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Cistus incanus (CYSTUS052) for treating patients with infection of the upper respiratory tract
A prospective, randomised, placebo-controlled clinical study

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ABSTRACT

In this prospective, randomized, placebo-controlled clinical study we aimed to investigate the clinical effect of a Cistus extract (CYSTUS052) in 160 patients with infections of the upper respiratory tract. The extract contains a high percentage of highly polymeric polyphenols. In cell culture and in a mouse model it exerts antiviral and antimicrobial activities. Principal active constituents of the genus Cistus are polyphenolic compounds. Plant-derived polyphenols have been shown to be strong antioxidants with potential health benefits. Various reports have appeared on the antiviral and antibacterial potential, including several reports describing the antiviral activity of polyphenols against influenza virus. Clinical studies on the effectiveness of Cistus incanus are scarce. Only one controlled application observation study demonstrated the effectiveness of a Cistus extract. The present randomised, placebo-controlled clinical study was designed to compare the symptom scores in patients with common cold treated either with CYSTUS052 or with placebo. A score of subjective symptoms decreased significantly over the course of treatment with Cistus, whereas treatment with placebo resulted in a less distinct decrease of symptoms. Among the inflammatory markers investigated, the C-reactive protein was mostly affected by Cistus and decreased significantly in the treatment group.

1. Introduction

The World Health Organization (WHO) has recently declared the influenza A (H1N1) of swine origin a global flu pandemic after holding an emergency meeting. It is the first flu pandemic in 40 years—the last in 1968 killed about one million people. Up to now, the current pandemic seems to be moderate and causing mild illness in most people. But the picture could change very quickly, for example in cases of drug resistant against the neuraminidase inhibitors such as oseltamivir or zanamivir. The development of alternative antiviral agents is necessary and one example could be Cistus incanus, which has shown better antiviral effects against influenza virus than oseltamivir in animals (Droebner et al., 2009). Principal active constituents of the genus Cistus are polyphenolic compounds. Polyphenols exhibit a wide range of antibacterial, antifungal, anti-inflammatory effects and have been shown to be strong antioxidants with potential health benefits. Various reports exist on antiviral and antibacterial potential (Cos et al., 2004; Urquiaga and Leighton, 2000; Arts and Hollman, 2005; Halliwell et al., 2005; Simeray et al., 1982; Chinou et al., 1994; Bouamama et al., 1999) including an antiviral activity of polyphenols against influenza virus (Nakayama et al., 1993).

Ehrhardt et al. (2007) and Droebner et al. (2007) described the antiviral activity of a specific Cistus incanus plant extract (CYSTUS052) against influenza A virus infections. But clinical studies on the effectiveness of Cistus incanus extracts are limited. One controlled observation study was performed on 53 patients, who suffered from painful infection in the mouth and throat area and demonstrated the effectiveness of a Cistus extract (Kiesewetter, 2002). Recently we were able to show in an open clinical randomised study that the treatment with Cistus was more effective in reduction of the average duration and severity of symptoms in patients with infection of the upper respiratory tract than treatment with Camilla sinensis (Kalus et al., 2009).

In the present prospective, randomized, placebo-controlled clinical study, we investigated the clinical effect of a Cistus extract in 160 patients with infections of the upper respiratory tract.

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2. Materials and methods

2.1. Patients and study design

We recruited 160 out-patients (age 7–81 years), who suffered from an infection of the upper respiratory tract by clinical signs. Throat-swabs were taken and subjected to a suitable bacterial culture medium regarding the pathogen of the infection. In cases in which no growth of bacteria was detectable a viral infection was suggested. A rapid test for the differentiated detection of Influenza A and B was applied (BioStar OIA FLU A/B, Inverness Medical). The further differentiation was performed by commercial serological test kits. Based on the findings 92 (57.5%) volunteers had a viral infection (11 patients with Influenza A and 7 patients with Influenza B) and 67 (41.8%) a bacterial infection.

The start of treatment was delayed maximally 1 day after the first visit. All test subjects were randomly assigned either to 6 × 2 tablets CYSTUS052 daily (approximately 220 mg polyphenols) or placebo. The lozenges dissolve in the saliva over roughly 10 min. Patients were observed and treated up to 7 days. The subjects were asked to judge the maximum severity of the following symptoms on a questionnaire provided by their physician: pain, cough intensity, cough frequency, sputum and sniffles. Each symptom was determined as follows: 0 = not present, 2 = slight, 4 = mild and 6 = severe. The total score was calculated by adding the five symptom scores and therefore ranged from 0 to 30. The score was recorded at the first visit prior to the start of treatment and daily until day 7. Additionally inflammatory blood markers were measured (Factor VIII activity, C-reactive protein) on days 1, 4 and 7.

2.2. Medications

The product investigated consisted exclusively of CYSTUS052 lozenges (Dr. Pandalis Urheimische Medizin GmbH & Co. KG, Germany). Each lozenge contained an extract from a distinct variety of Cistus incanus (Cistus incanus PANDALIS® = CYSTUS052), corn syrup, banana, beetroot and rosehip oil. CYSTUS052 extract was defined by the Manufacturer as having a content of more than 18 mg of polyphenols per lozenge.

The placebo capsules contained corn syrup, banana, beetroot and rosehip oil only. Verum treatment and placebo lozenges were matched for size and appearance.

2.3. Statistical analysis

The primary efficacy evaluation was performed as well as per-protocol and as intent-to-treat-analysis (last observation carried forward) using the software STATA for Windows, Version 10. For the symptom score, factor VIII activity and C-reactive protein, variance analyses were performed with type of medication (Cistus vs placebo) and type of infection (bacterial vs viral or Influenza A/B vs other viral infections, resp.) as between-subject factors and day of treatment as within-subject factor.

3. Results

Of the 160 participants in this study (56 men and 104 women), 129 patients completed the study, 82.5% of the Cistus group and 80.0% of the placebo group. The demographic data's of 160 patients receiving Cistus or placebo lozenges for treatment of bacterial or viral infections is shown in Table 1. The range of pathogens is shown in Table 2.

Table 1
The demographic data of the 160 patients.

	Body weight (kg)	Body height (cm)	Age (years)		
	Mean ± SD	Mean ± SD	Mean	min	max
Cistus	72.8 ± 16.0	170 ± 10.4	46	10	77
Placebo	77.4 ± 17.4	170 ± 10.6	43	7	81

Table 2
Range of pathogens of the participants.

	Placebo	Cistus	Total
Staphylococcus aureus	3	5	8
Streptococcus pneumoniae	26	19	45
Mycoplasma pneumoniae	1	1	2
Chlamydia pneumonia	0	3	3
Haemophilus influenzae	5	5	10
Influenza A Virus	4	7	11
Influenza B Virus	2	5	7
Virus, other	39	35	74
Total	80	80	160

3.1. Score of subjective symptoms

The score of subjective symptoms decreased significantly during observation ($p < 0.001$). The decrease was significantly more pronounced in the group of subjects treated with Cistus compared to placebo ($p < 0.001$). These effects were observed as well in the per-protocol as in the intent-to-treat analysis. Fig. 1 and Table 3 clearly demonstrate the improvement of the symptoms during treatment.

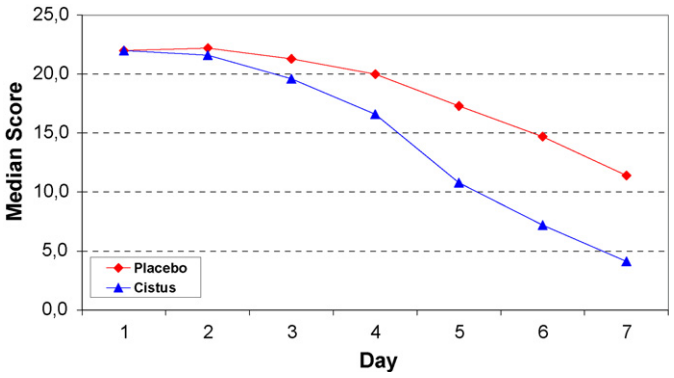

Fig. 1. Improvement of the symptoms following treatment with Cistus and placebo. The score was calculated by adding the five symptom scores (pain, cough intensity, cough frequency, sputum, sniffles) and ranged from 0 (no symptoms) to 30 (strong symptoms).

Table 3
Score, CRP and F VIII (Mean and SD).

Parameter	Cistus Mean ± SD	Placebo Mean ± SD
Score		
Day 1	22 ± 4.6	22 ± 4.6
Day 4	17 ± 6.3	20 ± 5.0
Day 7	4 ± 3.2	11 ± 3.6
CRP		
Day 1	37.6 ± 24.7	34.8 ± 23.1
Day 4	36.4 ± 25.9	39.4 ± 23.4
Day 7	8.8 ± 4.9	17.7 ± 8.8
F VIII		
Day 1	249 ± 61.1	275 ± 56.4
Day 4	289 ± 48.7	298 ± 53.2
Day 7	217 ± 42.2	242 ± 45.5

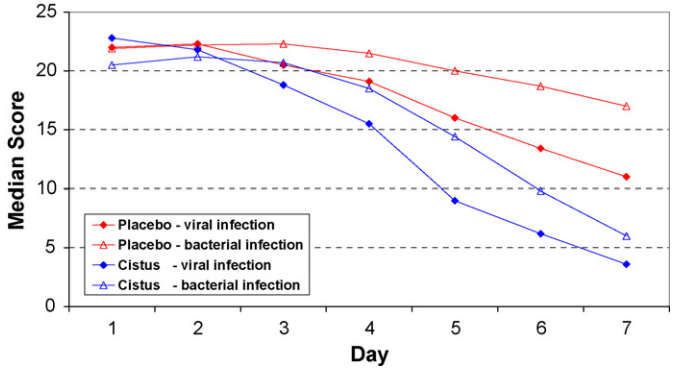

Fig. 2. Improvement of the symptoms separated for bacterial and virus infections following treatment with Cistus and placebo.

The improvement of the score was more pronounced in patients with viral infections in comparison to bacterial infections ($p < 0.001$) (Fig. 2). Again, this effect was observed as well in the per-protocol as in the intent-to-treat analysis. Within the virus group the score of subjective symptoms decreased significantly in the Influenza A/B as well as in the non-Influenza virus group ($p < 0.001$), but the decrease in the Influenza A/B group was more slowly ($p < 0.001$) (Fig. 3).

3.2. Laboratory parameters

Among the inflammatory markers we investigated the C-reactive protein (CRP) and the factor VIII activity (FVIII). Both markers showed a major decrease after day 4 (see Fig. 4 and Table 3). CRP decrease was more pronounced in the Cistus group

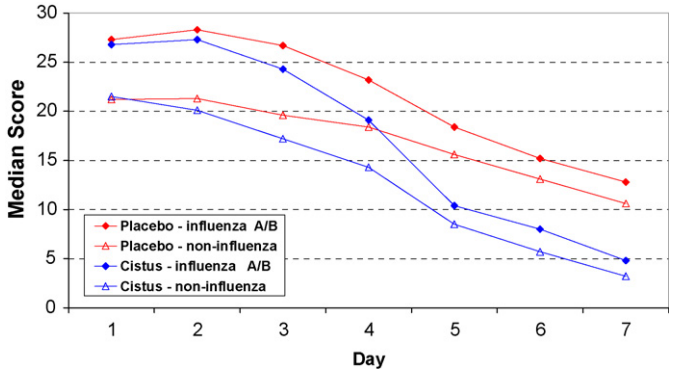

Fig. 3. Improvement of the symptoms separated for influenza A/B and non-influenza virus infections following treatment with Cistus and placebo.

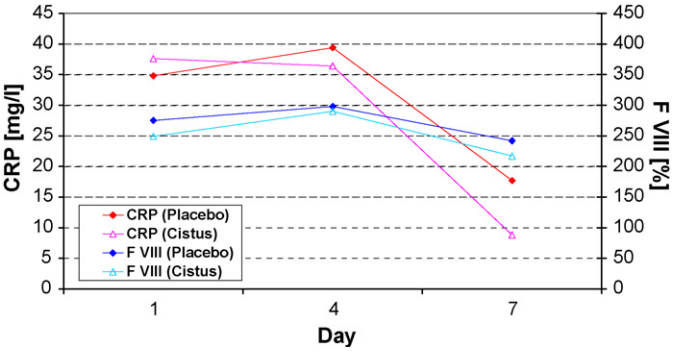

Fig. 4. Effects on the CRP-level and F VIII activity following treatment with Cistus and placebo.

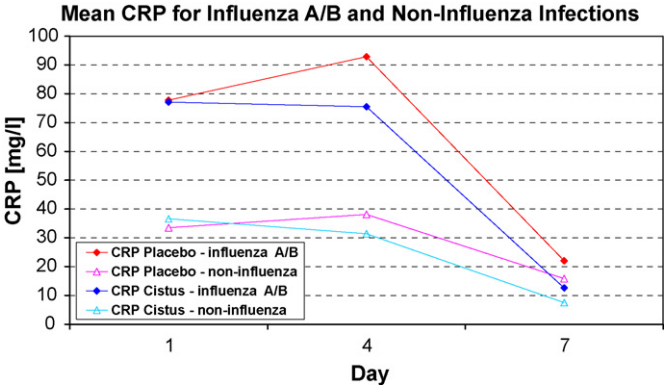

Fig. 5. Effects on the CRP-level separated for influenza A/B and non-influenza virus infections following treatment with Cistus and placebo.

Table 4
Adverse events.

Symptom	Cistus		Placebo	
	%	abs.	%	abs.
Nausea/dizziness	8.8	7/80	8.8	7/80
Stomach complaints	5	4/80	11.2	9/80

($p = 0.002$ in the intent-to-treat analysis, $p = 0.09$ in the per-protocol analysis). FVIII decrease was significantly higher in the Cistus group ($p = 0.002$ in the intent-to-treat analysis, $p = 0.008$ in the per-protocol analysis).

The decrease of both factors were significantly more pronounced in patients with viral infections compared to bacterial infections ($p < 0.001$ in the intent-to-treat analysis, $p = 0.004$ for CRP and $p = 0.026$ for F VIII in the per protocol analysis). Within the virus group the initial increase of CRP was more pronounced in Influenza A/B than in the non-Influenza A/B virus group (Fig. 5).

3.3. Adverse events

Approximately 17.0% (27/160) of the patients complained of adverse effects. Adverse effects were observed more significantly in the placebo group with 20.0% (16/80) than in the Cistus group with 13.8% (11/80) ($p < 0.001$; Fisher's exact test). By far, the most frequent adverse effects were nausea/dizziness and stomach complaints (Table 4).

4. Discussion

The most common diseases in the world are upper respiratory tract infections, resulting in substantial morbidity, mortality, and financial loss (Woodall, 2004; Islam and Carter, 2005). According to acute lower respiratory infections, viruses are reported to be the most important pathogens involved. Avian and swine flu have been responsible for poultry outbreaks worldwide and have resulted in numerous cases of human infection and death in recent years. The rapid spread has induced world-wide fears of a new pandemic. Several antiviral compounds have been developed but their long term efficacy is often limited because of their toxicity or the emergence of drug-resistant virus mutants. These have increased dramatically in recent years, for amantadine from a global prevalence of <2% prior to 2002 to currently >90% (Deyde et al., 2007). H1N1 influenza viruses with the H275Y mutation are resistant to the neuraminidase inhibitor oseltamivir and were able to spread globally in 2008 and 2009.

This highlights the urgent need for new or well-known alternative antiviral drugs. Herbal drugs are increasingly used due to

the facts that the compounds are natural products, well tolerable and lack appreciable side effects. Such a suitable herbal drug could be Cistus, which showed no tendency to induce viral resistance in vitro (Ehrhardt et al., 2007).

To our knowledge, the present study is the first clinical trial conducted in a prospective, placebo controlled manner to describe the effectiveness of Cistus incanus in the treatment of upper and lower respiratory tract infections. Cistus incanus, a genus belonging to the family Cistaceae provide a rich source of polyphenols (Droebner et al., 2007), and are used in folk medicine as anti-inflammatory, antiviral, antibacterial, and antifungal agents for centuries (Simeray et al., 1982; Chinou et al., 1994; Sánchez de Rojas et al., 1995; Yesilada et al., 1997; Bouamama et al., 1999; Attaguile et al., 2000). Plant-derived polyphenols have been shown to bind and to inactivate viruses and bacteria in several studies via a physical and unspecific interaction (Toda et al., 1991; Yamaguchi and Jie, 2001). Epigallocatechin gallate (EGCG) and theaflavin digallate, two high molecular polyphenols widespread in plants were shown to bind to the hemagglutinin of influenza virus and thus block its infectivity (Nakayama et al., 1993). Due to the overall poor absorption and low plasma concentrations of high molecular polyphenols, it is suggested that these phenols might exert mainly direct effects (Halliwell et al., 2005). Biologically active low molecular phenols like Resveratrol mainly affects intracellular signal pathways and possesses anti-inflammatory effects against influenza A viruses by reducing expression of late viral proteins (Palamara et al., 2005).

In the study presented here, treatment of patients with infection of the upper respiratory with Cistus was effective in reducing the average duration and severity of symptoms. The evaluation of disease severity was assessed by a subjective symptom score including pain, cough (intensity and frequency), sniffles, and sputum. The time period, in which the drug achieved improvement of the clinical symptoms, was significantly shorter for Cistus than for placebo. These effects occur in patients with bacterial as well as viral infections and depend obviously not on specific antibacterial or antiviral effects but rather on an unspecific and broad action directly against the pathogen, as it was shown by in vitro tests (Ehrhardt et al., 2007). The advantage of such an unspecific action may be that resistant variants cannot easily emerge and that the compound may also act against bacterial co-infections that represent a major complication in severe influenza virus infections. The median symptom score was lowered earlier in patients with virus than in patients with bacterial infections. This argues for direct physical interactions with proteins at the surface of the virus particle to avoid penetration of the virus in the cells. By this mechanism cells are protected against damage and the subjective feeling can be improved earlier than by intracellular antiviral or antibacterial effects of the polyphenols. Animal tests have demonstrated that the Cistus extract showed an antiviral effect only when administered before or parallel to virus infection, but not afterwards (Droebner et al., 2007).

It still remains unclear, how Cistus extract in the mouth can help to reduce spread of influenza virus in the lung by an exclusive binding effect. The efficiency may possibly be attributed to a combination of several biological effects. According to earlier in vitro and in vivo studies non-specific biological or pharmacological interactions could be ruled out (Ehrhardt et al., 2007; Droebner et al., 2007). A further explanation model could be the release of active substances in the throat from the lozenges, which are transported with the respiration into the upper respiratory tract as an aerosol. Another mode of action might be the prevention of a reinfection by virus particles in the nasopharyngeal cavity, which have been coughed up. Within the virus group the therapeutically effects of Cistus were observed in the Influenza A/B as well as in the non-Influenza group. The improvement occurred earlier in the non-Influenza than in the Influenza A/B group. Nevertheless a difference of efficiency over the total observation period is not detectable. The decrease of the symptom score took place faster in the non-Influenza group, however the severity of illness before treatment was more pronounced in the Influenza A/B group and the decrease of the symptoms overall during treatment with Cistus was more evident in the Influenza A/B group than in the non-Influenza group.

The inflammatory laboratory parameter C-reactive protein was decreased significantly upon Cistus treatment, but the F VIII activity was not. CRP has a half time of approximately 24 h and F VIIIc of approximately 12 h. Both are acute phase proteins, but CRP is a more sensitive parameter to proof or to monitor inflammations and correlate tighter to the process of inflammation. The coagulating activity may persist increased for a longer period after inflammation. The observation of the increased severity of illness in the Influenza A/B virus group compared to the non-Influenza group by the symptom score is confirmed by the marked elevation of CRP in the Influenza A/B group.

It is unknown, whether clinical active polyphenols are specific only for Cistus, which is known to mainly contain highly polymeric polyphenols (Petereit et al., 1991). These large molecules appear to bind pathogens and thus to inhibit these from penetrating into human cells (Ehrhardt et al., 2007). In a prior, not placebo-controlled study we could show, that Cistus (CYSTUS052) was more effective in reducing the average duration and severity of symptoms in patients than green tea. The average content of polyphenols in green tea was comparable to that of CYSTUS052 extract (Chen et al., 2008). The clinical improvement does obviously not depend on the overall amount of polyphenols. The difference in efficacy may be based on the nature of the containing phenolic compounds. In clinical studies polyphenol-rich plant extracts were much more effective than any isolated or composed mixture of pure polyphenols. This strongly suggests that a lot of components and most likely the entire composition may be responsible for the antiviral and antibacterial properties of medicinal herbs (Song et al., 2005).

In conclusion, Cistus was more effective in reducing the average duration and severity of symptoms in patients with infection of the upper respiratory tract than placebo. The results may stimulate further studies with the possibility to treat patients with severe respiratory infections.

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