determining the need for antibiotics in high-risk patients of group A *beta streptococcus pharyngitis* as although it has a specificity of 0.82, the post-test probability was 12-40%. In addition, acute pharyngitis is most commonly viral in origin, and bacterial causes account for only 5 to 10% of cases.[14] Use of the *Costus* extract in patients with acute pharyngitis and tonsillitis did not result in any reportable adverse effects. There is no available safety study in the literature for *C. speciosus* use in humans. However, there was a study on a different species of the *Costus* genus that was conducted by Ezejiofor et al.[15] That study reported that the aqueous extract of the leaves of *Costus afer Ker Gawl* may cause potential hepatotoxicity for chronic use of more than 28 days, but is non-toxic to the kidneys of the male albino wistar rat.

The limitations of the current study are the small sample size of 15 patients and the absence of a microbiological confirmation test, control group, and double-blind technique.

In conclusion, this pilot study revealed significant efficacy of the use of aqueous extract of *C. speciosus* rhizome in patients suffering from acute pharyngitis and tonsillitis. This intervention demonstrated an improvement in acute symptoms in 60% of the patients treated within the first 24 hours, and 93% complete remission on day 5 without the development of any adverse effects. This finding suggests that we may consider the extract of this rhizome as an alternative therapy to antibiotic management of acute pharyngitis and tonsillitis. We recommend conducting a randomized, double-blind trial with a larger group of patients to evaluate and compare the efficacy of *C. speciosus* in patients with acute upper respiratory tract infection.

Table 1 - The total score of 6 variants of symptoms (fever, throat pain, difficulty swallowing, headache, myalgia, and the inability to work) using 4-point scale for each symptom (0: none, 1: mild, 2: moderate, 3: severe) among the 15 patients suffering from acute pharyngitis and tonsillitis during the recorded period of 5 days.

Patient number	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
1st	17	13	5	1	0	0
2nd	14	9	4	2	0	0
3rd	9	7	4	2	1	0
4th	9	7	4	3	1	0
5th	7	5	2	0	0	0
6th	11	7	3	0	0	0
7th	10	8	5	1	0	0
8th	7	5	3	1	0	0
9th	6	4	1	0	0	0
10th	11	6	3	1	0	0
11th	13	11	8	3	1	0
12th	8	8	5	2	1	0
13th	7	7	3	1	1	1
14th	6	6	6	2	0	0
15th	9	9	9	4	1	0

Table 2 - The *p*-values between each of 2 consecutive days during the measured duration of 5 days among patients suffering from acute pharyngitis and tonsillitis.

Variable	*P*-value
The *P*-value of Day 0 and 1	0.062
The *P*-value of Day 1 and 2	0.041
The *P*-value of Day 2 and 3	0.043
The *P*-value of Day 3 and 4	0.112
The *P*-value of Day 4 and 5	0.205

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